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Obesity/Nutrition

Obesity and iron deficiency: a quantitative meta-analysis

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Summary

Hypoferraemia (i.e. iron deficiency) was initially reported among obese individuals several decades ago; however, whether obesity and iron deficiency are correlated remains unclear. Here, we evaluated the putative association between obesity and iron deficiency by assessing the concentration of haematological iron markers and the risks associated with iron deficiency in both obese (including overweight) subjects and non-overweight participants. We performed a systematic search in the databases PubMed and Embase for relevant research articles published through December 2014. A total of 26 cross-sectional and case–control studies were analysed, comprising 13,393 overweight/obese individuals and 26,621 non-overweight participants. Weighted or standardized mean differences of blood iron markers and odds ratio (OR) of iron deficiency were compared between the overweight/obese participants and the non-overweight participants using a random-effects model. Compared with the non-overweight participants, the overweight/obese participants had lower serum iron concentrations (weighted mean difference [WMD]: −8.37 μg dL^{-1}; 95% confidence interval [CI]: −11.38 to −5.36 μg dL^{-1}) and lower transferrin saturation percentages (WMD: 2.34%, 95% CI: −3.29% to −1.40%). Consistent with this finding, the overweight/obese participants had a significantly increased risk of iron deficiency (OR: 1.31; 95% CI: 1.01–1.68). Moreover, subgroup analyses revealed that the method used to diagnose iron deficiency can have a critical effect on the results of the association test; specifically, we found a significant correlation between iron deficiency and obesity in studies without a ferritin-based diagnosis, but not in studies that used a ferritin-based diagnosis. Based upon these findings, we concluded that obesity is significantly associated with iron deficiency, and we recommend early monitoring and treatment of iron deficiency in overweight and obese individuals. Future longitudinal studies will help to test whether causal relationship exists between obesity and iron deficiency.

Keywords: Anaemia, hypoferraemia, iron deficiency, obesity.

Abbreviations: BMI, body mass index; BMI-for-age, BMI% adjusted for age and gender; BMI-SDS, BMI-standard deviation score; CI, confidence interval; ID, iron deficiency; IDA, iron deficiency anaemia; IL-6, interleukin-6; OR, odds ratio; SMD, standard mean difference; sTfR, soluble transferrin receptor; TS, transferrin saturation; WAT, white adipose tissue; WMD, weighted mean difference.

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Introduction

A putative connection between obesity and hypoferraemia was first suggested more than half a century ago. In 1961, Wenzel *et al*. measured lower levels of serum iron in obese subjects compared with non-obese subjects (1). These findings were later supported by results reported by Seltzer and Mayer (2). Due to the epidemic increase in obesity worldwide, numerous studies were conducted in the past decade, specifically examining the association between obesity and iron deficiency (ID). Classic explanations for ID among obese individuals include inadequate dietary iron intake, increased iron requirements due to increased blood volume and physical inactivity (2–4). However, the latest research suggests that obesity-associated low-grade inflammation and the iron-regulatory protein hepcidin play a principal role in the regulation of endogenous iron homeostasis (5–9). An increased risk of developing ID has been reported in obese adults and children (3,10–13); however, other studies suggested that ID and obesity may not be correlated (14,15). Thus, whether obesity affects the risk of developing ID remains unclear.

Obese individuals who develop ID have an increased health burden. Initially presenting with iron depletion, ID can progress to iron-deficient erythropoiesis, eventually leading to iron deficiency anaemia (IDA) (16). The typical symptoms of anaemia include weakness, fatigue, dyspnoea and reduced exercise capacity; these symptoms can significantly hinder weight loss in obese patients. In addition, both ID and anaemia are known factors associated with increased heart failure and mortality (17).

Here, we investigated the putative association between obesity and ID by performing a meta-analysis of published studies in order to critically assess the differences in haematological iron markers and the risk of developing ID between overweight/obese populations and non-overweight populations.

Methods

Search strategy

The criteria for conducting and reporting a meta-analysis of observational studies have been reported previously (18). Two investigators (authors LZ and XZ) independently conducted a literature search in the databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Embase (http://www.embase.com) for articles published through 10 December 2014, using the following search terms: ('obesity' or 'obese' or 'overweight' or 'adipose' or 'adiposity' or 'body size') and ('iron' or 'anemia' or 'anaemia' or 'ferritin' or 'transferrin' or 'sTfR'). We restricted our search to articles that were written in English. No restriction with respect to the study type was applied for the search or inclusion criteria. The references included in the relevant original papers and review articles were also screened in order to identify potential publications. The selection procedure is summarized in Fig. 1.

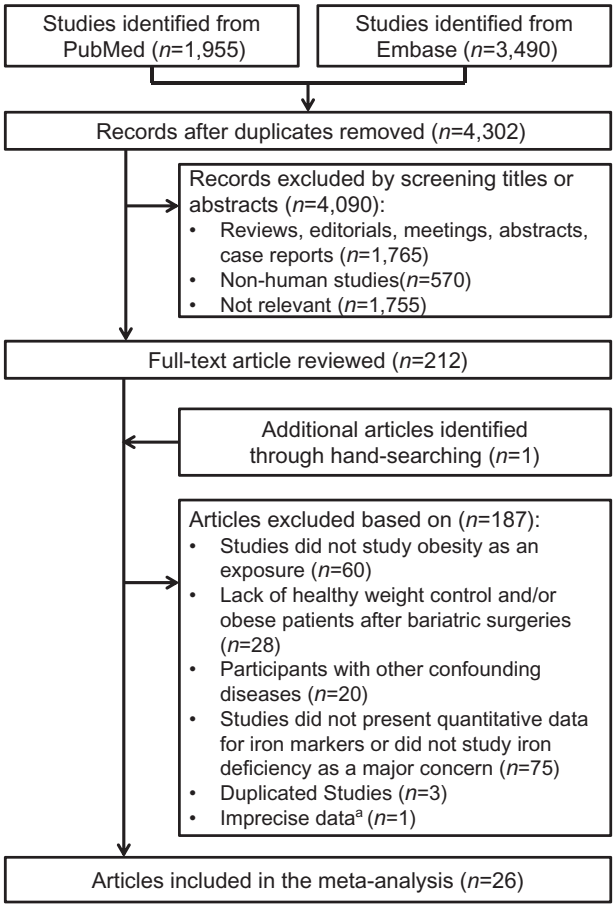

Figure 1 Flowchart depicting the literature search and selection of publications for inclusion in the meta-analysis. [a]'Imprecise data' refers to a high serum ferritin (outside of the normal range) reported in this one study (57).

Study selection

The following inclusion criteria were applied: (i) studies that evaluated the association between iron status and overweight/obesity; (ii) studies that included both an overweight and/or obese group and a non-overweight group and (iii) studies that (i) reported mean and standard deviation (SD) (or median and range) of any of the following haematological iron markers: serum iron, transferrin saturation percentage (TS%), serum ferritin or soluble transferrin receptor (sTfR), and/or (ii) reported the prevalence or risk estimate and corresponding 95% confidence interval (CI) of ID and/or IDA. In the event of multiple articles published using the same population, we selected the most informative article, which was usually the most recent publication.

