Association between iron deficiency and telogen effluvium: a systematic review and meta- analysis

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Abstract

Iron deficiency has been associated with telogen effluvium, but currently, the data regarding their association are conflicting. To derive a more precise estimation of this association, we performed a systematic review and meta-analysis to investigate serum ferritin level, serum iron level, and prevalence of ferritin deficiency in all published studies. Databases including PubMed, Google Scholar, Offshore Vessel Inspection Database, and Cochrane Library, were systematically searched. The association was assessed using standardized mean differences, odds ratios, and 95% confidence intervals. Statistical analysis was performed using Review Manager version 5.4.1. A total of 20 studies were identified. The results showed that in patients with telogen effluvium, including those with acute and chronic telogen effluvium, serum iron and serum ferritin levels were lower than those in the normal population. There was no significant difference in serum ferritin and iron levels between patients with acute and chronic telogen effluvium. In patients with chronic telogen effluvium, the prevalence of ferritin deficiency was higher than that in the general population when ferritin levels were 20 ng/dl and 30 ng/dl as the threshold for the diagnosis of iron deficiency. This meta-analysis revealed that iron deficiency is associated with telogen effluvium and clarified the critical serum ferritin level for defining iron deficiency in patients with telogen effluvium.

Introduction

Telogen effluvium is a diffuse, non-scarring alopecia characterized by the simultaneous loss of a large number of telogen hairs and was named by Kligman in 1961[1]. Changes in the hair follicle cycle, such as shortening or lengthening of the anagen and telogen phases and synchronous hair follicle cycling, can induce hair shafts to fall out synchronously during the telogen phase, resulting in telogen effluvium[2]. Telogen effluvium is common in non-menopausal women, with an incidence rate of approximately 30% in the United States, Britain, and Japan, which seriously increases the economic and psychological burden on patients[3, 4]. Telogen effluvium does not have a specific predisposing ethnicity, but women are more likely than men to seek medical attention for telogen effluvium[5]. Depending on the disease duration, it can be divided into acute and chronic[6]. When the onset of telogen effluvium is acute, the daily amount of hair loss is > 300 hairs, the incubation period is generally 2–3 months, and it can occur at any age [2, 7]. The course of the disease lasts for 4–6 months, and 95% of patients can control their hair loss within 6 months. Chronic telogen effluvium usually lasts for more than 6 months and up to 2–3 years, occurs most often in women aged 30–60 years, and has a long and fluctuating course[8, 9]. Although telogen effluvium is a common dermatological disease, the cause of hair loss remains unclear. However, this hypothesis is controversial. Telogen effluvium is associated with a variety of endogenous and exogenous factors, including surgery, bleeding, childbirth, severe illness, malnutrition, micronutrient deficiencies, drugs, and major stressful events[10–14].

Iron deficiency is a potential cause of hair loss. Many studies have investigated the association between iron deficiency and telogen effluvium. The studies have mainly focused on the association between the reduction in serum iron and ferritin levels and hair loss. Iron in the human body is divided into three components: iron storage, iron transport, and functional iron. Iron deficiency is divided into three stages: reduced iron storage, reduced iron storage plus transported iron, and iron deficiency anemia[15]. Serum iron is a marker of iron transport and can reflect the state of iron deficiency in the body. Serum ferritin is a complex formed between apoferritin and iron core Fe^{3+}, which is the storage form of iron, and ferritin is a marker of iron storage[16, 17]. Ferritin is the first to be affected when iron is deficient[18]. Serum ferritin can reliably reflect iron deficiency and is synchronized with bone marrow iron staining with high sensitivity and specificity[19]. However, there is currently no universally accepted serum ferritin level for defining iron deficiency. In studies on iron deficiency and alopecia, serum ferritin was used to define the cut-off value of iron deficiency ranging from 10 to 70 ug/L[1, 20, 21]. Studies evaluating the association between iron deficiency and telogen effluvium have yielded conflicting results, and the value of iron supplementation in patients remains unclear[22–24]. Currently, there is no published evidence-based medical evidence on the association between iron deficiency and telogen effluvium and accepted serum ferritin level for defining iron deficiency. Therefore, we conducted a meta-analysis of the relationship between iron deficiency and telogen effluvium.

Results

Study characteristics

We retrieved 1642 studies. After removing duplicates, 890 studies were evaluated. By reading the titles and abstracts and excluding irrelevant articles and reviews, the remaining 346 articles were further evaluated. After reading the full text, a total of 20 studies were included in the final meta-analysis. Seventeen were case-control studies[25-41], and three were cross-sectional studies[42-44]. The publication years ranged from 2005 to 2021, with a total of 3642 participants. The NOS results showed that the methodological quality was generally high. The vast majority of participants were young and middle-aged women, including people in Asia, Europe, and North America. Among them, Egypt, Turkey, and Iran included three studies; India and Iran included two studies; and Bangladesh, China, Jordan, Nepal, Pakistan, Saudi Arabia, and the United States included one study each. The included studies evaluated serum ferritin level, serum iron level, and prevalence of ferritin deficiency. The subjects were patients with acute and chronic telogen effluvium. We performed a subgroup analysis of different hair loss types to explore the similarities and differences in serum iron and ferritin levels. The subjects with acute and chronic telogen effluvium were placed in separate subgroups, and those with unclassified telogen effluvium were placed in the telogen effluvium group. The literature search flowchart is shown in Figure 1. Table 1 presents the characteristics of the included studies.

Table 1

Baseline characteristics of the included studies.

