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Pica practices, anemia, and oral health outcomes: a systemic review

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Abstract

Objectives Pica is a non-nutritive eating behavior. The potential impact of pica on oral health and the association between pica and anemia are understudied. We examined the current evidence on the relationship between pica practices, anemia, and oral health outcomes.

Methods We used Population, Intervention, Control, and Outcomes (PICO) terms to create MeSH terms to assess 1) the relationship between pica and iron deficiency anemia (IDA), 2) the relationship between IDA and oral health, and 3) the relationship between pica, anemia, and oral health outcomes. The review was registered on Prospero [CRD42022349022]. We searched databases including PubMed, Embase, Web of Science, Cochrane Library, and, clinicaltrials.gov in June 2022.

Results From 4,159 searched articles, 89 met the inclusion criteria. Studies were published between 1959 and 2022 from 33 countries. Nearly half of these studies (55.1%, $n=49$) were case reports. The most common picas included geophagia (soil/dirt) (44.9%, $n=40$ papers), pagophagia (ice) (22.5%, $n=20$), amylophagia (starch) (15.7%, $n=14$), paint/metal (5.6%, $n=5$), paper (5.6%, $n=5$) and others such as pica for foam and hair. Fifteen case reports and one intervention study showed the effects of pica practice on oral health, such as tooth abrasion, dental caries, and depapillated tongue. Furthermore, 81% of the papers reported the co-occurrence of pica with anemia and 15 papers reported a significant association ($p<0.05$) between pica and low hemoglobin levels ranging from < 12.0 to 2.7g/dL among all age groups, including among pregnant and postpartum women. Pica practices were strongly associated with IDA (serum ferritin < 15.0 – 4.3 mcg/ml) but showed a non-statistically significant trend of association with oral health outcomes.

Conclusion Pica was strongly associated with anemia and IDA. Tooth abrasion and dental caries were observed among pica users. Future studies could define the strength of the pica-oral health association, and the potential mediators, such as anemia.

Keywords Pica, Oral health, Anemia, Iron deficiency anemia, Interventions

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Introduction

Anemia is a common nutrition problem globally affecting about a third of the world's population [1]. Women of reproductive age, children, and pregnant women are the most at risk for anemia because of various physiological changes that increase iron needs such as menstruation, growth, and reproduction respectively [1–4]. In 2010, South Asia and Central, West, and East sub-Saharan Africa had the highest burden of anemia, and iron deficiency anemia (IDA) remained the most common cause [1]. Aside from anemia and IDA, a bidirectional relationship has been observed between oral and systemic health [5]. Specifically diabetes, metabolic syndrome, obesity, eating disorders, and adverse pregnancy outcomes [5, 6]. Other studies have connected oral health with immune and metabolic status as risk factors for caries and related cariogenic microbial growth [7]. Thus, risk factors for caries include body weight and body mass index [8].

Pica is the compulsive craving and/or ingesting non-nutritive substances including clay, dirt, paper, and laundry starch. Without treatment, this habit may lead to lethal health outcomes [9]. Pica and IDA may be interrelated, as pica has been reported as a symptom of IDA in 50% of IDA patients [9, 10]. Pica is a non-nutritive eating behavior among all age groups but is common among at-risk pregnant women [11–13]. Households are at the highest risk of experiencing food insecurity, which is often associated with micronutrient deficiencies such as anemia and non-nutritive eating behavior, like pica, posing a risk of systemic infections [11, 12] and birth outcomes. Toddlers and children with certain mental conditions, e.g. autism, may also have a higher propensity to practice pica, potentially persisting into adolescence. Infants, children, and adolescents practicing pica are at a higher risk for environmental intoxication from the ingestion of non-nutritive substances and persistent practice can lead to IDA [14, 15]. Like iron, other micronutrients including vitamins C, E, D, and A, omega-3 fatty acids, and minerals have demonstrated anti-oxidant and anti-inflammatory functions, affecting oral inflammatory diseases [6].

Chronic IDA may predispose patients to angular stomatitis or angular cheilitis, atrophic glossitis on the tongue, or spoon nails (koilonychia) [16], and potentially dry mouth [17]. The oral disease burden is disproportionately higher among minority and low-income populations. Over the years, less improvement has been reported. Isolation of microbes on some common pica substances such as clay confirms the impact on the oral microbiome, especially for cariogenic microorganisms [18, 19].

A few studies have demonstrated that iron or zinc therapy resolved symptoms of IDA, and pica [20–22]. Reinforcement and behavioral interventions were recommended forms of treatment for youths practicing pica [23]. A relationship between pica and IDA is also discussed when individuals consume substances containing lead such as soil or paint chips. Individuals with higher concentrations of lead in their blood have a higher risk for IDA because of the inverse relationship between lead and iron in the body [24].

Robust data defining the relationship between pica, anemia, and oral health is limited. This systematic review examined current evidence on the relationship between pica, IDA/anemia, and oral health among all physiological groups.

Material and methods

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. A protocol was developed and registered on PROSPERO with the ID: CRD42022349022.

Inclusion criteria

We included research papers or case reports on human studies and full article reports on all age groups. We included papers with study designs such as longitudinal studies, cross-sectional studies, cohort studies, case-control studies, case reports, retrospective studies, and clinical trials. Studies published on all age groups and pregnant women and lactating women were included.

Exclusion criteria

Papers on *in vitro* studies, animal studies, only abstracts, literature reviews, letters to the editor, editorials, patient handouts, and review papers were excluded.

Data sources and search strategy

Database searches were conducted in June 2022 to identify published studies that met the inclusion criteria. For this systematic review, the databases searched for the studies include PubMed, Embase, Web of Science, Cochrane, and clinicaltrials.gov. The search strategy used combinations of anemia, oral health, and pica, and a list of the types of pica to develop a comprehensive search MeSh. The complete search strategy is shown in the supplementary File 1.

The selection process of studies began by importing 4,159 articles studies, from all sites, into EndNote. Then, 551 duplicate studies were removed remaining 4,161 studies. Titles were assessed for exclusion criteria, additional studies were removed, and 225 articles remained. The abstracts of these studies were screened for inclusion and exclusion criteria and 131 more studies were removed, remaining 94 papers. The full-text papers were

screened, and five more papers were excluded. A total of 89 papers were included in the final review.

Paper selection and data extraction process

We identified papers using the search terms in the various databases and exported these to Endnote, and duplicates were removed. Three of the researchers served as article reviewers (BAZA, AM, and YW) and selected published studies for inclusion in the review. Using the eligibility criteria, all titles and abstracts were screened against the inclusion criteria. Spot checks were conducted on 10% of the excluded papers to assess the extent of agreement among all reviewers. Any disagreements were resolved through discussion with all reviewers. The three reviewers for the remaining articles retrieved full-text articles, and these were screened after reading the full articles against the eligibility criteria. This resulted in 225 potentially relevant papers for data extraction.

A data extraction form was developed and piloted to extract data from included studies. The form was revised after the pilot testing and used to extract information from the rest of the included papers. Data collected included the type of study design, study population, sample size, recruitment method, intervention, control, outcome measures, and key findings.

Eighty-nine (89) papers were included and extracted for data analysis. As shown in the PRISMA diagram Fig. 1 below.