In this study, we included the following diagnosis of overweight/obesity for adults: body mass index (BMI) or the Wetzel grid method (19); for children and adolescents, we included the following diagnosis of overweight/obesity: BMI (20), BMI percentage adjusted for age and gender (BMI-for-age), BMI-standard deviation score (BMI-SDS) or BMI *Z*-score. Acceptable quantitative analytical techniques for determining iron status were as followed: serum iron was measured using a colorimetric assay (the ferrozine method), inductively coupled plasma mass spectrometry or flame atomic absorption spectrometry; serum ferritin was measured using a chemiluminescent immunometric assay, immunoturbidimetric assay or immunoradiometric assay; sTfR was measure using an enzyme-linked immunosorbent assay or particle-enhanced nephelometry; TS% was calculated using one of the following formulas: ([serum iron/total iron-binding capacity] × 100), ([serum iron/transferrin] × 71.2) or ([serum iron/transferrin] × 70.9).

The following exclusion criteria were applied: (i) studies that did not use the diagnosis of overweight and/or obesity as the categorization standard for the study population; (ii) studies that lack a non-overweight group, and studies in which the control group contained both non-overweight and overweight subjects; (iii) studies that included obese patients who underwent bariatric surgery; (iv) studies that included participants with other confounding diseases such as metabolic syndrome, diabetes, hypertension, non-alcoholic fatty liver, cancer and/or haemochromatosis-related mutations; (v) studies that lacked sufficient quantitative data, including studies that did not report the mean and SD (or median and range) for haematological iron markers and studies that did not report the prevalence or risk estimates (and corresponding 95% CI) of ID or IDA; (vi) studies performed in animals and/or cell lines and (vii) non-original articles (including reviews, editorials and commentaries), abstracts, unpublished studies and duplicate studies.

Data extraction

The following data were extracted from each article selected: basic information (title, the first author's name and publication year); study characteristics (name of the study, study design and geographical location); participant characteristics (sample size, number of cases and non-cases, age, gender and race/ethnicity); standards for diagnosing obesity/overweight; mean and SD (or median and range) of haematological iron markers; quantitative analytical methods for measuring blood iron markers; the diagnosis standards for ID and/or IDA; and the prevalence or risk estimates (and 95% CI) of ID and/or IDA. When a study used several models to adjust for potentially confounding variables, the risk estimate based upon the most adjusted confounding variables was selected.

The quality of each study was assessed independently by two investigators in accordance with the Newcastle–Ottawa quality assessment scale (21). A maximum of nine points was assigned to each study, with scores of 0–3, 4–6 and 7–9 indicating low, moderate and high quality, respectively. Discrepancies were resolved by discussion until consensus was reached.

Statistical analyses

To analyse the haematological iron markers, the sample size and mean (with SD) of the marker concentration in the overweight/obese group were compared with the non-overweight group. For each marker, the most commonly used unit of measurement in the included studies was selected as a 'standard unit' (serum iron, serum ferritin and sTfR were reported in $\mu g\ dL^{-1}$, $ng\ mL^{-1}$ and $mg\ L^{-1}$, respectively). The other units were converted to the respective 'standard unit'. Studies with units that could not be reliably converted to the 'standard unit' were not excluded from the analysis. Effect size was calculated using the weighted mean difference (WMD) method and then assessed using a random-effects model. Specifically, due to the limited number of studies with sTfR results, we relaxed the criteria and included one additional study with units of measurement that could not be converted (22). Effect size for sTfR was calculated using standard mean difference (SMD) Hedge's g, then assessed using a random-effects model.

To analyse the risk of ID and IDA, multivariate-adjusted risk estimates were used. When adjusted ones are unavailable, original data were used to calculate a crude risk estimate. For studies that reported separate sets of risk estimates for non-overlapping overweight and obese groups (compared with a single group of non-overweight participants), the raw counts from the different weight categories were combined to obtain a single estimate for use in the comparison between overweight/obese and non-overweight subjects. The odds ratio (OR) was assessed using a random-effects model.

We conducted subgroup analyses stratified by age, gender, overweight/obese, the method of weight diagnosis, the analytical techniques for haematological iron markers or ID diagnosis methods, geographic area, ethnicity, sample size and study quality. In the subgroup analysis of sample size, the median sample size of 321 from all identified studies was used as the categorical criterion. In the subgroup analysis of study quality, we compared only the results from moderate-quality studies (i.e. a score of 4–6) and high-quality studies (i.e. a score of 7–9), as none of the included studies fell into the low-quality category. Between-strata *P*-values were obtained using an *F*-test from meta-regression. Heterogeneity among various studies was evaluated using the *I*-squared (I^2) statistic, which reports the percentage of variation among studies, due to hetero-

geneity rather than random chance (23,24). Publication bias was assessed using Egger's linear regression (25) and funnel plots (26). A sensitivity analysis was performed in order to examine the influence of individual studies; in this analysis, the meta-analysis estimate was computed after omitting one study at a time (27). All statistical analyses were conducted using STATA version 11.0 (STATA Corp, College Station, TX, USA) and the program R (28).

Results

Characteristics of included studies

Our initial search of PubMed and Embase identified a total of 4,302 potentially relevant studies. After screening the titles and abstracts, we selected 212 articles for further evaluation. After applying the inclusion and exclusion criteria, a total of 26 original studies were ultimately included in the meta-analysis (Fig. 1), including 21 cross-sectional studies (2,3,5,6,10–15,22,29–38) and 5 case–control studies (39–43); no cohort studies were include in the analysis.

Table 1 summarizes the characteristics of the 26 studies included in our analysis. In total, 13,393 overweight and/or obese subjects and 26,621 non-overweight subjects were included in these 26 studies. Fifteen studies reported serum iron levels (2,3,6,11,29–32,35,38–43), 10 reported TS% (2,6,11,22,30,32,35,40–42), 15 reported serum ferritin (5,6,11,14,22,31–37,39,40,42) and 4 reported sTfR (5,22,33,34). Fifteen studies evaluated the risk of developing ID among overweight/obese populations (2,3,5,6,10–15,22,30,31,33,36), and four studies evaluated the risk of developing IDA (11,31,32,36). Detailed information regarding the weight diagnoses and outcomes is summarized in Supporting Information Table S1. The total quality scores of all included studies ranged from 4 to 8, with a median score of 6.5 (Supporting Information Table S2).

