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A meta-analysis of pica and micronutrient status

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Abstract

Objectives—Pica is the craving for and consumption of non-food items, including the ingestion of earth (geophagy), raw starch (amylophagy), and ice (pagophagy). Pica has long been associated with micronutrient deficiencies, but the strength of this relationship is unclear. We aimed to evaluate the association between pica behavior and the risk of being anemic or having low hemoglobin (Hb), hematocrit (Hct), or plasma zinc (Zn) concentrations.

Methods—We systematically reviewed studies in which micronutrient levels were reported by pica status. We calculated the pooled odds ratio for anemia or weighted mean difference in Hb, Hct, or Zn concentrations between groups practicing or not practicing pica behaviors.

Results—Forty-three studies including 6407 individuals with pica behaviors and 10,277 controls were identified. Pica was associated with 2.4 times greater odds of anemia (95% CI: 1.94–2.85, $p<0.001$), lower Hb concentration (−0.65 g/dL, 95% CI: −0.83–−0.48 g/dL, $p<0.001$), lower Hct concentration (−1.15%, 95% CI: −1.61–−0.70%, $p<0.001$), and lower Zn concentration (−34.3 μg/dL, 95% CI: −59.58–−9.02 μg/dL, $p=0.008$). Statistical significance persisted after excluding outliers and in subgroup analyses by pica type and life stage.

Conclusions—Pica is significantly associated with increased risk for anemia and low Hb, Hct, and plasma Zn. Although the direction of the causal relationship between pica and micronutrient deficiency is unknown, the magnitude of these relationships is comparable to other well-recognized causes of micronutrient deficiencies. Pica warrants greater public health attention; specifically a potential physiological mechanism causing the relationship between pica and micronutrient deficiencies merits further study.

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Conflict of Interest
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Keywords

Anemia; Pica; Meta-Analysis; Hemoglobin; Micronutrients

Introduction

Pica is the craving and purposeful consumption of non-food substances (Young et al., 2010). It includes geophagy (consumption of earth), amylophagy (consumption of raw starch), pagophagy (consumption of ice), and other forms of non-food consumption. Pica was first described in 400 BCE by Hippocrates (Hippocrates, 1839), and has since been observed in human populations worldwide (Anell and Lagercrantz, 1958; Laufer, 1930) and in hundreds of non-human animal species (Krishnamani and Mahaney, 2000; Young et al., 2011). In the United States, reported prevalence of pica behaviors has ranged from 4.0% among men and women at an outpatient weight loss clinic (Delaney et al., 2014) to 68% among pregnant women (Horner et al., 1991) to 18.5% among children (Barltrop 1966).

Pica behavior is sometimes, but not always, found in conjunction with micronutrient deficiencies, and the direction of this relationship is not well understood (Young et al., 2010; Young et al., 2011). There are two mechanisms by which pica may cause these deficiencies. Pica materials may bind to the mucosal layer of the gut, thereby preventing absorption of micronutrients (Hunter, 1973). These materials may also absorb micronutrients in ingested food, preventing them from being metabolized (Cavdar et al., 1983). Conversely, it has been suggested that micronutrient deficiencies cause humans to seek out minerals from non-food substances (Cavdar et al., 1983; Hunter, 1973; Prasad et al. 1961). Others have suggested that pica may be a nonadaptive response to micronutrient deficiencies, perhaps operating through neurological disturbances (Chishom and Martin, 1981; Prasad et al., 1961; von Bonsdorff, 1977; Youdim and Iancu, 1977).

Further, the strength of the association between pica and micronutrient deficiencies has been inconsistent. In a recent review of 28 cross-sectional studies of the association between pica and iron deficiency and/or anemia, pica was associated with iron deficiency or increased risk for anemia in only 19 (Young et al., 2010). Data from the few available intervention studies are also inconclusive. Some case series have noted that iron and zinc supplementation were associated with cessation of pica behaviors (Bhalla et al., 1983; Chen et al., 1985; Coltman, 1969; Lofts et al., 1990), but these studies lacked controls and rigorous blinding. The two controlled double-blind studies of the effect of iron supplementation on geophagy found no effect (Gutelius et al., 1962; Nchito et al., 2004). The only experimental support for a causal relationship between pica and anemia is in rats. Anemic rats consumed more ice (pagophagy) than water compared to non-anemic controls, and recovery from anemia eliminated pagophagy (Woods and Weisinger, 1970).

This conflicting evidence suggested the need to clarify the nature of the relationships between pica and micronutrient deficiencies. Specifically, in this first meta-analysis of pica and micronutrient deficiencies, our objectives were to estimate the strengths of the associations with biomarkers most commonly associated with pica (anemia, hemoglobin, hematocrit, and plasma zinc) and to determine if the associations were dependent upon an

individual's life stage (age, pregnancy status) or the type of material (earth, ice, and/or starch) consumed.

