

# Effect of Bariatric Surgery on the Circulating Level of Adiponectin, Chemerin, Plasminogen Activator Inhibitor-1, Leptin, Resistin, and Visfatin: A Systematic Review and Meta-Analysis

## Authors

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## ABSTRACT

Different adipokines secreted from adipose tissue, exert a range of physiological effects. The aim of present systematic review and meta-analysis was to critically investigate the consequence of bariatric surgery on circulating adipokines, that is, adiponectin, leptin, visfatin, resistin, plasminogen activator inhibitor, and chemerin. After systematically checking the following electronic databases: ISI web of Science, Scopus and PubMed without limitation in time and language up to February 2019, a pool based on a random effect model was established. Eighty-five eligible studies were entered for quantitative analysis. Our meta-analysis revealed that circulating adiponectin increased significantly after bariatric surgery [Standardized mean difference (SMD)= 1.401, 95% CI: 1.101, 1.701,  $p < 0.001$ ]; whilst leptin (SMD= -2.178, 95% CI: -2.433, -1.923,  $p < 0.001$ ), PAI-1 (-14.928 ng/ml 95% CI: -21.794, -8.063,  $p < 0.001$ ), and chemerin (-50.238 ng/ml 95% CI: -85.708, -14.768,  $p < 0.001$ ) decreased. However, serum visfatin (2.05 ng/ml, 95% CI: -5.07, 9.17,  $p = 0.573$ ) and resistin (-2.080 ng/ml, 95% CI: -5.352, 1.192,  $p = 0.21$ ) were unchanged. In conclusion, bariatric surgery is associated with a reduction in specific adipokines including leptin, chemerin, and PAI-1, whereas adiponectin is raised, adaptations that could be indicative of improved fat mass and function.

## Introduction

Obesity, which is defined as excessive expansion of white adipose tissue, is a global health problem with reported prevalence of more than 1.9 billion around the world [1]. It is associated with a range of health-related problems and major chronic diseases including cancer, cardiovascular diseases (CVD), and diabetes mellitus (DM) [2–4]. There is thus an urgent need for patients with obesity to get rid of their excess fat. Many conservative therapies such as restricted diet take time and do not result in sustained weight loss [5], whereas bariatric surgery appears to have a better outcome [6, 7]. Food intake is reduced following bariatric surgery as a consequence of either reducing the size of stomach through insertion of a gastric band, or the removal of a part of the stomach or reducing the length of the small intestine. Long-term studies indicate this type of surgery, is not effective for weight loss [5], but also ameliorate a variety of obesity-related diseases such as DM and CVD [8]. However, some adverse effects may be expected due to the magnitude of the procedure [9]. Moreover, whether it also has further benefits due to an improved profile of circulating adipokines remains to be fully clarified.

Adipose tissue is a loose connective tissue, which is mainly composed of adipocytes. It acts as an energy storing for lipids and is recognized as the biggest endocrine organ of the human body, secreting several soluble factors, known as adipokines [10]. These are critical regulators of systemic lipid and glucose homeostasis, although most are associated with obesity-related health problems such as insulin resistance, beta-cell dysfunction, endothelial dysfunction, and atherosclerosis [11–14]. Although leptin can regulate energy balance by inhibiting hunger, obesity results in a loss of sensitivity [15]. Adiponectin is a protein hormone with an anti-inflammatory role that can modulate glucose and lipid homeostasis [16]. Chemerin, is a chemoattractant protein, that is necessary for adipogenesis, which when elevated in adipose tissue may be a marker for the onset of DM [17]. Visfatin is an enzyme that activates insulin and has insulin-mimetic effects [18], whereas plasminogen activator inhibitor-1 (PAI-1), is the primary inhibitor of tissue- and urokinase-type plasminogen activators, and considered to be a critical regulator of the fibrinolytic system [19]. Finally, resistin promotes hepatic production of low density lipoproteins (LDL), which degrades LDL receptors [20].

Weight loss after bariatric surgery is mainly due to the loss of visceral fat [21], but whether the secretion of adipokines is then modulated remains to be fully established as the response varies [22–24] and is not always significant [25–30]. We, therefore, conducted a meta-analysis and systematic review to investigate the effect of different types of bariatric surgeries on these adipokines.

## Materials and Methods

This meta-analysis and systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [31].

