See corresponding editorial on page 739.

Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies[1–3]

Paige E Miller and Vanessa Perez

Abstract

Background: Replacement of caloric sweeteners with lower- or no-calorie alternatives may facilitate weight loss or weight maintenance by helping to reduce energy intake; however, past research examining low-calorie sweeteners (LCSs) and body weight has produced mixed results.

Objective: The objective was to systematically review and quantitatively evaluate randomized controlled trials (RCTs) and prospective cohort studies, separately, that examined the relation between LCSs and body weight and composition.

Design: A systematic literature search identified 15 RCTs and 9 prospective cohort studies that examined LCSs from foods or beverages or LCSs consumed as tabletop sweeteners. Meta-analyses generated weighted mean differences in body weight and composition values between the LCS and control groups among RCTs and weighted mean correlations for LCS intake and these parameters among prospective cohort studies.

Results: In RCTs, LCSs modestly but significantly reduced all outcomes examined, including body weight (−0.80 kg; 95% CI: −1.17, −0.43), body mass index [BMI (in kg/m^2): −0.24; 95% CI: −0.41, −0.07], fat mass (−1.10 kg; 95% CI: −1.77, −0.44), and waist circumference (−0.83 cm; 95% CI: −1.29, −0.37). Among prospective cohort studies, LCS intake was not associated with body weight or fat mass, but was significantly associated with slightly higher BMI (0.03; 95% CI: 0.01, 0.06).

Conclusions: The current meta-analysis provides a rigorous evaluation of the scientific evidence on LCSs and body weight and composition. Findings from observational studies showed no association between LCS intake and body weight or fat mass and a small positive association with BMI; however, data from RCTs, which provide the highest quality of evidence for examining the potentially causal effects of LCS intake, indicate that substituting LCS options for their regular-calorie versions results in a modest weight loss and may be a useful dietary tool to improve compliance with weight loss or weight maintenance plans. *Am J Clin Nutr* 2014;100:765–77.

INTRODUCTION

Over the past several decades, the worldwide prevalence of overweight and obesity has increased markedly (1, 2). Because overweight and obesity are major causes of comorbidities, including cardiovascular disease, hypertension, type 2 diabetes, certain cancers, and other health conditions (3), identifying strategies that help regulate body weight is imperative. Replacement of caloric sweeteners (herein referred to as sugar) with lower-calorie alternatives is one such strategy that may help reduce energy intake, thereby facilitating weight loss, weight maintenance, or prevention of weight gain (4). Low-calorie sweeteners (LCSs)[4] may improve adherence to weight loss or maintenance plans by preserving the palatability of foods and beverages with fewer calories than sugar (5). Conversely, a hypothesis that LCS intake promotes, rather than prevents, weight gain by altering taste and metabolic signaling, decreasing satiety, and increasing appetite, hunger, sweets cravings, and ultimately food intake emerged nearly 3 decades ago (6, 7). However, a recent review of randomized controlled trials (RCTs) (8), and new findings from an RCT that examined the effect of low-calorie sweetened beverages (LCSBs) on overall dietary patterns (9), failed to support this hypothesis.

LCSs are classified into 2 categories: *1*) nonnutritive sweeteners, which are also referred to as high-intensity, high-potency, and intense sweeteners and *2*) bulk sweeteners or sugar alcohols (eg, polyols). Nonnutritive sweeteners have an intense sweet taste, contribute negligible to zero calories as consumed, and are used in minimal quantities to replace a larger amount of sugar. Polyols replace the bulk of sugar but are generally less sweet (with the exception of xylitol and maltitol); therefore, they are often used in combination with nonnutritive sweeteners. As delivered, polyols contribute 0 to 3.0 kcal/g, compared with 4 kcal/g from sugar (10, 11). LCSs allowed in the United States by the Food and Drug Administration include acesulfame potassium, aspartame, luo han guo extract, neotame, saccharin, steviol glycosides, and sucralose; other nonnutritive sweeteners, such as cyclamate, thaumatin, neohesperidin dihydrochalcone,

[1] From the Center for Epidemiology, Biostatistics, and Computational Biology, Exponent Inc, Chicago, IL.

[2] Supported by the North American Branch of the International Life Sciences Institute.

[3] Address reprint requests and correspondence to V Perez, Exponent Inc, 525 West Monroe Street, Suite 1050, Chicago, IL 60661. E-mail: vperez@exponent.com.

[4] Abbreviations used: LCS, low-calorie sweetener; LCSB, low-calorie sweetened beverage; RCT, randomized controlled trial; SSB, sugar-sweetened beverage; WGMC, weighted group mean correlation; WGMD, weighted group mean difference.

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and alitame, are authorized for use in other countries (4, 12, 13). Among the polyols, the Food and Drug Administration has approved the use of erythritol, hydrogenated starch hydrolysates, isomalt, lactitol, maltitol, mannitol, sorbitol, and xylitol (11, 13); polyglycitol syrup is authorized for use by the European Commission (14).

Overall, research into the potential health effects of LCSs is complicated by the diversity of available LCSs and the growing number of foods and beverages sweetened with one or more LCSs (8, 15). Contributing to this complexity, the composition of LCSs in foods and beverages and consumer preference for particular LCSs continue to change over time. Although past reviews on LCSs and weight control have been published (16–19), none to date have provided a quantitative evaluation of the evidence from both RCTs and prospective cohort studies, examined all types of LCSs, investigated body-composition outcomes, or included several RCTs published in recent years (20–24). Therefore, the purpose of the current study was to systematically review and quantitatively evaluate results from RCTs and prospective cohort studies, separately, that examined the relation between LCSs and body weight, fat mass, BMI, and waist circumference.

MATERIALS AND METHODS

Literature search and study selection

This systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (25). No prespecified protocol was followed for this study. A comprehensive literature search using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was performed to identify RCTs and prospective cohort studies through 16 September 2013 with no lower date limit. The complete search string can be found elsewhere (*see* Supplemental Figure 1 under "Supplemental data" in the online issue). In brief, a combination of MeSH and relevant free text terms designed to capture the following were used: all individual LCSs (generic and name brands) approved for use globally; food and beverage sources of LCS such as "diet soda"; different names for LCS such as "intense sweetener" and "polyol"; body weight and composition parameters (eg, "waist circumference" and "fat mass"); and relevant study designs, including "cohort" and "controlled trial." The MeSH terms included "sweetening agent," "body mass index," "adipose tissue," "adiposity," "body weight," "cohort studies," and "randomized controlled trial." Supplementary literature searches involved examining the reference lists of all relevant studies and pertinent review articles to identify articles not captured in the initial search. Established guidelines for systematic reviews provided by the Agency for Health Care Research and Quality (26) were followed, and special considerations for reviews in the field of nutrition (27) were addressed.