Methods

Study Identification

We conducted a systematic search for pica studies among humans using the keywords "pica," "amylophagy," "clay eating," "chalk eating," "cachexia Africana," "citta," "mal d'estomac," "malacia," "erde essen," "aarde eten," "dirt-eating," "starch eating," "amylophagia," "ice-eating," "pagophagy," "pagophagia," "geophagy," and "geophagia" in Agricola, Dissertation Abstracts, Google Scholar, Human Relation Area Files, ISI Web of Science, JSTOR, Library of Congress, LexisNexis, OCLC, Proquest Historical Newspapers, and Pubmed. Titles and abstracts were examined to exclude irrelevant articles. A minority of articles were obtained by expert referral, specifically those not in catalogued databases. We then checked the reference lists of retrieved articles to identify other relevant articles. Full texts of relevant articles were obtained to extract information on pica behavior, micronutrient status, and population studied. Publication format was not an exclusionary criterion, but all references were either articles published in peer-reviewed journals or baccalaureate, masters, or doctoral theses. Non-English articles were translated as needed and included in the analysis. The literature search was conducted independently in December 2012 and July 2013 to ensure that all relevant articles were included in the meta-analysis.

Inclusion/Exclusion

A study was considered eligible for inclusion if an effect size of pica could be calculated from the data presented, i.e. if data were reported on the prevalence of anemia or Hb, Hct, or Zn concentrations between individuals with pica and otherwise comparable individuals who did not engage in pica. Studies were included in anemia analyses if counts for anemic individuals with pica and without pica and for non-anemic individuals with pica and without pica were reported or could be calculated. Studies were included in the Hb, Hct, and Zn analyses if mean and SDs for the biomarker was reported by pica status. The corresponding authors of papers with missing counts for anemia and pica status or missing means and SDs for Hb, Hct, and Zn concentrations were contacted once by email for additional data necessary for meta-analysis, but a response was received for only one study (Young et al., 2010).

Definitions

Pica classifications were made based on authors' definitions of pica within each article (Supplemental Table 1). Because definitions for pica can vary among studies, sub-analyses were conducted for geophagy, pagophagy, and amylophagy. The current DSM-5 definition of pica includes consumption of nonfood, nonnutritive substances only, which includes geophagy but not pagophagy or amylophagy (Hartmann et al., 2012), while historically, consumption of large amounts of ice or raw starch has been considered as a pica behavior (Danford, 1982; Young, 2010).

Anemia was defined according to the authors' designation in each study; these definitions varied slightly across studies (Supplemental Table 1). These definitions were generally but not always in agreement with WHO definitions for anemia, which are Hb <11.0 g/dL or Hct <33% in children 6–59 months, Hb <11.5 g/dL or Hct <34% in children 5–11 years, Hb <120 g/dL or Hct <36% in children 12–14 years, Hb <12.0 g/dL or Hct <36% in non-pregnant women, Hb <11.0 g/dL or Hct <33.0% in pregnant women, and Hb <13.0 g/dL or Hct <39% in men (WHO, 2001). Anemia was analyzed separately from Hb and Hct because many studies only provided data on presence or absence of anemia.

For sub-analyses by life stage, "children" was also defined according to the authors' designations (Supplemental Table 1). "Children" ranged in age from 6 months to 15 years, and one study included individuals up to age 18 (Geissler et al., 1998). Three of the twelve studies among children included ages in which ingestion of non-food items could be considered mouthing behaviors (<2 years), but these studies were not excluded because young children comprised small minorities of the samples. Pregnancy was established by most authors by the fact of a woman attending an antenatal clinic.

For analyses by pica type, a study was included if pagophagy, amylophagy, or geophagy were reported as the most common type of pica in each study. The prevalence of pagophagy ranged from 44.4% to 100% in the eligible pagophagy studies, 63.7% to 100% for amylophagy, and 59.1% to 100% for geophagy. Repeated analyses defining pica types as study populations limited to those exclusively reporting geophagy, amylophagy, or pagophagy yielded no qualitative changes to the results in this study.

Data Extraction

We gathered data on the geographical location and year of study, population characteristics, type of pica, prevalence of pica, sample size, effect size, and significance level for each study using a standardized form (Supplemental Table 2). If significance level was not reported, we calculated a p-value using a chi-squared test for anemia with counts of patients with and without anemia or a two-sample t-test with unpooled variance for Hb, Hct, and Zn using mean, SD, and sample size for pica and non-pica groups (Supplemental Table 2). All included studies were either observational studies gathering information on pica status along with anemia status and Hb, Zn, or Hct concentrations, or intervention trials comparing the effects of supplementation on micronutrient status in populations with pica. For studies involving clinical treatment of pica behavior, only data on patients' micronutrient statuses prior to treatment were included. Two readers worked independently to extract data from each study under supervision by S. L. Y. for accuracy.

Statistical Analysis

Our primary outcome of interest was differences in micronutrient status between populations of individuals who practiced pica behavior and those who did not. Data were available on anemia (binary categorical variable), Hb (g/dL) (untransformed continuous variable), Zn (μg/dL) (untransformed continuous variable), and Hct (%) (untransformed continuous variable). All meta-analyses of the association between pica behavior and micronutrient deficiency were performed with micronutrient data in the same units (counts of individuals

for anemia, g/dL of Hb, μg/dL of Zn, or % Hct), so effect sizes did not require additional adjustment. Sub-analyses were also conducted by life stage (children, adults, pregnant women) and pica type (amylophagy, pagophagy, and geophagy) when at least 5 studies were eligible.

We used the "metan" function in Stata/MP 12.1 (StataCorp) to calculate all pooled effect sizes, study weights, and forest plots, and "metafunnel" to generate all funnel plots to assess publication bias from inputs of frequencies of anemic individuals by pica behavior or mean and standard deviation of Hb, Hct, or Zn concentrations by pica behavior. For analyses of anemia, the primary outcome was a pooled OR of an individual being anemic, whereas the primary outcome for the continuous variables (Hb, Hct, and Zn) was the weighted mean difference (WMD), which is the difference in average concentration between pica and non-pica groups. Studies were weighted according to the inverse of their variances (Higgins et al., 2011).