Differences in blood iron markers in overweight/obese subjects

Compared with the non-overweight group, the serum iron and TS% values were significantly different in the overweight/obese population (Fig. 2). Specifically, serum iron concentration was significantly lower in the overweight/obese group (WMD: −8.37 μg dL^{-1}; 95% CI: −11.38 to −5.36 μg dL^{-1}). TS% was also significantly lower in the overweight/obese group: (WMD = −2.34%; 95% CI: −3.29% to −1.40%). Previous studies suggested a tendency towards higher levels of serum ferritin, a major iron storage protein (44). Our meta-analysis revealed a marginally significant difference in the serum ferritin level between obese/overweight population subjects ad non-overweight subjects (WMD: 9.65 ng mL^{-1}; 95% CI: −0.80 to 20.10 ng mL^{-1}) (Fig. 3a). We also evaluated whether the concentration of sTfR differed between the overweight/obese group and the non-overweight group; however, no significant difference was observed (SMD: −0.09 mg L^{-1}; 95% CI: −1.08 to 0.90 mg L^{-1}) (Fig. 3b).

Risk of developing iron deficiency in the overweight/obese population

The risk of developing ID was higher in the overweight/obese subjects, with a pooled OR of 1.31 (95% CI: 1.01–1.68), suggesting a significant association between ID and high body weight (Fig. 4a). Notably, the method used to diagnose ID differed among the 15 studies that were included in the association analysis; the details of ID diagnose in each study are summarized in Supporting Information Table S1. TS%, serum iron concentration and serum ferritin concentration were used as diagnostic indices for ID in 14 studies; the study by Aeberli *et al*. diagnosed ID using sTfR level (5). Our analysis of blood markers revealed that the direction of the differences in TS% and serum iron between the two groups was opposite to the direction of the difference in serum ferritin. Thus, we divided the studies into two groups, depending on whether each study based their ID diagnosis on serum ferritin or not. Based upon the eight studies that used a ferritin-based ID diagnosis, the association between ID and overweight/obesity was not significant (OR: 1.04; 95% CI: 0.69–1.56). In contrast, the pooled OR calculated from the seven studies that did not use a ferritin-based ID diagnosis was significant (OR: 1.49; 95% CI: 1.19–1.85) (Fig. 4b,c).

Risks of developing iron deficiency anaemia in the overweight/obese population

Four studies examined the risk of developing IDA among overweight/obese subjects. Similar to ID, the diagnosis of IDA differed among the included studies; the details are given in Supporting Information Table S1. Manios *et al*. diagnosed IDA using TS% and haemoglobin and reported a significantly higher risk of IDA in their overweight/obese group (11). In contrast, two groups used a ferritin-based IDA diagnosis and reported that obesity may play a protective role on the development of IDA (31,36). The pooled OR of IDA in overweight/obese individuals was 1.09 (95% CI: 0.57–2.10) (Fig. 5).

Subgroup analyses

Subgroup analyses of iron haematological markers

Subgroup analyses were performed both on haematological iron markers and on ID risk stratified by relevant factors (see Table 2). For the three blood markers, the pooled effect size of the differences between the overweight/obese and non-overweight groups remained significant in a majority of subgroups. Notably, the differences in serum iron, TS% and serum ferritin were larger in the obese subjects (serum iron:

Table 1 Characteristics of the 26 studies included in the meta-analysis

Author	Year	Country/Study name*	ST	Healthy-weight group			Overweight/Obese group			WD	Extracted outcomes (markers/ risk estimates)	QS
				N	Age†	F/M	*N*	Age†	F/M			
1. Aeberli *et al.* (5)	2009	Switzerland/–	CS	33	10.0 (2.7)	20/13	85	10.26 (1.84)	42/43	BMI-SDS	Serum ferritin, sTfR/ID	6
2. Altunoglu *et al.* (29)	2014	Turkey/–	CS	45	44 (13.3)	29/16	206	40.9 (15.9)	176/30	BMI	Serum iron/–	6
3. Ausk and Ioannou (6)	2008	USA /NHANES III	CS	5,108	18 and up	–	3,681	18 and up	–	BMI	Serum iron, TS%, serum ferritin/ ID,	8
4. Azab *et al.* (39)	2014	Egypt/–	CC	80	8.1 (1.9)	40/40	80	7.8(2.3)	44/36	BMI *Z*-score	Serum iron, serum ferritin/–	7
5. Brotanek *et al.* (10)	2008	USA /NHANES II-IV	CS	5,766	1–3	–	1,339	1–3	–	BMI-for-age	–/ID	7
6. Cepeda-Lopez *et al.* (30)	2011	Mexico/NNS-2	CS	W:240 C: 921	W:29.1 (8.1) C: 8.23 (1.88)	C:47.8%/52.2%	W: 381 C:253	W: 33.1 (7.6) C:8.0 (1.9)	C:50.2%/ 49.8%	W:BMI; C:BMI *Z*-score	Serum iron, TS%/ID	7
7. Chang *et al.* (15)	2014	China/–	CS	377	11.9 (2.3)	189/188	271	10.9 (2.3)	154/117	BMI-for-age	-/ID	7
8. Chang *et al.* (31)	2014	China/NAHSIT	CS	543	49.9 (0.8)	Female	628	56.8(1.0)	Female	BMI	Serum iron, serum ferritin/ID, IDA	7
9. del Giudice *et al.* (40)	2009	Netherland/–	CC	50	10.7 (2.7)	25/25	60	11.3 (2.5)	29/31	BMI-SDS	Serum iron, TS%, serum ferritin/–	6
10. Demircioglu *et al.* (41)	2014	Turkey/–	CC	30	12.7 (2.8)	17/13	80	12.1 (2.6)	44/36	BMI-for-age	Serum iron, TS%, serum ferritin/–	6
11. Eftekhari *et al.* (32)	2009	Iran/–	CS	291	16.1 (3.8)	Female	107	16.9 (1.6)	Female	BMI-for-age	Serum iron, TS%, serum ferritin/IDA	8
12. Fanou-Fogny *et al.* (33)	2011	Mali/FONIO	CS	32	15–49	Female	16	15–49	Female	BMI	Serum ferritin, sTfR / ID	7
13. Ferrari *et al.* (34)	2014	Europe‡/HELENA-CSS	CS	695	12.5–17.5	–	181	12.5–17.5	–	BMI	Serum ferritin, sTfR/–	7
14. Fricker *et al.* (42)	1990	France/–	CC	20	30.5 (7.0)	Female	20	30.8 (9.3)	Female	BMI	Serum iron, TS%, serum ferritin/–	6
15. Ghadiri-Anari *et al.* (35)	2014	Iran/–	CS	131	34 (13)	–	275	43.3 (12.8)	–	BMI	Serum iron, TS%, serum ferritin/–	5
16. Karl *et al.* (22)	2009	USA/–	CS	135	20 (4)	Female	72	22 (5)	Female	BMI	TS%, serum ferritin, sTfR/ID	5
17. Kordas *et al.* (14)	2013	Colombia/ENSIN	CS	1,883	13–49	Female	1,374	13–49	Female	W:BMI; G:BMI *Z*-score	Serum ferritin/ID	8
18. Laillou *et al.* (36)	2014	Vietnam	CS	892	15–49	Female	300	15–49	Female	BMI	Serum ferritin/ID, IDA	7
19. Manios *et al.* (11)	2013	Greece/Healthy Growth Study	CS	1,436	9–13	751/685	1,056	9–13	500/556	BMI	Serum iron, TS%, serum ferritin/ ID, IDA	7
20. Nead *et al.* (12)	2004	USA/NHANES III	CS	7,285	2–16	–	2,413	2–16	–	BMI-for-age	–/ID	7
21. Pinhas-Hamiel *et al.* (3)	2003	Israel/–	CS	136	10.5 (3.2)	93/43	185	12.0 (3.7)	114/71	BMI-SDS	Serum iron/ID	5
22. Revenga-Frauca *et al.* (37)	2009	Spain/–	CS	46	8.32 (2.13)	–	80	10.1 (2.4)	–	BMI	Serum ferritin/–	4
23. Seltzer *et al.* (39)	1963	USA/–	CS	264	14.9 (2.0)	129/135	57	14.6 (2.2)	32/25	Weight and Height	Serum iron, TS%/ID	4
24. Suliburska *et al.* (38)	2013	Poland/–	CS	20	15.2 (1.7)	11/9	78	14.5 (1.8)	42/36	BMI-for-age	Serum iron/–	5
25. Tascilar *et al.* (43)	2011	Turkey/–	CC	33	10.59 (2.9)	18/15	34	10.71 (2.07)	18/16	BMI	Serum iron/–	4
26. Tussing-Humphreys *et al.* (13)	2009	USA/NHANES 2003–2004	CS	129	14.5 (1.6)	Female	81	14.5 (1.7)	Female	BMI-for-age	–/ ID	7