Prospective cohorts and RCTs were eligible if the following criteria were met: *1*) study population was generally healthy (ie, not hospitalized or acutely ill); *2*) dose or intake data for at least one LCS (nonnutritive sweetener or polyol) or delivery vehicle of LCS were provided; *3*) the effect of LCS, compared with the control arm, could be examined independently of other intervention components; and *4*) outcome data for at least one measure of body weight or composition were available. Child and adult populations were eligible. A minimum study duration of ≥2 wk for RCTs (28) and ≥6 mo for prospective cohorts (29) was selected to be consistent with past published meta-analyses that were similar in design (28, 29) and to be inclusive in an area of research with a relatively small pool of studies.

Data extraction

The following information was extracted from each RCT or prospective cohort: first author, publication year, geographic location, demographic and health characteristics, sample size, source and type of LCS, and outcomes measured. For RCTs, additional information on the intervention and control regimens, dose of specific LCS (or LCS source), and means and SDs of changes in the outcomes from baseline to trial end for all study arms were obtained. To avoid double-counting results from 3 studies that had more than one control arm (23, 24, 30), we extracted results a priori from the most relevant comparison group, ie, the one that was most comparable with the other included studies. This included sugar-sweetened beverages (SSBs) in 2 studies (23, 30) and a usual diet that included 280-kcal caloric beverages/d other than milk in the third study (24). When change SDs were unavailable, methods described in the Cochrane Handbook for Systematic Reviews of Interventions (31) were relied on to calculate or estimate SDs from other statistics in the published articles (eg, SDs were calculated from SEs or CIs). For studies with missing measures of variance for mean change, SDs were estimated by using the correlation coefficient (r) method, in which the average correlation coefficient ($r = 0.965$) between baseline and trial-end values from all other included studies was used. For one study with missing baseline, trial-end, and change SDs (32), values for change SD were imputed from the average change SD among the other RCTs included in the meta-analysis. Sensitivity analyses evaluated the change in overall study results by removing *1*) the RCT by Kanders et al (32) that had imputed SDs for change in the outcome measurements and, in a separate analysis, *2)* the RCT by Knopp et al (33) that had an inherently different intervention design (aspartame capsules were provided rather than LCSs in foods or beverages or as tabletop sweeteners).

Additional data extracted from prospective cohort studies included cohort name, dietary-assessment method, year in which diet was assessed, exposure unit, intakes within each exposure category, statistical adjustments, and results data as presented by the author, which were as follows: the β estimate, SE, and associated t statistic for change in the outcome per unit increase in the baseline exposure (estimated from linear regression models) or the change in outcome and SE in each category of intake. Two studies reported outcome data as RRs and 95% CIs: one for risk of overweight/obesity (34) and the other for risk of elevated waist circumference (35); these data were extracted and reviewed but were not included in the meta-analysis because ≥2 studies were required to pool results. Authors were contacted up to 3 times, if needed, for missing data and study details.

Statistical analysis

A meta-analysis was performed by using random-effects modeling with Comprehensive Meta-Analysis Software (version 2.2.046; Biostat). The primary meta-analyses for the RCTs evaluated the mean change in body weight, fat mass, BMI, or waist circumference (mean value at follow-up minus the mean

value at baseline for both groups) between the LCS intervention group and the comparator arm. Two or more RCTs by outcome were required to generate weighted group mean differences (WGMDs), 95% CIs, and corresponding *P* values for heterogeneity. The degree of inconsistency between studies was evaluated by using the I^2 statistic ($0\% \leq I^2 \leq 100\%$, where increasing values correspond to greater heterogeneity) (36).The same outcomes measured on different scales were converted to the same unit (eg, pounds to kilograms) for comparability between studies (31). Meta-analyses by the following subgroups were performed: *1*) age group [children compared with adults (>18 y)], *2*) sex, *3*) source of LCS (beverage, foods, or tabletop sweetener), and *4*) whether the LCS intervention resulted in significantly lower energy intake compared with the comparator arm.

The primary meta-analyses of the prospective cohort studies evaluated the reported or calculated *t* statistics (regression slope divided by its SE) and specified the effect direction as determined by a positive or negative regression coefficient. This analysis allowed for the synthesis of the regression slopes based on a standardized metric (37).Two or more studies by outcome were required to generate weighted group mean correlations (WGMCs), 95% CIs, corresponding *P* values for heterogeneity, and the I^2 statistic. Whenever possible, subgroup analyses were conducted as done for the RCTs and according to whether the studies provided *1*) total energy-adjusted results and *2*) baseline BMI-adjusted analyses (adjustments for other baseline body-composition variables were eligible but not performed).

Pooled summary estimates from the random-effects models were compared with the results from fixed-effects models to examine the potential for small-study bias. Potential publication bias was examined by visual inspection of funnel plots and with Egger's regression test (38). The *x* axis in the funnel plots represents the effect size of each RCT or the Fisher-transformed correlation value of each prospective cohort study. The *y* axis represents the SE of the effect size or correlation value of the corresponding study. The solid vertical line is the pooled summary estimate from the meta-analysis. In the absence of publication bias, the plot resembles a symmetrical inverted funnel, and Egger's regression test will fail to reject the null hypothesis of no funnel plot asymmetry.