Author (year)	Type of study	Sample size(P/C)	country	Sex (P/C)	Age(P/C) (mean ± SD, y)	Type	Diagnosis	Data collected	NOS
Alizadeh et al.2021	Case-control	83/83	Iran	Female	36.78±5.88	CTE	History, physical examination, pull test,dermoscopy	serum ferritin, prevalence of ferritin deficiency	7
Cheng et al.2021	Cross-Sectional	193/183	China	NA/Female	28.37±5.11/29.11±5.46	TE, ATE, CTE	History, physical examination, pull test,dermoscopy	serum iron, serum ferritin	7
Chisti et al.2012	Case-control	100/100	India	Female	26.6±7.25/26.83±9.97	ATE, CTE	History, physical examination	serum ferritin	7
Elethawi et al.2012	Case-control	38/25	Iraq	Female	30.15±6.5	CTE	History, physical examination, pull test	serum ferritin	7
Ertug et al.2018	Case-control	455/196	Turkey	Female	29.01±8.71/31.29±8.7	TE	History, physical examination, pull test	serum iron	7
Fatani et al.2015	Cross-Sectional	160/425	Saudi Arabia	Female	28.94±10.6/34.24±11.4	TE	History, physical examination	serum ferritin	6
Hamad et al.2010	Case-control	34/26	Egypt	Female	22.95±7.31/19.06±9.82	TE	History, physical examination, pull test, trichogram	serum iron	7
Hasseeb et al.2020	Case-control	53/26	Iraq	Female	Range 18–45	ATE, CTE	History, physical examination	serum iron, serum ferritin	7
Hodeib et al.2017	Case-control	40/20	Egypt	Female	28.10±4.65/27.45±6.41	TE, ATE, CTE	History, physical examination, pull test,dermoscopy	serum iron, serum ferritin	7
Karadag et al.2011	Case-control	63/50	Turkey	Female	29.1±11.9/28.4±9.4	TE, ATE, CTE	History, physical examination, dermoscopy	serum ferritin	7
Karim et al.2010	Case-control	30/30	Bangladesh	Female	25.4 ±7/24.8 ±5.6	TE	History, physical examination, pull test	serum ferritin	7
Moeinvaziri et al.2009	Case-control	30/30	Iran	Female	28.1±8.5/29.4±8.2	CTE	History, physical examination, trichogram	serum iron, serum ferritin, prevalence of ferritin deficiency	7
Naser et al.2021	Cross-sectional	60/60	Iraq	Female	32.6±6.47/41.3±4.59	CTE	History, physical examination, pull test	serum ferritin, prevalence of ferritin deficiency	7
Obaidat et al.2005	Case-control	72/30	Jordan	Female	26±9.2/32±11.6	CTE	History, physical examination, pull test	serum ferritin, prevalence of ferritin deficiency	7
Olsen et al.2010	Case-control	381/76	USA	Female	Range 18-65	TE	History, physical examination	serum ferritin, prevalence of ferritin deficiency	7
Pradhan et al.2018	Case-control	60/60	Nepal	Female	33.93±11.02/34.97±10.42	TE	History, physical examination	serum ferritin	7
Rasheed et al.2013	Case-control	80/40	Egypt	Female	29.8 ± 9.3/30.8 ± 8.56	TE	History, physical examination, pull test,	serum ferritin	7

							trichogram, dermoscopy		
Sarkar et al.2013	Case-control	40/40	India	Female	24.28 ± 6.17/23.11±4.67	CTE	History, physical examination, pull test, trichogram	serum ferritin, prevalence of ferritin deficiency	7
Ullah et al.2019	Case-control	50/50	Pakistan	Female	26±7.61/31.88±6.62	TE	History, physical examination, pull test	serum ferritin	7
Yavuz et al.2018	Case-control	40/30	Turkey	NA/Female	NA	CTE	NA	serum iron	7

Abbreviations: P, patients; C, control; TE, telogen effluvium; ATE, acute telogen effluvium; CTE, chronic telogen effluvium; NA, not applicable.

Main results

Serum ferritin level in telogen effluvium

Ten studies measured serum ferritin level in telogen effluvium[27,28,30,31,34,35,37,39,43,44]. Significant heterogeneity was observed ($P < 0.00001$, $I^2 = 93\%$), and a random-effects model was applied. These results showed that serum ferritin levels were lower in the telogen effluvium group than in the control group ($P < 0.00001$, SMD = −1.09, 95% CI = −1.50 to −0.69). Four studies measured serum ferritin level in acute telogen effluvium[26,28-30]. Heterogeneity was observed ($P = 0.04$, $I^2 = 63\%$). A random-effects model was used. The acute telogen effluvium group had a lower serum ferritin level than the control group ($P = 0.03$, SMD = −0.53, 95% CI = −1.00 to −0.06). Nine studies measured serum ferritin level in chronic telogen effluvium[26,28-30,32,33,36,40,42]. Heterogeneity was observed ($P = 0.0001$, $I^2 = 75\%$). A random-effects model was used. The chronic telogen effluvium group had lower serum ferritin level than the control group ($P < 0.0001$, SMD = −0.73, 95% CI = −1.06 to −0.40). Serum ferritin levels were lower in patients with different types of telogen effluvium than in the normal population. The results are shown in Figure 2.

Serum iron level in telogen effluvium

Three studies had a measurement of serum iron level in telogen effluvium[27,28,39]. Heterogeneity was found ($P < 0.00001$, $I^2 = 93\%$), and the random-effects model was applied. These results showed that serum iron level was reduced in the telogen effluvium compared to the control group ($P = 0.03$, SMD =−1.09, 95% CI =−2.06 to −0.11). Only two studies had a measurement of serum iron level in acute telogen effluvium[28,29]. No significant heterogeneity was observed ($P = 0.52$, $I^2 = 0\%$). To maintain the consistency of the results, we used the random-effects model. The acute telogen effluvium group had significantly lower serum iron level than the control group ($P = 0.001$, SMD = −0.77, 95% CI = −1.25 to −0.30). We also switched the fixed-effects model analysis, which is consistent with the random-effects model. Three studies had a measurement of the serum iron level in chronic telogen effluvium[28,29,32]. Heterogeneity was observed ($P = 0.04$, $I^2 = 68\%$). A random-effects model was applied. The chronic telogen effluvium group had significantly lower serum iron level than the control group ($P = 0.005$, SMD = −0.84, 95% CI = −1.42 to −0.26). In patients with different types of telogen effluvium, serum iron levels were lower than those in the normal population. The results are shown in Figure 3.