### Search strategy

PubMed/Medline and Scopus were searched from inception to January 2019 using the following terms in titles and abstracts: ((*leptin*

[Title/Abstract]) OR (*adiponectin* [Title/Abstract]) OR (*PAI-1* [Title/Abstract]) OR (“*Plasminogen activator inhibitor-1*” [Title/Abstract]) OR (*visfatin* [Title/Abstract]) OR (“*pre-B cell colony-enhancing factor-1*” [Title/Abstract]) OR (*PBEF* [Title/Abstract]) OR (“*nicotinamide phosphoribosyltransferase*” [Title/Abstract]) OR (*Nampt* [Title/Abstract]) OR (*Chemerin* [Title/Abstract]) OR (*resistin* [Title/Abstract]) OR (“*adipocyte secreted factor*” [Title/Abstract]) OR (*ADSF* [Title/Abstract]) OR (*FIZZ-3* [Title/Abstract])) AND (“*Bariatric Surgery*” [Mesh]) OR (“*Gastric Bypass*” [Title/Abstract]) OR (“*Gastrectomy*” [Title/Abstract]) OR (“*Bariatric Surgery*” [Title/Abstract]) OR (“*Biliopancreatic Diversion*” [Title/Abstract]) OR (*Gastroplasty* [Title/Abstract]) OR (*bariatric* [Title/Abstract]) OR (*Roux-en-Y* [Title/Abstract]) OR (*RYGB* [Title/Abstract]) OR (“*Sleeve gastrectomy*” [Title/Abstract]) OR (“*Gastric sleeve*” [Title/Abstract]) OR (“*gastric band*” [Title/Abstract]) OR (*Lap-Band* [Title/Abstract]) OR (“*duodenal switch*” [Title/Abstract])). As we did not want to miss any relevant articles, all the reference list of eligible articles, related reviews, and meta-analyses were hand-searched.

### Eligibility criteria

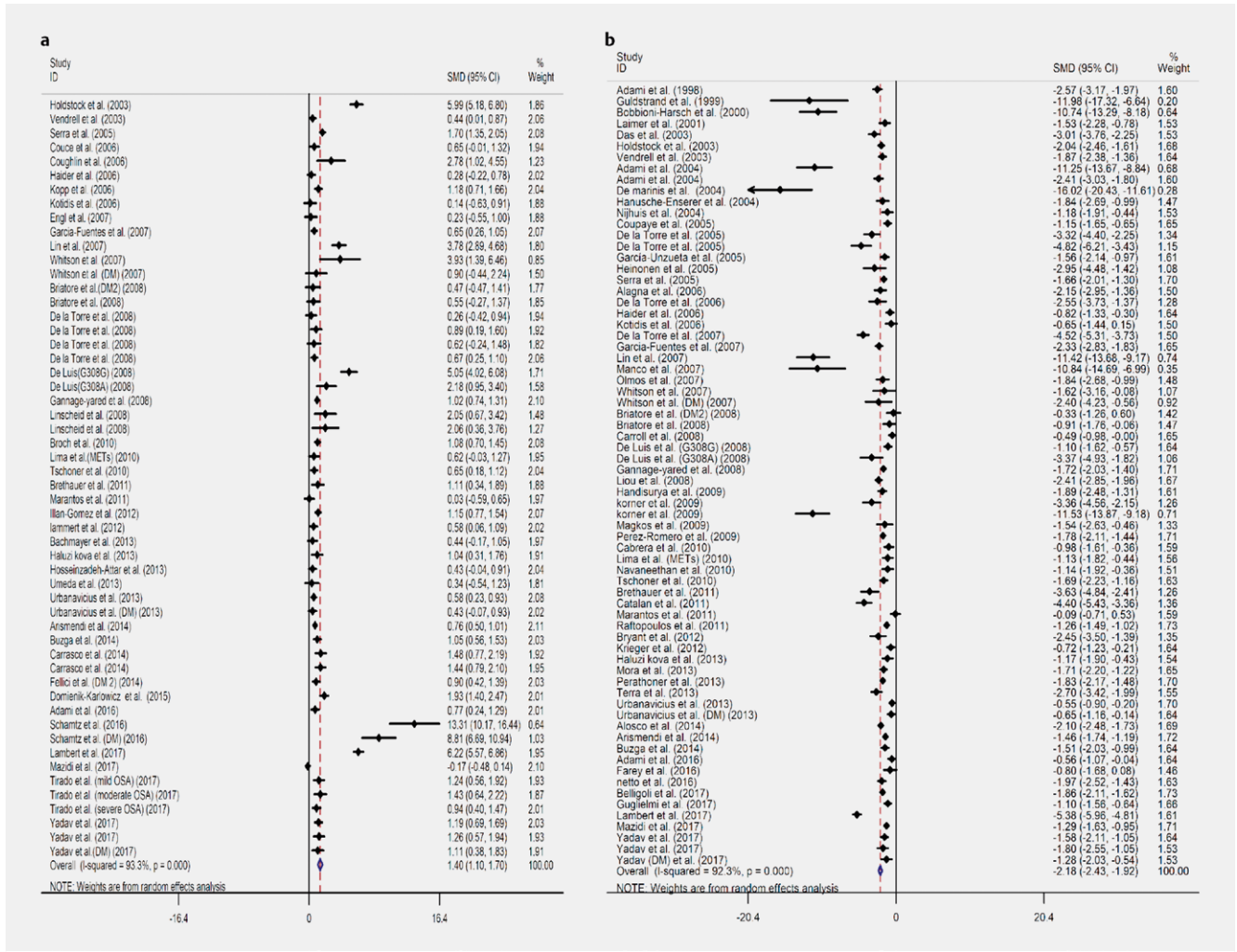
Title and abstract of all retrieved articles in the initial search were screened separately by two different reviewers. Studies were included if they met the following criteria (1) reported baseline BMI and at least one of the following measures; leptin, adiponectin, PAI-1, visfatin, chemerin, and resistin before and after surgical intervention, (2) performed one of the common bariatric surgeries [Roux-en-Y gastric bypass (RYGB); SG, gastric bypass (GBP); vertical banded gastroplasty (VBG); GB, Biliopancreatic diversion (BPD)], and (3) bariatric surgery were performed only for treatment of obesity and not any other reason. Articles were excluded if they had the following exclusion criteria: (1) the reason of surgery was not obesity, (2) had insufficient data for the outcomes of interest in individuals, and (4) experimental and animal studies. All editorials, reviews, letters to editors, conference papers, animal studies, and molecular studies were excluded.