RESULTS

Literature search and study characteristics

The PubMed search yielded 522 references, of which 93 articles were retained for full-text screening. Fifteen RCTs (20–24, 30, 32, 33, 39–45) and 9 prospective cohorts were ultimately eligible for inclusion in the meta-analysis (**Figure 1**). Primary characteristics of the 15 included RCTs are provided in **Table 1**. A total of 1951 participants were included in the meta-analysis; individual trial size ranged from 19 adults (42) in a crossover study to 632 children in a parallel-design trial (20). Most studies were conducted in adult populations; 4 studies were conducted in children (20, 21, 33, 39). Study duration varied widely [3 wk (30) to 78 wk (20)], as did the mean age of the participants [4 y (20) to 65 y (24)]. The mean BMI (in kg/m^2) across the studies varied from 22.5 (44) to 37.7 (32) (median: 29.1), with the exception of one study among young children aged 4–11 y (20), in which the mean BMI was 16.8 (0.03 *z* score for age) (20). Eight of the trials were conducted solely in overweight or obese populations (21–24, 32, 40, 43, 45). Nine studies presented

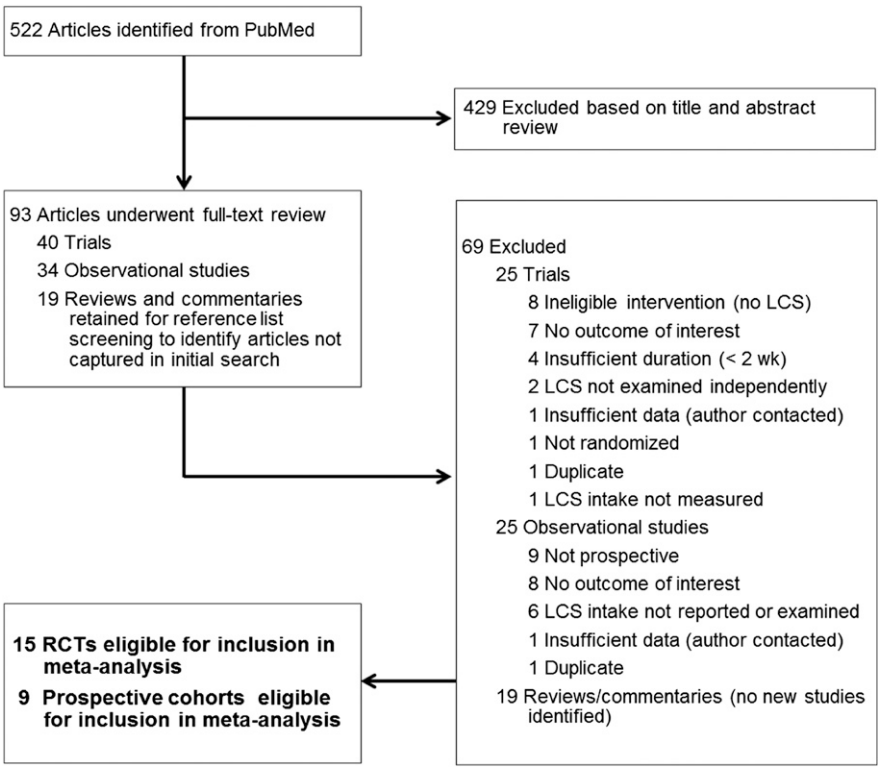

FIGURE 1. Study selection process. http://www.ncbi.nlm.nih.gov/pubmed. LCS, low-calorie sweetener; RCT, randomized controlled trial.

TABLE 1
Characteristics of the randomized controlled trials included in the meta-analysis[1]

				Intervention details				
Study, year (ref)	Age[2]	Sex (M/F)	Mean BMI	Control group	LCS group	LCS dose/d[3]	Duration[4]	Outcome
	y		*kg/m*^{2}				*wk*	
Blackburn et al, 1997 (40)	20–60	0/136	37.3	Energy-reduced diet with sucrose-sweetened foods and beverages plus table sugar for sweetener	Energy-reduced diet with aspartame-sweetened foods and beverages plus aspartame sweetener	285 ± 235 mg aspartame	16	BW
de Ruyter et al, 2012 (20)	4–11	343/289	16.8 (0.03 *z* score)	8 oz/d SSB	8 oz/d LCSB	34 mg sucralose + 12 mg ACK	78	BMI *z* score, BW, fat mass,[5] WC
Ebbeling et al, 2006 (39)	13–18	47/56	25.3	Usual diet, which included ≥ 1 SSB/d	Up to 4 cans or bottles of LCSBs and water per day	21.7 oz LCSB	25	BMI
Ebbeling et al, 2012 (21)	14–16	124/100	30.3	Usual diet, which included ≥ 1 SSB or fruit juice/d	LCSBs and water	10.8 oz LCSB	52	BMI, BW, fat mass[5]
Gatenby et al, 1997 (41)	18–50	0/65	23.1	Usual diet that did not include habitual consumption of reduced-sugar foods	Detailed instructions provided for substituting conventional sugar-containing foods with those containing LCS	NR	10	BW
Gostner et al, 2005 (42)	21–53	7/12	NR	Sucrose-sweetened foods as part of an otherwise typical Western-style diet (low fiber, high fat)	Isomalt-sweetened foods as part of an otherwise typical Western-style diet (low fiber, high fat)	30 g isomalt	4	BW
Kanders et al, 1988 (32)	26–60	11/45	37.7	Energy-reduced diet without any aspartame- or saccharin-sweetened products	Energy-reduced diet with aspartame-sweetened foods and beverages plus aspartame sweetener	383 mg aspartame	12	BW, BMI, fat mass[5]
Knopp et al, 1976 (33)	10–21	4/51	NR[6]	Energy-reduced diet plus lactose capsules	Energy-reduced diet plus aspartame capsules	2700 mg aspartame	13	BW
Maersk et al, 2012 (23)	20–50	17/30	32.1	SSB	Aspartame-sweetened soda	33.8 oz LCSB	26	BW, fat mass[7]
Njike et al, 2011 (22)[8]	52 ± 11	6/33	30.3	Sugar-sweetened hot cocoa	ACK- and aspartame-sweetened hot cocoa	16 oz LCSB	6	BW, BMI, WC

(Continued)

TABLE 1 (*Continued*)

Study, year (ref)	Age[2]	Sex (M/F)	Mean BMI	Intervention details		LCS dose/d[3]	Duration[4]	Outcome
				Control group	LCS group			
Raben et al, 2002 (43)	20–50	6/35	27.8	Sugar-sweetened food and beverages	Food and beverages with LCS (by weight, 54% aspartame, 22% ACK, 23% cyclamate, and 1% saccharin)	480–670 mg aspartame + ACK + cyclamate + saccharin	10	BW, fat mass[5]
Reid et al, 2007 (44)	20–55	0/133	22.5	SSB	Aspartame- and ACK-sweetened soda	34 oz LCSB	4	BMI
Reid et al, 2010 (45)	20–55	0/53	27.5	SSB	Aspartame- and ACK-sweetened soda	34 oz LCSB	4	BW
Tate et al, 2012 (24)	18–65	50/268	36.2	Usual diet, which included 280-kcal caloric beverages/d other than milk	Replacement of caloric beverages with LCSB (population consumed ≥ 280-kcal caloric beverages/d other than milk before intervention)	24–32 oz LCSB	26	BW, WC
Tordoff and Alleva, 1990 (30)[8]	22.9 ± 3.7	21/9	25.2	SSBs	Aspartame-sweetened soda	38 oz LCSB	3	BW

[1] 1 oz = ~30 mL. ACK, acesulfame potassium; BW, body weight; LCS, low-calorie sweetener; LCSB, low-calorie sweetened beverage; NR, not reported; ref, reference; SSB, sugar-sweetened beverage; WC, waist circumference.