The I^2 statistic was calculated to determine between-study heterogeneity, where I^2 >50% was evidence for between-study heterogeneity (Harris et al., 2008). When I^2 was >50%, a random effects model was used to generate the DerSimonian and Laird (D-L) pooled OR or WMD (DerSimonian and Laird, 1986; Harris et al., 2008). Where I^2 was <50%, a fixed effects model was used to generate the inverse variance (I-V) pooled OR or WMD to increase power to detect significant differences between groups (Harris et al., 2008).

We investigated the possibility of publication bias using funnel plots (Sterne and Harbord, 2004). For anemia, log OR was plotted on the x-axis and standard error of the log OR was plotted on the y-axis. For the other biomarkers, WMD was plotted on the x-axis and inverse variance on the y-axis. This choice of axes allowed straight lines to be drawn to define a region within which 95% of studies would be expected to fall in the absence of heterogeneity and publication bias (Palmer et al., 2008; Sterne and Egger, 2001). Additionally, we tested for small-study effects using Harbord's test for binary outcomes (anemia), and Egger's test for small-study effects for meta-analysis with continuous outcomes (Hct, Hb, and Zn) (Palmer et al., 2008). Egger's regression line was plotted on all funnel plots as a visual test for funnel plot asymmetry (Harbord et al., 2009).

Assessment for robustness was carried out by excluding outliers that tended to overestimate effect size. Outliers were defined as studies with values lying outside of the 95% confidence limits on a funnel plot. All statistical tests were two-sided and significance was set at α <0.05.

Throughout, we present our findings with pica as the independent variable and micronutrient deficiencies as the dependent variables, although a causal relationship has not been established (Young, 2010). However, because recalled information necessarily refers to past behavior and a blood draw occurs after the behavior was reported, this presentation was the most logical.

Results

Study Characteristics

Fifty-four full-text articles and dissertations were assessed for eligibility after initial screening of abstracts for inclusion/exclusion criteria (Figure 1), and 43 were ultimately included in this meta-analysis (Table 1 for included studies and Supplemental Table 3 for excluded studies). The 43 studies in this analysis included data from a total of 6407 individuals with pica behavior and 10,277 controls who did not exhibit the behavior (mean study size: 347.6 individuals; median 143). Nineteen studies were conducted in North America, 9 in Africa, 5 in South America, 1 in Europe, and 9 in Asia.

Pica and anemia

Pooled analysis of the relationship between pica and anemia indicated that individuals reporting pica were 2.34 times more likely to be anemic (D-L pooled OR=2.34, 95% CI 1.94–2.85, p<0.001) (Figure 2A). There was no evidence of publication bias using Harbord's test for small-study effects (p=0.811) or upon visual examination of the funnel plot (Supplemental Figure 1A). After excluding outlying studies favoring high OR, a statistically significant association between anemia and pica persisted OR 1.94 (I-V 95% CI 1.69–2.18, p<0.001) (data not shown).

The relationship between anemia and specific types of pica indicated some heterogeneity in the magnitude of the relationship, but all sub-analyses indicated a strong relationship between pica behavior and anemia. Practicing geophagy was associated with 2.1 times greater odds of anemia (Figure 2B, D-L pooled 95% CI: 1.55 –2.74, p<0.001), pagophagy with 1.5 times greater odds (Figure 2C, I-V pooled 95% CI: 1.01–2.11, p=0.042), and amylophagy with 3.1 times greater odds (Figure 2D, D-L pooled 95% CI: 1.75–5.54, p<0.001).

The OR of being anemic was approximately twice as high among children (Figure 2E, D-L pooled OR=4.23, 95% CI 1.52–11.78, p=0.006) than among pregnant women (Figure 2F, I-V pooled OR=1.92, 95% CI: 1.68–2.19, p<0.001).

The relationship between pica and anemia persisted when restricting studies to those defining anemia as Hb or Hct at or below the WHO thresholds, though the strength of the OR was lower than when including all studies (I-V pooled OR=2.07, 95% CI 1.80–2.37, p<0.001) (data not shown).

Pica and hemoglobin concentration

Pica behavior was significantly associated with lower levels of Hb across all populations (D-L pooled WMD=−0.65 g/dL, 95% CI: −0.83 - 0.48 g/dL, p<0.001) (Figure 3A). There was no evidence of bias using Egger's test or in the funnel plot (p=0.960) (Supplemental Figure 1B). After excluding outlying studies, the pooled WMD for the relationship between pica and Hb decreased slightly to −0.57 (I-V pooled 95% CI: −0.66–−0.49 g/dL, p<0.001). The relationship between Hb and pica was stronger in those practicing geophagy (D-L pooled WMD=−0.95 g/dL, 95% CI: −1.34–−0.55 g/dL, p<0.001), in children (D-L pooled WMD=

−1.17 g/dL, 95% CI: −1.86–−0.48 g/dL, p=0.001), and in pregnant women (I-V pooled WMD=−0.68 g/dL, 95% CI: −0.76–−0.61 g/dL, p<0.001) (Figures 3B-D).