### Data extraction

Two independent researchers (MAE and GH) did the study selection, whereas to resolve any controversies, a chief investigator (SA) was present. The following data were acquired from each study; first author's name; year of publication; study location; study duration; number of participant's, participant's age and gender; study design; weight and BMI before and after intervention; participant's health status; mean and SD of serum or plasma levels of leptin, adiponectin, PAI-1, visfatin, chemerin, and resistin. Also if all individuals just had the same disease, it was reported (► **Fig. 1,2**).

### Assessment of study quality

Two authors independently assessed the quality of included studies by the Newcastle-Ottawa Quality Assessment Scale (NOS). This scale comprising of three quality factors: selection (maximum 4 stars), comparability (maximum 2 stars), and outcome (maximum 3 stars). A maximum of 9 stars represents the highest quality. A total score of 7 or more was considered to indicate high-quality studies [32, 33].



**Fig. 1** Forest plot presenting mean difference (MD) and 95 % confidence intervals for the impact of bariatric surgery on **a** adiponectin and **b** leptin. Results from Hedges' g analysis.

## Statistical analysis

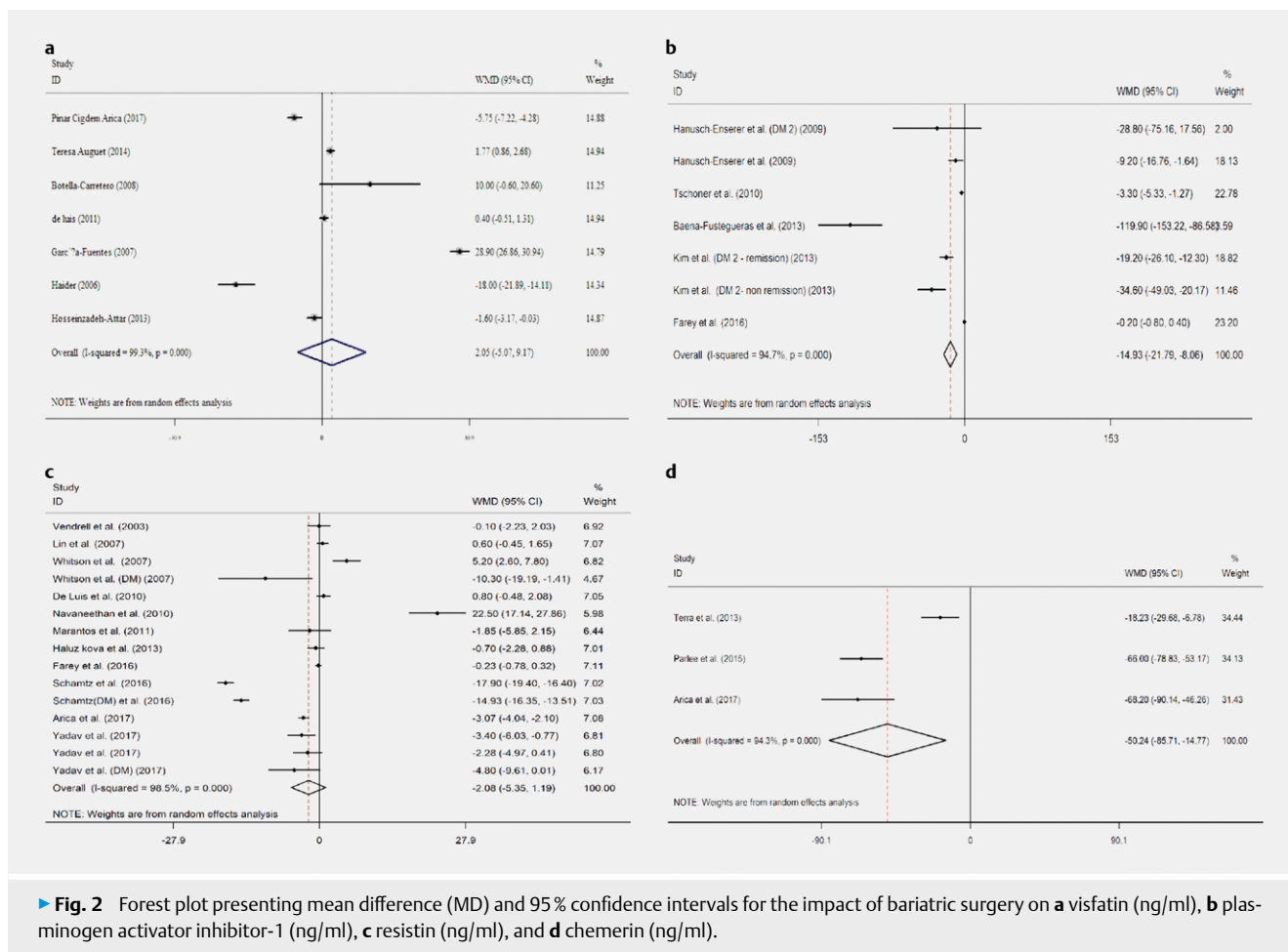
Mean difference was used as the effect size and a random effects model was utilized for the meta-analysis [34]. Using random-effects model, effect sizes were acquired as the weighted mean difference (WMD) and 95% CI by DerSimonian–Laird method. When reported variable could not be pooled, Hodges's adjusted g was used to calculate overall estimate of effect size. A test for heterogeneity was performed (using Q statistic and  $I^2$ ) [35]. The subgroup analysis (▶ **Table 2S**) was conducted to find out possible sources of heterogeneity among included studies. Meta-regression analysis was performed to investigate whether participant baseline BMI and also duration of follow up could explain the heterogeneity across studies and also affect measured effect size. Publication bias was investigated by visual inspection of the funnel plot as well as by using the Egger's regression method. In case of publication, bias trim and fill analysis were performed. This specific analysis was conducted for evaluating the possible effect of publication bias on overall estimate of effect size based on possible relevant unpublished studies [36]. We used the sensitivity analysis to assess the effect of each study on the overall effect size by removing each individual

study in turn. All statistical analyses were carried out using Stata MP V.14.0 (StataCorp, College Station, Texas, USA).

## Results

### Study selection

PRISMA flow diagram of the search process is depicted in (▶ **Fig. 1S**) (Supporting Information). A total of 2071 papers were found. After removing duplicates, 1706 abstracts were selected for a more detailed review. Following screening based on the title and abstract, 1599 articles were excluded: 1) 1493 unrelated topics, 2) 28 animal studies, 3) 78 letters, reviews, and book sections. One hundred and seven citations remained after screening for title and abstracts. After full-text evaluation a further 22 studies were also excluded: 1) combination with other treatments (n = 3), and 2) with not enough information (n = 19). Finally, 83 prospective and 2 retrospective studies remained for the systematic review (▶ **Table 1S**) (Supporting Information).



