Review Article

Are Adults Over 18 Years of Age with Anaemia More Likely to Develop Chronic Periodontitis Than Adults Without Anaemia? - A Systematic Review and Meta-Analysis

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ABSTRACT

Aims and Objectives: Periodontitis is a chronic disease affecting the supporting tissues of the teeth and exhibits bidirectional relation with systemic diseases. This study aims to determine the association between chronic periodontitis and erythrocyte functional measures: total red blood cells (RBCs), hemoglobin (Hb) concentration, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) by systematic review and meta-analysis. **Materials and Methods:** A systematic search of the electronic databases PUBMED, OVID, Embase, Web on Science, and Google Scholar was undertaken from inception to July 2022. English language studies that evaluated the erythrocyte functional measures in periodontitis and health were selected. Other review reports, letters/opinion articles, studies without a definition of periodontitis, and the concomitant presence of systemic conditions (diabetes, kidney disease, cancer) were excluded. Two reviewers determined full-text eligibility in a blinded process. Meta-Essentials software was used to generate forest plots and to determine heterogeneity and publication bias. **Results:** Twenty-six studies involving 1082 patients with chronic periodontitis and 980 healthy controls were analyzed. Pooled results showed lower Hb concentration (Hedges' $g = -1.16$; 95% confidence intervals [CI], −1.7 to −0.62), RBC counts (Hedges' $g = -0.85$; 95% CI, −1.31 to −0.38) and packed cell volume (−0.56; 95% CI, −1.02 to −0.11) in patients with chronic periodontitis. **Conclusion:** This meta-analysis showed a decreasing trend in the hematological parameters, including hemoglobin concentration, number of erythrocytes, and hematocrit in patients with chronic periodontitis compared to healthy controls.

Keywords: *Anemia, periodontitis, red blood cell parameters, risk factors*

Introduction

Periodontitis is a chronic polymicrobial inflammatory disease of the periodontium (i.e., the tooth-supporting tissues).[1,2] Clinically, it is characterized by bleeding gums, periodontal ligament destruction, and alveolar bone loss. Several modifiable and nonmodifiable risk factors contribute to the clinical significance of periodontal diseases.[3] Case-control and correlational studies have suggested an association between chronic periodontitis and anemia, a hematological abnormality in which the number of red blood cells (RBCs) or their oxygen-carrying capacity is insufficient to meet physiological requirements.[4-6]

Several hypotheses have been proposed to support a bidirectional relationship between chronic periodontitis

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and anemia.[7] Chronic loss of blood from bleeding gums could reduce hemoglobin and lead to anemia.[8,9] Anemia due to dietary deficiencies (iron, vitamins) is the most common form worldwide. In this context, it is relevant to note that periodontal pathogens such as *Porphyromonas gingivalis* use iron for growth and thereby deplete iron and precipitate anemia.[10] Furthermore, chronic periodontitis is typically associated with elevated production of inflammatory cytokines such as IL1, IL6, and tumor necrosis factor-α. Mechanistically, these cytokines could suppress erythropoiesis, shorten RBC survival, and blunt erythropoietin response.[2,11] Anemia of chronic disease is the most prevalent anemia after iron deficiency anemia and is a result of the body's response to an inflammatory disease.[12] A population-based study on the quality of life of the elderly also supports the association between pro-inflammatory cytokines and C-reactive protein, and unexplained anemia.[13] Hence, it is likely that the elevated immune/inflammatory responses in chronic periodontitis can induce or perpetuate systemic effects of anemia of chronic disease. Hematocrit and other related blood parameters have been shown to improve after treatment in chronic generalized periodontitis patients with anemia, further supporting a relationship between the two conditions.[14,15]

Although several studies, including a few reviews, have reported associations between the circulating hemoglobin concentration and the clinical measures of chronic periodontitis,[9,16] comprehensive analyses of the relationship between all hematological parameters of anemia and chronic periodontitis are lacking. In addition to hemoglobin concentration and total RBC count, indices that define the size and hemoglobin content of RBCs including the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and MCH concentration (MCHC) are critical determinants of anemia.[17] The objective of this study is to determine the association between all erythrocyte functional measures and chronic periodontitis by systematic review and meta-analysis for better evaluation of anemia as a risk factor for periodontitis.

Materials and Methods

The PRISMA 2020 guideline[18] was used to report the systematic review with the use of Sample, Phenomenon of Interest, Design, Evaluation, and Research Type (SPIDER) as a tool to structure the research question: "Is there a specific association between specific erythrocyte functional measures and periodontitis?" The erythrocyte functional measures included (total RBC, hemoglobin [Hb] concentration, MCV, and MCHC).[19]

Search strategy

Five databases including PUBMED, OVID (Medline), Embase, Web on Science, and Google Scholar were searched from inception to July 2022 for studies published in English.[18,19] The search terms used in each of the databases included the following: (periodontitis or "periodontal diseases" or "chronic periodontitis") and ("anemia/anemia" or "hemoglobin" or "Hb" or "red blood cell counts" or "RBC" or "MCV" or "mean corpuscular volume" or "MCH" or "mean corpuscular hemoglobin" or "MCHC" or "mean corpuscular hemoglobin concentration" or "erythropoietin"). All data extraction was conducted by two investigators independently (RM and MS).

Inclusion and exclusion criteria

	Criteria	Inclusion	Exclusion
	Language	English	Non-English
S	Sample	Periodontitis (adults)	Periodontitis with the following conditions: Age <18 year; pregnant or lactating woman; absence of the definition of periodontitis; subjects with other chronic infections or inflammatory diseases; presence of systemic diseases such as diabetes, kidney diseases, and cancer
PI	Phenomenon of interest	Anemia	Studies not evaluating anemia; subjects with inherited anemias including sickle-cell anemia, thalassemia, and Fanconi's anemia; absence of evaluation of blood samples
D	Design of study	Cohort studies, case-control studies, comparative cross-sectional studies, observational studies, RCT/non-RCTs	Reviews, opinion-based studies, letter to editors, commentaries
E	Evaluation	Hb, hematocrit, RBC counts, MCV, MCH, MCHC	Studies not evaluating Hb, hematocrit, RBC counts, MCV, MCH, MCHC
	Research type	Qualitative studies, quantitative studies, mixed-method studies	

Study selection

Both authors participated in the literature search. Each reference was initially screened by titles and abstracts of all the articles after the exclusion of duplicates. Independent lists generated by each author were cross-referenced and any disagreement was resolved by consensus. Then full-text eligibility was determined based on inclusion and exclusion criteria by the two reviewers in a blinded process for final selection. A 100% agreement rate was obtained between the two authors.