Pica and hematocrit concentration

Individuals practicing pica had significantly lower hematocrit levels (I-V pooled WMD= −1.15%, 95% CI: −1.61–−0.70%, p<0.001 (Figure 4A). Egger's test did not yield evidence of publication bias (p=0.921), and the funnel plot appeared generally symmetrical (Supplemental Figure 1C). Although exclusion of outliers decreased the magnitude of the effect size, it remained significant (I-V pooled WMD=−1.05%, 95% CI: −1.57–−0.53%, p<0.001). The difference in WMD between pica and non-pica groups was slightly weaker among pregnant women than in all studies (I-V pooled WMD = −0.99%, 95% CI: −1.55–−0.43%, p=0.001) (Figure 4B).

Pica and plasma zinc concentration

Plasma Zn was significantly lower in the pica than in the non-pica group (D-L pooled WMD=−34.3 μg/dL, 95% CI: −59.6–−9.02 μg/dL, p=0.008) (Figure 5). There was no evidence of bias using Egger's test (p=0.478), though the funnel plot shows a number of outliers to the left of the 95% CI (Supplemental Figure 1D). Exclusion of outliers favoring lower plasma Zn concentrations caused the pooled WMD to increase to −19.63 μg/dL, and the association between pica behavior and lower plasma zinc levels was no longer statistically significant (D-L pooled 95% CI: −48.2–8.93 μg/dL, p=0.178) (data not shown).

Discussion

Pica has been an enigma for more than 2000 years due to its unclear associations with human health (Young, 2012). This meta-analysis represents an advance in our understanding of correlates of pica by providing evidence of statistically significant and biologically important associations with micronutrient deficiencies. Pica behavior was associated with 2.4 times increased odds of anemia, a lower Hb concentration (-0.65 g/dL), lower Hct (−1.2%), and lower plasma Zn (−34 μg/dL) compared to similar control individuals without pica. These associations persisted in subgroups of individuals practicing geophagy, pagophagy, amylophagy, as well as in children and pregnant women. Further, these results were also robust to exclusion of outliers favoring large effect size, except in the case of plasma Zn, though this may have been due to the exclusion of 2 of 5 studies from the original meta-analysis.

The magnitude of the effect size of pica on anemia (Figure 2A) is comparable to or larger than other known risk factors for incident anemia, including dietary deficiencies of dietary iron (Fe), vitamin B-12, and folate among American women (ORs 1.13, 1.16, and 1.12, respectively) (Thomson et al., 2011), biofuel smoke exposure among children in developing countries (OR 1.57, 95% CI 1.49–1.67) (Kyu et al., 2010), and geohelminth infection among pregnant women (OR 2.13, 95% CI 1.10–4.13) (Larocque et al., 2005). Similarly, the effect sizes of pica on Hb, Hct, and Zn are of biological importance. Considering that in adult women, the normal range of Hb is 12.1–15.1 g/dL and of Hct is 36.1 − 44.3% (Bunn, 2011) pica-associated decreases in Hb of 0.65 g/dL and Hct of 1.15% are large. For reference,

meta-analyses found that daily Fe supplementation increased Hb by 0.99 g/dL in pregnant women (86) and 0.78 g/dL in children aged 0–12 (Iannotti et al., 2006). Thus, the effect of pica on Hb observed in this study is slightly greater than that observed in iron supplementation studies. Lastly, the normal range for plasma Zn is 76–125 μg/dL for both sexes, so the effect size of 34.3 μg/dL observed here is very large.

Although this work cannot determine if pica is causally related to micronutrient deficiencies, it does suggest that pica is a clear marker of risk for these conditions, all of which have serious health consequences. For example, reviews of anemia outcomes have found strong associations with increased risk of pre-term birth and low birth weight in pregnancy (Allen, 2000) and long-lasting neural and behavioral defects in infants (Lozoff et al., 2008). Zinc deficiencies have been found to lead to multiple morbidities as well, including diminished immune function and insufficient reproductive hormone synthesis (Salguiero et al., 2000).

These strong associations between pica and micronutrient deficiencies suggest that pica status could be used as a preliminary clinical indicator for micronutrient deficiency. The prevalence of pica is difficult to estimate due to varying definitions of pica and the reluctance of individuals to report cravings for and ingestion of unusual materials, but estimated prevalences among the studies included in this meta-analysis, which were conducted in populations at risk for pica behaviors, range from 11% to 76.5% (SI Table 2). Estimated prevalences among populations most at risk for pica behavior in the United States have been as high as 68% in pregnant women (Horner et al., 1991) and 18.5% in children (Barltrop, 1966). Screening for pica behavior could be a proxy for identifying risk of anemia or Zn deficiency, of particular use in low-resource settings.

Strengths of this analysis include the use of data from a large number of studies with study populations of diverse age, geographic location, type of pica, and time period, providing power to detect significant effects of pica behavior. There was also no evidence for publication bias in any meta-analyses (Supplemental Figure 1). The funnel plot for Zn appeared unbalanced, but this was not unusual due to the small number of studies in this analysis (n=5), where Egger's test may be underpowered (Geissler et al., 1998). We were unable to find any sources of unpublished data, and despite the lack of evidence for publication bias, unpublished data that would otherwise be eligible for inclusion in the meta-analysis could change the associations found in this study.