Qualitative assessments of papers include

The National Institutes of Health (NIH), National Heart Lung Blood and Quality Assessment Tool was used to assess the quality of the observational cohort, cross-sectional, case-control, and intervention studies [26]. The 40 included papers were categorized as "Good", "Fair" and "Poor" depending on the complete information and clarity of the study design approach and control confounder. Quality assessments were not conducted for the 49 case reports. Overall ($n=40$), 16 papers were categorized as "poor", 21 were "fair" and three (3) were classified as

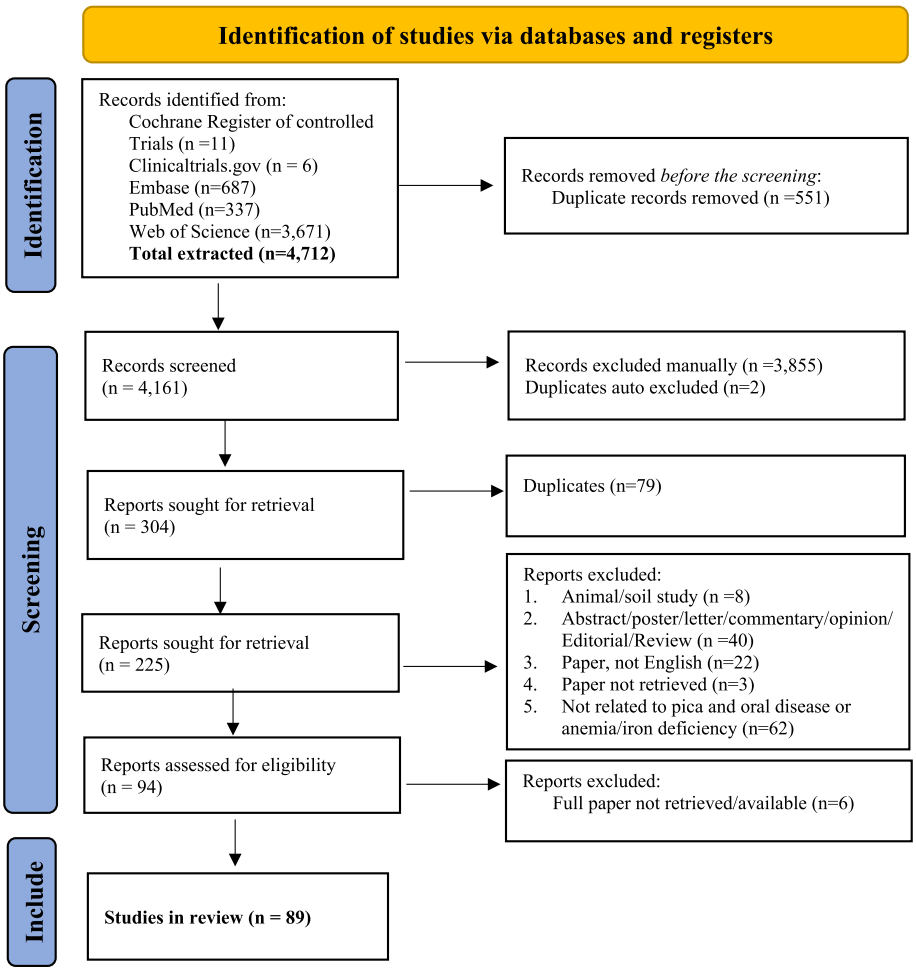

Fig. 1 PRISMA diagram and screening process [25]

"good". Quality assessment categories are placed in the last column of Tables 1, 2, 3, 4. Two of the researchers (BAZA and YW) conducted the quality assessment.

Data synthesis approach

A narrative approach was used to synthesize the extracted data from the included studies. Discussions and consensus were used to agree on various themes for the qualitative synthesis to align with the review objectives.

Groups were categorized as young children ≤ 8 years old; Preadolescents = 8 years − 12 years; Adolescents = 13 years − 18 years; non-pregnant Women of Reproductive Age (WRA) = 18 years − 45 years; Adults Males = 18 years − 60 years; Adult females = 45 years − 60 years, older adults > 60 years pregnant women and postpartum women.

Results

Overview of the papers in the review

Of the 4,159 articles, 89 articles [10, 27–114] were included in the review. Half 55.1% ($n=49$) of the qualified papers were case reports, and quality assessments were done on the remaining 40 (44.9%) papers. Of these 40 papers, 18.0% ($n=16$) were cross-sectional studies, 11.2% ($n=10$ papers) were cohort studies, 4.5% ($n=4$) were case-control studies, 10.1% ($n=9$) were interventional studies and only 1.1% ($n=1$) was a retrospective chart review. No randomized control trials on IDA/ anemia pica and oral health were identified. Papers were published from 1959 to 2022 using data from 33 countries. Data are categorized into the following subgroups; 34 (38.2%) papers reported the co-occurrence of pica with IDA in Table 1 [27–60], 72 (81.0%) reported co-occurrence with anemia in Table 2 [27–98], 16 (18.0%) papers reported the co-occurrence of pica and oral diseases in Table 3 [29, 32, 35, 36, 40, 49, 50, 58, 63, 72, 74, 87, 94, 99–101] and 39 (43.8%) reported interventions implemented to address pica and/or IDA in Table 4 [27, 29–33, 35–37, 39–41, 44, 49, 56, 58–63, 66, 67, 69–72, 94–99, 102–107]. In the last column of all tables' quality assessments for cohort, case-control, intervention, and cross-sectional studies are included.

Pica and iron deficiency anemia (IDA)

Out of the 34 (38.2%) with data on the relationship between pica and IDA, 2.9% ($n=1$) were case-control studies, 67.6% ($n=23$) were case reports, 8.8% ($n=3$) were cross-sectional studies, 11.8% ($n=4$) were cohort studies, 5.9% ($n=2$) were intervention trial and 2.9% ($n=1$) was a retrospective chart review of patients who underwent a Laparoscopic Roux-en-Y gastric bypass (LRYGP). As assessed by serum ferritin, iron status ranged from 1.5 mcg/L to 66.5 mcg/L. Only two papers reported pica practices and IDA among pregnant [37, 55]. Both studies showed pica for freezer frost [37] and the cohort study reported pica additional pica ice, and clay [55]. Of the 200 pregnant women in the cohort study, 17.5% reported pica and confirmed that pica was significantly associated with IDA ($p=0.05$) [55]. Similarly, in a cohort study, young children including those breastfeeding had pica for paper, clay, and uncooked starches, and mean serum ferritins of 9.2 mcg/L [57]. In the two intervention studies conducted among adult females, ice was the most common type of pica, and serum ferritin levels ranged between 4.23 to 21 6 mcg/L [59, 60]. Overall, three studies reporting data on young children, adult females, and pregnant women with pica prevalence ranging between 8.1% −74.0% reported statistically significant pica association with serum ferritin levels [47, 54, 55].

Relationship between pica and anemia

Out of the 72 (80.9%) reporting data on the relationship between pica and anemia, 5.6% ($n=4$) papers were case-control studies, 55.5% ($n=40$) were case reports, 11.1% ($n=8$) were cohort studies, 16.7% ($n=12$) were cross-sectional studies, 59.7% ($n=7$) were intervention trials and 1.4% ($n=1$) was a retrospective chart review of patients who underwent an LRYGP as shown in Table 2. Of the 37 case reports across different ages, 33 of the cases reported that pica was associated with low hemoglobin levels between 3.3 to 11.0 g/dL, and 4 papers reported anemia diagnosis without indicating the actual levels assessed. Similarly, in cross-sectional studies, pica was also observed in children and adults with hemoglobin levels between 3.0g/dL and 12.7g/dL. Low hemoglobin levels were similarly reported among pica practice in a cohort study. In the intervention studies, pica was reported among individuals with hemoglobin ranging from 7.0 to 10.0 g/dL. The commonest pica observed were pica for ice, clay, and uncooked starches such as rice, corn, and oats. In twelve papers (16.7%), hemoglobin levels were not reported although anemia diagnoses were indicated in the paper [28, 47, 48, 50, 54, 66, 73, 79, 82, 89, 93, 96].

Thus, across the life stages irrespective of the study design, pica was associated with low hemoglobin levels. Eleven (11) papers using a case report, cross-sectional, case-control, cohort, and intervention study designs confirmed a statistically significant relationship ($p<0.01$ and ($p<0.05$) between pica and anemia ($p<0.005$) [47, 54, 55, 80, 81, 85, 88, 90, 91, 94, 97]. These observations were also observed for pregnant [55, 88] and postpartum [81, 91] women.