Serum ferritin and iron levels in acute and chronic telogen effluvium

Four studies had a measurement of serum ferritin level in acute and chronic telogen effluvium[26,28-30]. Only two studies had a measurement of serum iron level in acute and chronic telogen effluvium[28,29]. No significant heterogeneity was observed, and the fixed-effects model was applied. There was no significant difference in serum ferritin level between acute and chronic telogen effluvium ($P = 0.62$, SMD = 0.08, 95% CI = −0.23–0.38), nor were serum iron levels ($P = 0.26$, SMD = 0.26, 95% CI = −0.19–0.72). The results are shown in Figure 4.

Prevalence of ferritin deficiency and telogen effluvium

Six studies on chronic telogen effluvium have reported the prevalence of ferritin deficiency, which has not been publicly reported in patients with acute telogen effluvium. Due to the small number of included studies, we directly used a random-effects model for analysis. Three studies reported the prevalence of ferritin deficiency and chronic telogen effluvium with ferritin level below 10–15 μg/L (ng/mL)[25,32,41]. There was no significant difference between the chronic telogen effluvium and control groups ($P = 0.51$, SMD = 1.57, 95% CI = 0.41–5.95). Two studies reported the prevalence of ferritin deficiency and chronic telogen effluvium with ferritin levels of 20 μg/L[33,36], 30 μg/L[32,42], 40 μg/L[25,41], and ≤ 70 μg/L[41,42]. The prevalence of ferritin deficiency in the chronic telogen effluvium group was significantly higher than that in the control group at serum ferritin levels of 20 μg/L ($P = 0.0002$, SMD = 4.32, 95% CI = 1.99–9.38) and 30 μg/L ($P < 0.00001$, SMD = 18.62, 95% CI = 8.28–41.90). No significant difference was observed between the chronic telogen effluvium and control groups with ferritin levels of 40 μg/L ($P = 0.43$, SMD = 1.22, 95% CI = 0.74–2.00) and ≤ 70

μg/L (P = 0.54, SMD = 1.97, 95% CI = 0.23–16.74). In patients with chronic telogen effluvium, the prevalence of iron deficiency was higher than that in the general population with ferritin levels at thresholds of 20 μg/L and 30 μg/L, and the difference was statistically significant. The results are shown in Figure 5.

Sensitivity analysis

The contribution of each study to the pooled estimate was evaluated to assess the sensitivity of the analyses. Yavuz et al. had an undue influence on the summary SMD under the serum iron level in acute telogen effluvium[38]. This was excluded from the analysis. Other studies did not substantially change the pooled point estimates. We also converted the random- and fixed-effects models in all studies. No substantial changes were observed in these data. These results confirm the reliability of the present study.

Publication bias

Funnel plots were used to evaluate the publication bias. In the study of serum ferritin and iron levels in patients with telogen effluvium, the funnel plot was symmetrical, suggesting that the overall publication bias was small (Figure 6). In the studies on the prevalence of serum ferritin deficiency, because only two to three studies were included in each subgroup, the number was relatively small, and no further publication bias testing was performed.

Discussion

This study used evidence-based medicine to assess the association between iron deficiency and telogen effluvium, including studies from several countries in Asia, Europe, and the United States. The serum ferritin and iron levels of patients with acute and chronic telogen effluvium were lower than those of controls. There was no significant difference in serum ferritin levels or serum iron reduction levels between patients with acute and chronic telogen effluvium. In patients with chronic telogen effluvium, the prevalence of ferritin deficiency is higher than that in the general population when ferritin levels are 20 ng/dl and 30 ng/dl as the threshold for the diagnosis of iron deficiency.

However, the mechanism by which iron affects hair growth remains unclear. Iron metabolism is the basis of the interaction between oxidative stress and antioxidants[45]. Iron can regulate the oxidative activity of tyrosinase, which is significantly associated with hair whitening[46]. Iron is a cofactor of ribonucleotide reductase, the rate-limiting enzyme in DNA synthesis. Iron deficiency prevents the normal function of this enzyme, thus inhibiting proliferation and other iron-dependent enzymes and leading to hair loss[47]. The level of ferritin in non-dividing cells, such as hair follicle stem cells and terminal differentiated cells, increased, whereas the level of ferritin in rapidly proliferating hair follicle stromal cells was low, and the level of free iron was high. This balance between ferritin and iron is partially controlled by the transcription factor c-myc, and overexpression of c-myc may cause hair loss[48, 49]. Some genes in the human hair follicles may be regulated by iron. Iron deficiency may have an effect on gene expression, but its specific mechanism remains unclear[50].

Currently, the majority of the women in the current study are premenopausal, and therefore are more like to have hair loss due to loss of iron stores through menstruation. The research subjects were mainly young and middle-aged female patients, and only one study explicitly identified premenopausal and postmenopausal female patients with telogenic hair loss[41]. This study defined iron deficiency as ferritin ≤ 15 μg/L or ≤ 40 μg/L and found no significant difference in the prevalence of iron deficiency in women with chronic telogen effluvium or female pattern hair loss compared with controls and premenopausal or postmenopausal iron deficiency. There was no significant difference in the prevalence.