*DHS, Demographic and Health Survey; ENSIN, Encuesta Nacional de la Situacion Nutricional en Colombia 2005; FONIO project (EU/INCO no. 0015403); HELENA-CSS, Healthy Lifestyle in Europe by Nutrition in Adolescence–Cross Sectional Study; NAHSIT, Nutrition and Health Survey in Taiwan; NHANES, National Health and Nutrition Examination Survey; NNS, Mexican National Nutrition Survey.†Age is presented as mean (SD) or range.‡The Ferrari *et al.* study (35) was conducted in the following nine European countries: Greece, Germany, Belgium, France, Hungary, Italy, Sweden, Austria and Spain.C, Children; CC, case–control study; CS, cross-sectional study; E, Egypt; F, Female; G, Girls; M, Male; M, Mexico; *N*, numbers of participants; P, Peru; QS, quality score; ST, study type; W, Women; WD, weight diagnosis.

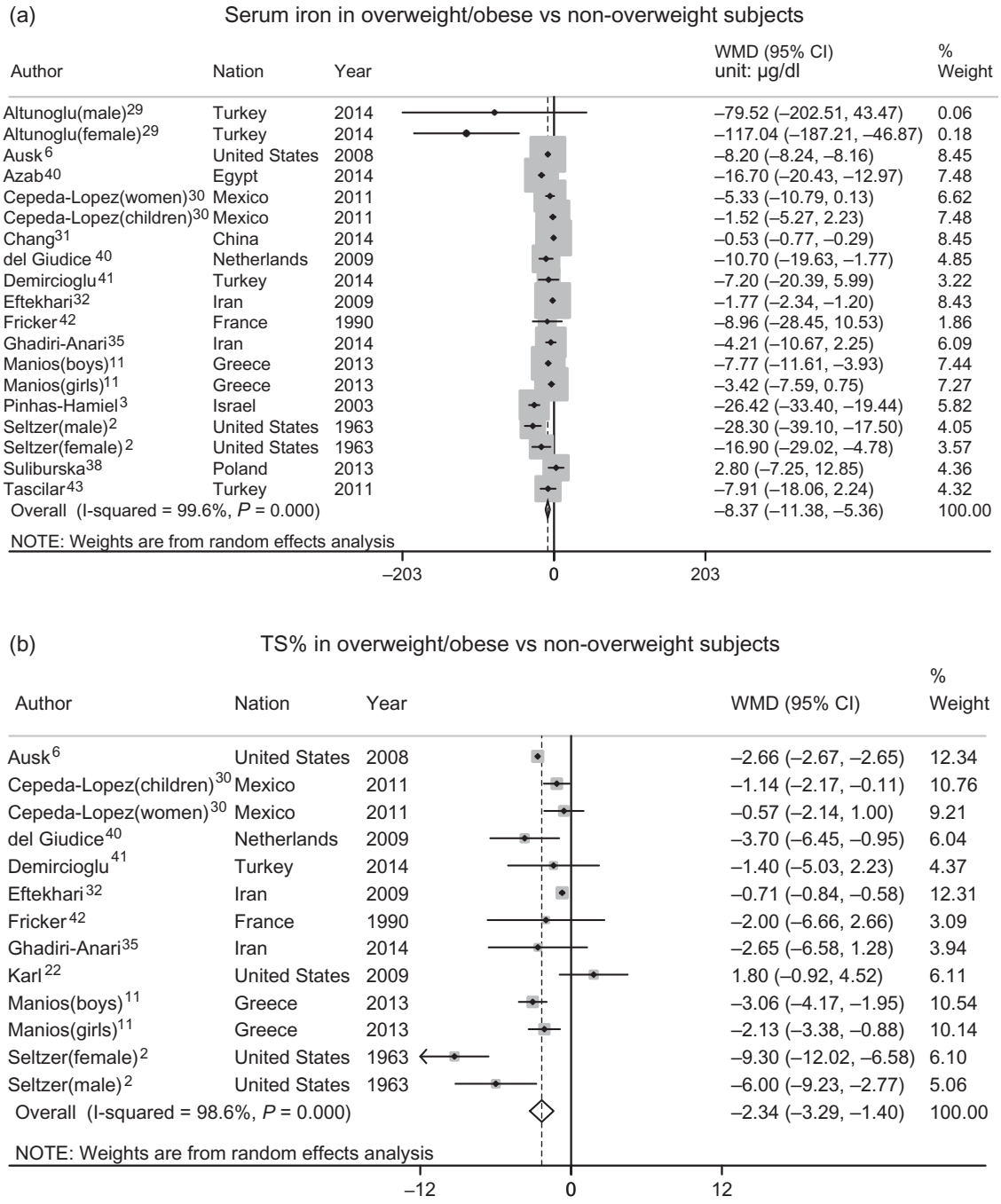

Figure 2 Meta-analysis of studies reporting the effect of obesity/overweight on serum iron concentration (a) and transferrin saturation (TS%, panel b). In this and subsequent figures, the black circles, horizontal lines and grey boxes represent the effect size, the 95% CI and the weighted percentage, respectively, of the corresponding study. The vertical dashed line indicates the location of the pooled effect estimate, and the diamond in the bottom row ('overall') represents the pooled effect size and 95% CI. WMD was analysed for both blood iron markers, and the random-effects model was used.