Data extraction, risk of bias assessment, and statistical analysis

To assess the aim of the review, the following data were collected: information on the selected publications, including the last name of the first author, year of publication, country of study, purpose of study, sample size, characteristics of subjects included, definition of periodontitis, and outcome measures. Periodontitis definitions proposed by the 2007 CDC/AAP working group for use in population-based surveillance were applied in selecting studies.[20] Quality assessment was conducted using the Newcastle-Ottawa scale (NOS) based on three broad perspectives (selection, comparability, and exposure/outcome), with a maximum of nine scores by both authors independently. The outcomes were all continuous variables, including hemoglobin concentration, RBC counts, packed cell volume, MCV, MCH, and MCHC data provided as the mean and SD were extracted. The meta-essentials tools were used for statistical analyses.[21] We determined the standardized mean difference by calculating Hedges' g effect size and 95% confidence intervals (CIs) to assess the levels of these parameters in chronic periodontitis and control subjects. Because the sample size was small and different in the included studies, we used Hedges' g to measure the effect size. The Cochran's Q test, I^2 statistic, and P value were used to assess the heterogeneity. Random effects model was applied and a $P \geq 0.1$ or $I^2 \leq 50\%$ was considered as no significant heterogeneity. We used the sensitivity analysis to assess the robustness. Begg and Muzumdar test was used to assess the asymmetry of the funnel plot and $P < 0.05$ was considered publication bias. If present, the trim-and-fill method was adopted to determine the influence of publication bias on the results. Subgroup analyses were used to stratify the studies by covariables including gender, direction of change, and sample size to explore potential sources of heterogeneity.

Results

Initially, 2387 articles were collected from databases and a general Google search using the specific search terms for anemia and chronic periodontitis provided in the "Methods" section. After removing duplicates and irrelevant references, 128 studies remained. Following a comprehensive evaluation of titles and abstracts, 77 articles were excluded. Subsequently, a full-text review was conducted on 51 studies and this process resulted in the exclusion of 25 studies including five studies on aggressive periodontitis, five due to the absence of a definition of periodontitis, nine due to studies assessing only gingival crevicular fluid or saliva, and six studies to lack of control groups. Twenty-six articles remained for final analysis. PRISMA 2020 flowchart detailing this process is depicted in Figure 1.

Characteristics of included studies and quality assessment

In the current meta-analysis, a total of 26 studies with 2062 study participants were included to assess anemia as reported in patients with chronic periodontitis. By design, all except one were case-control studies and the number of test participants per study ranged between 5 and 100. Interestingly, although there was no geographic area restriction in our search criteria, 21 of the 26 studies were originated from India (1324 participants), two studies from Iraq (120 participants), one study each from Germany (127 participants), UK (82 participants), and Brazil (63 participants). All 26 studies reported circulating hemoglobin levels, >70% of studies reported additionally total RBC counts, MCV, and MCH and 40% of studies reported additionally total hematocrit and MCHC values. The criteria for the diagnosis of periodontitis and the control group used in each study are also given (Supplementary Table S1).[4-6,8,12,22-42] The quality score of each primary study, based on the Newcastle-Ottawa quality score assessment, was moderate to high for all 26 articles assessed.

Meta-analysis Results

Combined data on the analysis of the association between periodontitis and alterations of hematological parameters are provided in Table 1.

Analysis of hemoglobin (Hb)

In a pooled analysis of all 26 studies (gender cohort is reported separately in the studies by Hutter *et al.*[4] and Nibali *et al.*[22] and were included in the analysis as separate studies), the results revealed that there was a decreasing trend in Hb concentration in periodontitis subjects compared to the control group (−1.24 [−1.8 to −0.67]). However, there was significant heterogeneity among the studies (I^2 = 94.2%). Sensitivity analysis by excluding studies one by one at a time showed that neither the magnitude nor the direction of the effect size was substantially altered. We showed that the pooled Hedges' g was stable and reliable, implying lower Hb

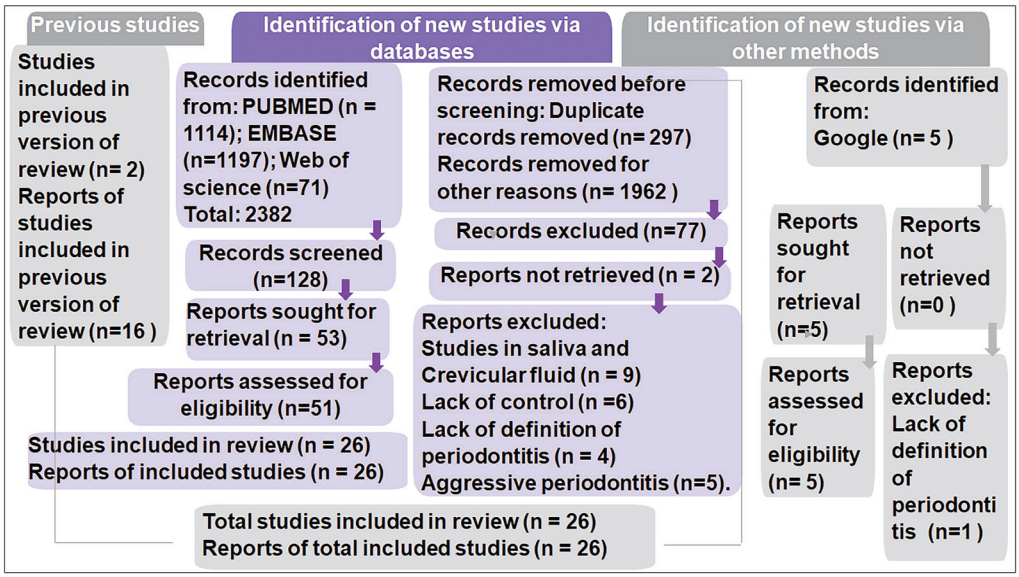

Figure 1: PRISMA 2020 flow diagram of study selection

Table 1: Meta-analysis of the association between periodontitis and anemia.

Hematological parameters	Number of studies	Number of subjects Test, Control	Hedges's g (95% CI)	Cochranes' Q	I^2
Hemoglobin	26	1082, 980	-1.16 (-1.7, -0.62)	456.43	94.08%
RBC counts	23	1000, 921	-0.85 (-1.31, -0.38)	302.39	92.06%
MCV	21	934, 889	-0.03 (-0.27, 0.21)	100.3	78.37%
MCH	20	917, 804	-0.31 (-0.88, 0.27)	288.34	93.06%
MCHC	18	8,37,748	-0.20 (-0.49, 0.09)	121.8	84.40%
PCV	14	661, 553	-0.56 (-1.02, -0.11)	102.28	85.23%

CI = confidence interval, Q = Chi-squared statistic, I^2 = Cochrane

levels in periodontitis [Figure 2A]. No publication bias was observed based on Begg and Muzumdar test [Figure 2B] ($z = -3.91$; $P = 0.00$). To explore the sources of heterogeneity, we performed subgroup stratification on variables, including gender, sample size, and country of studies. The lower Hb level in the chronic periodontitis cohort was consistent in gender studies restricted to males or including both sexes. However, based on the population studied, the trend towards lower Hb level in periodontitis was observed only in studies originating from India ($N = 20$), but not in studies from other regions ($N = 6$) suggesting low heterogeneity of later studies [Table S1].