This meta-analysis has some weaknesses. Definitions of anemia, pica, and children varied among studies, though these variable definitions should not have biased the results of our meta-analysis in a particular direction. While this diversity contributed to the generalizability of results, these differences may also make comparisons among studies difficult. While the main analyses in this study used a broad definition of pica that encompassed consumption of nonfood items and consumption of unusual quantities of ice or raw starch, the association between pica behavior and increased risk of anemia and decreased Hb concentration persisted when applying the stricter DSM-5 definition of pica and examining only individuals practicing geophagy. Subgroup analyses, which indicated that all associations were upheld within pica types and life stages, attempted to decrease between-study heterogeneity and control for confounding factors, but we could not measure

all potential confounders. For example, past studies have proposed that pica behavior is related to psychosocial stress, e.g. a smaller social support network (Edwards et al., 1994). We were unable to control for this factor because social relationships of the subjects were not documented in any of the included studies. Additionally, other previous studies have found that pica is more common among those with low socioeconomic status (Rose et al., 2000). Thus, it is possible that socioeconomic status is associated with both low micronutrient status and pica behavior, creating the semblance of a direct association between micronutrient status and pica. Lastly, it is possible that illness causes individuals to practice pica, and inflammation is sometimes associated with micronutrient deficiencies. These variables may be interesting to investigate in future studies on the relationship between pica and micronutrient deficiency.

A clear next step for understanding the nature of the public health consequences of pica is determining if the relationship between pica and micronutrient deficiencies is causal, and if so, the nature of causality, and the mechanisms by which the relationships manifest. The effect sizes observed here provide strong evidence that pica is of major public health concern. A more thorough investigation of both the prevalence, especially among children and pregnant women, as well as the physiological relationships with micronutrient deficiencies is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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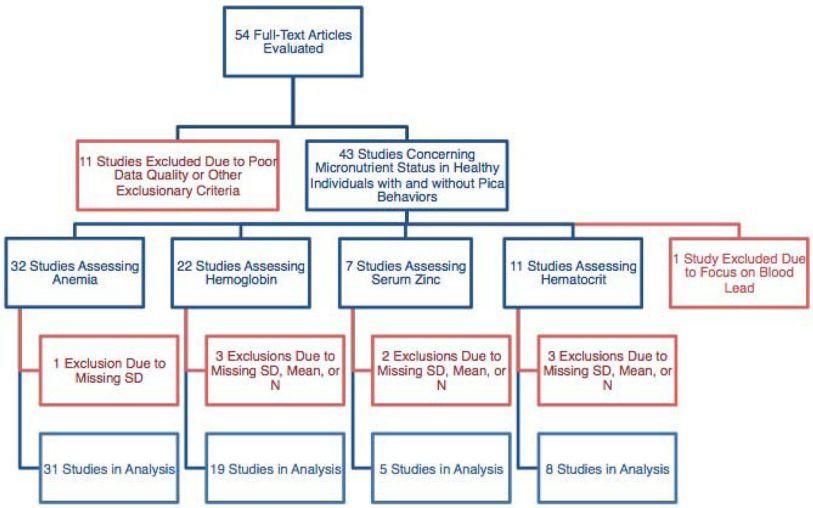

Fig. 1. Flowchart of study selection process

* Several articles measured more than one biomarker, so the number of studies used in each analysis do not sum to 43.