[2] Mean ± SD is shown when age range was not reported by the authors.

[3] The dose of the LCS source (beverages) is shown when the actual dose of LCS was not reported in the study.

[4] Reflects the length of time in each study arm, not the duration of the entire study in the case of crossover trials.

[5] Measured by bioelectrical impedance analysis.

[6] Study population was overweight, on average, but mean BMI was not provided.

[7] Measured by dual-energy X-ray absorptiometry.

[8] Crossover design.

results for males and females combined, 2 studies reported results separately (30, 32), and 4 studies were conducted only in women (40, 41, 44, 45).

Most of the LCS intervention regimens exclusively evaluated LCSBs (20–24, 30, 39, 44, 45); information on the LCS composition in these beverages was available in 5 of the studies [aspartame alone (23, 30) or aspartame plus acesulfame potassium (22, 44, 45)]. Of the remaining 6 trials, 2 assigned participants to diets with aspartame-sweetened foods and beverages plus aspartame for tabletop sweetener (32, 40), 1 provided aspartame capsules (33), 1 had participants substitute conventional sugar-containing foods with those containing LCS (41), 1 provided isomalt-sweetened foods (42), and 1 provided participants with foods and beverages sweetened with aspartame, cyclamate, acesulfame potassium, and saccharin (43). The group that received SSBs or sugar-sweetened foods or the group assigned to follow a habitual (usual) diet that contained SSBs and sugar-sweetened foods was evaluated as the control arm for most studies (20–24, 30, 39–45). The other control arms consisted of groups that received lactose capsules (33) or an energy-reduced diet (similar to the intervention) that did not include LCSs (32).

The main characteristics of the prospective cohort studies are shown in **Table 2**. The number of subjects in each study ranged from 465 (46) to 51,603 (47), with a total of 103,940 subjects across the 9 cohorts. Four studies were conducted in children and adolescents (48–51) and 5 in adults (34, 35, 46, 47, 52). Five studies provided results for men and women combined (34, 35, 46, 49, 51), 2 provided results for each sex separately (48, 50), and 2 examined women only (47, 52). Most of the cohort studies reported only one outcome (35, 46–48, 51, 52), and the outcome reported by each of these 6 studies varied: BMI (48), body weight (46, 47, 52), fat mass (51), and risk of elevated waist circumference (35). The other studies examined BMI and fat mass (50), BMI and body weight (49), and BMI and incidence of becoming overweight/obese or obese (34). Only 2 types or sources of LCS were examined across the cohorts—beverages sweetened with LCS (34, 35, 47–51) or saccharin (46, 52).

Meta-analysis results from RCTs

Body weight

Shown in **Figure 2** are the effect sizes, 95% CIs, and precisions of each study from the meta-analysis of RCTs examining LCSs and body weight among all subjects (forest plot A) and by age group (forest plot B), sex (forest plot C), and source of LCS (forest plot D). In the meta-analysis of all subjects, LCS reduced body weight by 0.80 kg (95% CI: −1.17, −0.43; fixed-effect WGMD = −0.61) compared with the comparator arm. Removal of data from Kanders et al (32) and Knopp et al (33), in separate analyses, marginally affected the results: −0.79 kg (95% CI: −1.17, −0.42; fixed-effect WGMD = −0.60) and −0.79 kg (95% CI: −1.18, −0.41; fixed-effect WGMD = −0.60), respectively. In stratified models by age group, LCSs decreased body weight in children (−1.06 kg; 95% CI: −1.57, −0.56; fixed-effect WGMD = −1.06) and adults (−0.72 kg; 95% CI: −1.15, −0.30; fixed-effect WGMD = −0.52). Results among children with data from Knopp et al (33) removed [−1.09 kg (95% CI: −1.70, −0.48); fixed-effect WGMD = −1.06] and results among adults with data from Kanders et al (32) removed [−0.71 kg (95% CI: −1.14, −0.28); fixed-effect WGMD = −0.51] were not appreciably different from the results with these studies included. Analyses by sex showed significant reductions in body weight with LCSs among women (−0.72; 95% CI: −1.19, −0.25; fixed-effect WGMD = −0.62); the summary estimate for men was null but based on only 2 trials (no evidence of small-study bias was observed) (30, 32). Meta-analyses examining change in body weight by source of LCS were also limited because most studies examined LCSBs rather than foods or tabletop sweeteners (no evidence of small-study bias was observed; forest plot D).

BMI, fat mass, and waist circumference

The effects of LCS on BMI (kg/m^2; forest plot A), fat mass (kg; forest plot B), and waist circumference (cm; forest plot C), compared with the comparator arm, are shown in **Figure 3**. LCS significantly reduced BMI (−0.24 kg/m^2; 95% CI: −0.41, −0.07; fixed-effect WGMD = −0.24), fat mass (−1.10; 95% CI: −1.77, −0.44; fixed-effect WGMD = −1.41), and waist circumference (−0.83; 95% CI: −1.29, −0.37; fixed-effect WGMD = −0.83). Additional results from subgroup analyses are shown elsewhere (*see* Supplemental Table 1 under "Supplemental data" in the online issue).

Meta-analysis results from prospective cohort studies

Meta-analyses of the prospective cohort studies were limited largely by differences across the individual studies; the models that were feasible are shown in **Figure 4** and elsewhere (*see* Supplemental Table 2 under "Supplemental data" in the online issue). Modest statistically significant positive associations between baseline LCS intake and change in BMI (WGMC: 0.03; 95% CI: 0.01, 0.06; fixed-effect WGMC = 0.03) are shown in Figure 4 (forest plot A). In the meta-analysis of LCS intake and weight gain (Figure 4; forest plot B) and fat mass (*see* Supplemental Table 2 under "Supplemental data" in the online issue), no statistically significant associations were observed, and statistical evidence for small-study bias was lacking (data not shown). Only one prospective cohort study examined waist circumference (specifically, risk of elevated waist circumference) (35); therefore, a meta-analysis examining the effect of LCS on waist circumference was not possible.