Analysis of RBC

Pooled analysis of all 25 studies showed a significant decrease in RBC counts in periodontitis subjects compared to healthy controls (−0.86 [−1.31 to −0.38]; $P = 0.00$). There was significant heterogeneity among the studies ($I^2 = 92\%$) [Figure 3A]. In the sensitivity analysis by excluding studies one by one at a time, neither the magnitude nor the direction of the effect size was substantially altered. We showed that the pooled Hedges' g was stable and reliable, implying lower RBC counts in periodontitis. Significant publication bias was observed in this analysis as determined by the Begg and Muzumdar test ($P = 0.001$) [Figure 3B]. Trim-and-fill method in the random effects model using the leftmost/rightmost run estimator to adjust for publication bias was performed yielding an adjusted effect size of 0.37 (95% CI, −0.23 to 0.98] four missing studies). Subgroups analyses showed that the lower RBC counts were maintained in studies with both genders (Hedges' $g = -0.85$ [−1.36 to −0.35]) but not in studies evaluating only the male population (Hedges' $g = -0.81$ [−1.77 to 0.14]). Similarly, studies from India supported lower RBC counts in periodontitis ($N = 18$; Hedges' $g = -1.15$ [−1.7 to −0.6]) as compared to studies from other regions ($N = 5$; Hedges' $g = -0.04$ [−0.34 to 0.26]) [Table S2].

Analysis of PCV

The PCV is a measure of the proportion of blood that is made up of cells, expressed as a percentage or fraction.[31] Reduced PCV has been associated with anemia. In a pooled analysis of 14 studies, the results revealed that the PCV exhibited a decreasing trend in periodontitis subjects compared to the control group (Hedges' $g = -0.56$ [−1.02 to −0.11]) [Figure 4A]. A moderate

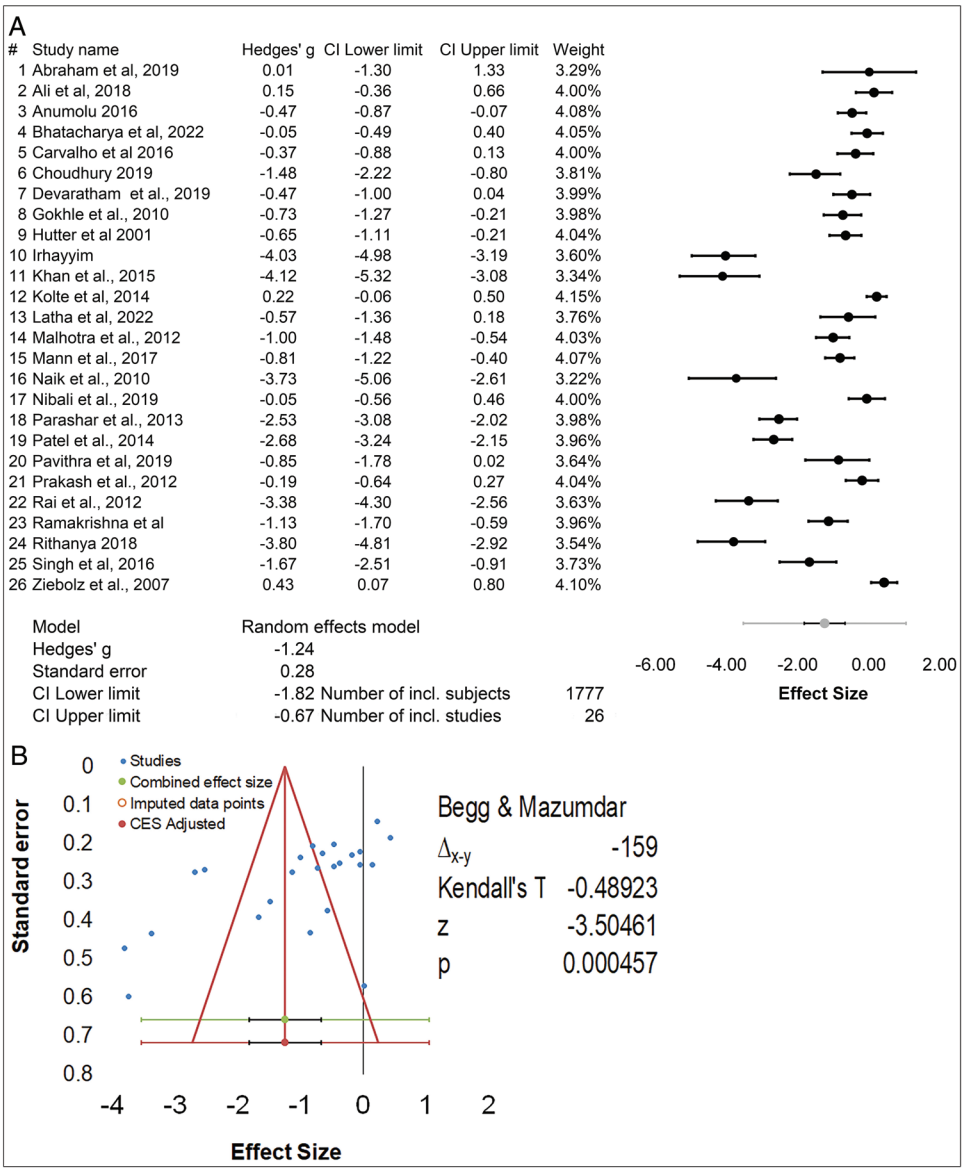

Figure 2: (A) Forest plot analysis of studies reporting hemoglobin concentration in chronic periodontitis and control subjects. Hedges' *g*, 95% confidence interval, and data of random effects model including % weight of each study are shown. (B) Publication bias of 26 studies reporting the observations of Hb concentration in patients with periodontitis

degree of heterogeneity was detected among the studies (I^2 = 85%). In sensitivity analysis by excluding studies one by one at a time, neither the magnitude nor the direction of the effect size was altered. We showed that the pooled Hedges' *g* effect size was stable and reliable, implying lower PCV in periodontitis. In this analysis, no publication bias was observed as determined by Begg and Muzumdar test (P = 0.05) [Figure 4B]. In subgroups analyses, the lower PCV counts were maintained in studies from India (Hedges' g = −0.78 [−1.33 to −0.24]) but not in studies from other regions (Hedges' g = −0.11 [−0.57 to 0.36]) that also exhibited lower heterogeneity (I^2 = 72%). Similarly, including only males exhibited lower PCV in periodontitis (N = 7; Hedges' g = −0.77 [−1.47 to −0.06]) [Table S3].

Analysis of MCV

Red cell indices including MCV, MCH, and MCHC are valuable in the morphologic classification of anemias in terms of size and hemoglobin content.[28,43] In a pooled analysis of 23 studies, the results revealed that the MCV was not significantly altered between the periodontitis and control groups (Hedges' g = −0.08 [−0.38 to 0.22]). A moderate degree of heterogeneity was detected among the studies (I^2 = 83.6%) [Figure 5A]. No publication bias was observed in this analysis as determined by Begg and Muzumdar test (P = 0.3) [Figure 5B]. In sensitivity analysis by excluding studies one by one at a time, neither the magnitude nor the direction of the effect size was altered. Subgroup analysis of the MCV