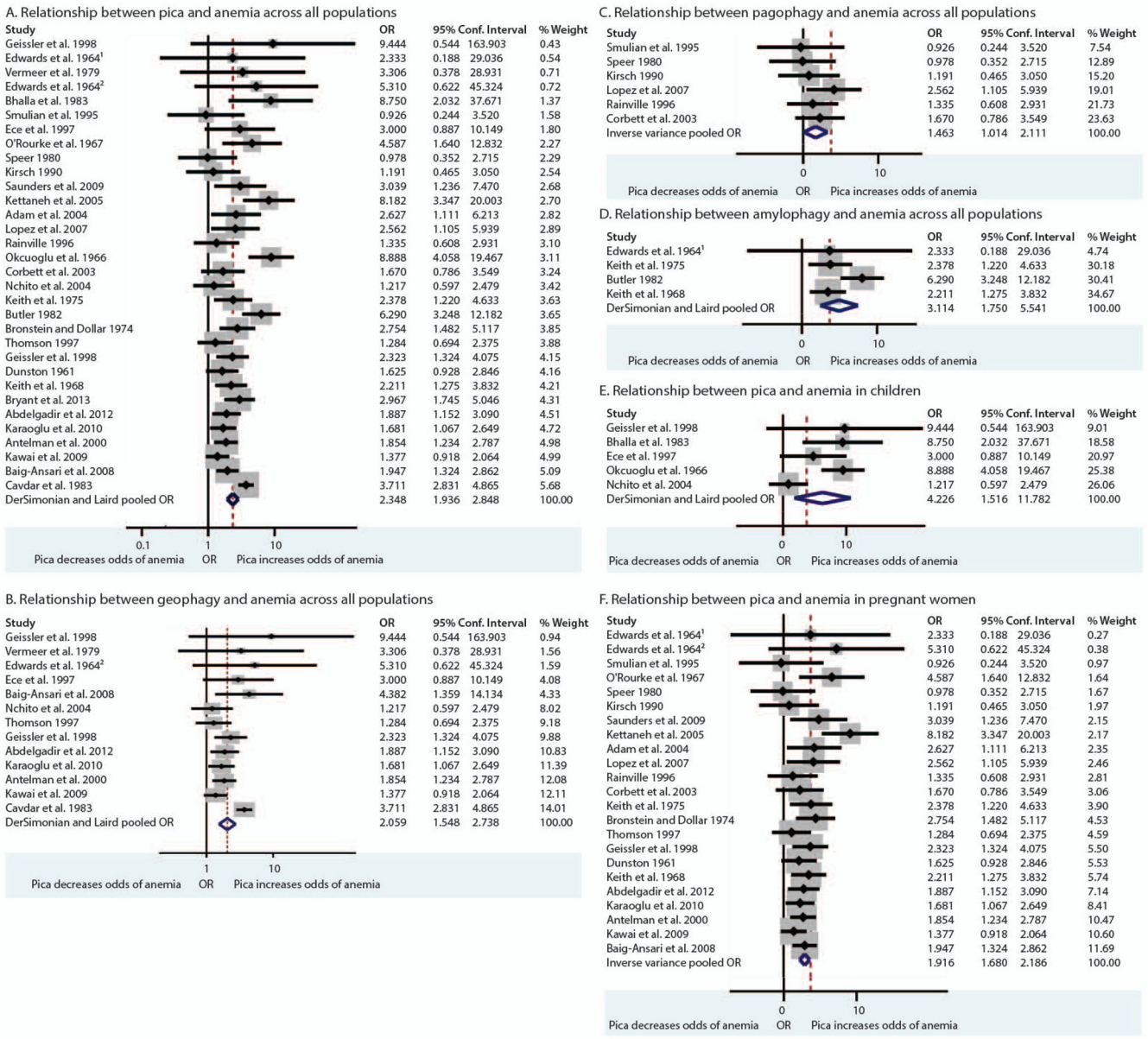

Fig. 2. Forest plots of effect of pica on anemia

Horizontal displacement of squares represents odds ratio (OR) with square size proportional to study weight in the meta-analysis. Horizontal lines represent 95% CI. Studies are organized by increasing weight. The hollow diamond indicates the pooled OR and 95% CI. **(A)** Pooled estimate of OR of pica behavior associated with anemia is shown for n=32 studies. **(B)** Pooled estimate of OR of geophagy behavior associated with anemia (n=12). **(C)** Pooled estimate of OR of pagophagy behavior associated with anemia (n=6) **(D)** Pooled estimate of OR of amylophagy behavior associated with anemia (n=4) **(E)** Pooled estimate of OR of pica behavior associated with anemia in children (n=5). **(F)** Pooled estimate of OR of pica behavior associated with anemia in pregnant women (n=23).

[1]Data for amylophagy only. [2]Data for geophagy only.