Table 1 Description/distribution of Pica and IDA [*n* = 34 papers]

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed; Serum Ferritin (SF) Serum Iron (SI) mcg/L Mean Corpuscular Volume (MCV) fl	Type of pica	Pica Prevalence Percentage (p-value)	Pica Consumption Pattern and Quantity (Frequency)	Quality Assessments
[27]	Retrospective chart review	Patients who underwent Laparoscopic Roux-en-Y gastric bypass (LRYGP) from 2001–2011 (959)	SF = 5	Ice, salt cravings, and burnt popcorn	1.7		Poor
[28]	Case-control	Children (400)	IDA diagnosis reported, SF NR	Clay/soil/dirt, cloth, paper, pencils, plaster, hair, toothpaste, starch	28.8		Fair
[29]	Case report	Female child (1)	SF = 8. ng/ml	Brick piece			NA
[30]	Case report	Female child (1)	MCV = 67.4	Furniture foam			NA
[31]	Case report	Female preadolescent (1)	SF = 1.5	Hair			NA
[32]	Case report	Adult male (2)	SF = 8.0	Uncooked rice Cement and dirt			NA
[33]	Case report	Female Teenage (1)	SF = 32.0	Stones and eggshells			NA
[34]	Case report	Female young child (1)	SI = 0.7	Paper			NA
[35]	Case report	Adult female (1)	SF = 14.0	Laundry starch		1–2 boxes/day	NA
[36]	Case report	Female teenage (1)	SF = 5.2	Plastic			NA
[37]	Case report	Pregnant woman (1)	SF = 2.4	Freezer frost		24–36 /week	NA
[38]	Case report	Adults (3)	SF = 8.0	Ice/cold bottled water and rubber bands			NA
[39]	Case report	Older adult female (1)	SF = 15.0	magnesium carbonate			NA
[40]	Case report	Adult Female (1)	SF = 8.0	Laundry starch			NA
[41]	Case report	Young children female (2)	SF = 6.0 SI = 55.0	Hair			NA
[42]	Case report	Adult female (1)	SF = 5.0	Unpeeled lemons			NA
[43]	Case report	Children with Trichuris infection (10)	SI = 23.0	Specific not mentioned			NA
[44]	Case report	Adult male (1)	SI = 14.0	Specific not mentioned			NA
[45]	Case report	Adult female (1)	SF = 3.0	Ice and salt			NA
[46]	Case report	Non-pregnant adult females (10)	SI = 20.7	Clay and laundry starch		250 −1300gm/day	NA
[47]	Case report	Young children (200)	SF = 2.2–46.0		74.0 ($p = 0.504$)		NA
[48]	Case report	Adult Female (1)	IDA diagnosis reported, SF NR	Clay/dirt/earth			NA
[49]	Case report	Female adult (1)	SI = 2.5	Raw rice		300-400g/day	NA

Table 1 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed; Serum Ferritin (SF) Serum Iron (SI) mcg/L Mean Corpuscular Volume (MCV) fl	Type of pica	Pica Prevalence Percentage (p-value)	Pica Consumption Pattern and Quantity (Frequency)	Quality Assessments
[50]	Case report	Adults and older adults (7)	SI = 25.7	Ice			NA
[51]	Case report	Adults (21)	SI = 26–56	Clay/dirt/earth	100.0		NA
[52]	Cross-sectional	Adolescents (2,647)	SF = 34.1	Clay/soil/termite mounds, ice, uncooked rice/ starch	12.4		Fair
[53]	Cross-sectional	Young children (1,367)	SF = < 19.6	Clay/soil/termite mounds, ice, uncooked rice/ starch	11.0		Fair
[54]	Cross-sectional	Adult Female (553)	SF = 21.4	Ice	8.1 ($p = 0.0001$)	0.5–2 cups/week	Fair
[55]	Cohort	Pregnant women (200)	SF = 66.5	Ice, Freezer frost, and clay	17.5 ($p = 0.05$)		Fair
[56]	Cohort	Young children and teenagers (144)	SF = 11.6	Specific not mentioned	2.0		Fair
[57]	Cohort	Young children Breastfeeding (15)	SF = 9.2	Paper	7.0		Poor
[58]	Cohort	Children (21)	SI = 32.4	Clay, dirt, and plaster	100.0		Fair
[59]	Intervention	Adult females with IDA (12)	SF = 6 (2.0–21.0)	Ice, sawdust, knitting rope, dry oats, Chewing gum, pickles.	88.9		Poor
[60]	Interventional	Adult female (35)	SF = 4.23	Ice	32.4		Fair

NR Data not reported, *Hgb* hemoglobin, *MCV* Mean Cell Volume, *SF* Serum Ferritin, *SI* Serum Iron, *N/A* Not applicable. Young child= < 8years old; Preadolescents = 8 years - 12 years; Adolescents = 13 years – 18 years; Women of Reproductive Age (WRA) = 18 years – 45 years; Adults Males = 18 years – 60 years; Adult females = 45 years – 60 years and Older adults = > 60 years

Pica, IDA/anemia and oral health outcomes

Sixteen (16) published papers reported pica practice related to oral diseases, and all papers were case reports [29, 32, 35, 36, 40, 49, 50, 58, 63, 72, 74, 87, 94, 99–101] except one intervention study [94] as reported in Table 3. Cases were mostly female aged from 7 to 77 years old, and mostly non-pregnant WRA ($n = 10/16$), one study each reported on pregnant women, regular long-term blood donors, and patients with polycythemia. These papers reported various levels of oral health impacts from pica practices. For instance, 66.3% ($n = 9/16$) reported teeth abrasion [29, 32, 40, 49, 63, 66, 72, 99–101], 25.0% ($n = 4/16$) reported dental caries, [29, 40, 49, 63, 72, 101] 12.5% ($n = 2/16$) reported depapillated tongue and 18.8% ($n = 3/16$) case reports were on patients with both teeth abrasions and caries [29, 63, 101] and 3/16 papers showed no significant impact on oral health [50, 87, 94]. The median number of carious teeth is 3. Tooth abrasions were widespread, up to 16 teeth in the reported cases. Other reported oral diseases include aggressive periodontitis ($n = 1/16$), and chronic and alveolar abscess ($n = 1/16$). One study reported no pica-related oral disease although surgery was done for a mandibular fracture related to hitting ($n = 1/16$). These highlight the close correlation between pica practice and tooth abrasion as shown in Table 3. Common pica associated with abrasions included bricks, gravels, stones, uncooked rice, ice, and seashells.

Eleven out of the 16 papers (68.8%) showed a relationship between anemia and oral health outcomes and corresponding hemoglobin levels ranged from 3.5 g/dL to 9.1 g/dL [29, 32, 35, 36, 40, 49, 63, 74, 87, 94] or serum ferritin > 15.0 mcg/ml [66]. Uniquely, oral diseases such as caries were associated with low hemoglobin ranging