## Findings from systematic review

Characteristics of eligible studies are summarized in **Table 1S**, with a sample size of between 5 and 180 participants who underwent bariatric surgery (total sample size of studies;  $n = 3512$ ).

Sixty-one studies reported leptin [22, 23, 25, 27, 28, 30, 37–91], 40 adiponectin [22, 23, 26, 28–30, 40, 43, 46, 47, 49, 54, 56, 57, 61, 62, 67, 72–74, 78, 79, 89–106], 11 resistin [23, 24, 27, 30, 62, 74, 78, 82, 91, 105, 107], 7 visfatin [24, 25, 57, 61, 100, 108, 109], PAL-1 [27, 65, 89, 110, 111], and 3 chemerin [24, 88, 112]. Across the included studies 8 were performed on patients with DM [30, 47, 65, 90, 91, 99, 105, 111], one study was on the metabolic syndrome [73], one on obstructive sleep apnea [106], another study stratified subjects based on different polymorphisms of tumor necrosis factor- $\alpha$ -G308A genotype [107] and other studies were carried out just on participants with obesity [22–29, 37–46, 48–64, 66–72, 74–89, 92–98, 100–104, 108–110, 112].

Across the included studies 26 were on patients with a Roux-en-Y gastric bypass (RYGB) [29, 30, 42, 45–48, 51, 63, 67–69, 73, 74, 76, 79, 80, 86, 87, 91, 95, 99, 104, 105, 110, 111], 18 after various forms of surgery [22, 43, 54, 56, 57, 72, 78, 81–83, 88, 89, 92, 100, 103, 106, 108, 109], 14 bilio-pancreatic diversion (BPD) [25, 28, 37–41, 54, 55, 58, 77, 97, 107, 112], 8 gastric bypass (GBP) [23, 53, 54, 93, 94, 96, 98, 101], 6 adjustable gastric banding (AGB) [24, 52, 64, 69, 70, 90], 6 gastric banding (GB) [26, 61, 65, 66,

71, 104], 5 laparoscopic sleeve gastrectomy (LSG) [27, 44, 49, 62, 85], 4 after vertical banded gastroplasty (VBG) [54, 60, 84, 102], 2 sleeve gastrectomy (SG) [59, 94], 1 laparoscopic gastric banding (LGB) [50], and 1 laparoscopic minigastric bypass surgery (LMGBP) [75].

In addition, studies were performed in subjects with different baseline BMIs, 7 were in subjects between 30–39.9 kg/m<sup>2</sup> [29, 40, 72, 75, 94, 99, 111], 21 in subjects between 40–44.9 kg/m<sup>2</sup> [26, 27, 38, 45, 49, 50, 55, 56, 62, 67, 69, 71, 77, 78, 80, 85, 89, 94, 104–106], 44 in subjects between 45–49.9 kg/m<sup>2</sup> [23, 24, 37, 39, 41–44, 46–48, 51, 52, 54, 58–61, 64, 66, 68–70, 73, 74, 81–84, 87, 88, 90, 92, 93, 98, 100–103, 106–108, 110, 112], and 17 studies in subjects over than 50 kg/m<sup>2</sup> [22, 28, 53, 57, 76, 86, 91, 95–97, 99, 109], whilst 4 studies did not report BMI [30, 54, 65, 79].

Twenty studies were on females only [25, 26, 45, 51, 52, 54, 55, 60, 62, 71, 73, 77, 78, 94, 96, 98, 101, 102, 108, 109] and 2 on males only [41, 81] and the rest included studies conducted on both genders [22–24, 27–30, 37–40, 42–44, 46–50, 53, 56–59, 61, 63–70, 72, 74–76, 79, 80, 82–93, 95, 97, 99, 100, 103–107, 110–112].