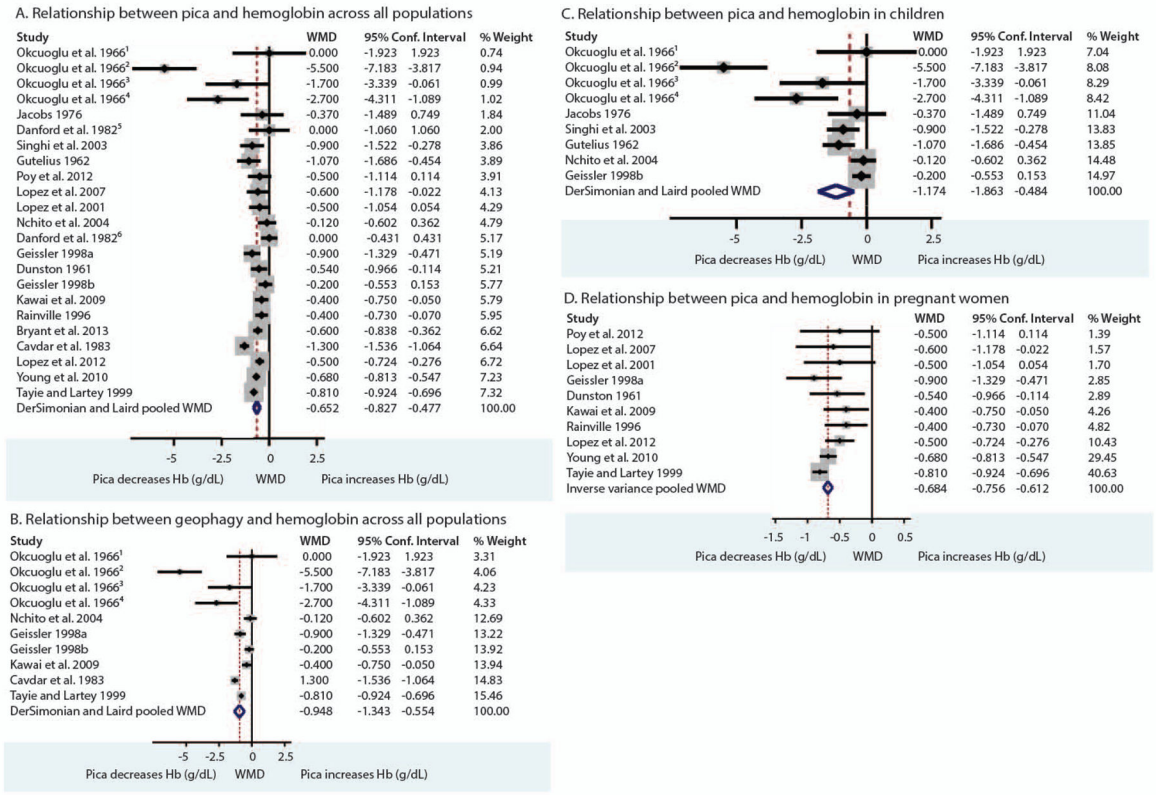

Fig. 3. Forest plots of effect of pica on hemoglobin

Horizontal displacement of squares represents weighted mean difference (WMD), with square size proportional to study weight in the meta-analysis. Horizontal lines represent 95% CI. Studies are organized by increasing weight. The hollow diamond indicates the pooled OR and 95% CI. **(A)** Pooled estimate of WMD of pica behavior associated with hemoglobin (Hb) concentration (g/dL) for n=23 studies **(B)** Pooled estimate of WMD of geophagy behavior associated with Hb concentration (n=11). **(C)** Pooled estimate of WMD of pica behavior associated with Hb concentration in children (n=10). **(D)** Pooled estimate of WMD of pica behavior associated with Hb concentration in pregnant women (n=9).
[1]Children aged 6 months to 3 years with clay pica. [2]Children aged 4 to 15 years with dirt and plaster pica. [3]Children aged 6 months to 3 years with dirt and plaster pica. [4]Children aged 4 to 15 years with clay pica. [5]Males only. [6]Females only.

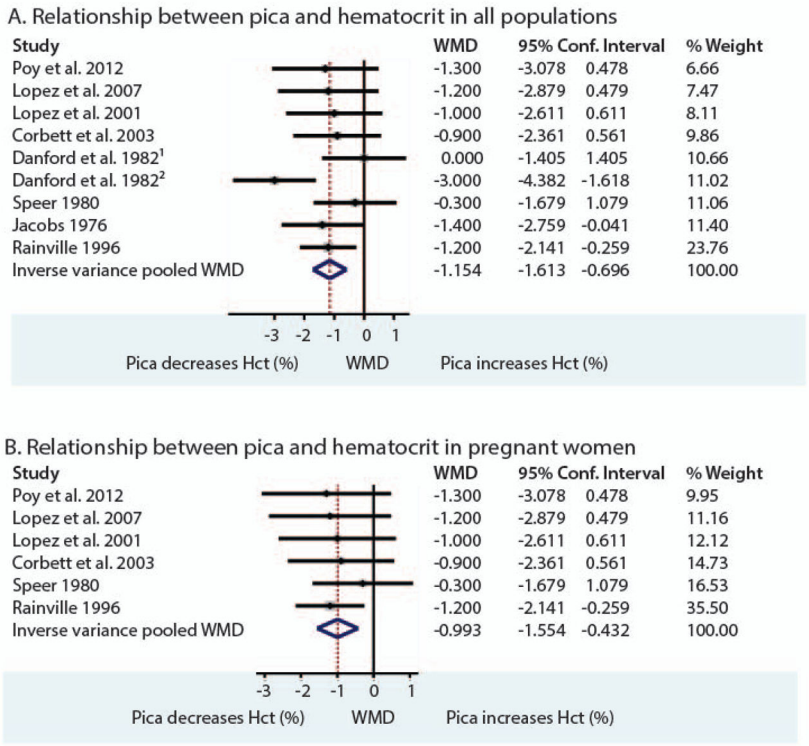

Fig. 4. Forest plots of effect of pica on hematocrit

Horizontal displacement of squares represents weighted mean difference (WMD), with square size proportional to study weight in the meta-analysis. Horizontal lines represent 95% CI. Studies are organized by increasing weight. The hollow diamond indicates the pooled OR and 95% CI. **(A)** Pooled estimate of WMD of pica behavior associated with hematocrit (Hct) (%) for n=9 studies. **(B)** Pooled estimate of WMD of pica behavior associated with Hct (%) in pregnant women (n=6).

[1]Males only. [2]Females only.

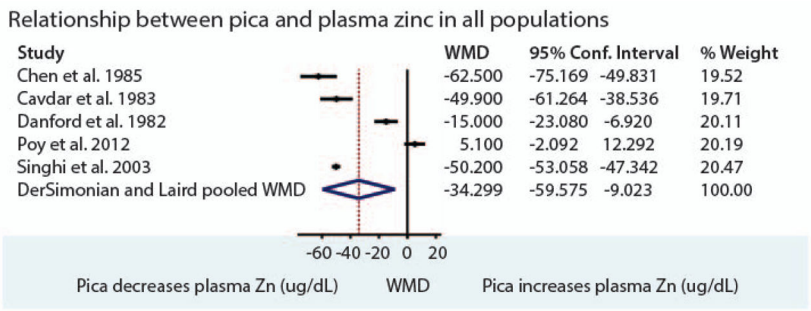

Fig. 5. Forest plots of effect of pica on plasma zinc

Horizontal displacement of squares represents weighted mean difference (WMD), with square size proportional to study weight in the meta-analysis. Horizontal lines represent 95% CI. Studies are organized by increasing weight. The hollow diamond indicates the pooled OR and 95% CI. Pooled estimate of WMD of pica behavior associated with plasma zinc (Zn) (ug/dL) for n=5 studies.