Table 2 Relationship between Pica and Anemia ($n = 72$)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed; Hemoglobin/ Anemia indicator g/dL	Type of pica	Pica Prevalence Percentage % (p-value)	Pica Consumption Pattern: Quantity (Frequency)	Quality Assessments
[27]	Retrospective chart review	Patients who underwent Laparoscopic Roux-en-Y gastric bypass (LRYGP) (959)	10.5	Ice, salt cravings, and burnt popcorn	1.7		Poor
[29]	Case report	Female child (1)	8.0	Brick piece			N/A
[61]	Case report	Adult F (1)	8.5	Clay			N/A
[30]	Case report	Female child (1)	10.8	Furniture foam			N/A
[31]	Case report	Female preadolescent (1)	7.5	Hair			N/A
[62]	Case report	WRA (1)	5.1	Metallic coins			N/A
[63]	Case report	WRA (1)	8.6	Pieces of bricks and gravel			N/A
[64]	Case report	Preadolescents and adults (12)	5.5	Clay, soil			N/A
[65]	Case report	Adult male (1)	7.0	Clay, ice			N/A
[66]	Case report	Older adult (1)	Reported but not specified	Pieces of bricks and gravel			N/A
[32]	Case report	Adult male (2)	8.9	Uncooked rice Cement and dirt			N/A
[33]	Case report	Female Teenage (1)	8.4	Stones and eggshells			N/A
[67]	Case report	Adolescents (4)	9.4	Ice			N/A
[68]	Case report	WRA (1)	6.6	Toilet air freshener			N/A
[34]	Case report	Female young child (1)	4.8	Paper			N/A
[35]	Case report	Adult female (1)	8.9	Laundry starch		1–2 boxes/day	N/A
[36]	Case report	Female teenage (1)	9.1	Plastic			N/A
[69]	Case report	WRA (1)	11.0	Paper			N/A
[37]	Case report	Pregnant woman (1)	9.0	Freezer frost		24–36 /week	N/A
[38]	Case report	Adults (3)	8.4	Ice/cold bottled water and rubber bands			N/A
[70]	Case report	Older adult female (1)	> 12.0	Metallic objects	3–8		N/A
[71]	Case report	Young children (12)	7.9	Clay, soil, and pieces of brick and wood			N/A
[39]	Case report	Older adult female (1)	2.7	magnesium carbonate			N/A
[72]	Case report	WRA (1)	> 12	Uncooked rice and wheat			N/A
[40]	Case report	Adult Female (1)	3.5	Laundry starch			N/A
[41]	Case report	Young children female (2)	4.9	Hair			N/A
[73]	Case report	Adults (3)	Reported but not specified	Soil, toothpicks			N/A
[42]	Case report	Adult female (1)	3.3	Unpeeled lemons			N/A
[43]	Case report	Children with Trichuris infection (10)	6.9	Specific not mentioned			N/A

Table 2 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed; Hemoglobin/ Anemia indicator g/dL	Type of pica	Pica Prevalence Percentage % (p-value)	Pica Consumption Pattern: Quantity (Frequency)	Quality Assessments
[74]	Case report	WRA (1)	9.1	Soil			N/A
[75]	Case report	Adult male (1)	9.3	Metallic coins			N/A
[44]	Case report	Adult male (1)	8.7	Specific not mentioned			N/A
[45]	Case report	Adult female (1)	10.9	Ice and salt			
[46]	Case report	Non-pregnant adult females (10)	6.3	Clay and laundry starch		250–1300 gm/ day	N/A
[76]	Case report	Adult male (1)	8.7	Roofing plates			N/A
[47]	Case report	Young children (200)	Reported but not specified	Reported but not specified	74.0 ($p=0.504$)		N/A
[48]	Case report	Adult Female (1)	Reported but not specified	Clay/dirt/earth			N/A
[49]	Case report	Female adult (1)	7.9	Raw rice		300–400 g/day	N/A
[50]	Case report	Adults and older adults (7)	Reported but not specified	Ice	57.0		N/A
[51]	Case report	Adults (21)	3.0	Clay/dirt/earth	100.0		N/A
[77]	Case report	Children (29)	4.6	Clay, soil, some plaster	100.0		NA
[78]	Cross-sectional	Children (58)	7.2	Reported but not specified	27.6		Poor
[54]	Cross-sectional	Adult Female (553)	Reported but not specified	Ice	8.1 ($p=0.0001$)	0.5–2 cups/week	Good
[52]	Cross-sectional	Adolescents (2,647)	< 11.5 g/dL	Clay/soil/termite mounds, ice, uncooked rice/ starch	12.4 (12.8% of girls and 18.6% of boys)		Fair
[79]	Cross-sectional	Children (440)	Reported but not specified	Soil	9.4		Poor
[53]	Cross-sectional	Young children (1,367)	11.8	Clay/soil/termite mounds, ice, uncooked rice/ starch	11.0		Fair
[80]	Cross-sectional	Children (253)	7.9	Reported but not specified	41.0 ($p<0.05$)		Poor
[81]	Cross-sectional	Postpartum women (1,014)	11.2	Ice, clay, soap, toothpaste, and chalk	23.2 ($p<0.001$)		Poor
[82]	Cross-sectional	Previously pregnant women (552)	Reported but not specified	Clay, dirt, soil	31.9		Fair
[83]	Cross-sectional	Adults (1,498)	12.7	Soil	12.0		Fair
[84]	Cross-sectional	Adolescents and adults (13,172)	8.6	Ice, cement, dusting powder, chalk, coal,	88.0		Fair
[85]	Cross-sectional	Adult female (368)	> 12.0	Specific substances not mentioned	73.7% (< 0.05)		Poor
[86]	Cross-sectional	WRA (462)	10.0	Reported but not specified			Poor
[87]	Case-control	Adult and older adults (1,133)	> 12.0	Reported but not specified	8.0		Fair
[88]	Case-control	Pregnant women (64) Adults (94)	10.4	Clay, ice, raw rice	27.0 ($p<0.001$)		Fair

Table 2 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed; Hemoglobin/ Anemia indicator g/dL	Type of pica	Pica Prevalence Percentage % (p-value)	Pica Consumption Pattern: Quantity (Frequency)	Quality Assessments
[28]	Case-control	Children (400)	Reported but not specified	Clay/soil/dirt, cloth, paper, pencils, plaster, hair, toothpaste, starch	28.8		Fair
[89]	Case-control	Adolescents and WRA (281)	Reported but not specified	Clay/soil, salt	71.0		Fair
[58]	Cohort	Children (21)	5.1	Clay, dirt, and plaster	100.0		Fair
[55]	Cohort	Pregnant women (200)	11.0	Ice, clay, Freezer frost and ice	17.5 ($p=0.05$)		Fair
[90]	Cohort	Adults (371)	11.1	Soil	51.5 ($p<0.001$)		Good
[56]	Cohort	Young children and teenagers (144)	10.4	Specific not mentioned	2.0		Fair
[91]	Cohort	Postpartum (281)	11.2	Ice, freezer frost, baking soda, baking powder, cornstarch, baby powder	76.5 ($p<0.01$)		Fair
[92]	Cohort	Children (2,976)	Reported but not specified	Soil	69.0	100–5000 mg/ day	Poor
[93]	Cohort	Young children (60)	Reported but not specified	Soil	100.0		Poor
[57]	Cohort	Young children Breastfeeding (15)	8.0	Paper	7.0		Poor
[94]	Interventional trial	WRA (50)	9.1	Reported but not specified	24.0 ($p=0.007$)		Fair
[95]	Interventional trial	Children (38)	7.0	Clay, soil	100.0		Fair
[60]	Interventional trial	Adult female (35)	10.0	Ice	32.4		Fair
[96]	Interventional trial	Children and pre-adolescents (50)	Physical symptoms reported	Soil	10.0		Poor
[97]	Interventional trial	Children and Pre-adolescent (100)	8.2	Reported but not specified	100.0 ($p<0.001$)		Poor
[59]	Intervention trial	Adult females with IDA (12)	9.4	Ice, sawdust, knitting rope, dry oats, Chewing gum, pickles.	88.9		Poor
[98]	Interventional trial	Adults and older adults: mean age is 38.2 ± 15.9 (100)	8.7	Ice	25.0	1.7 ± 3.5 cubes of ice/day	Fair

NR Data not reported; in a few cases pica practices were reported but the specific pica was not stated. *Hgb* hemoglobin; *SF* Serum Ferritin; *SI* Serum Iron, *N/A* Not applicable. Young children ≤ 8 years old; Preadolescents = 8 years - 12 years; Adolescents = 13 years – 18 years; Women of Reproductive Age (WRA) = 18 years – 45 years; Adults Males = 18 years – 60 years; Adult females = 45 years – 60 years and Older adults = > 60 years

from 3.5 g/dL to 8.6 g/dL. Additionally, about a third of the papers ($n=6/16$) papers specifically showed a correlation between pica, IDA, and oral health outcomes. Serum ferritin was reported in these studies and ranged from 4.6 mcg/ml to 15.0 mcg/ml [29, 32, 35, 40, 49, 66, 74]. In addition, physical symptoms of IDA, such as cold intolerance, hair loss, and decreased growth and thinning of nails, were reported and correlated with oral diseases and pica concurrently as shown in Table 3 [32, 49]. Despite the reported anemia diagnosis among pica users, no studies have assessed the association between all three categories: pica practice, anemia, and oral diseases.