Serum ferritin levels are the most specific and effective measure of whole-body iron stores and are commonly used[51]. The prevalence of reduced serum ferritin levels (< 30–40 μg/L) appears to be higher in women with telogen effluvium than in the general population[52]. Serum ferritin levels below 30 μg/L were found in 40–50% of women in Cambodia[53], Portugal [54], Norway, and Denmark [55]. Although values < 12–15 μg/L can confirm iron deficiency, serum ferritin level < 30 μg/L is more widely used due to its higher sensitivity (92%) and similar specificity (98%) [16, 56, 57]. This study shows that if serum ferritin ≤ 15 μg/L or ≤ 70 μg/L is used as the cut-off value for the diagnosis of iron deficiency in patients with chronic telogen effluvium, the prevalence of iron deficiency in the telogen effluvium group and the control group was not statistically different. If serum ferritin level was 20 μg/L or 30 μg/L for the diagnosis of iron deficiency, the prevalence of iron deficiency was statistically different compared to that in the non-alopecia population.

There are few intervention trials of iron supplementation in patients with alopecia, which may be due to conflicting conclusions from previous studies on whether patients with alopecia are iron-deficient. Several studies have been published using different interventions, including iron with L-lysine[24, 58], iron alone[59], and iron with spironolactone[60]. Two studies targeted interventions with ferritin levels > 50 μg/L[61] or 70 μg/L[23]. These studies were limited by small sample sizes and differences in ferritin levels. However, monitoring serum iron levels is important in patients taking oral iron supplements. Taking iron supplements without monitoring is associated with a risk of potentially serious complications[62, 63].

This study has certain limitations. First, there were ethnic differences among the included participants, different dietary habits, and differences in their intake of iron. Second, ferritin levels can be elevated in diseases such as inflammation, chronic kidney disease, and tumors[64, 65]. Although this study was screened, there may still have been some selection bias. Third, the sample size of the included population was small, and there may be differences

in the examination methods of serum ferritin, which reduces the reliability of the conclusion of this study. However, this study also has some clinical significance. This study is the first to use evidence-based medicine to confirm that serum iron and serum ferritin levels are decreased in patients with telogen effluvium. This study also found that in some studies using ferritin to define iron deficiency, the prevalence of alopecia was not significantly lower than that of the non-alopecia population, which may be due to the selection of a critical value that is significantly low or significantly high.

Conclusion

This study shows that iron deficiency is associated with telogen effluvium and provides evidence-based medical evidence for the treatment of telogen effluvium with iron supplementation. Simultaneously, this study clarified the critical value of serum ferritin to define iron deficiency in patients with telogen effluvium and provided a reference value for the screening of iron deficiency in patients with alopecia.

Materials And Methods

The study was carried out based on the principles of the PRISMA statement[66]. This protocol was registered in PROSPERO (ID 42022310129). The raw data and fully reproducible code are available on the OSF (https://osf.io/d58at/).

Literature search

We searched for literature describing the association between iron deficiency and telogen effluvium. Literature was retrieved by a formal search of electronic databases (PubMed, Offshore Vessel Inspection Database, Cochrane Library, and Google Scholar) and by manually searching the reference lists of related articles. The computer searches were limited before February 2022, using the keywords: “iron” OR “ferrum” OR “ferritin” AND “hair loss” OR “alopecia” OR “telogen effluvium”. The language used was limited to English. There were no ethnic restrictions.

Inclusion criteria

The diagnosis of telogen effluvium was based on the examination results of physical examination, pull test, history, dermoscopy, and/or trichogram. The inclusion criteria were as follows: (1) published literatures related to the association of serum iron level, serum ferritin level, or prevalence of ferritin deficiency with telogen effluvium; (2) independent case-control or cross-sectional studies; and (3) original studies providing the mean and standard of serum iron level and the number of each group, serum ferritin level, or prevalence of ferritin deficiency.

Exclusion criteria

The exclusion criteria were as follows: (1) studies with original data that could not be extracted; (2) studies with duplicated data; and (3) studies with study participants having specific diseases that may have an effect on serum iron or ferritin, such as acute infections, fever, and chronic wasting disease; with patients undergoing bariatric surgery, or with patients with cancer.

Data extraction

Two authors (J.Z.Z. and M.M.G.) independently extracted the original data. They independently decided whether to include each study. Disagreements were resolved by discussion with the third investigator (L.D.). The extracted data consisted of the following items: the first author’s name, year of publication, method of diagnosis, type of study, sample size, sex, age, country, and measures of iron deficiency.

Quality assessment

Study quality was assessed using the Newcastle-Ottawa Scale (NOS)[67]. Three aspects were considered in the NOS criteria: (1) selection of research objects (0–4 stars), (2) comparability of research objects (0–2 stars), and (3) exposure or outcome (0–3 stars). NOS scores range from 0 (worst) to 9 stars (best); a score equal to or higher than 7 indicated that the study was of good quality. Two investigators (Y.D. and Y.X.M.) independently assessed the quality of each included study. Disagreements were resolved by discussion with the participation of the third investigator (T.T.L.).

Statistical analyses

Review Manager 5.41 (The Nordic Cochrane Centre, Copenhagen) was used to perform the meta-analysis. Continuous variables were analyzed using standardized mean differences (SMDs) with 95% confidence intervals (CIs). Dichotomous data were analyzed using odds ratios (ORs) corresponding to 95% CI. Heterogeneity among the studies was assessed using the I^2 statistic[68]. If heterogeneity existed among the studies ($P < 0.10$ and $I^2 > 50\%$), the random effects model was used to estimate[69]. Otherwise, a fixed-effects model was adopted[70]. Sensitivity analysis was performed to assess the robustness and heterogeneity of the combined results. Funnel plots were used to assess the potential publication bias.

Declarations

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Conflicts of interest

The authors declared no competing interests exist.

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Author Contributions

J.Z. Z. and X.J.K. designed the study. J.Z.Z., M.M.G. and L.D. screened the articles, extracted the data. Y.D., Y.X.M., and T.T.L. assessed the risk of bias, and analysed and interpreted the data. J.Z. Z. wrote the first draft of the manuscript. X.J.K. reviewed the subsequent versions and the final draft. All authors approved the final version.