## Meta-analysis results

### Effect of bariatric surgery on circulating adiponectin

Fifty-four prospective studies including a total of 1862 participants reported circulating adiponectin after bariatric surgery. Overall, combined results showed that circulating adiponectin increased

following bariatric surgery (Hedges'  $g = 1.401$ , 95% CI: 1.101, 1.701,  $p < 0.001$ ) (► **Fig. 1a**). Due to a significant heterogeneity between studies ( $I^2 = 99.3\%$ ,  $p < 0.001$ ), subgroup analyses were performed based on gender (female/both), type of surgery (RYGB/GB/GBP/BPD/miscellaneous/various), baseline BMI ( $< 45 \text{ kg/m}^2$ / $\geq 45 \text{ kg/m}^2$ ), follow-up period ( $\leq 3$  months/6–11 months/12 months/ $> 12$  months). This revealed that the effect of bariatric surgery on adiponectin remained significant in all subgroups except for GB type of surgery, although a lack of eligible studies in this type of surgery must be considered before making any conclusion.

### Effect of bariatric surgery on circulating leptin

Seventy prospective and retrospective studies including a total of 2751 participants reported leptin as an outcome measure. Pooled effect size showed that circulating leptin decreased significantly following bariatric surgery (Hedges'  $g = -2.178$ , 95% CI:  $-2.433$ ,  $-1.923$ ,  $p < 0.001$ ) (► **Fig. 1b**). There was significant heterogeneity among included studies ( $I^2 = 92.3\%$ ,  $p < 0.001$ ). Subgroup analysis also was performed (► **Table 2S**) and showed a significant association in all subgroups for gender, baseline BMI, type of surgery, and follow-up duration.

### Effect of bariatric surgery on circulating resistin, visfatin, PAI-1, and chemerin

Seven prospective articles with 330 participants reported resistin as an outcome measure. Pooled effect size indicated no effect of bariatric surgery on circulating resistin ( $-2.080 \text{ ng/ml}$ , 95% CI:  $-5.352$ ,  $1.192$ ,  $p = 0.21$ ) (► **Fig. 2c**). There was no significant heterogeneity between studies ( $I^2 = 98.5\%$ ,  $p < 0.001$ ), and subgroup analysis revealed no association for baseline BMI, type of surgery, and follow-up period (► **Table 2S**).

Overall, 8 studies with 171 participants assessed PAI-1 as an outcome measure. Pooled effect size showed that serum PAI-1 decreased significantly following bariatric surgery ( $-14.928 \text{ ng/ml}$ , 95% CI:  $-21.794$ ,  $-8.063$ ,  $p < 0.001$ ) with significant heterogeneity among included studies ( $I^2 = 94.7\%$ ,  $p < 0.001$ ) (► **Fig. 2b**).

Finally, three studies reported chemerin as an outcome measure following bariatric surgery, that resulted in reduced circulating concentrations ( $-50.238 \text{ ng/ml}$ , 95% CI:  $-85.708$ ,  $-14.768$ ,  $p < 0.001$ ) with significant heterogeneity between included studies ( $I^2 = 0.0\%$ ,  $p < 0.001$ ) (► **Fig. 2d**).

Seven studies assessed circulating visfatin following bariatric surgery ( $2.05 \text{ ng/ml}$ , 95% CI:  $-5.07$ ,  $9.17$ ,  $p = 0.573$ ). Between-study heterogeneity was significant ( $I^2 = 99.3\%$ ,  $p < 0.001$ ) (► **Fig. 2a**).

### Sensitivity analysis

Sensitivity analysis revealed that overall estimates of effect size were not excessively influenced by any of included studies significantly for adiponectin, leptin, chemerin, PAI-1, and visfatin. Pooled effect size for resistin showed significant effect following elimination study of Navaneethan et al. [82] ( $-3.63 \text{ ng/ml}$ , 95% CI:  $-6.87$ ,  $-0.39$ ,  $I^2 = 98.3\%$ ).

### Publication bias and trim and fill analysis

Publication bias analysis was found for studies reporting adiponectin and leptin. Therefore, following trim and fill analysis were performed for these two factors. The modified estimate of pooled ef-

fect size for adiponectin, from 64 hypothesized studies changed but remained significantly increased following bariatric surgery ( $0.819$ , 95% CI:  $0.45$ ,  $1.188$ ,  $p < 0.001$ ). Trim and fill sensitivity analysis for leptin showed that overall estimate of effect size from 70 hypothesized negative unpublished studies did not change ( $-2.178$ , 95% CI:  $-4.33$ ,  $-1.923$ ), and remained significant ( $p < 0.001$ ). Publication bias did not appear to affect these results. There was no evidence of publication bias for studies examining the effect of bariatric surgery on PAI-1 ( $p = 0.453$ , Begg's test), resistin ( $p = 0.4$ , Begg's test), and visfatin ( $p = 0.54$ , Begg's test).