Table 3 Pica, Anemia/IDA, and Oral Health ($n=16$ papers)

Article/Authors	Country	Age (years)	Study design	Oral Health	Pica Substance	Biomarkers Analyzed: Hemoglobin Hgb (g/dL) Serum ferritin (SF) (mcg/ml)	Quality Assessments
[29]	India	7	Case report	Caries & teeth abrasions	Brick pieces	SF = 8.0 Hgb = 8.0	N/A
[63]	India	30	Case report	Caries & teeth abrasions	Bricks pieces and gravel	Hgb = 8.6	N/A
[72]	India	26	Case report	Tooth abrasions	Raw rice and wheat	Normal Hgb	N/A
[66]	UK	56	Case report	Tooth abrasions	stones and grit	Stress, SF = 15.0	N/A
[32]	USA	39	Case report	Tooth abrasions	uncooked milled basmati rice, drying cement, and dirt	Physical symptoms of IDA are evidenced by severe fatigue and hair loss decreased growth and thinning of nails. Hgb = 8.2 SF = 8 .0	N/A
[35]	USA	18	Case report	No reported oral health outcome related to pica. Oral and maxillofacial surgery due to bilateral mandibular fractures after hitting.	Laundry starch	Hgb = 8.9 SF = 14.0	N/A
[99]	USA	45	Case report	Tooth abrasions	ice and freezer frost	N/A	N/A
[40]	USA	47	Case report	Caries & chronic alveolar abscess	laundry starch	Hgb = 3.5 SF = 8.0	N/A
[36]	Tunisia	17	Case report	Soft tissue pathology	Plastic	Hgb = 9.1	N/A
[100]	Chile	77	Case report	Tooth abrasions	white beach shells	NR	N/A
[49]	Malaysia	32	Case report	Tooth abrasions	Uncooked rice	Physical symptoms of IDA Hgb = 7.9 SF = 4.6	N/A
[101]	UK	36	Case report	Tooth abrasions, caries, and missing teeth	Sand	NR	N/A
[74]	Turkey	26	Case report	Bleeding on probing & Aggressive periodontitis	Dirt	Stress, SF = 11.0	N/A
[87]	Sweden	20–59 regular long-term blood donors ($N=1133$)	Case report	No significant prevalence of Sore tongue	8% pica, specifics NR	Hgb <12.0 Report ID	N/A
[50]	USA	polycythemia vera patients with venesection ($N=7$)	Case report	No glossitis, cheilosis, or dysphagia	4 (57%), Ice	Chronic ID reported	N/A
[94]	India	Pregnant women 18–40 ($N=50$)	Intervention study (500 mg Dhatri Lauha for 4 weeks)	Tasteless and glossitis which improved after therapy	24% pica, Specifics NR	Hgb < 10.0–7.0	Fair

NR Data is not reported; *Hgb* Hemoglobin, *SF* Serum Ferritin, *N/A* Not applicable. Young children ≤ 8years old; Preadolescents = 8 years - 12 years; Adolescents = 13 years – 18 years; Women of Reproductive Age (WRA) = 18 years – 45 years; Adults Males = 18 years – 60 years; Adult females = 45 years – 60 years and Older adults = > 60 years

Table 4 Interventions and outcomes for pica practices ($n = 39$)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed Hemoglobin/ Serum ferritin (SF) /Anemia indicator g/dL	Type of pica	Intervention	Key Findings related to IDA and Anemia	Comments on IDA and pica Post-intervention	Other outcomes	Quality Assessment
[27]	Retrospective chart review	Patients who underwent Laparoscopic Roux-en-Y gastric bypass (LRYGP) (959)	Meal Hgb = 10.5	Ice, salt cravings, and burnt popcorn in 16/959 = 1.7%	Intravenous iron treatment	Pica resolved in all patients	All patients with pica had severe IDA levels.	-	Poor
[72]	Case report	WRA (1)	Hgb is > 12.0 normal	Uncooked rice and wheat	Pharmacological treatment for Obsessive-compulsive disorder (OCD)	Pica resolved	-	Reported pica during previous pregnancies	N/A
[102]	Case report	Adult Female (1)	NR	Burn matches	Oral zinc sulfate 220 mg per day for 10 weeks	-	-	zinc level and taste acuity back to normal	N/A
[29]	Case report	Female child (1)	SF = 8.0 Hgb = 8.0	Brick piece	Deworming, iron, zinc, and calcium, supplements	-	-	Iron, calcium and zinc (serum zinc levels (40 µg/10 ml) deficiency	N/A
[61]	Case report	Adult Female (1)	Hgb = 8.5	Clay/stones	Oral and parenteral iron supplementations and antiretroviral treatments	Partially effective 12.5	-	-	N/A
[30]	Case report	Female child (1)	Hgb =10.8	Furniture foam	Ferrous fumarate syrup at 45 mg thrice daily after food for six weeks	-	-	-	N/A
[31]	Case report	Female preadolescent (1)	Hgb = 7.5 SF = 1.5	Trichophagia - Hair	Oral iron	-	-	-	N/A
[62]	Case report	Women of Reproductive Age (WRA) (1)	Hgb = 5.1	Metallic coins	copper sulfate 2 mg daily	Resolved the hematological issues	-	Zinc-induced copper deficiency	N/A
[63]	Case report	WRA (1)	Hgb = 8.6	Pieces of bricks and gravel	Diet counseling and referral for iron deficiency treatment	-	-	Malnourished patient had kyphosis	N/A

Table 4 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed Hemoglobin/ Serum ferritin (SF) /Anemia indicator g/dL	Type of pica	Intervention	Key Findings related to IDA and Anemia	Comments on IDA and pica Post-intervention	Other outcomes	Quality Assessment
[66]	Case report	Older adult W(1)	SF = 15.0	Pieces of bricks and gravel	Combined fixed and removable prostheses. Iron supplements and hormone replacement therapy.	Pica resolved	-	Diagnosed with stress	N/A
[32]	Case report	Adult male (2)	Mean Hgb = 8.9 Mean SF = 6.5	Uncooked rice, drying cement and dirt	Intolerant of oral iron supplements and thus was treated with intravenous iron (Fe = 1500mg) and iron dextran therapy. The other was treated with intravenous iron (1000mg total).	Pica resolved after the first infusion of 500mg of iron	Physical symptoms of anemia evidenced by severe fatigue and hair loss moderate pallor and fatigue, dizziness, cold intolerance, hair loss, and decreased growth and thinning of nails	Related IDA to multiparty and menorrhagia	N/A
[103]	Case report	Adult males (4) and WRA (7)	Hgb = 9.7	Clay	Intravenous fluids	9 of the 11 were diagnosed with anemia	-	Related pica to hunger	N/A
[104]	Case report	WRA (1)	Hgb >12.5	Ice, freezer frost, and iced drinks	tablet venlafaxine 50 mg along with capsule B-complex, Distraction and Psychological family counseling	Pica did NOT resolve	-	Hemoglobin, serum calcium, and stool examination were normal.	N/A
[33]	Case report	Female Teenage (1)	Hgb = 8.4	Stones and eggshells	Oral iron supplement Tested negative for psychological test	Hgb increased to 12.4	-	partial intestinal obstruction	N/A
[67]	Case report	Adolescents (4)	Hgb = 9.4	Ice	Tested negative for psychological test	-	-	-	N/A