Publication bias

The symmetric funnel plot of RCTs that examined LCS and body weight (**Figure 5**; plot A), which was the largest set of studies, does not provide evidence of publication bias—a finding supported by Egger's regression test ($P = 0.164$). There was some evidence of publication bias among the prospective cohorts that examined BMI (the largest set of cohort studies), based on a visual assessment of the funnel plot (Figure 5; plot B), although this was not supported by Egger's regression test ($P = 0.818$).

DISCUSSION

The current meta-analysis provides a rigorous evaluation of the scientific evidence on LCS and body weight and composition. Findings from the meta-analysis of 15 RCTs—the gold standard study design in medical research—indicate that substituting LCS for sugar modestly reduces body weight, BMI, fat mass, and waist circumference. Although the mean reduction in body

TABLE 2
Characteristics of the prospective cohorts included in the meta-analysis[1]

Study, year (ref)	Cohort	Age[2]	Sex (M/F)	BMI (mean)	Follow-up	Year diet assessed	Dietary-assessment method	LCS source or type	Results, energy-adjusted	Results, BMI-adjusted[3]	Outcome[4]
		y			*y*						
Berkey, 2004 (48)	GUTS	9–14	5067/6688	NR	1	1997–1998	Validated youth FFQ	LCSB	Yes	Yes	BMI
Colditz, 1990 (52)	NHS	30–55	0/31,940	23.4[5]	4	1980	Validated FFQ	Saccharin	Yes	Yes	BW
Fowler, 2008 (34)	SAHS	25–64	1421/1950	27.4	7.5	1979–88	24-h recall + survey questions	LCSB	No	Yes	BMI, overweight/ obesity incidence
Johnson, 2007 (51)[6]	CIF	7	471 (M+F)	16.2 (0.10 *z* score)	2	1999	3-d food records	LCSB	No	Yes	Fat mass[7]
Laska, 2012 (50)	IDEA + ECHO	10–17	276/286	22.0	2	2006–2008	4 validated survey questions	LCSB	Yes	No	BMI, fat mass[8]
Nettleton, 2009 (35)[9]	MESA	45–84	1307/1121	27.9	3–7	2000–2002	1 FFQ question	LCSB	Yes	No	Risk of elevated WC
Newby, 2004 (49)	ND WIC Program	2.9 ± 0.7	675/670	16.6	0.5–1	1995–1998	Validated FFQ	LCSB	Yes	No	BMI, BW
Parker, 1997 (46)	PHHP	18–64	176/289	26.5	4	1986–1987	Validated FFQ	Saccharin	Yes	Yes	BW
Schulze, 2004 (47)	NHS II	24–44	0/51,603	24.5	4	1991–1999	3 validated FFQ questions	LCSB	No	Yes	BW

[1] BW, body weight; CIF, Children In Focus; ECHO, Etiology of Childhood Obesity; FFQ, food-frequency questionnaire; GUTS, Growing Up Today Study; IDEA, Identifying Determinants of Eating and Activity; LCS, low-calorie sweetener; LCSB, low-calorie sweetened beverage; MESA, Multi-Ethnic Study of Atherosclerosis; ND WIC, North Dakota Women, Infants, and Children; NHS, Nurses' Health Study; NR, not reported; PHHP, Pawtucket Heart Health Program; ref, reference; SAHS, San Antonio Heart Study; WC, waist circumference.

[2] Mean ± SD when the age range was not reported.

[3] Adjustment for other baseline body-composition measures was eligible but not performed in any studies.

[4] Reflects change in the measure from baseline, unless noted otherwise.

[5] Mean BMI was estimated from categorical data provided in the article.

[6] Findings among 7-y-olds are shown; authors also report findings among a smaller sample of the population at 5 y.

[7] Measured by dual-energy X-ray absorptiometry.

[8] Measured by bioelectrical impedance analysis.

[9] Met eligibility criteria but was not included in the meta-analysis because it was the only study with risk of elevated WC as an outcome.