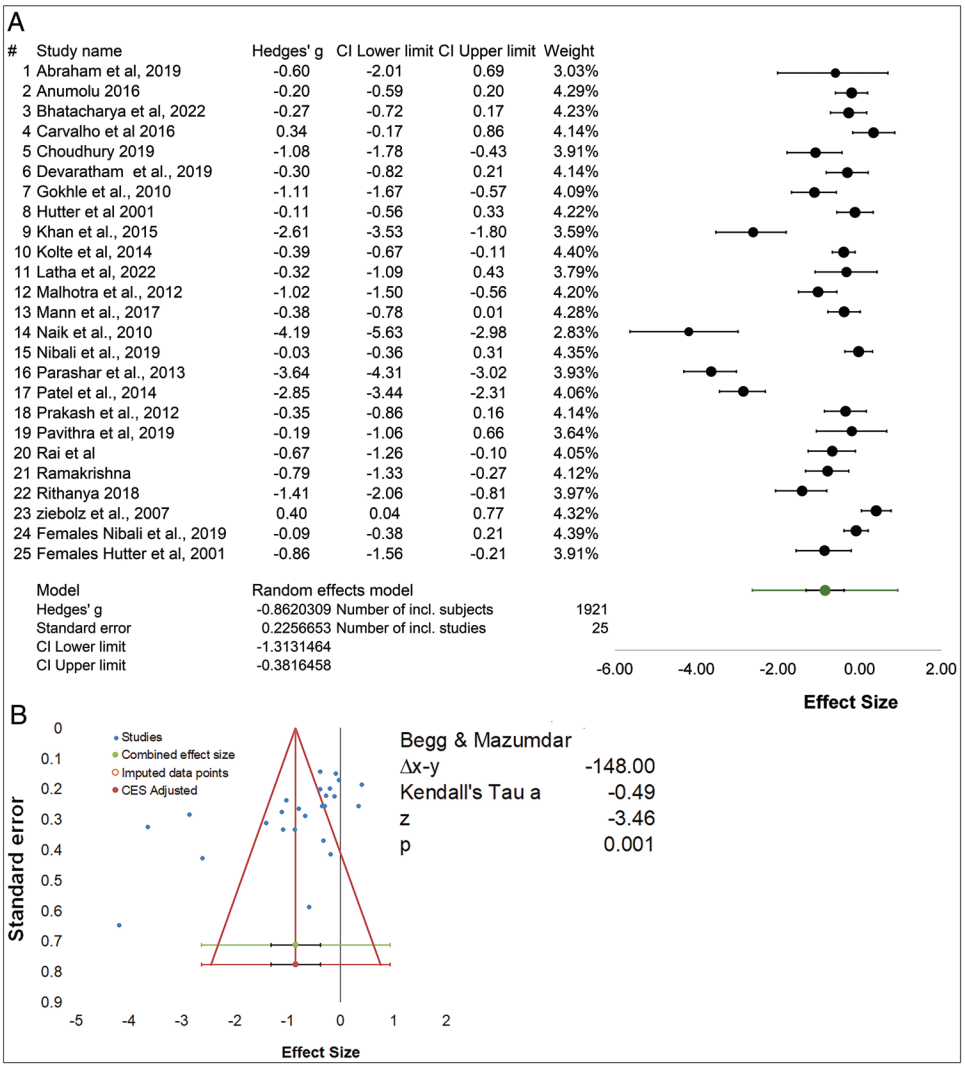

Figure 3: (A) Forest plot analysis of a total of 23 (male and female groups from Hutter *et al.*[4] and Nibali *et al.*[22] studies are included independently) reporting RBC counts in chronic periodontitis and control subjects. Hedges' *g*, 95% confidence interval, and data of random effects model including % weight of each study are shown. (B) Publication bias of 23 studies reporting the observations of RBC counts in patients with periodontitis

measure also suggested no significant difference in MCV values between groups [Table S4].

Analysis of MCH

In a pooled analysis of all 19 studies (Hutter *et al.*[4] and Nibali *et al.*[22] reported results as separate cohorts for each gender and hence were included as independent studies for analysis), the results revealed that there was a decreasing trend of MCH in periodontitis subjects compared to the control group (−0.31 [−0.88 to 0.27]; p_Q = 0.00) [Figure 6A]. There was significant heterogeneity among the studies (I^2 = 93%) and sensitivity analysis did not affect the magnitude or the direction of the effect size. No publication bias was observed in this analysis [Figure 6B]. Subgroup analysis of MCH showed that the Cochrane Q of studies from countries other than India suggested a homogenous population (Q = 2.6; P = 0.46) [Table S5].

Analysis of MCHC

In a pooled analysis of 18 studies, the results revealed that the MCHC was lower in periodontitis subjects compared to the control group, the decrease being significant (−0.20 [−0.49 to 0.09]; P = 0.00) [Figure 7A]. A significant degree of heterogeneity was detected among the studies (I^2 = 84.4%). In sensitivity analysis, neither the magnitude nor the direction of the effect size was altered. The visual inspection of the funnel plot indicated slight asymmetry [Figure 7B] but using trim and fill did not change the magnitude of the effect size. In the stratified analyses, it was observed that the studies recruiting both genders (N = 10/18) exhibited low heterogeneity (I^2 = 43.4%) with potentially decreased contribution of studies recruiting only males to the combined effect size [Table S6]. Subgroup analysis further suggested that the heterogeneity across

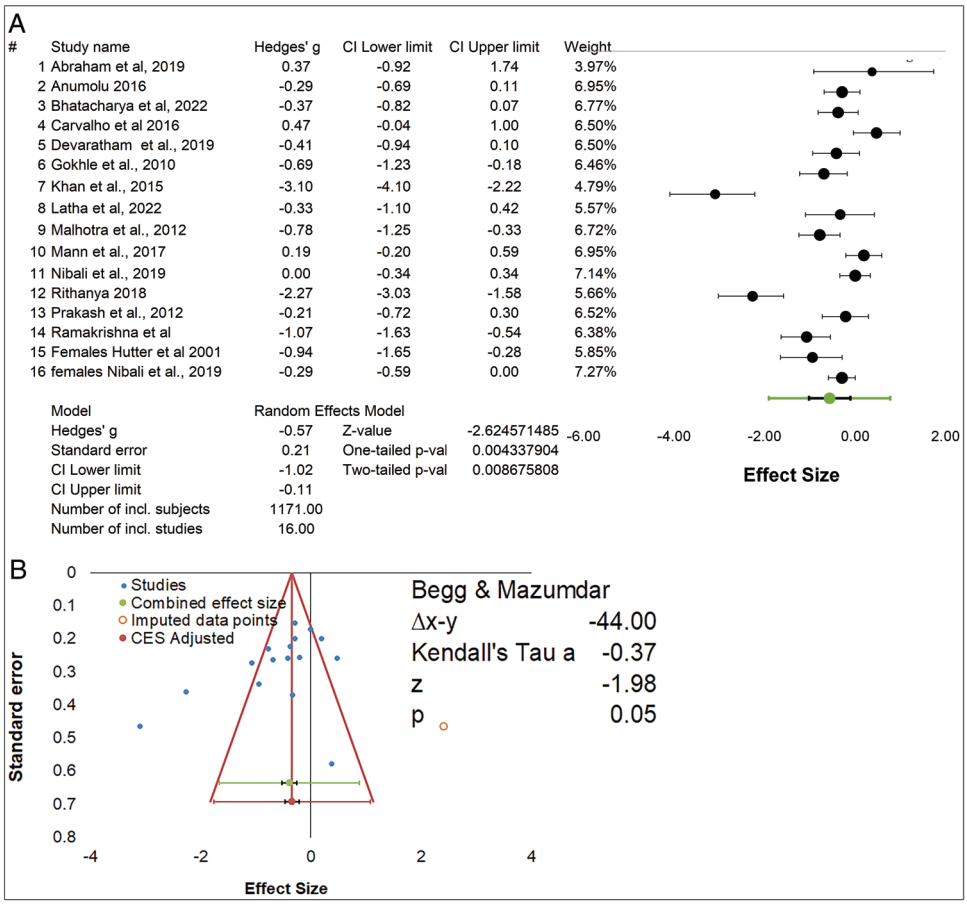

Figure 4: (A) Forest plot analysis of 14 studies (gender cohort is reported separately in Hutter *et al.*[4] and Nibali *et al.*[22] studies and hence the two studies are listed as two studies) reporting PCV in chronic periodontitis and control subjects. Hedges' *g*, 95% confidence interval, and data of random effects model including % weight of each study are shown. (B) Funnel plot analysis of publication bias of 14 studies reporting PCV in periodontitis patients

studies was high in the "India" group (I^2 = 87.4%) and low in the "other" group. countries outside of India.