### Meta-Regression analysis

Meta-regression indicated that there was not a linear association between the change in serum adipokine with baseline BMI of participants [i. e., adiponectin ( $p = 0.41$ ), leptin ( $p = 0.49$ ), PAI-1 ( $p = 0.31$ ), and resistin ( $0.33$ )]. Moreover, no significant associations with follow up duration and changes in adiponectin ( $p = 0.85$ ), leptin ( $p = 0.39$ ), PAI-1 ( $p = 0.82$ ), visfatin ( $p = 0.61$ ), and resistin ( $p = 0.4$ ) were found. There was a significant association between the change in visfatin and baseline BMI of participants ( $\beta$  coefficient =  $3.6$ ,  $p = 0.026$ ).

## Discussion

Our comprehensive meta-analysis has shown that circulating leptin, chemerin, and PAI-1 decreased after bariatric surgery, whereas adiponectin decreased, and both visfatin and resistin were unchanged.

Adiponectin is an adipokine, which is not secreted exclusively by the adipose tissue [113], but a range of human tissues [114]. Obesity is associated with decreased adiponectin, that in turn is linked to reduced insulin sensitivity [115]. Increased adiponectin status, mediated by enhanced action, or function of adiponectin receptors (AdipoR) [116], or pharmacological elevation of adiponectin can relieve obesity-related health problems [114]. For instance, thiazolidinediones (TZDs) or other medicinal herbs like Zataria or astragaloside II can increase circulating adiponectin, and improve insulin sensitivity [117–120]. In addition to pharmacological interventions, exercise and training can also raise plasma adiponectin [121–123], and would be predicted to ameliorate obesity-related health problems like DM and CVD, given the cardio-protective effects of adiponectin [124]. The positive effect of all types of bariatric surgery on circulating adiponectin, irrespective of baseline BMI and gender, would therefore be expected to represent a beneficial outcome, as would the decrease in leptin, that has a range of physiological functions including appetite regulation, and energy homeostasis [125]. Serum leptin level is correlated with resting metabolic rate (RMR) in some but not all studies [126], and obesity is accompanied with leptin resistance [127]. Raised leptin has also been found with insulin resistance, DM [128], and thickening of the intima-media thickness with the onset of atherosclerosis [128]. Reduced leptin with bariatric surgery, occurs concurrently with loss of body fat, and has also been seen with exercise and dietary interventions [128, 129].

Increased circulating PAI-1 with obesity is well documented [130], and is an established risk factor for coronary artery disease, atherosclerosis, and stroke [131, 132]. Conversely lowering PAI-1

reduces the risk of CVD [133], so the decrease with bariatric surgery would be expected to be beneficial. Resistin is a pro-inflammatory cytokine that can modulate substrate metabolism through blocking the action of insulin [134], as well as the onset of CVD, due to inflammation, endothelial and smooth muscle cell dysfunction, thrombosis, and angiogenesis [134, 135]. It was, however, unaffected by bariatric surgery as was visfatin. This adipokine can modulate inflammation, and is raised with obesity, DM, metabolic syndrome, and CVD [18, 136, 137]. Chemerin also contributed to adipogenesis, glucose homeostasis, food intake, and body weight; and elevated chemerin with obesity has been implicated in the onset of DM [138–140]. Bariatric surgery decreased chemerin, but the lack of eligible studies for chemerin and significant sensitivity analysis for resistin suggests these findings must be interpreted with caution, and larger scale studies are needed.

Our meta-analysis has both strengths and limitations, and is the first such study of its kind. Although there were sufficient studies investigating the effects of bariatric surgery on leptin and adiponectin the lack of eligible studies for the other adipokines limits the interpretation of this data. In addition, the effects of confounding factors including, genetic background and other lifestyle modification remained unclear, together with the potential effects of different types of bariatric surgery.

## Conclusion

In conclusion, our meta-analysis of prospective and retrospective studies show that bariatric surgery has a beneficial effect on several adipokines including reduced leptin, chemerin and PAI-1, and increased adiponectin, but has no effect on resistin and visfatin. However, these results must be interpreted with caution especially for adipokines with fewer eligible studies for quantitative analysis.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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