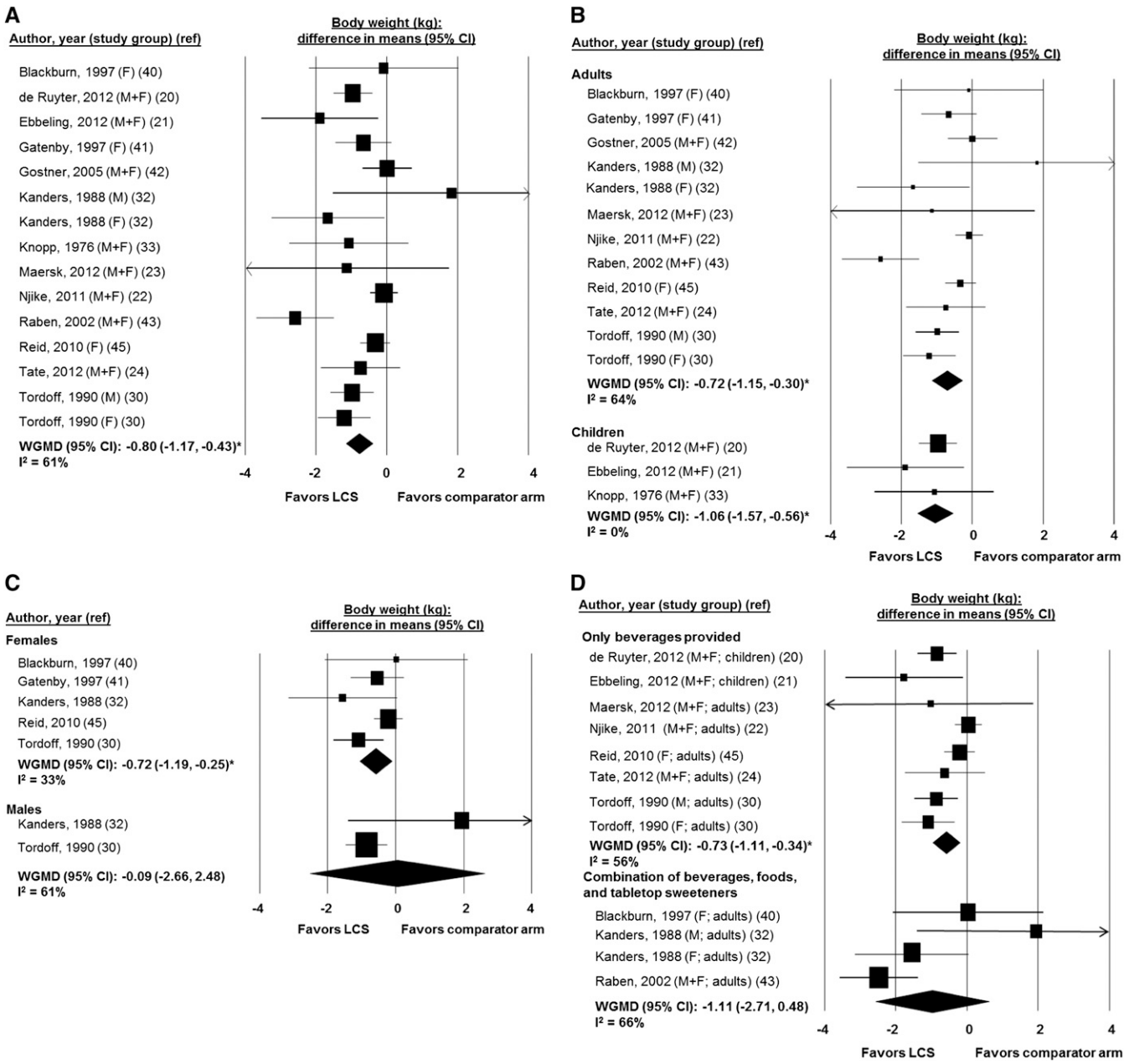

FIGURE 2. Forest plots derived from random-effects models depicting the effect of LCS on body weight in RCTs among all subjects (A) and by age (B), sex (C), and source of LCS (D). Squares represent mean change in body weight within the individual studies; 95% CIs are represented by horizontal lines. Square size is proportional to the weight of each study. Diamonds represent the WGMD. $^*P < 0.05$. LCS, low-calorie sweetener; RCT, randomized controlled trial; ref, reference; WGMD, weighted group mean difference.

weight was modest (0.80-kg decrease), it would not be expected for a single dietary change, ie, replacement of sugar with LCS, to cause clinically meaningful weight loss (53). Rather, leading nutrition and health authorities recommend a multifaceted approach to weight loss and weight maintenance—one that includes an overall healthy dietary pattern, physical activity, and other lifestyle behavior changes (54, 55). By maintaining the palatability of foods and beverages with fewer calories than sugar, LCS could help improve adherence to weight-loss or maintenance plans (5).

The current meta-analysis also examined the relation between LCS intake and body weight and composition among prospective cohort studies because experimental and observational research methods can be complementary tools in understanding diet-health relations. This meta-analysis showed statistically nonsignificant associations between LCS intake and body weight and fat mass, but a significant, albeit modest, positive association with BMI. Compared with findings from well-controlled, randomized trials, wherein reported effects can be attributed to the dietary intervention under investigation (56), findings from observational studies in the field of nutrition are not easily interpreted. Specifically, the meta-analysis of prospective cohort studies was limited because few studies (46, 48, 52) adequately controlled for potential confounding by other diet and lifestyle factors. Only 3

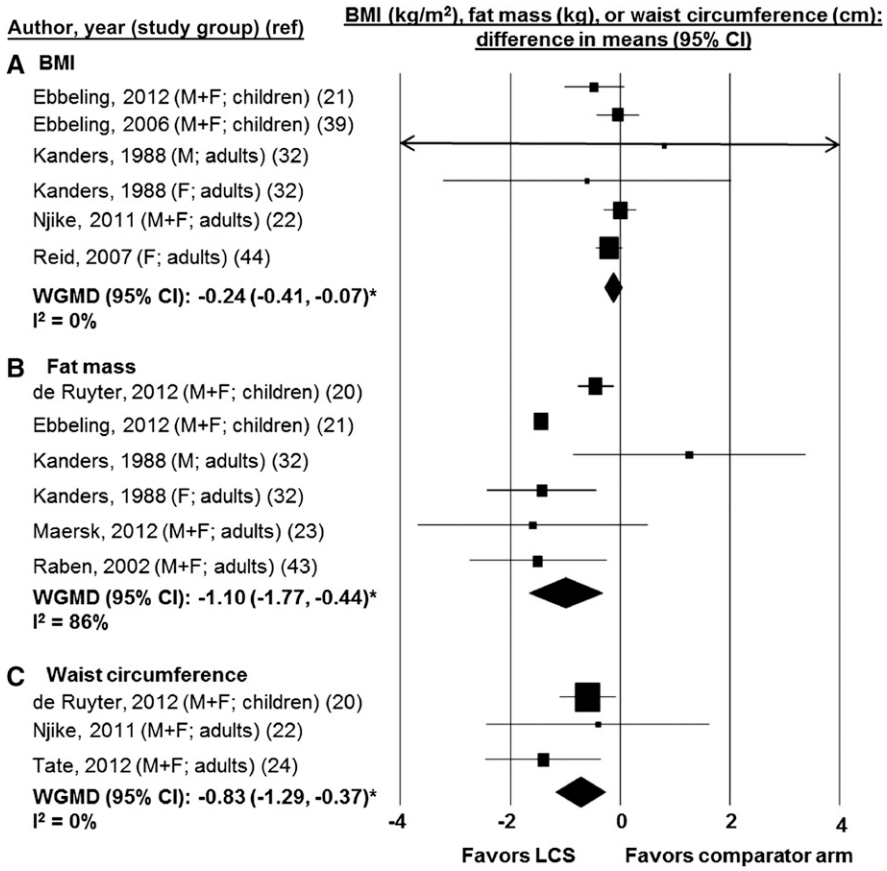

FIGURE 3. Forest plots derived from random-effects models depicting the effects of LCS on BMI (A), fat mass (B), and waist circumference (C) in RCTs. Squares represent mean change within the individual studies; 95% CIs are represented by horizontal lines. Square size is proportional to the weight of each study. Diamonds represent the WGMD. *$P < 0.05$. LCS, low-calorie sweeteners; RCT, randomized controlled trial; ref, reference; WGMD, weighted group mean difference.

studies (46, 48, 52) controlled for both total energy intake and a measure of baseline body weight or composition. Several other potential sources of bias include the possibility of reverse causality and dietary measurement error (57)—2 methodologic issues that were not sufficiently addressed in most studies included in the meta-analysis. Importantly, 7 (35, 46–50, 52) of the prospective cohorts assessed LCS intake at baseline, and only a few survey or food-frequency questionnaire questions pertained to LCS intake (largely consumption of diet soda). This insufficient measurement of LCS intake provides limited information on individual intakes and, as a result, may have biased the reported associations with body weight and composition (58).