Discussion

This meta-analysis included 26 studies with a total of 2062 participants to evaluate the association between chronic periodontitis and anemia. The hematological parameters of Hb concentration, RBC counts, and PCV were assessed in 26, 25, and 18 studies, respectively. Greater than 75% of the studies reported a significant decrease in Hb and RBC counts in the periodontitis population. Further, while the combined effect size for each of these hematological parameters supports lower values in periodontitis, the reduction did not reach statistical significance. This contrasts with the significant decrease in Hb concentration and RBC counts in periodontitis reported in previous meta-analyses by de Carvalho Franca *et al.*[16] (nine studies) and that by Wu *et al.*[44] (11 studies). The lower trend in hematocrit or packed cell volume observed in our meta-analysis corroborated with that reported by these previous meta-analyses. Low MCV (microcytic), MHC (hypochromic), and MCHC RBCs are commonly observed in iron deficiency anemia.[12] However, the observed lack of statistical significance of the reduction in the combined effect size for these red cell indices was observed in our analysis and in previous studies. de Carvalho Franca *et al.*[16] and Wu *et al.*[44] (11 studies) could be attributed to the cohorts including different degrees of periodontitis as well as to the interlaboratory variations in measurements.

A significant observation from our systematic search is that nearly 79% of the studies and participants originated from India. This could be attributed to the increased prevalence of both anemia and periodontitis in the Indian population. However, considerable systematic and empirical assessment of the global burden of diseases suggests that the prevalence of anemia is increasing worldwide, particularly in the aging population.[3,17] Cumulative analysis of the National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2018 suggests that the prevalence of

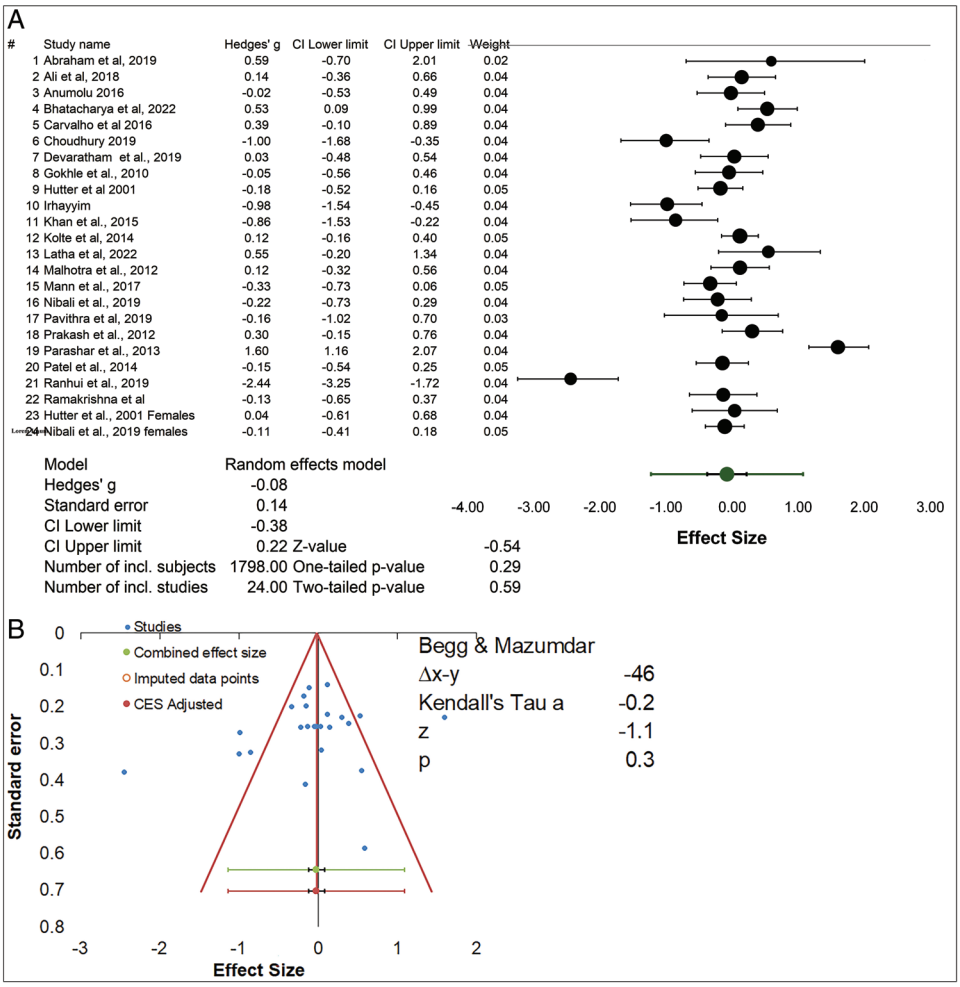

Figure 5: (A) Forest plot analysis of studies reporting MCV in chronic periodontitis and control subjects (gender cohort is reported separately in Hutter *et al.*'s[4] and Nibali *et al.*'s[22] studies and hence the two studies are listed as two studies). Hedges' *g*, 95% confidence interval, and data of random effects model including % weight of each study are shown. (B) Publication bias of 23 studies reporting the observations of MCV in patients with periodontitis

anemia is between 5.71% and 7.85% in the United States, with a statistically significant increasing trend. Further, the average prevalence in 60+ years old is much higher than that in individuals below 60 years of age.[45]

Much like anemia, the global prevalence of periodontal disease also varies considerably by country. While socioeconomic status, nutritional status, sample size, sampling technique, and disease measurement method/diagnostic technique are common factors that could contribute to the varied prevalence of both diseases, the definition of clinical characteristics and the timing of the study with respect to the disease process are additional factors that could modulate the data for periodontal diseases.[17] In a recent analysis of data retrieved from the World Health Organization (WHO) oral health data bank where periodontal health is assessed using the community periodontal index (CPI), Nazir *et al.*[3] reported that the global prevalence of periodontal disease increased with age from adolescents to adults. Interestingly, the highest prevalence of severe periodontal disease (periodontal depth >4 mm) was observed in high-income countries potentially attributable to the increase in longevity and in older population. Significantly, not only the prevalence of chronic periodontitis is higher in older individuals but also the relative risk of systemic diseases increases to 44% among individuals aged 65 years and over. Pertinently, the prevalence of unexplained anemia has been shown to be higher in older populations in developed countries.[46]

Strengths and limitations

Meta-analysis is a statistical method that allows the quantitative synthesis of results from different studies to estimate a common summary effect and reduce the probability of spurious associations. Additional potential advantages include the opportunities to evaluate and measure the degree of consistency or heterogeneity of the reported associations across the