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Figures

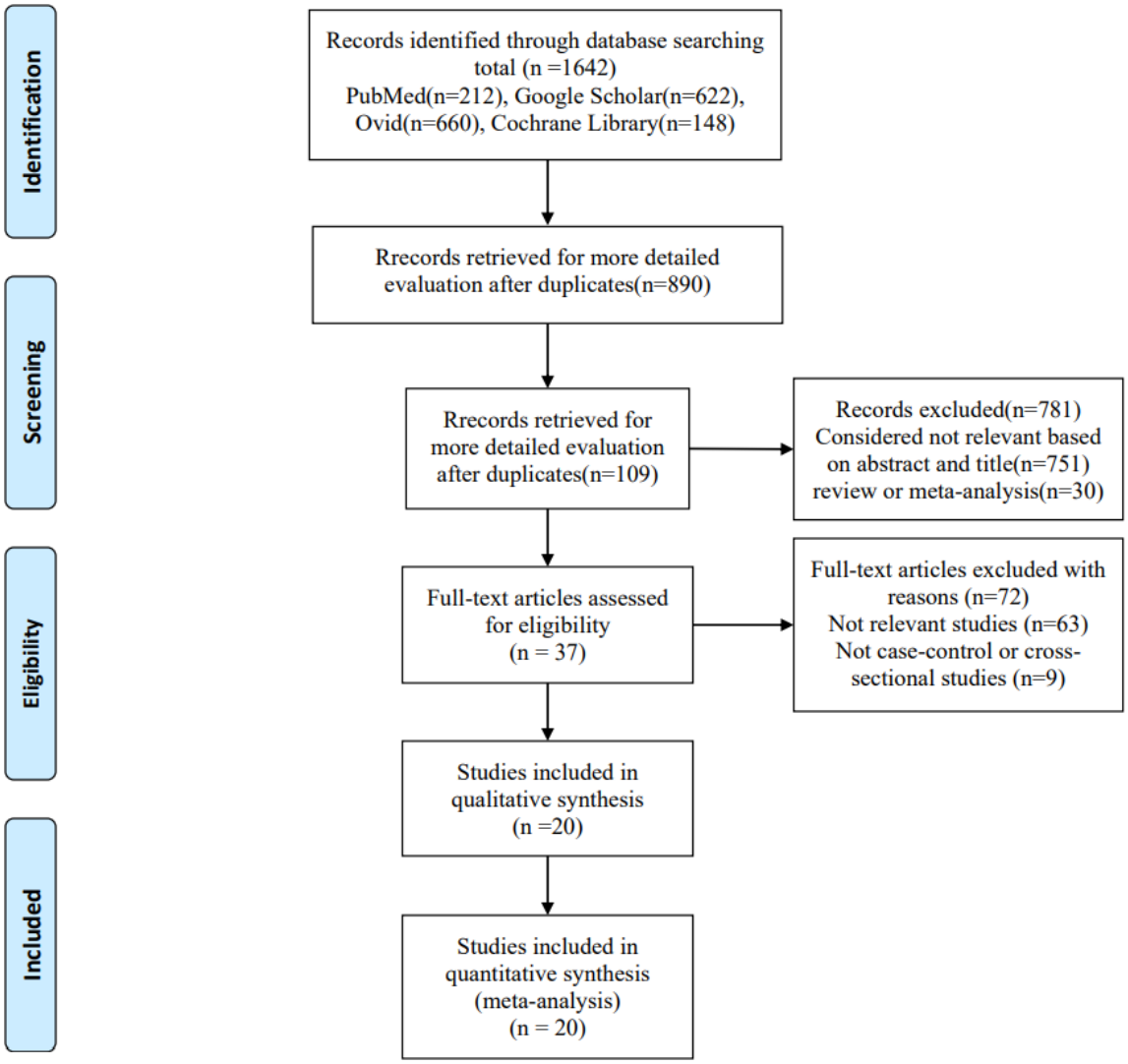

Figure 1

Flow of the selection of literature that reported the relationship of iron deficiency and telogen effluvium.