Table 4 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed Hemoglobin/ Serum ferritin (SF) /Anemia indicator g/dL	Type of pica	Intervention	Key Findings related to IDA and Anemia	Comments on IDA and pica Post-intervention	Other outcomes	Quality Assessment
[105]	Case-report	WRA (25)	mean Hgb = 9.36 +/- 1.45	Ice	one dose of parenterally iron on ice consumption, over 3 weeks, IM injection of 5cc saline, and then 5cc iron dextran	Mean Hgb increased to 13.2		Diagnosed with severe hypermenorrhea	N/A
[49]	Case report	WRA (1)	Hgb =7.9 SF = 4.6	Raw rice	oral iron and Hgb improved after 3 weeks and	Pica cravings partially resolved	Presented with symptoms of fatigue and lethargy. PCOS and menorrhagia	-	N/A
[35]	Case report	WRA (1)	Hgb = 8.9	Laundry starch	330mg of ferrous sulfate 3x/day	Hgb = 10.0	-	-	N/A
[44]	Case report	Adult male (1)	Hgb = 8.7	Reported but not specified	Extensive iron and liver extract therapy,	Pica improved and Hemoglobin increased to 14.0	-	at 12 years old, a cavernous hemangioma was removed, at age 14 pica and hemochromic anemia were detected	N/A
[36]	Case report	Adolescent F (1)	Hgb = 9.1	Plastic	daily iron supplement	-	-	-	N/A
[37]	Case report	Pregnant woman (1)	Hgb = 9.0 SF = 2.4	Freezer frost A traditional tamarind jelly candy in a brown glazed ceramic pot	Oral chelation with Succimer (dimercaptosuccinic acid) and coincidentally with Triphasil (oral contraceptive).	-	-	-	N/A

Table 4 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed Hemoglobin/ Serum ferritin (SF) /Anemia indicator g/dL	Type of pica	Intervention	Key Findings related to IDA and Anemia	Comments on IDA and pica Post-intervention	Other outcomes	Quality Assessment
[69]	Case report	WRA (1)	Hgb =11.0	Paper	Laparotomy and a transfusion of three units of blood 14 days after the operation and a week later started taking folic acid and iron polymaltose complex (Ferrum H).	Hgb increased to 14.2 six weeks later	-	-	N/A
[106]	Case report	Young child Male (1)	SF = 4.30	Stones and pebbles- litho-bezoar	Use of laxatives and a rectal washout, and the pebbles were excreted over 3 days. Oral iron therapy was also commenced with the cessation of pica.	Hgb increased to 14.2	-	Concurrent acute intestinal obstruction	N/A
[99]	Case report	Pregnant woman	NR	Ice and freezer frost	Composite resins were selected as interim restorations.	-	-	Concurrent bulimia	N/A
[70]	Case report	Older adult male (1)	Hgb = 3.0	Metallic objects	n-acetylcysteine and sodium bicarbonate followed by intravenous copper sulfate	Hgb increased to > 12.0	Refused surgery, experienced sepsis and multiorgan failure, and died	Concurrent schizophrenic	N/A
[71]	Case report	Young children B. (12)	Mean Hgb =7.9 ± 2.64	Clay, soil, pieces of bricks black coal, and pieces of wood	Iron-Dextran compound (Imferon)	8 children showed increased hemoglobin levels (mean Hgb = 11.43). All pica resolved	-	-	N/A

Table 4 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed Hemoglobin/ Serum ferritin (SF) /Anemia indicator g/dL	Type of pica	Intervention	Key Findings related to IDA and Anemia	Comments on IDA and pica Post-intervention	Other outcomes	Quality Assessment
[39]	Case report	Older adult female (1)	Hgb = 2.7	magnesium carbonate	Transfused twice, counseled, and replaced with 1200 mg of parenteral iron	Hgb increased to 5.7	-	Recurrent IDA	N/A
[40]	Case report	Adult Female (1)	Hgb = 3.5 SF = 8.0	Laundry starch	1. Transfused with 4 units of packed red blood cells and started on intravenous iron dextran therapy to replace her iron deficit. 2. Tooth no. 6 was removed under local anesthesia without complication. 3. prescriptions for ferrous sulfate 325 mg three times daily and multivitamins	-	-	The patient reported being introduced to eating soap at the age of 13 years by her mother.	N/A
[41]	Case report	Young children female (2)	Mean Hgb = 4.9	Hair - trichotillomania and trichophagia	transfused with packed red blood cells, and laparotomy /surgery for removal of a 255 gm trichobezoar, then receiving iron therapy.	Mean Hgb increased to 13.1	-	-	N/A

Table 4 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed Hemoglobin/ Serum ferritin (SF) /Anemia indicator g/dL	Type of pica	Intervention	Key Findings related to IDA and Anemia	Comments on IDA and pica Post-intervention	Other outcomes	Quality Assessment
[56]	Cohort	Young children and teenagers (144)	Mean Hgb = 10.4	Specific not mentioned	Oral iron therapy and ferric carboxymaltose (with pts with poor response to iron therapy)	Mean Hgb increased to 12.9. three had pica at presentation but symptoms disappeared with FCM administration	-	-	Fair
[58]	Cohort	Children (21)	Hgb = 5.1	Clay, dirt, and plaster	Some were given oral iron supplements	Report IDA but SF is not included. Hgb increased to 12.0	-	-	Fair
[60]	Intervention	WRA (35)	Hgb = 10.0	Ice	8 weeks of oral iron therapy in the form of ferrous sulfate tablets. Average dietary iron intake was 16.5mg/day	Pica resolved	-	Pica practice was significantly associated with the age of menarche	Fair
[107]	Intervention	Young children (44) and adolescents (975)	NR	Soil – 85/1019	Diet (tablespoon of minced meat) and a tablet of calcium daily	Pica resolved	-	-	Poor
[95]	Interventional trial	Children B, (38)	Mean Hgb = 7.0	Mostly Clay, soil, and others not indicated	Intervention: given 6mg/kg ferrous fumarate, Control group: multivitamin drops	Intervention group hemoglobin increased (mean Hgb =10.9), and pica resolved within 2 weeks	-	-	Fair
[94]	Interventional trial	WRA (50)	Hgb = 9.1	Reported but not specified	Dhatri Lauha with a dose of 500 mg 3x a day	Pica resolved ($p=0.0007$) and Hemoglobin increased to 9.5 ($p<0.0001$	-	Tastelessness (not sig, $p=0.057$) and glossitis (not sig, $p=0.083$) improved after treatment	Fair

Table 4 (continued)

Article/Authors	Study Design	Target population (Sample Size)	Biomarkers Analyzed Hemoglobin/ Serum ferritin (SF) /Anemia indicator g/dL	Type of pica	Intervention	Key Findings related to IDA and Anemia	Comments on IDA and pica Post-intervention	Other outcomes	Quality Assessment
[59]	Intervention trial	Adult females with IDA (12)	Mean Hgb = 9.4	Ice, sawdust, knitting rope, dry oats, Chewing gum, pickles.	Oral iron replacement therapy 3/9 and intravenous replacement were used in (6/9) patients	Pica was resolved on 8/9. Mean hemoglobin was 12.7	-	-	Poor
[97]	Interventional trial	Children and Pre-adolescent (100)	Mean Hgb = 8.2	Reported but not specified	Group A received an iron and zinc supplement. Group B received a placebo supplement for six weeks	80% resolved ($p < 0.0001$) pica and IDA in the intervention group. The mean hemoglobin was 8.6	-	Zinc with iron significantly improved pica	Poor
[96]	Interventional trial	Children and pre-adolescents (50)	Physical symptoms reported - pallor of the skin, mucous membranes, and nail beds	Soil/Dirt – in 10%	patients received either cobalt-iron preparation orally or in a liquid/tablet form, 20–40 mg of cobalt chloride with 37.5–75 mg ferrous sulfate for 10–16 weeks	Cobalt-iron treatment improved blood values more than the purely iron supplement.	All patients showed a marked pallor of the skin, mucous membranes, and nail beds	22 pts displayed evidence of malnutrition. cobalt may improve the absorption of iron	Poor
[98]	Interventional trial	Adults and older adults: mean age is 38.2 ± 15.9 (100)	Hgb = 8.7	Ice	A single dose of 2 mg/kg ferrous sulfate and 64 mg of iron and H. Pylori treatment	Pica was resolved 1 month after the iron replacement is all 55 with IDA. 1 report pica resolved after H. Pylori treatment	-	-	Fair

NR Data not reported, *Hgb* hemoglobin, *SF* Serum Ferritin, *N/A* Not applicable, *OCD* Obsessive-compulsive disorder, Young children ≤ 8years old; Preadolescents = 8 years - 12 years; Adolescents = 13 years – 18 years; Women of Reproductive Age (WRA) = 18 years – 45 years; Adults Males = 18 years – 60 years; Adult females = 45 years – 60 years and Older adults = > 60 years

Lastly, case reports on non-pregnant adult women [66, 74] indicated stress as a risk factor for the association between pica, IDA, and oral health diseases.