Variations in overall dietary patterns among subjects in observational studies should be considered in the study of LCSs and body weight and composition because individuals who consume LCSs may have differential patterns of eating compared with those who do not (59). Recent findings from the Choose Healthy Options Consciously Everyday RCT provide supporting evidence that LCS intake plays a role in influencing overall dietary patterns (9). In this 6-mo study, replacement of regular-calorie beverages with either water in one study arm or LCSBs in a second study arm resulted in significant changes in other food and nutrient intakes. Both groups consumed less total energy, whereas intakes of desserts, caloric sweeteners, and alcohol were significantly reduced in the LCSB group but not in the water group. This finding provides suggestive evidence that LCSs do not, contrary to past hypotheses (6, 7), increase the desire or inclination to consume more sweet foods. Taken together, observational and experimental investigations into LCS intake as part of overall dietary patterns provide useful insight into how individuals are currently consuming LCSs and the effect of LCS intake on dietary patterns. In turn, these findings may be useful in informing the development of dietary guidelines and public health recommendations.

In both the prospective cohort studies and RCTs, the sources and types of LCSs investigated were limited. Seven (34, 35, 47–51) of the 9 prospective cohorts examined intakes of LCSBs, which is just one of many sources of LCS in the diet. The other 2 cohort studies (46, 52) investigated intakes of only one type of LCS (saccharin). There was more diversity in the sources and types of LCS evaluated among the RCTs, although 9 (20–24, 30, 39, 44, 45) of the 15 studies exclusively examined LCSBs. The others evaluated aspartame (32, 33, 40), unspecified LCSs (41), isomalt (42), and a combination of aspartame, cyclamate, acesulfame potassium, and saccharin (43). In addition to the limited types and sources of LCS examined, far fewer studies examined the effect of LCSs on BMI, fat mass, and waist circumference compared with body weight. Nevertheless, the direction of effects was the same across the different outcomes, and all reductions were statistically significant.

Only one RCT (33) examined the effect of capsules of LCS (specifically aspartame) on body weight. The main research objective in the RCT by Knopp et al (33)—to evaluate potential

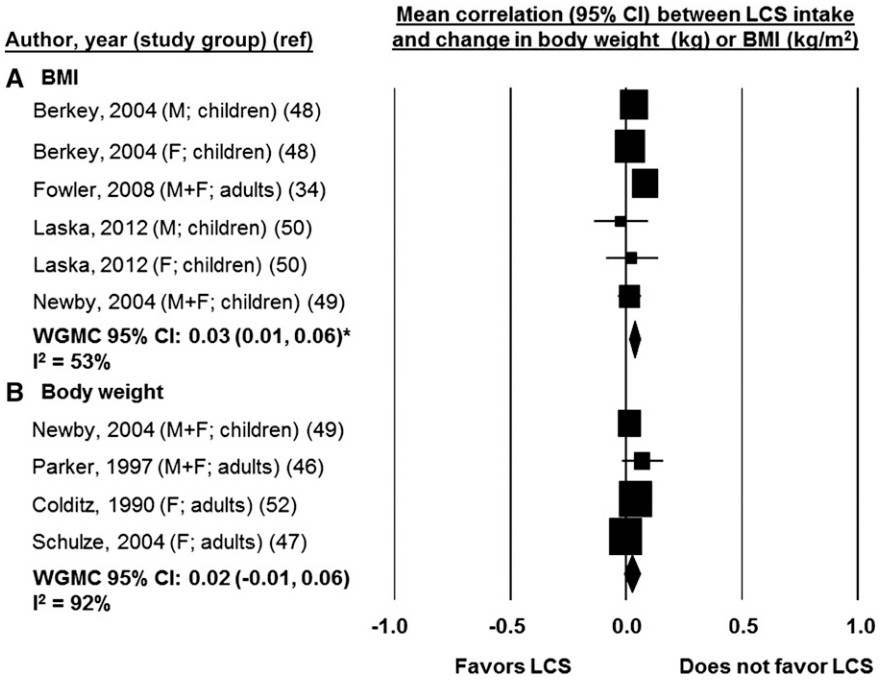

FIGURE 4. Forest plots derived from random effects models summarizing results from the meta-analysis of prospective cohort studies that examined LCS intake and change in BMI (A) or body weight (B). The squares represent the mean correlation within each study, with 95% CIs represented by horizontal lines. Square size is proportional to the weight of each study. Diamonds represent the WGMC. Reference numbers are shown in parentheses. *$P < 0.05$. LCS, low-calorie sweetener; ref, reference; WGMC, weighted group mean correlation.

toxicity from aspartame intake administered in capsule form—is inherently different from the objectives in the other RCTs, which were designed to examine the effects of LCS as a sugar substitute (provided in foods, in beverages, or as tabletop sweeteners). Body weight was not a primary outcome in the study by Knopp et al; however, because it was measured and the study met a priori inclusion criteria, it was included in the current meta-analysis. Knopp et al found nonstatistically significant reductions in body weight, and removal of this RCT from the meta-analysis did not appreciably influence the summary findings.

Past reviews examining the relation between LCS and body weight have focused solely on one type of LCS (18) or have been qualitative in nature (5, 16, 17, 19, 60). Two of the recent qualitative reviews (16, 19) noted a lack of evidence to draw firm conclusions and called for additional research, including long-term relatively large trials, to advance understanding and address key questions. The current systematic review and meta-analysis aimed to address many of these questions by quantitatively summarizing results from RCTs, 5 of which have been published since 2011 (20–24). One of these trials (20)—the largest (n = 641 enrolled) and longest (18 mo) to date—found that replacement of SSBs with LCSBs reduced weight gain and fat accumulation in normal-weight children aged 4–11 y.