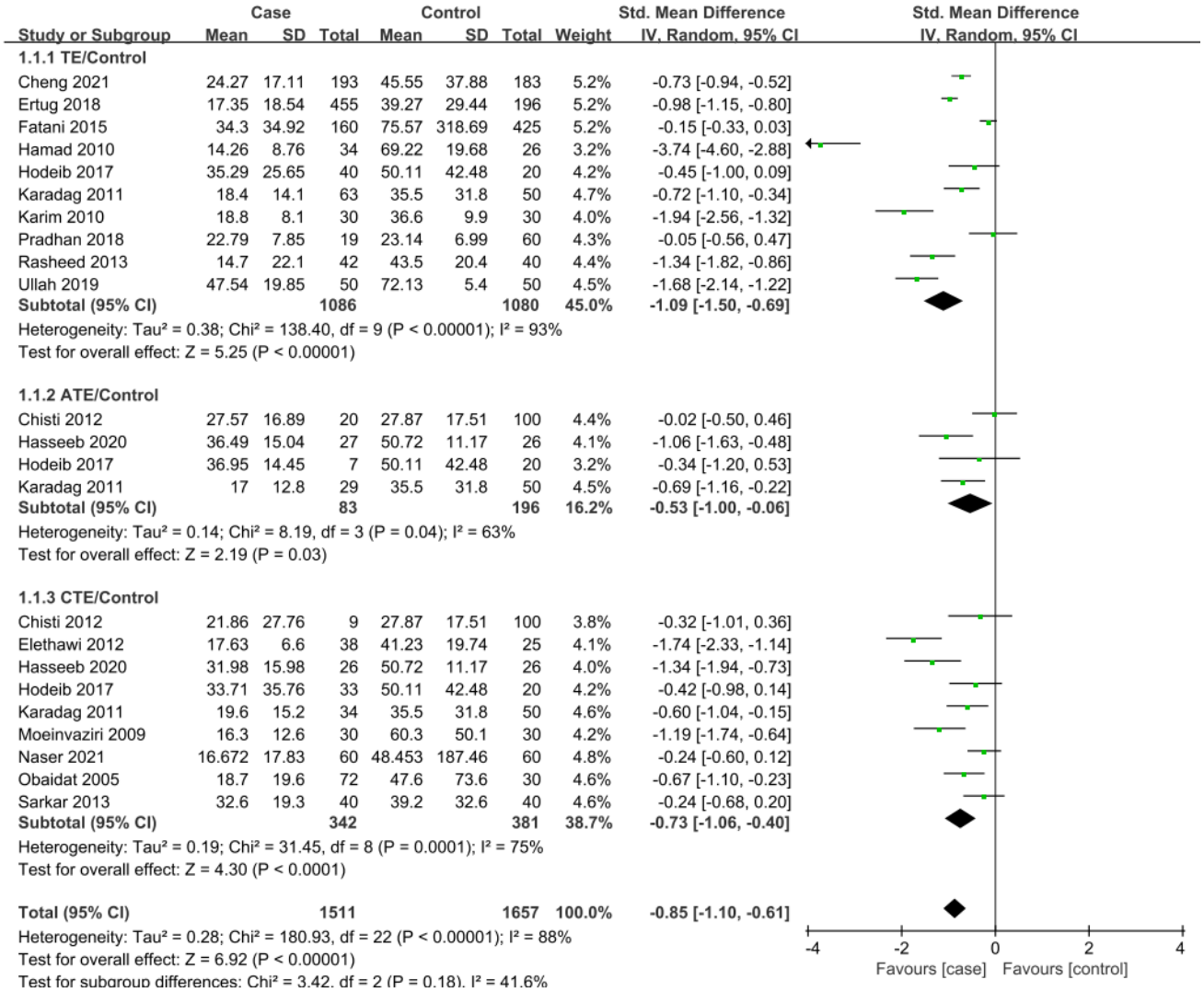

Figure 2

Forest plot of the serum ferritin level in different types of telogen effluvium compared to the control groups.

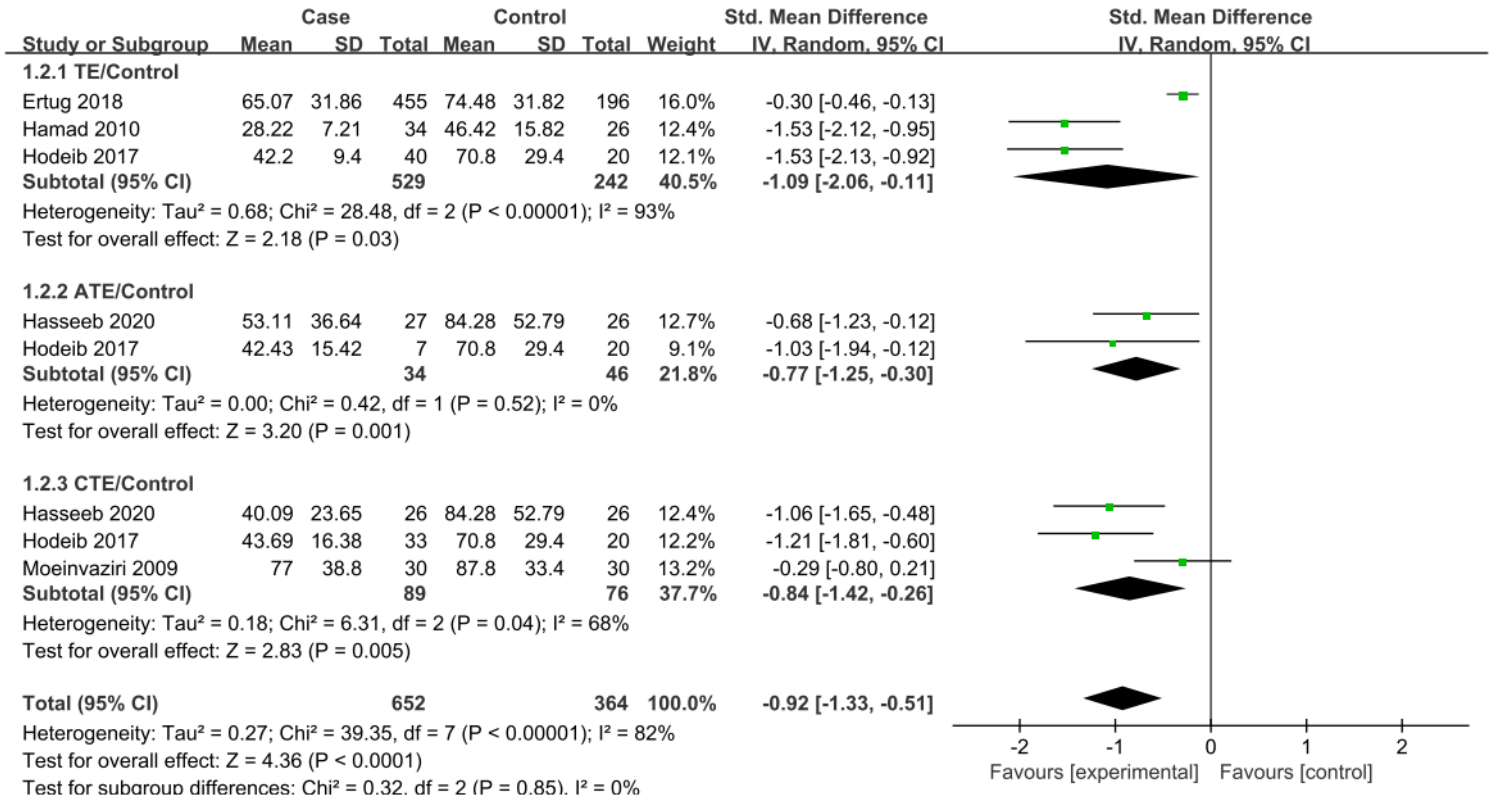

Figure 3

Forest plot of the serum iron level in different types of telogen effluvium compared to the control groups.