Interventions to address pica

Out of the 89 papers in this review, 39 (43.8%) used diverse interventions to manage pica practices. The papers with intervention components included 1 (2.6%) retrospective chart review [27], 28 (71.8%) case reports [29–33, 35–37, 39–41, 44, 49, 61–63, 66, 67, 69–72, 99, 102–106], 2 (5.1%) cohort studies [56, 58], and 8 (20.5%) intervention studies [59, 60, 94–98, 107]. From the retrospective study involving intravenous (IV) iron treatment after LRYGP, pica resolved in all patients. Similarly, iron repletion in the form of ferrous fumarate or ferrous sulfate or iron through oral, intramuscular, or intravenous routes completely resolved pica among WRA, adult females, preadolescents, and children with results as soon as within two to 10 weeks of treatment. In two studies [94, 97] pica resolved as hemoglobin levels improved to normal (> 12g/dL) levels ($p < 0.005$). Partial resolution of pica was also reported in two studies both case reports [49, 61].

Although iron-alone treatments seem effective in treating pica, a few studies combined iron with other micronutrient supplements such as zinc [29, 97], calcium [29, 97, 104, 107], cobalt [96], and copper [62, 70]. Other mechanisms of pica treatment included deworming [29], anti-retroviral treatments (ARTs) [61], hormone therapy [66], B complex [104], and pharmaceuticals meant for OCD [72]. Interestingly, in one intervention study, Cobalt-iron treatment improved blood values more than the purely iron supplement [96].

Iron therapy was widely used in the treatment of pica. The iron dosage used as supplements or infusions varied widely although just an infusion of 500 mg resolved pica among adult males, 64 mg single dose of oral iron supplement, and average dietary iron intake was 16.5 mg/day. In a few instances, multivitamins were prescribed alongside iron supplements [40, 95].

In three studies, pica conditions were treated using nutrition and dietary interventions. The first study used mainly diet, specifically they study gave one tablespoon of minced meat to young children and preadolescents [107], liver extract therapy on adults made with pica [44], and dietary counseling but complemented with calcium or iron supplements [63]. In these three studies, both hemoglobin and pica were observed to improve after these treatments.

Aside from these interventions, one intervention trial used a single dose of 2 mg/kg ferrous sulfate and 64 mg of iron and H. Pylori treatment concurrently among adults and older adults [98] to treat pica. After 1 month of the iron treatment, pica resolved in all 55 patients but for one patient, pica resolution only occurred when the H Pylori treatment was done. In another study [40], an adult female who had a pica for laundry starch was provided iron treatment, counseling, and tooth removal under local anesthesia. The outcome of this treatment on pica practices was however not reported in the case report. The only treatment that showed no impact on pica practices (for ice) in a WRA was the use of venlafaxine 50 mg tablets that were administered along with capsule B-complex, distraction, and psychological family counseling [104].

Pica seemed to co-exist and/or be associated with hunger [103], malnutrition [96], multi-parity [32], menorrhagia [32, 49, 105], age of menarche [60], intestinal obstruction [33, 106], eating disorders like bulimia [99], obese individuals who underwent Laparoscopic Roux-en-Y gastric bypass [27], tastelessness and glossitis [94, 102], and mental conditions such as schizophrenia [70] and OCD [72]. These results were observed across diverse age groups.

Discussion

We reviewed publications assessing the relationship between pica and iron deficiency anemia (IDA), pica, and oral health outcomes, and the relationship between IDA/anemia and oral health. The co-occurrence of pica and anemia was reported in 72 of the 89 papers included in the review indicating a high association. About a third of the papers also reported pica and IDA correlations. Sixteen papers reported pica with teeth abrasions and caries. Caries were common oral conditions for patients practicing amylophagia i.e. pica of starches such as uncooked rice or oats, while teeth abrasions were common among people who had geophagia i.e. pica for soil, clay, and stones. Severe IDA (serum ferritin < 15 mcg/ml) was uniquely observed among six case reports of oral conditions and pica. Reported pica practices were closely related to anemia, specifically with IDA as confirmed in < 18 papers that indicated pica resolution when hemoglobin or iron levels were improved after iron repletion or treatment although the quality of evidence was fair or poor. Overall, 40% ($n = 16$ papers) were categorized as "poor", 52.5% ($n = 21$) were "fair" and 7.5% ($n = 3$) were classified as "good" evidence. The 49 case reports did not go through quality assessment.

Anemia and pica were concurrently reported in 80.9% of the papers in this review. In all study designs, pica practices were more likely to be associated with low hemoglobin levels. Reported significant levels were observed [47, 54, 80, 81, 88, 90, 91, 94, 97] for mostly severe anemia (6.5 to 7.9 g/dL) or even life-threatening anemia (< 6.5 g/dL) [115]. Anemia can be caused by

nutritional and non-nutritional factors [113]. Risk factors for anemia can be exacerbated when an existing infection exists, the person lives with a chronic condition or individuals have undergone weight loss surgery [2, 4]. In a retrospective chart review of 959 obese patients who had undergone LRYB, 1.7% pica was reported and the mean hemoglobin showed mild anemia (10 g/dL) [27]. Conversely, in a case report of 10 children with Trichuris infection, severe anemia was observed [43]. These observations suggest strongly that pica practices are more likely to occur in untreated or persistent anemia. Additionally, a study comparing oral microbiota between 24 IDA patients and 24 healthy individuals in China reported that iron deficiency led to lower internal diversity in the oral flora that increased oral *streptococci* [116]. Similarly, IDA patients showed significantly higher levels of microorganisms such as *Lactococcus, Enterococcus, Pseudomonas*, and *Moraxella* frequently reported as antibiotic-resistant [116].

Pica and IDA seem to have a cause-and-effect relationship. For instance in the case of pica for dirt, in a cohort of 21 children, the mean serum iron was very low [58]. Understandably, some pica substances such as clay or stones have been known to be microbial carriers [18, 19] that may cause infections, further increasing iron needs through immune responses and increased inflammation [117–120]. In cross-sectional studies, cohort, and intervention studies, the mean serum ferritin for pica practices was consistently low (1.5–46.0 mcg/L) across all age groups [115]. Serum ferritin was uniquely low for young female children, female preadolescents, teen females, and pregnant women but not for older adult females. In adult women, IDA was commonly associated with parity and menorrhagia. The observed association is to be expected as females have physiological needs related to growth, puberty, and childbearing [15, 121–124]. Conversely, IDA has been shown to cause pica practices, evidenced by the resolution of pica when iron alone or iron combined with other nutrients or diet therapy was introduced in at least 14 studies where hemoglobin and/or iron status improved [27, 32, 44, 56, 59, 60, 66, 71, 72, 94, 95, 97, 98, 107].

The relationship between pica and oral health outcomes was consistent. Of the 16 papers, 11 mostly case reports on females showed a relationship between oral health conditions with both mild and severe anemia cases [29, 32, 35, 49, 63]. One of the reported cases was with life-threatening anemia in a 47-year-old woman from the United States [40]. Types of pica showed a trend in the nature of oral conditions or symptoms reported. For instance, pica for stones, bricks, and clay seems to show a trend of direct impact on oral health manifested as teeth abrasions. Stones and gravel are harder and may destroy the enamel, thus their use as pica substances may cause physical deterioration on the tooth surface. These types of pica substances may also increase the risks of worm infections since the soil or clay may have a microbial load on them [18, 19]. Pica for raw uncooked starches seemed to be commonly reported with concurrent caries in India, the USA and Malaysia. Similar to ultra-processed foods and sugars, uncooked starches may serve as substrates for microbial organisms such as *Candida albicans* and *Streptococcus Mutans* [125]. The effect of such pica substances on the salivary properties or microbiome changes is currently unknown.