WMD: –9.98 µg dL^{-1}; 95% CI: –14.82 to –5.13 µg dL^{-1}; TS%: WMD: –2.59%; 95% CI: –4.80% to –0.38%; serum ferritin: WMD: 8.33 ng mL^{-1}; 95% CI: –6.86 to 23.53 ng mL^{-1}) than in the overweight subjects (serum iron: WMD: –4.05 µg dL^{-1}; 95% CI: –6.48 to –1.63 µg dL^{-1}; TS%: WMD: –1.51%; 95% CI: –1.94% to –1.09%; serum ferritin: WMD: 6.27 ng mL^{-1}; 95% CI: –8.86 to 21.40 ng mL^{-1}). However, no significant difference was observed between each stratum using meta-regression, with the exception of age in our analysis of serum ferritin. Significant differences in serum ferritin concentration were measured between overweight/obese subjects and the non-

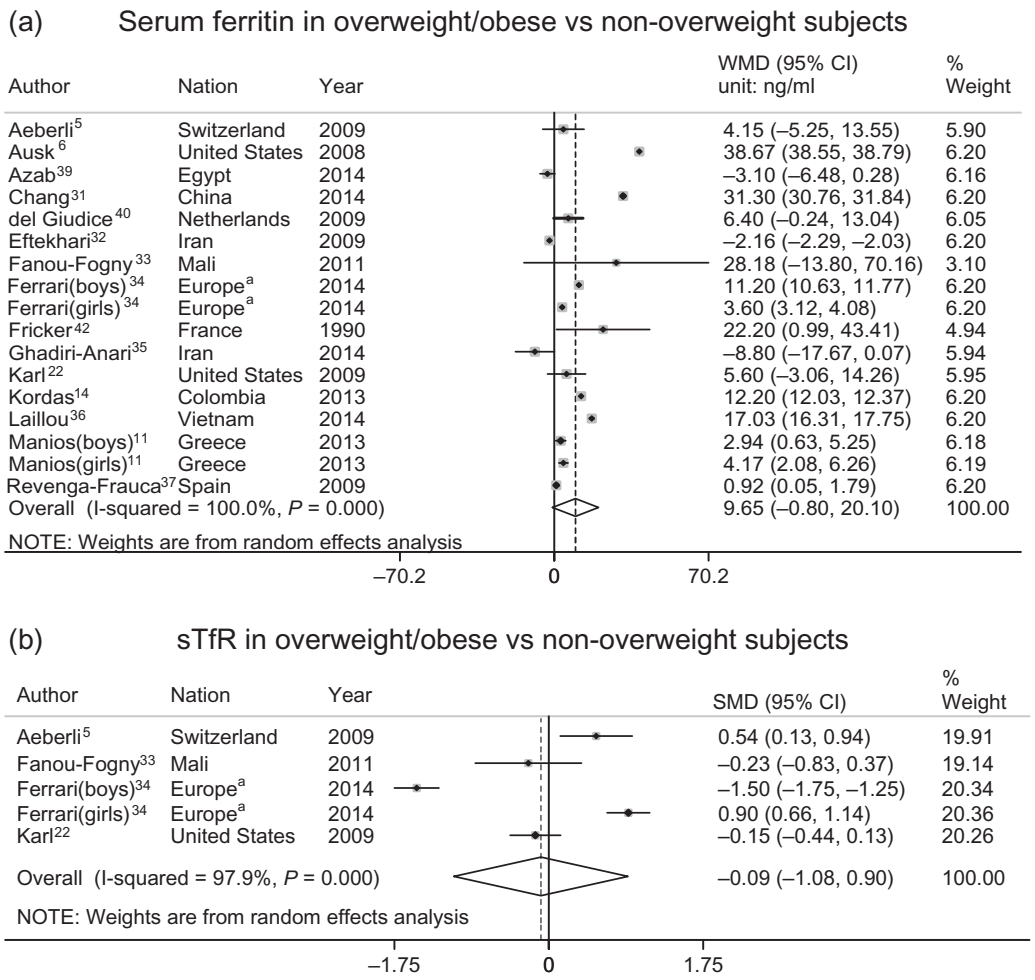

Figure 3 Meta-analysis of studies reporting the effect of obesity/overweight on the serum ferritin concentration (a) and sTfR concentration (b). WMD was analysed for serum ferritin, and SMD was analysed for sTfR. A random-effects model was used. [a]The Ferrari *et al.* study was conducted in nine European countries: Greece, Germany, Belgium, France, Hungary, Italy, Sweden, Austria and Spain.

overweight subjects in studies with subjects under 18 years of age (WMD: 3.75 ng mL^{-1}; 95% CI: 0.07–7.43 ng mL^{-1}) and subjects 18 of age and older (WMD: 19.30 ng mL^{-1}; 95% CI: 3.21–35.39 ng mL^{-1}), with a between-strata *P* value of 0.040. The results of our subgroup analysis with significant between-stratum differences are shown graphically in Supporting Information Fig. S3. Other stratified factors including gender, analytical techniques and overweight/obese had no clear effect on the results.

Subgroup analysis of the association between obesity and iron deficiency

Age, weight diagnostic methods and ethnicity were all found to be meaningful stratified factors in the association analysis between overweight/obesity and the risk of developing ID. Significant differences were found between studies with subjects under 18 years of age (OR: 1.78; 95% CI: 1.37–2.30) and subjects 18 of age and older (OR: 0.92; 95% CI: 0.59–1.44, between-strata $P = 0.025$); between studies with 'BMI'-based obesity diagnosis (OR: 1.00; 95% CI: 0.77–1.28), studies with 'BMI-for-age'-based obesity diagnosis (OR: 2.25; 95% CI: 1.77–2.85) and other indicator-based obesity diagnosis (OR: 1.42; 95% CI: 0.98–2.05, between-strata $P = 0.032$); and between studies with 'Caucasian' (OR: 1.69; 95% CI: 1.22–2.35) and 'Non-Caucasian' (OR: 0.97; 95% CI: 0.72–1.32, between-strata $P = 0.038$) of sample ethnicity (Supporting Information Fig. S3). The risk of developing ID remained significant in obese subjects compared with non-overweight subjects (OR: 1.66; 95% CI: 1.08–2.54), but not significant compared with overweight subjects (OR: 1.08; 95% CI: 0.86–1.36), suggesting that iron metabolism is more severely perturbed when one has excessive bodyweight. No subgroup analysis was performed for sTfR and the risk of developing IDA due to insufficient numbers of eligible studies.