Although the body of evidence on LCSs and body weight has grown in recent years, several research questions remain. Examinations into specific LCSs, particularly understudied yet commonly used LCSs such as polyols, sucralose, and steviol glycosides, are warranted. Research into the role of LCSs as part of overall dietary patterns would provide important insight for developing guidelines and public health recommendations. Few studies provided separate estimates for men and women, which limited evaluations of sex-specific effects. Observational studies that use new dietary-assessment tools, such as those that integrate technology in mobile phones with image processing, visualization, and food and nutrient databases (61), have the potential to substantially improve the quality and validity of dietary intake data and thus studies that depend on these observational data. In addition, the inclusion of additional LCSs and products sweetened with LCS into food and nutrient databases would facilitate comprehensive investigations into the relation between LCS intake and body weight and composition.

In conclusion, the meta-analysis of observational studies showed a small positive association between LCS intake and BMI, but no association with body weight or fat mass. On the other hand, data from RCTs, which provide the highest quality of evidence for examining the potentially causal effects of LCS intake on body weight, indicate that substituting LCSs for calorically dense alternatives results in a modest reduction of body weight, BMI, fat mass, and waist circumference. Compared with the consistent findings among the RCTs, results from prospective cohort studies were limited and more difficult to interpret, particularly because of inadequate control of important confounders, including total energy intake and baseline differences between LCS consumers and nonconsumers in body weight and composition. On the basis of the available scientific literature to date, substituting LCS options for their regular-calorie versions results in a modest weight loss and may be a useful dietary tool to improve compliance with weight-loss or weight-maintenance plans.

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The authors' responsibilities were as follows—PEM: conceptualized the study, conducted the literature review, extracted the study data, and designed the study; VP: conducted a separate data extraction for quality control and

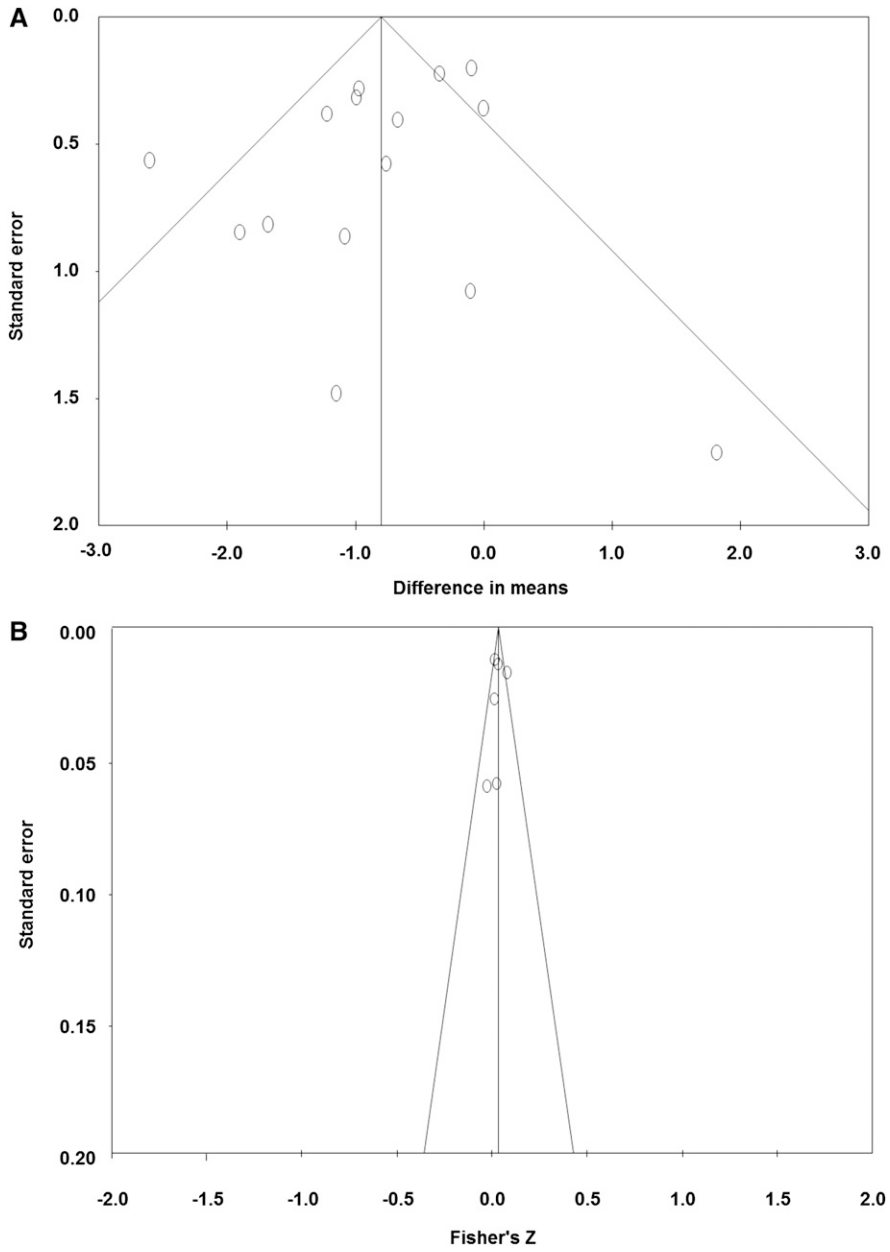

FIGURE 5. Funnel plots for the detection of publication bias among RCTs that examined body weight (A) and prospective cohort studies that examined BMI (B). The *x* axis represents the effect size of each RCT (A) or the Fisher-transformed correlation value of each prospective cohort study (B). The *y* axis represents the SE of the effect size (A) or the correlation value (B) of the corresponding study. The solid vertical line is the pooled summary estimate from the meta-analysis. RCT, randomized controlled trial.

conducted the meta-analyses; PEM and VP: interpreted the results; PEM: drafted the manuscript, with substantial support from VP; and both authors critically reviewed the manuscript for intellectual content. PEM and VP received funding to conduct this research from the North American Branch of the International Life Sciences Institute (ILSI). ILSI had no role in the study design, data collection and analysis, interpretation of the data, or preparation of the manuscript. At the time this research was completed, PEM was employed at Exponent. Neither of the authors had a conflict of interest.

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