The relationship between IDA/anemia and oral health, although moderately shown in six case studies is very significant. Common pica substances included pica for stones, raw uncooked starches, and uncooked rice. Reported IDA status was strongly associated with serum and salivary ferritin levels and the increased risk of oral microbial growth [126–128]. Additionally, a study showed that salivary metals, including iron increased candida growth [128, 129]. In the first study published in 2018, Norris and co-authors observed that next to zinc, salivary iron copper, and manages were the most abundant in the saliva from medically healthy adults aged 21 to 80 years of age [128]. Iron strongly influenced *S. mutans* in biofilm formation. Since *S. mutans* species is the main causative agent of caries, the ability to form biofilm on the surface of teeth promotes disease risks [130]. Similarly, preliminary findings from *in vivo* studies show that iron even in the saliva has an impact on the growth and hyphal formation of *C. albicans* implicated in caries disease formation. This makes IDA status a critical risk marker for consideration when treating oral diseases [130, 131].

Lastly, pica treatments were inconsistent but showed a trend of treatment with iron repletion. For many case reports and intervention studies, oral iron supplements significantly improved hemoglobin levels [127, 132] and pica practices [27, 56, 60, 66, 72, 107]. Only two studies i.e. a case report and intervention study of dietary approaches and counseling were used to treat IDA and pica [44, 107]. In an intervention study consisting of 44 young children and 975 adolescents, one tablespoon of minced meat and a tablet of calcium daily improved hemoglobin and pica practices [107]. In fact, younger children (ages 2 to 6 years) and males quit the soil-eating habit the fastest. Overall males quit in 10 days while females in 12 days [107]. In the case report, an anemic adult male who practiced pica was given extensive but unspecified amounts of iron and liver extract therapy. This treatment concurrently improved hemoglobin and pica [44]. Meat contains heme iron that improves iron status. However, food sources containing

glucose, lactose, soy protein, and iron have been showed to increase *S. mutans* [130]. Although this is a positive finding, the recent results on the behaviors of *C. albicans and S. Mutans* in the presence of iron pose concerns for the resultant individual microbial effect and interaction of both microorganisms [126]. A broader concern about the use of oral iron supplements has an unknown effect on the oral microbiome. In some cases, iron supplements were used in addition to replenishing other iron-inducing nutrients such as zinc, calcium, and copper. For WRA who are prone to recurrent IDA, a sustainable treatment approach may be critical for this population. Aside from the evolving role of processed foods, and sugars, diet and nutrition education could play an important role in addressing pica, and IDA status. High sugars negatively affect the diversity and balance of oral microbiota [125, 133]. Conversely, ultra-processed foods negatively affect the gut microbiome [125, 134], it is unknown how these foods will affect the oral microbiome.

Strengths and limitations of this review

This review has many strengths. First, concurrently evaluating data from the association between pica, IDA and oral health is a novel approach. Remarkably, a few papers (16) included in the review presented results in all three outcomes. All but one of the 16 papers were case reports. We separated serum ferritin/ iron and hemoglobin outcomes allowing the assessment of the relationships between oral health and anemia and IDA separately. Additionally for this review, we did not limit papers to a specific year. This approach allowed for a comprehensive review of pica, IDA/anemia, and oral health among all ages and physiological groups across 63 years [1959 to 2022] representing data from 33 countries.

Some limitations are however observed. An overwhelming 55.0% ($n=49$) of papers included in this review were case reports. Of the 40 papers (45.0%) assessed for quality, 16 papers were considered "poor", 21 were "fair" and three (3) were categorized as "good". These findings indicated the need for high-quality research on the topic. Specifically, studies with RCT study designs are lacking on this topic. Lastly, inconsistent result reporting introduced a high level of heterogeneity thus making it impossible to run pooled odds ratios or weighted mean differences. These meta-analyses if conducted would have provided further insight on the observed relationships of pica, anemia/IDA, and oral health.

Conclusions and recommendations

The relationship between pica and IDA

A larger proportion (80%) of papers reported strong associations between pica and anemia. A third of those papers also confirmed an association between pica and low serum ferritin levels. These findings were confirmed in about 18 studies indicating the concurrent improvement of hemoglobin levels and resolution of the documented pica practices. A trend of high pica, IDA, and anemia was observed in mainly female case studies, including WRA. Additionally, some disagreement about the causes of pica was observed. For instance, it was unclear if iron alone was the most effective treatment of pica, and if other micronutrients were critical for pica treatment. Further, some papers discussed pica as a cause of IDA while others suggested pica practices were an effect of IDA. The direction of the causative effect is yet unknown from this review. Future studies using RCT to deduce causal inferences about pica are critical. The overall moderate to poor evidence as assessed in this review points to the relationship between pica and hemoglobin and ferritin levels. The data, however, is unclear if a dose-response relationship exists for these observed relationships. The current evidence sometimes failed to distinguish between cravings and actual consumption of non-food or pica substances. In some papers, both the craving for food and non-foods were assessed as pica, suggesting the need for studies on sensitive measurement tools for pica. Lastly, no paper included in this review examined the microbial or metal composition of pica substances reported. This unavailable microbial or metal composition data would have enabled an assessment of potential exposure to worm infestation or exposure to metals that may be serve as a barrier or facilitator of iron bioavailability.

For the relationship between pica and oral health outcomes

Tooth abrasion and dental caries were observed among pica users. Teeth abrasions were associated with geophagia while caries was associated with amylophgia. This review also revealed various gaps in research on the effects of pica and IDA on oral health. Future studies could focus on and define the strength of the pica-oral health association and the potential mediators, such as anemia and type of pica as many of these samples may influence the salivary metal composition, pH, or serve as substrates for cariogenic and microbial growth. The review also found limited research discussing pica, and oral health conditions among high-risk populations including pregnant women and low-income participants. Future research in this pica and oral health area could help answer questions relating to the effect of pica on low-income individuals, the associated oral conditions, and the relationship between pica, dietary intake, and oral diseases especially during perinatal stages. Such studies would also allow an assessment of the potential impact of pica on birth outcomes, and eventual oral health of exposed children, especially their caries risks.

Lastly, the relationship between IDA/anemia and oral health

A relationship between oral diseases and anemia was reported in 13 papers. Low serum ferritin levels indicative of IDA were reported in six (6) of the 16 papers that included oral health outcomes. Irrespective of the pica type, IDA and anemia were still associated with oral health outcomes and oral diseases such as caries. Additionally, for interventions to address anemia and pica in the context of oral diseases the only intervention study included in this review used surgical removal of the carious tooth and oral iron supplements on 50 women. This treatment significantly resolved pica while improving anemia status. However, it is unclear how such exposure to iron during pica treatment will affect the oral microbiota and ecosystem since these were not assessed. Randomized Control Trials are needed to investigate the potential impact of iron supplements on the oral microbiome and cariogenic microorganisms.

Abbreviations

Hgb	Hemoglobin
IDA	Iron Deficiency Anemia
LRYGP	Laparoscopic Roux-en-Y gastric bypass
MCV	Mean Cell Volume
OCD	Obsessive-Compulsive Disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trials
SF	Serum Ferritin
SI	Serum Iron
WRA	Women of Reproductive Age

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

B.A.Z.A conceptualized the idea. Drafted the main manuscript text. A. M., Y.W. and B.A.Z.A conducted the screening and data extraction. B.A.Z.A and Y.W. conducted the quality assessments of the papers. B.A.Z.A., J.X., D.C. and R.B. developed the search strategy and completed the search. T.W., K.F., S.G., and J.X. made critical inputs in the data analysis process and reviewed the drafted manuscript. All authors reviewed and approved the final manuscript.

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Data availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study. The search strategy has been included as supplementary material. Data extraction sheets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval and consent of participants were addressed in the published papers included in the study.

Consent for publication

Not Applicable

Competing interests

The authors declare no competing interests.

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