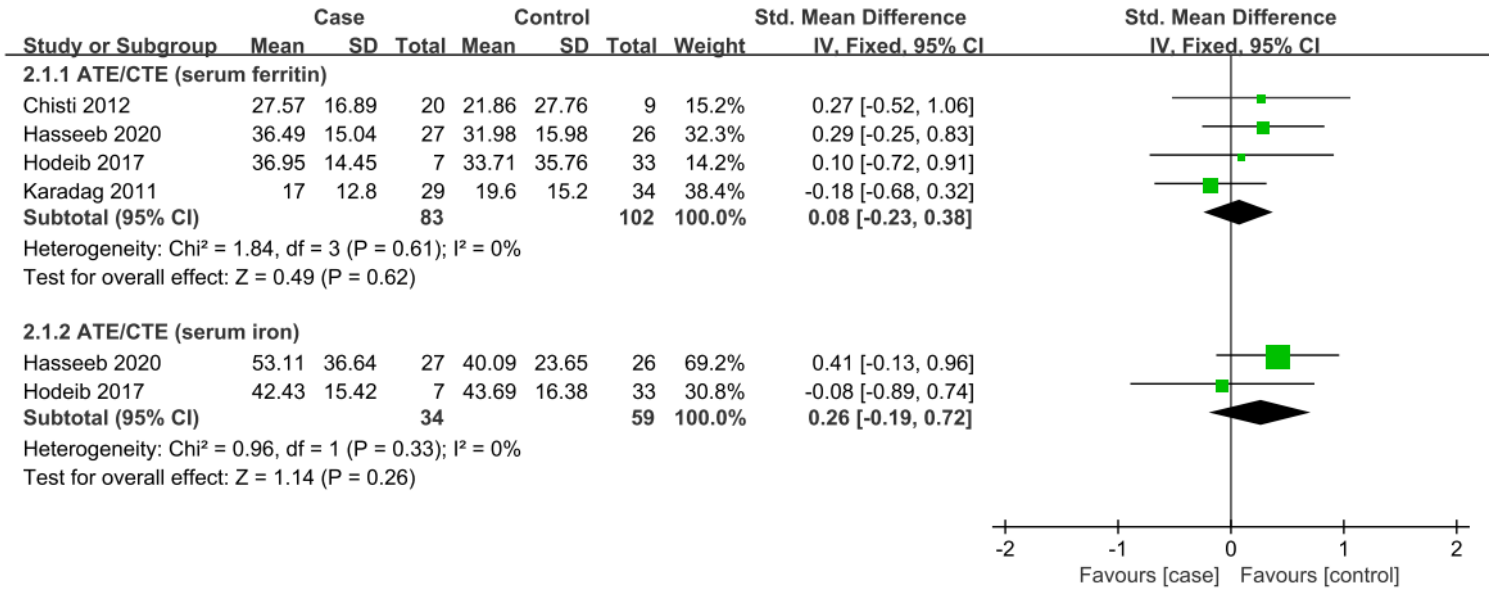

Figure 4

Forest plot of the serum ferritin and iron level in acute telogen effluvium compared to chronic telogen effluvium.