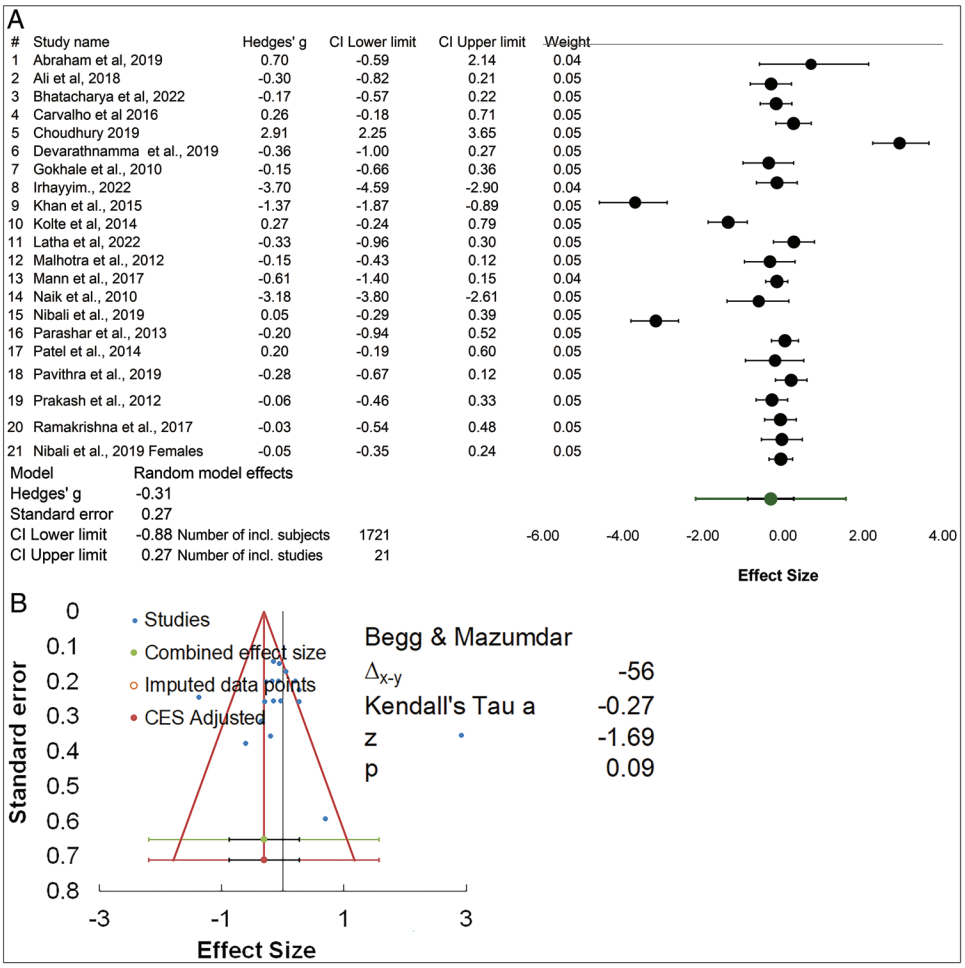

Figure 6: (A) Forest plot analysis of studies reporting MCH in chronic periodontitis and control subjects (gender cohort is reported separately in Hutter *et al.*'s[4] and Nibali *et al.*'s[22] studies and hence the two studies are listed as two studies). Hedges' *g*, 95% confidence interval, and data of random effects model including % weight of each study are shown. (B) Funnel plot analysis of publication bias of 14 studies reporting PCV in periodontitis patients

combined studies.[16,21] The main strength of our meta-analysis is the higher number of studies when compared to previous studies that assessed the association between periodontitis and anemia. In addition, secondary analysis regarding the gender, sample size, and geographic origin of the studies provides a deeper understanding of the pooled result.

In addition to being a nonregistered systematic report, there are a few unavoidable limitations of our study. First, significant heterogeneity was observed in all hematological parameters assessed, but the source of heterogeneity was not identified by stratified analyses. Second, the sample sizes included in some studies were small with six studies including less than 20 members per cohort. Third, the diagnostic criteria for periodontitis varied among the included studies contributing to the discrepancy in hematological measures. Fourth, we did not examine the severity of periodontal disease and the hematological parameters in the included studies, which might lead to heterogeneity and deviation in this analysis. Fifth, less than 25% of the included studies recruited individuals with an age range reaching 60 years and above, the population more likely to exhibit anemia. Sixth, 21 of the 28 studies originated from India. Since nutritional and socioeconomic status contributes to the development of anemia, caution must be exercised in generalizing the observed associations.

Conclusions

In conclusion, this meta-analysis composed of 26 case/control studies in 2062 patients with chronic periodontitis and 980 healthy controls showed a decreasing trend in the hematological parameters including hemoglobin concentration, number of erythrocytes, and hematocrit in patients with chronic periodontitis when compared to healthy controls. Variations in sample size, varied severity of periodontitis, and restricted geographic