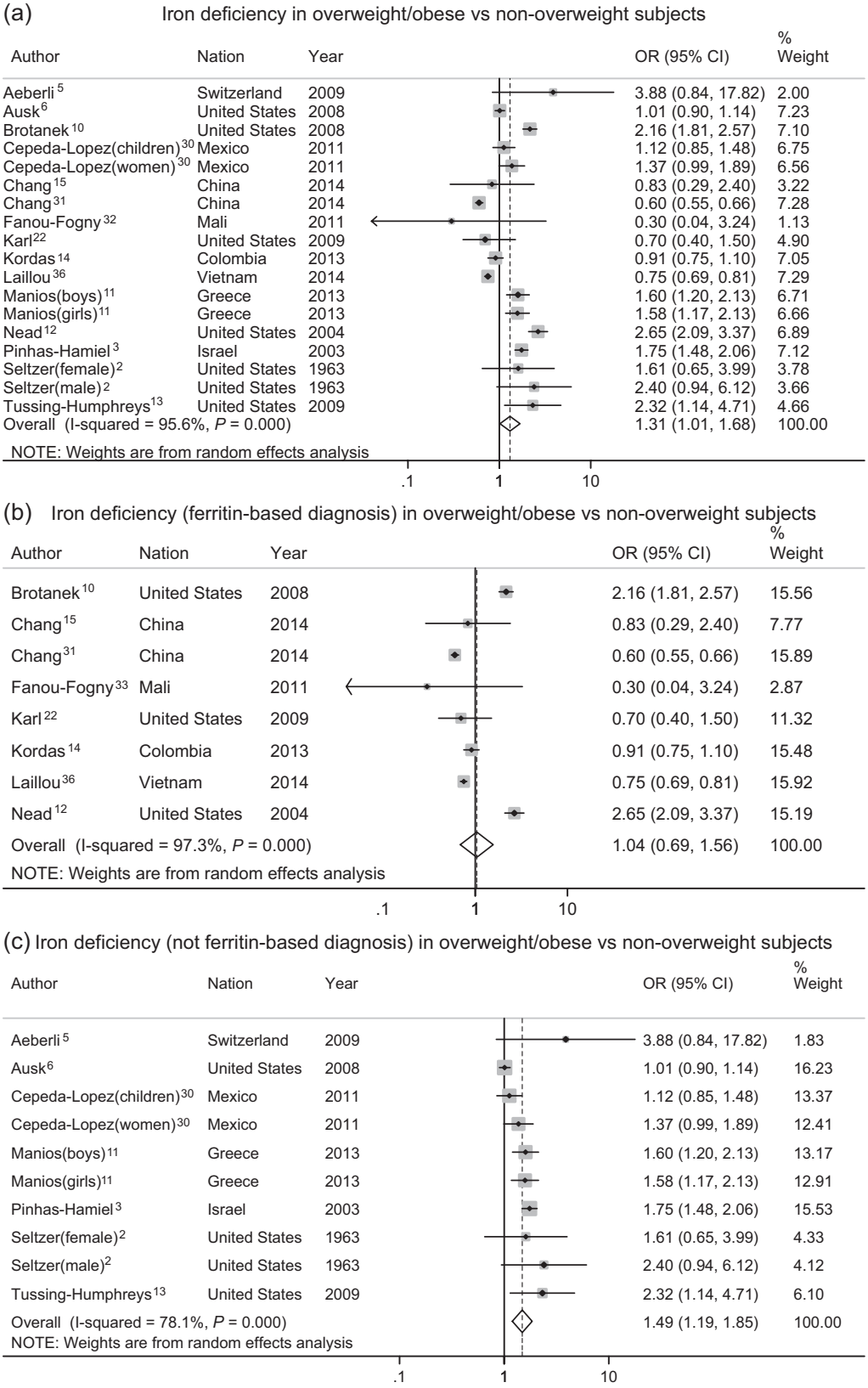

Figure 4 Association between obesity and ID. Forrest plots for pooled risk estimates with 95% CI of ID based on any diagnosis (a), ferritin-based diagnose (b) and non-ferritin-based diagnose (c). A random-effects model was used.

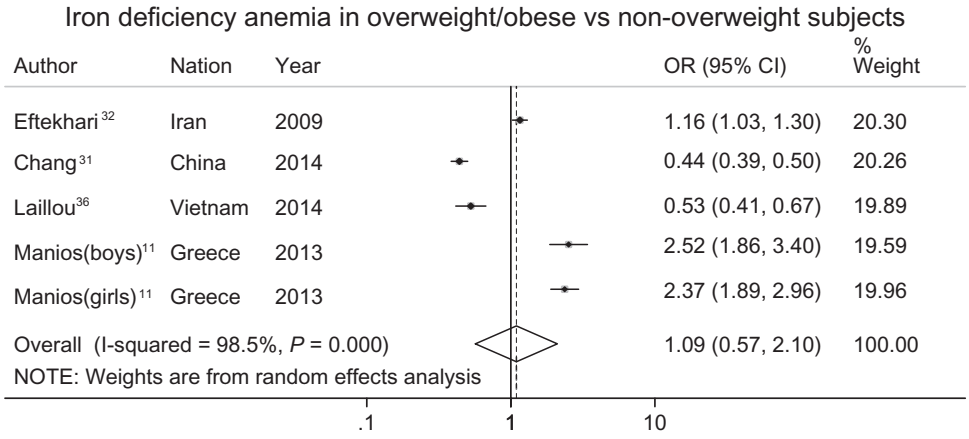

Figure 5 Association between obesity and iron deficiency anaemia. Forrest plots of pooled risk estimates with 95% CIs for iron deficiency anaemia in overweight/obese subjects compared with non-overweight subjects. A random-effects model was used.

Heterogeneity, publication bias and sensitivity analysis

High heterogeneity was found in all of the meta-analyses performed in our study (Figs 2–5). This heterogeneity may be due to the inherent differences in methodologies among the selected studies, including the sample selection strategy and geographical location. We therefore attempted to dissect the causes of heterogeneity by performing an exhaustive subgroup analysis (Table 2). Our analysis revealed that studies conducted in Europe, studies with a sample size below the median for the entire group of studies and studies with a total quality score <7 had relatively less heterogeneity.

We also examined publication bias using funnel plots (Supporting Information Fig. S1) and by performing Egger's test. Our analysis revealed no evidence of publication bias (Egger's test: serum iron: $P = 0.350$; TS%: $P = 0.349$; serum ferritin: $P = 0.771$; sTfR: $P = 0.903$; ID: $P = 0.649$; IDA: $P = 0.508$).

Lastly, our sensitivity analysis showed no evidence that any individual study affected the pooled results of total effect size (Supporting Information Fig. S2).

Discussion

The results of our meta-analysis show that the prevalence of hypoferraemia is higher among overweight and obese populations compared with non-overweight populations. Our meta-analysis of haematological iron markers revealed significant differences in serum iron concentration and TS%, both of which are markers used to measure the level of transferrin-bound circulating iron. Consistent with this finding, our association study revealed a positive correlation between obesity and the risk of developing ID.

Because the diagnosis of ID is currently not well defined, it can be difficult to interpret relevant results obtained from different research groups. Nevertheless, our results suggest that studies that use a ferritin-based diagnosis of ID are more likely to conclude that obesity is not associated with – or may even play a protective role in – the development of ID. Previous studies suggest that the level of serum ferritin increases in response to inflammation (45). Obesity is associated with low-grade inflammation of white adipose tissue (WAT) due to chronic activation of the innate immune system (46). Both WAT and infiltrated macrophages can be a major source of inflammatory cytokines, such as tumour necrosis factor-α, which is an activator of ferritin transcription (47). Therefore, patients with obesity-related ID may have normal or even elevated levels of serum ferritin.