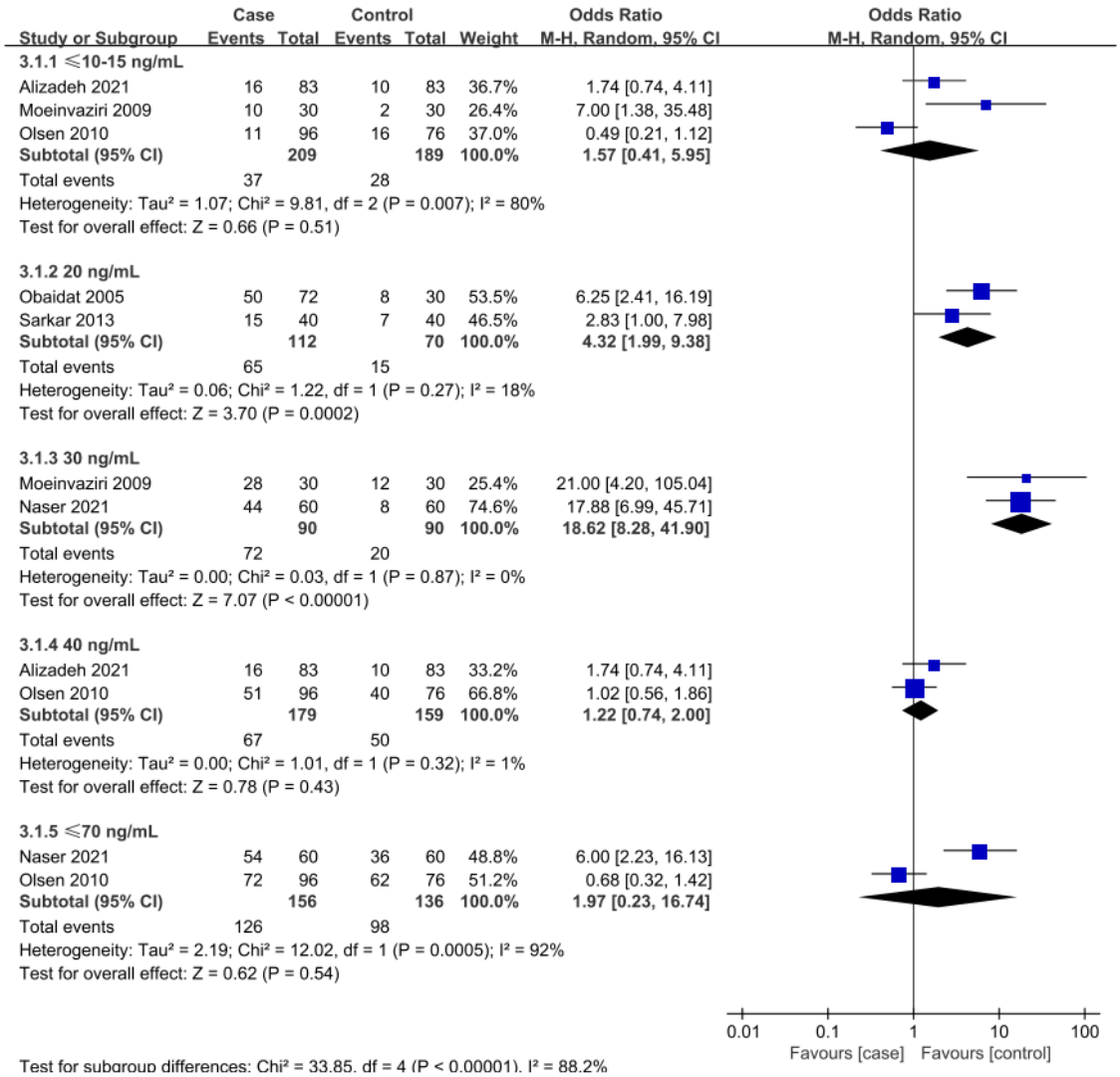

Figure 5

Forest plot of the prevalence of ferritin deficiency in chronic telogen effluvium compared to the control groups.

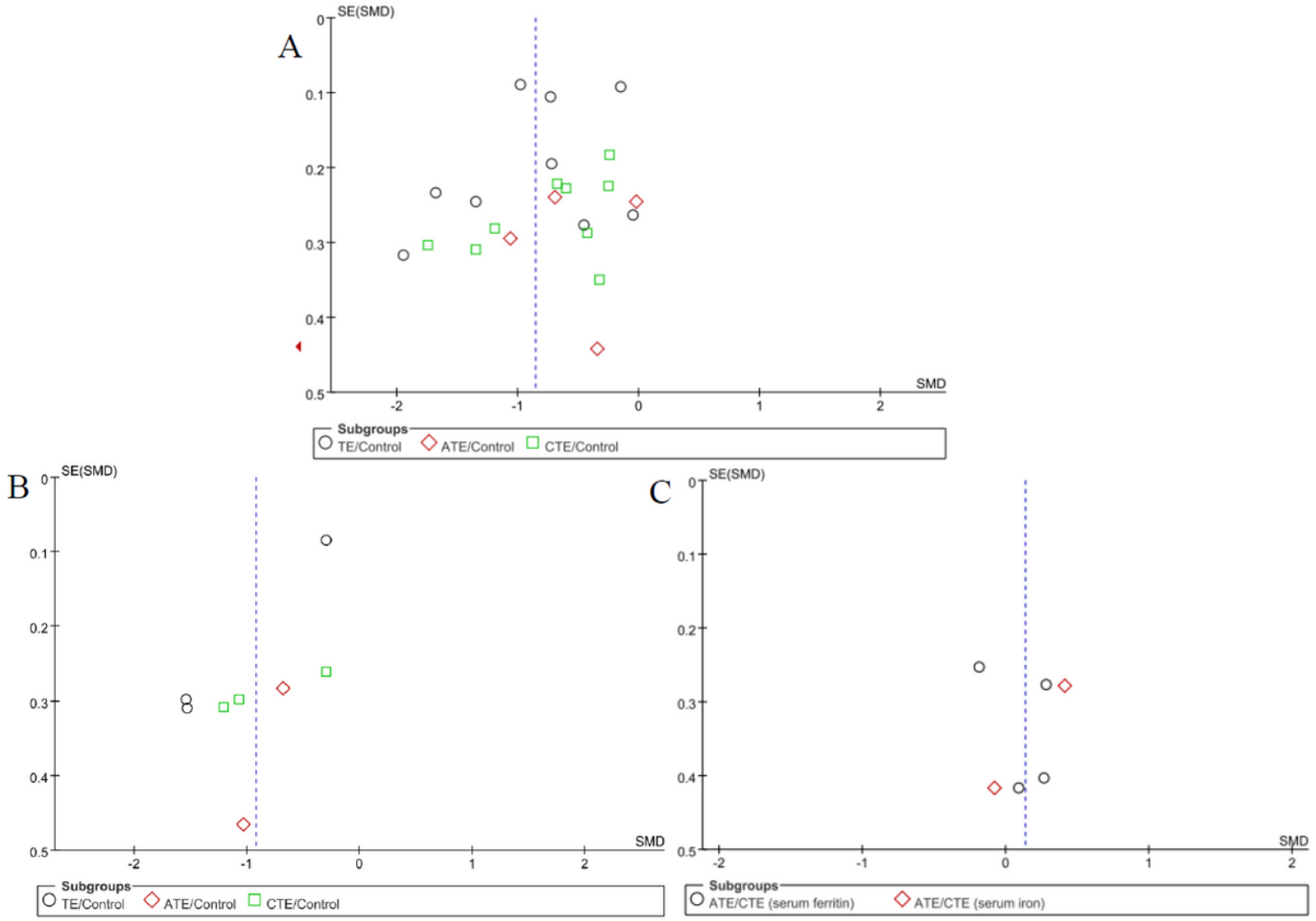

Figure 6

Funnel plot for publication bias tests. Each point represents a separate study for the indicated association. (a): serum ferritin level in different types of telogen effluvium vs. control groups; (b): serum iron level in different types of telogen effluvium vs. control groups; (c): serum ferritin and iron level in acute telogen effluvium vs. chronic telogen effluvium.