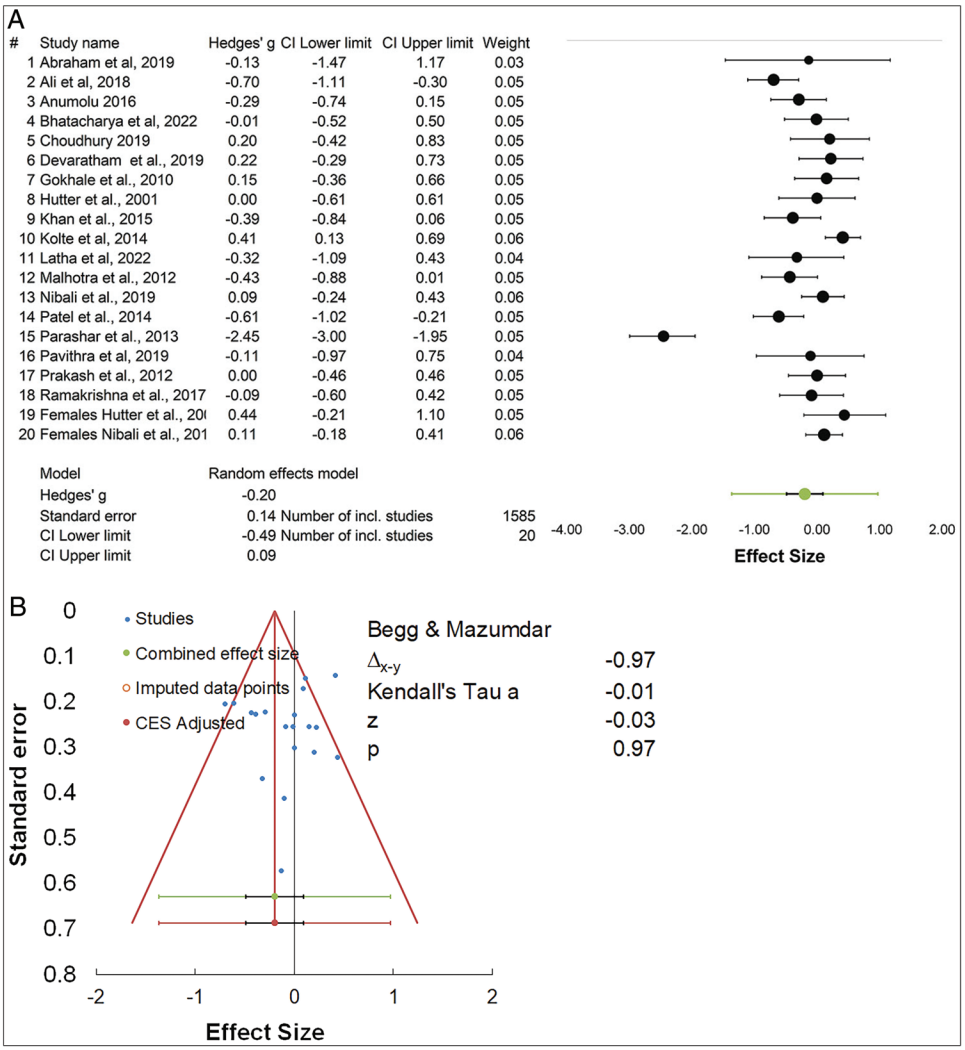

Figure 7: (A) Forest plot analysis of a total of 18 (Male and female groups from Hutter *et al.*'s[4] and Nibali *et al.*'s[22] studies are included independently) reporting MCHC concentration in chronic periodontitis and control subjects. Hedges' *g*, 95% confidence interval, and data of random effects model including % weight of each study are shown. (B) Funnel plot analysis of publication bias of 18 studies reporting MCHC in periodontitis patients

origin are limitations that preclude generalization of the observed effects. In the future, electronic medical and dental records could offer valuable resources for evaluating the relationship between periodontitis and anemia in a broader population.

Future study recommendations

Further research and more powered prospective studies that assess anemia and periodontitis among diverse populations with particular attention to the growing older population are needed.

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Conflicts of interest

There are no conflicts of interest.

Authors contributions

Not applicable.

Ethical policy and institutional review board statement

Not applicable.

Patient declaration of consent

Not applicable.

Data availability statement

The data that support the study results are available from the author Dr. Mythily Srinivasan, e-mail: mysriniv@iu.edu, on request.

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Table S1: Characteristics of the studies included in the meta-analysis

#	References	Case/control	Criteria of CPD	Criteria of Control	NOS
1	Abraham *et al*., 2019.[8]	5/5	AAP Classification 1999	AAP Classification 1999	6
2	Ali *et al*., 2018[22]	30/30	PD ≥ 4mm and CAL:1-2mm or more	Healthy periodontium	6
3	Anumolu *et al*., 2016.[23]	50/50	PD ≥ 5mm (30% sites) and CAL ≥ 2mm	GI: 0-1	6
4	Bhattacharya *et al*., 2022.[24]	40/40	PD ≥ 6mm	Periodontal pocket depth < 6mm	6
5	Carvalho *et al*., 2016.[25]	33/30	PD ≥ 5mm and AL ≥ 6mm	No periodontal infection	6
6	Choudhury *et al*., 2019.[26]	20/20	PD ≥ 5mm (30% sites) and CAL ≥ 2mm	GI: 0-1	6
7	Devarathnam *et al*., 2019.[27]	30/30	PD ≥ 6mm (30% sites) and BL ≥ 50%	Periodontal health	6
8	Gokhale *et al*., 2010.[28]	30/30	PD ≥ 6mm (30% sites); BL ≥ 50%	PD < 3mm	5
9	Hutter *et al*., 2001.[4]	Male: 50, 104 Female: 71, 121	≥7 teeth with ≥50% bone loss	not missing > 1 tooth/ quadrant (excluding 3rd molar), <2 mm on bite-wing x-rays <1 year old.	7
10	Irhayyim *et al*., 2020.[29]	30/30	PD ≥ 4mm and CAL loss of 1-2mm	Healthy periodontium	6
11	Khan *et al*., 2015[30]	20/20	PD ≥ 4mm, CAL ≥ 5mm	Clinically healthy gingiva	6
12	Kolte *et al*., 2014.[12]	100/100	PD ≥ 5mm	PD≤ 3mm	6
13	Latha *et al*., 2015.[31]	14/14	PD ≥ 4mm, CAL ≥ 1mm	PD < 3mm CAL: 0% sites	6
14	Malhotra *et al*., 2012.[32]	20/20	PD ≥ 5mm, CAL ≥ 3mm	No periodontal infection	6
15	Mann *et al*., 2017.[5]	50/50	PD ≥ 5mm	Periodontal health	6
16	Muppalla *et al*., 2016.[33]	30/30	CAL ≥ 5mm in > 30% sites	No attachment loss	6
17	Naik *et al*., 2010.[34]	15/15	CAL: 30% sites ≥ 5mm, or most sites ≥ 6mm	CAL: 0% sites	7
18	Nibali *et al*., 2019.[35]	121/225	PD and CAL ≥ 5mm	PD and CAL < 5mm (≥20 teeth)	6
19	Parashar *et al*., 2013.[6]	50/50	PD ≥ 6mm (10% sites) and CAL ≥ 5mm (30%)	CAL: 0% sites	6
20	Patel *et al*., 2014.[36]	50/50	PD ≥ 2mm and CAL ≥ 2mm (30% sites)	PD < 3mm CAL: 0% sites	6
21	Pavithra *et al*., 2019.[37]	50/50	PD ≥ 5mm (30% sites) and CAL ≥ 2mm	GI: 0-1	6
22	Prakash *et al*., 2012.[38]	90/50	CAL ≥ 2mm	PD < 3mm CAL: 0% sites without BL	6
23	Rai *et al*., 2012.[39]	20/32	CAL≥6mm	CAL≤ 5mm	5
24	Rithanya *et al*., 2019.[40]	25/24	CAL ≥ 5mm in > 30% of sites	CAL<5mm	5
25	Singh *et al*., 2013.[41]	50/50	CAL ≥ 5mm in > 30% of sites	CAL<5mm	6
26	Ziebolz *et al*., 2007.[42]	80/47	CPI score of 3 or 4	CPI of 0 or a CPI score 2 on the lingual aspects of lower anterior teeth	6

CAL: Clinical attachment loss; CPD: Chronic periodontal disease; PD: pocket depth; AAP: American association of periodontists; NOS: Newcastle-Ottawa scale.