We detected a marginal difference in serum ferritin, with a biased 95% CI. Our sensitivity analysis showed that this difference in ferritin became significant when certain studies are excluded from the analysis, such as the Ausk *et al.*'s study or Eftekhari *et al.*'s study. Moreover, age was a confounding factor in the ferritin analysis (48); specifically, compared with non-overweight subjects, ferritin concentration was significantly higher in overweight/obese subjects in both the under-18 age group and the 18-years-and-older age groups.

sTfR is a truncated form of the erythroid precursor surface transferrin receptor, and an increase in sTfR levels usually reflects a decrease in iron supply from the circulation (49). Previous studies suggest that sTfR levels do not rise under inflammatory conditions and is therefore a suitable marker for diagnosing ID in patients with concomitant inflammation (50–52). Nevertheless, the sTfR assay is not used universally due to variability among reported ranges from different manufacturers. In our analysis, we failed to detect a significant difference in sTfR concentration in the four studies that were eligible for analysis.

Interestingly, our stratification analysis between overweight and obese subjects detected a weight-dependent effect on iron levels. Specifically, we found that obese individuals have larger differences in the levels of haematological iron markers, and these individuals have a

Table 2 Subgroup analyses of three haematological iron markers and ID risks in overweight/obese subjects vs. non-overweight subjects

	Serum iron				TS%				Serum ferritin				Iron deficiency			
	N	ES (95% CI)	I^2 (%)	*P**	*N*	ES (95% CI)	I^2 (%)	*P**	*N*	ES (95% CI)	I^2 (%)	*P**	*N*	ES (95% CI)	I^2 (%)	*P**
Overall	15	–8.37 (–11.38, –5.36)	99.6	–	10	–2.34 (–3.29, –1.40)	98.6	–	15	9.65 (–0.80, 20.10)	100	–	15	1.31 (1.01, 1.68)	95.6	–
Age																
Below 18	7	–6.77 (–11.65, –1.88)	83.1	0.157	4	–2.2 (–3.16, –1.25)	47.7	0.877	6	3.75 (0.07, 7.43)	98.8	0.040	7	1.78 (1.37, 2.30)	76.5	0.025
18 and up	6	–5.63 (–11.09, –0.17)	99.8		4	–1.96 (–3.35, –0.57)	56.5		5	19.30 (3.21, 35.39)	100		3	0.92 (0.59, 1.44)	96.7	
Gender																
Male	3	–18.95 (–38.89,0.98)	85.2	0.579	2	–4.12 (–6.89, –1.35)	64.9	0.444	2	7.15 (–0.94, 15.24)	97.8	0.555	2	1.66 (1.26, 2.18)	0.0	0.179
Female	7	–2.02 (–3.59, –0.46)	84.1		6	–1.99 (–3.84, –0.14)	89.3		8	10.87 (2.19, 19.54)	100		7	1.00 (0.69, 1.46)	87.9	
Overweight/Obese																
Overweight	8	–4.05 (–6.48, –1.63)	99.1	0.208	7	–1.51 (–1.94, –1.09)	88.0	0.995	8	6.27 (–8.86, 21.40)	100	0.592	10	1.08 (0.86, 1.36)	79.0	0.097
Obese	13	–9.98 (–14.82, –5.13)	99.8		7	–2.59 (–4.80, –0.38)	99.7		10	8.33 (–6.86, 23.53)	100		7	1.66 (1.08, 2.54)	94.4	
Methods of weight diagnosis																
BMI	8	–5.82 (–10.12, –1.52)	99.8	0.520	6	–1.92 (–2.85, –1.00)	67.4	0.100	10	12.27 (1.01, 23.54)	100	0.375	7	1.00 (0.77, 1.28)	93.6	0.032
BMI-for-age	3	–1.77 (–2.33, –1.20)	0.0		2	–0.71 (–0.84, 0.58)	0.0		1	–2.16 (–2.29, –2.03)	–		4	2.25 (1.77, 2.85)	44.5	
Others	5	–16.36 (–25.38, –7.33)	91.9		3	–4.92 (–8.85, –0.98)	91.6		4	4.98 (–4.61, 14.57)	96.4		5	1.42 (0.98, 2.05)	83.7	
Analytical techniques of iron markers or ID diagnosis																
Major method†	10	–9.33 (–13.02, –5.63)	99.7	0.326	8	–2.78 (–3.87, –1.69)	98.9	0.466	9	7.86 (–0.16, 15.88)	99.8	0.507	8	1.04 (0.69, 1.56)	97.3	0.110
Others	5	–6.25 (–13.18, 0.68)	86.7		2	–0.99 (–1.83, –0.15)	0.0		4	11.54 (–8.37, 31.45)	100		7	1.49 (1.19, 1.85)	78.1	
Geographic area																
Europe	4	–5.51 (–9.29, –1.72)	36.8	0.650	3	–2.72 (–3.50, 1.93)	0.0	0.788	6	5.23 (1.38, 9.08)	98.7	0.552	2	1.62 (1.32, 1.98)	0.0	0.123
North America	3	–9.58 (–14.6, –4.20)	86.0		4	–2.69 (–4.41, –0.96)	90.5		2	22.43 (–9.97, 54.83)	98.2		7	1.54 (1.10, 2.15)	91.1	
Asia	7	–4.25 (–6.57, –1.92)	91.6		3	–0.71 (–0.85, –0.58)	0.0		4	9.55 (–10.62, 29.73)	100		4	0.91 (0.58, 1.41)	97.6	
Others	1	–16.70 (–20.43, –12.97)	–		–	–	–		3	6.81 (–7.40, 21.01)	97.5		2	0.90 (0.75, 1.09)	0.0	
Ethnicity																
Caucasian	10	–9.91 (–13.17, –6.65)	98.0	0.156	8	–2.78 (–3.87, –1.69)	98.9	0.284	10	6.95 (–8.44, 22.33)	100	0.132	8	1.69 (1.22, 2.35)	90.0	0.038
Non-Caucasian	5	–3.63 (–7.70, 0.52)	67.4		2	–0.99 (–1.83, –0.15)	0.0		5	15.98 (5.65, 26.31)	99.9		7	0.97 (0.72, 1.32)	95.2	
Sample size																
≥Median	8	–7.77 (–11.28, –4.26)	99.8	0.149	5	–1.78 (–2.90, –0.66)	99.3	0.293	9	10.62 (–2.14, 23.38)	100	0.865	9	1.22 (0.91, 1.62)	96.8	0.345
<Median	7	–10.21 (–18.30, –2.11)	72.0		5	–3.48 (–6.95, –0.02)	86.1		6	1.95 (–1.88, 5.78)	64.2		6	1.59 (1.07, 2.36)	49.3	
Quality score																
≥7	6	–5.57 (–9.39, –1.74)	99.8	0.130	4	–1.73 (–2.89, –0.57)	99.4	0.288	9	12.39 (–0.62, 25.40)	100	0.242	11	1.24 (0.94, 1.63)	96.2	0.422
4–6	9	–13.66 (–21.72, –5.61)	80.2		6	–3.38 (–6.40, 0.35)	83.4		6	2.58 (–1.99, 7.14)	60.3		4	1.57 (0.99, 2.48)	54.0	