Table S2: Stratified analysis of pooled Hedges' *g* effect size for Hb concentration

Hb Stratified analysis		I^2	Analysis of variance			
	Hedges' *g* (95% CI)			Sum of squares Q	df	*P*
Gender			**Between/model**	0.58	1	0.445
Males	−0.99 (−1.74, −0.23)	95.6%	**Within/residual**	36.39	26	0.05
Both	−1.36 (−2.09, −0.63)	94%	**Total**	36.97	27	0.058
Combined	−1.18 (−3.24, 0.88)	94%	**Pseudo R^2**	1.58%		
Sample Size						
>50	−1.43 (−2.09, −0.77)	92.1%	**Between/model**	3.61	1	0.057
<50	−0.65 (−1.40, −0.09)	95.7%	**Within/residual**	40.41	26	0.036
Combined	−1.06 (−3.11, 0.99)	94. %	**Total**	44.03	27	0.021
			Pseudo R^2	0.02%		
Geographic origin						
India	−1.41 (−2.01, −0.82)	93.9%	**Between/model**	5.04	1	0.025
Other	−0.54 (−1.46, 0.38)	92.4%	**Within/residual**	44.89	26	0.012
Combined	−1.05 (−3.10, 1)	94.1%	**Total**	49.93	27	0.005
			Pseudo R^2	10.10%		

Table S3: Stratified analysis of pooled Hedges' *g* effect size in total erythrocyte counts

RBC Stratified analysis		(I^2)	Analysis of variance			
	Hedges' *g* (95% CI)			Sum of squares Q	df	p
Gender			Between/Model	0.01	1	0.94
Males	−0.81 (−1.77, 0.14)	94.51%	Within/Residual	37.03	23	0.03
Mixed	−0.85 (−1.36, −0.35)	91.18%	Total	37.04	24	0.04
Combined	−0.84 (−2.91,1.22)	92%	Pseudo R^2	0.02%		
Sample Size						
<50	−0.7 (−1.16, −0.24)	85.00%	Between/Model	0.36	1	0.58
≥50	−0.98 (−2.13, 0.17)	96.96%	Within/Residual	38.95	23	0.03
Combined	−0.74 (−2.8, 1.32)	92%	Total	39.31	24	0.04
			Pseudo R^2	0.82%		
Geographic location						
India	−1.15 (−1.7, −0.6)	92.25%	Between/Model	17.8	1	0
Other	−0.04 (−0.34, 0.26)	59.73%	Within/Residual	34.06	23	0.06
Combined	−0.57 (−2.63, 1.5)	92.06%	Total	51.86	24	0.001
			Pseudo R^2	34.32%		

Table S4: Stratified analysis of pooled Hedges' *g* effect size for PCV

PCV Stratified analysis		I^2	Analysis of variance *P* value			
	Hedges' *g* (95% CI)			Sum of squares *Q*	*df*	*P*
Gender						
Males	−0.77 (−1.47, −0.06)	86.3%	Between/Model	0.36	1	0.527
Mixed	−0.54 (−1.09, 0.01)	84.1%	Within/Residual	19.23	13	0.09
Combined	−0.63 (−2.77,1.52)	88.44%	Total	20.61	14	0.112
			Pseudo R^2	1.84%		
Sample Size						
<50	−0.74 (−1.34, −0.14)	87.28%	Between/Model	6.35	1	0.012
≥50	−0.05 (−0.52, 0.43)	65.54%	Within/Residual	19.32	14	0.153
Combined	−0.37 (−2.55, 1.81)	87%	Total	25.67	15	0.042
			Pseudo R^2	24.74%		
Geographic location						
India	−0.78 (−1.33, −0.24)	86.98%	Between/Model	5.04	1	0.025
Other	−0.11 (−0.57, 0.36)	71.08%	Within/Residual	21.44	14	0.091
Combined	−0.43 (−2.56, 1.7)	85.33%	Total	26.48	15	0.033
			Pseudo R^2	19.02%		

Table S5: Stratified analysis of pooled Hedges' *g* effect size for MCV

MCV Stratified analysis		(I^2)	Analysis of variance			*P*
	Hedges' *g* (95% CI)			Sum of squares *Q*	*df*	
Gender						
Males	0.1 (−0.36, 0.56)	84.14%	Between/ Model	0.79	1	0.37
Mixed	−0.12 (−0.36, 0.11)	63.91%	Within/Residual	22.91	21	0.35
Combined	−0.08 (−2.15, 2.00)	74.6%	Total	23.7	22	0.36
			Pseudo R^2	3.33%		
Sample Size						
<50	−0.19 (−0.52, 0.13)	78.97%	Between/Model	2.24	1	0.14
≥50	0.23 (−0.33, 0.78)	90.37%	Within/Residual	29.48	22	0.13
Combined	−0.05 (−2.12, 2.02)	84%	Total	31.7	23	0.11
			Pseudo R^2	7.05%		
Geographic origin			Between/ model	0.71	1	0.4
India	−0.01 (−0.3, 0.29)	82.85%	Within/residual	22.02	21	0.4
Other	0.15 (−0.3, 0.01)	0%	Total	22.73	22	0.42
Combined	0.12 (−2.19,1.96)	78.07%	Pseudo R^2	3.12%		

Table S6: Stratified analysis of pooled Hedges' *g* effect size for MCH

MCH Stratified analysis						
Subgroup	**Hedges' *g* (95% CI)**	**Heterogeneity (I^2)**	**Analysis of variance *P* value**			
				Q	***df***	***P***
Gender						
Males	−0.67 (−1.33, 0.01)	92.44%	Between/ Model	1.96	1	0.16
Mixed	−0.08 (−0.96, 0.8)	93.56%	Within/Residual	32.16	19	0.02
Combined	−0.45 (−2.54, 1.65)	93%	Total	34.12	20	0.02
			Pseudo R^2	5.75%		
Sample Size						
<50	−0.38 (−1.12, 0.36)	91.53%	Between/ Model	0.66	1	0.56
≥50	−0.15 (−0.39, 0.1)	67.73%	Within/Residual	34.58	19	0.02
Combined	−0.17 (−2.26, 1.91)	89%	Total	35.24	20	0.03
			Pseudo R^2	1.87%		
Geographic origin						
			Between/ model	3.36	1	0.07
India	−0.426 (−1.8, 0.23)	94.00%	Within/residual	31.41	19	0.04
Other	0.07 (−0.11, 0.25)	0%	Total	34.77	20	0.02
Combined	0.12 (−2.19,1.96)	78.07%	Pseudo R^2	9.67%		

Table S7: Stratified analysis of pooled Hedges' *g* effect size for MCHC

MCHC Stratified analysis						
	Hedges' *g* (95% CI)	I^2	Analysis of variance *P* value			
Gender				*Q*	*df*	*P*
Males	−0.46 (−1.07, 0.14)	91.71%	Between/ Model	2.05	1	0.15
Mixed	0.03 (−0.22, 0.16)	43.38%	Within/Residual	14.14	15	0.52
Combined	−0.15 (−2.27, 1.97)	86%	Total	16.19	16	0.44
			Pseudo R^2	12.65%		
Sample Size				*Q*	*df*	*P*
<50	−0.08 (−0.22, 0.06)	0.00%	Between/ Model	1.44	1	0.23
≥50	−0.5 (−1.33, 0.32)	95.41%	Within/ Residual	19.02	18	0.39
Combined	−0.09 (−2.18, 2.0)	84%	Total	20.46	19	0.37
			Pseudo R^2	7.05%		
Effect size direction				*Q*	*df*	*P*
Negative	−0.30 (−0.69, 0.09)	89.18%	Between/ Model	1.46	1	0
Positive	−0.02 (−0.28, 0.23)	39.16%	Within/Residual	19	18	0.61
Combined	−0.11 (−2.22, 2.00)	84%	Total	20.46	19	0.08
			Pseudo R^2	7.13%		
Geographic location				*Q*	*df*	*P*
India	−0.29 (−0.64, 0.05)	87%	Between/ Model	4.26	1	0.04
Other countries	0.13 (−0.03, 29)	0%	Within/ Residual	15.59	18	0.62
Combined	−0.06 (−2.15, 2.04)	84%	Total	19.84	19	0.40
			Pseudo R^2	21.45%		