**P*-value for between-strata differences.†The major methods for analytical techniques and ID diagnosis are the methods most commonly used in all included studies. Major techniques for analysing serum iron, TS% and serum ferritin are colorimetric assay, serum iron/TIBC (both serum iron and TIBC are measured by colorimetric assay) and chemiluminescent immunometry, respectively. The major method for ID diagnosis is ferritin-based diagnosis.ES, effect size; *N*, number of studies.

higher risk of developing ID, compared with overweight subjects. Future studies that include a more detailed categorization of overweight individuals (e.g. based upon grades of obesity) will be helpful for determining whether body weight has a 'dose-dependent effect' on ID.

The aetiology of obesity-associated ID remains unclear. Previous hypotheses have included the consumption of a poorly balanced diet by obese individuals (2,3); increased iron requirement due to larger blood volume and/or body size (4); decreased levels of myoglobin (an iron-binding protein expressed in muscle tissue) due to decreased physical activity (2) and genetic predisposition (12). Nevertheless, several relatively recent studies examined daily dietary iron intake in obese and non-overweight individuals and found no significant difference between these two groups (5,7,13,30,53).

On the other hand, the role of hepcidin-mediated iron sequestration in obesity-related ID has received increasing attention in recent years (5–9). Hepcidin is a 25-amino acid peptide secreted primarily by the liver (54). Hepcidin drives the internalization and degradation of ferroportin, a key iron exporter, thereby decreasing iron absorption and release (55). Under normal conditions, secretion of hepcidin by the liver is stimulated by high transferrin saturation via a negative feedback loop. However, elevated concentrations of hepcidin were detected in obese populations, despite the presence of hypoferraemia (5,40,56,57). Thus, hepcidin may play a critical role in the development of obesity-related hypoferremia.

The mechanisms that override the dynamic regulation of circulating iron via hepcidin expression in obese individuals are currently unclear. One hypothesis suggests that hepcidin is stimulated by adipocytokines such as interleukin-6 (IL-6) and leptin, the secretion of which is increased from WAT in obese individuals (5,40,44). A couple of studies examined the putative association between hepcidin, IL-6 and leptin in obese populations but yielded conflicting results (5,40). Alternatively, the increased volume of adipose tissue in obese individuals may directly cause increased hepcidin expression. For example, Bekri *et al*. reported that in addition to liver, adipose tissue is also able to express hepcidin (58). However, a subsequent study by Tussing-Humphreys *et al*. suggested that the source of excessive hepcidin measured in obese people was in fact the liver, rather than adipose tissue (56). Thus, additional research is needed in order to understand better the mechanisms underlying obesity-related ID and the role of hepcidin in this process.

Our stratified analysis detected a strong correlation between obesity and the risk of developing ID in subjects under the age of 18. Consistent with this finding, the association between obesity and ID remained significant in studies that used BMI-for-age for diagnosing obesity, a method commonly used to diagnose childhood obesity. One possible explanation for this association is that the high iron demand in children and adolescents – which is driven by accelerated body growth – makes these individuals more susceptible than adults to potential iron depleting factors (59). Thus, obesity-related ID is more likely to develop in this age group. Moreover, our subgroup analysis revealed a lack of association between obesity and ID in adults, as well as a lack of association between ID and other obesity diagnosis groups, as suggested by our subgroup tests. However, given the limited number of available studies and the high heterogeneity among the studies, it remains unclear whether the relationship between obesity and ID risk varies with age and/or obesity diagnosis. Future studies of categorized age groups and/or unified obesity diagnose are needed in order to test the effect of age and obesity diagnosis criteria on the prevalence of obesity-related hypoferraemia.

To our surprise, we did not detect an association between obesity and IDA. Generally speaking, ID can eventually progress to IDA, as iron is the key element in the synthesis of haem. However, the risks of ID and IDA are not always linked. Haemoglobin, a widely used diagnostic indicator of anaemia, is a late-stage marker that develops slowly (45). Only 1% of circulating erythrocytes are replaced each day, and only after ≥10% of erythrocytes become hypochromic are commonly used haemoglobin tests able to detect the change. Thus, it is conceivable that a fraction of the obese population with latent ID or early phase IDA may not present with clinically identifiable anaemia (2).

Our study had several limitations that warrant discussion. Firstly, high heterogeneity was found among the included studies for most of the analyses performed. This heterogeneity may have been due to the research design and sample used in these studies. Nevertheless, significant differences in haematological markers and ID risks remained in the majority of subgroups with lower heterogeneity, suggesting that the pooled results are likely reliable. Secondly, blood iron status can be influenced by a variety of factors, including the contents of the meal consumed prior to sampling, medications, inflammation, infection and neoplasia. Although all of the studies included in our analysis controlled for one or more factors during sample selection, other confounders were likely present. Finally, although we detected a significant association between obesity and ID, based upon evidence obtained from cross-sectional and case–control studies, no causal relationship can be inferred. Thus, longitudinal research is required in order to test the putative causal relationship between obesity and ID.

In conclusion, our meta-analysis provides compelling evidence supporting an association between obesity and hypoferraemia. Therefore, we recommend that overweight and obese individuals undergo periodical screening for iron status, particularly given that some patients may already have latent ID or even early stage IDA, without overt clinical changes or laboratory findings. Long-term monitoring of haematological iron markers is strongly

recommended, particularly among individuals in specific age and/or gender categories for whom adequate iron intake is extremely important, including school-age children, adolescents and women of childbearing age. Moreover, the methods used to diagnose of ID in overweight and obese individuals must be standardized. Our results suggest that serum ferritin is not a sufficiently sensitive index for diagnosing ID in obese patients. One should therefore consider avoiding the use of ferritin (or raising the diagnostic threshold for depleted iron stores) when diagnosing ID in obese and/or overweight individuals. sTfR is a promising candidate in detecting ID, although a standardized assay system is still required. Finally, future longitudinal studies are needed in order to test the putative causal relationship between obesity and hypoferraemia.

Conflict of interest statement

No conflict of interest was declared.

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Authors' contributions

The authors' responsibilities were as follows: LZ and FW designed the research; LZ, XZ, YS and XF conducted the research, analysed the data and performed the statistical analyses; LZ, YW and FW drafted the manuscript. All authors reviewed and approved the final manuscript.

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12323

Figure S1. Funnel plots for publication bias.
Figure S2. Sensitivity analysis.
Figure S3. Forrest plots for subgroup analysis.
Table S1. Detailed information for weight diagnosis and outcomes of included studies.
Table S2. Quality assessments of included studies.

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