Table 1

Studies describing pica and micronutrient deficiencies included in meta-analysis*

Authors	Year of Publication	Location of Study	Study Population	Sample Size	Biomarkers Analyzed
Dunston	1961	New York, NY, USA	Pregnant women	100 pica 100 non-pica	Anemia**, Hb
Gutelius et al.	1962	Washington, DC, USA	Children aged 2–5	30 pica 28 non-pica	Hb
Edwards et al.	1964	Tuskegee, AL, USA	Pregnant women	14 amylophagy (pica) 40 geophagy (pica) 7 non-pica	Anemia
Okcuoglu et al.	1966	Ankara, Turkey, USA	Children aged 0.5–15***	63 pica 32 non-pica	Hb, Anemia
O'Rourke et al.	1967	Augusta, GA, USA	Pregnant women	37 pica 11 non-pica	Anemia
Keith et al.	1968	Chicago, IL, USA	Pregnant women	345 pica 642 non-pica	Anemia
Bronstein and Dollar	1974	Augusta, GA, USA	Pregnant women	65 pica 345 non-pica	Anemia
Keith et al.	1975	Chicago, IL, USA	Pregnant women	152 amylophagy (pica) 374 non-pica	Anemia, Hb
Jacobs	1976	Murray, UT, USA	Children aged 1–6	17 pica 16 non-pica	Anemia, Hb, Hct
Vermeer and Frate	1979	Holmes County, MS, USA	Women and children	19 pica 363 non-pica	Anemia
Speer	1980	Houston, TX, USA	Pregnant women	20 pagophagy 20 non-pica 32 pica 32 non-pica	Anemia, Hct
Cavdar et al.	1980	Ankara, Turkey	Children age 5+	32 geophagy (pica) 20 non-pica	Zn
Butler	1982	Pitt County, NC, USA	Adults (mean age 25)	66 pica 124 non-pica	Anemia
Danford et al.	1982	Waltham, MA, USA	Mentally retarded adults	60 pica 6 non-pica	Hb, Hct, Zn
Cavdar et al.	1983	Ankara, Turkey	Turkish women and children for anemia Turkish people aged 3–24 for zinc	725 pica and 525 non- pica for anemia and hemoglobin 32 pica and 20 non-pica for zinc	Anemia, Hb, Zn
Bhalla et al.	1983	Kanpur, India	Children aged 9 months-7 years	20 pica 22 non-pica	Anemia

Authors	Year of Publication	Location of Study	Study Population	Sample Size	Biomarkers Analyzed
Chen et al.	1985	Beijing, China	Children aged 1–6 years	47 pica 94 non-pica	Zn
Kirsch	1990	Atlanta, GA, USA	Pregnant women	26 pica 83 non-pica	Anemia
Smulian et al.	1995	Camden, NJ, USA	Pregnant women	707 pagophagy (pica) 627 non-pica	Anemia
Thomson	1997	Eastern Caprivi, Namibia	Pregnant women	75 pica 96 non-pica	Anemia
Rainville	1996	Houston and Prairie View, TX, USA	Pregnant women	215 pagophagy (pica) 66 non-pica	Anemia, Hb, Hct
Ece et al.	1997	Manisa, Turkey	Children aged 1–14	14 pica 110 non-pica	Anemia
Geissler	1998a	Kilifi, Kenya	Pregnant women	154 pica 121 non-pica	Anemia, Hb
Geissler	1998b	Usigu, Kenya	Children aged 10–18	114 pica 42 non-pica	Anemia, Hb
Tayie and Lartey	1999	Accra, Ghana	Pregnant women	143 geophagy (pica) 261 non-pica	Hb
Antelman et al.	2000	Dar es Salaam, Tanzania	Pregnant women	250 pica 572 non-pica	Anemia
Lopez et al.	2001	Buenos Aires, Argentina	Pregnant women	82 pica 72 non-pica	Hb, Hct
Corbett et al.	2003	North Carolina, USA	Pregnant women	48 pica 87 non-pica	Anemia, Hct
Singhi et al.	2003	Chandigarh, India	Children aged 1.5–4 years	31 pica 60 non-pica	Hb, Zn
Nchito et al.	2004	Lusaka, Zambia	Children aged 7–15 years	302 geophagy (pica) 104 non-pica	Anemia, Hb, Hct
Adam et al.	2004	New Halfa, Sudan	Pregnant women	35 pica 84 non-pica	Anemia
Kettaneh et al.	2005	Bondy, France	Men and women (mean age 37)	42 pica 116 non-pica	Anemia
Lopez et al.	2007	Buenos Aires, Argentina	Pregnant women	71 pica 71 non-pica	Hb, Hct
Baig-Ansari et	2008	Hyderabad, Pakistan	Pregnant women	639 pica 714 non-pica	Anemia
Kawai et al.	2009	Dar es Salaam, Tanzania	Pregnant women	277 geophagy (pica) 694 non-pica	Anemia, Hb

Authors	Year of Publication	Location of Study	Study Population	Sample Size	Biomarkers Analyzed
Saunders et al.	2009	Rio de Janeiro, Brazil	Pregnant women	30 pica 178 non-pica	Anemia
Karaoglu et al.	2010	Malatya, Turkey	Pregnant women	34 geophagy (pica) 189 non-pica	Anemia
Young et al.	2010	Zanzibar, Tanzania	Pregnant women	38 geophagy (pica) 773 amylophagy (pica) 86 geophagy and amylophagy (pica) 1470 non-pica	Hb
Abdelgadir	2012	Geizera, Sudan	Pregnant women	98 pica 194 non-pica	Anemia
Poy et al.	2012	Buenos Aires, Argentina	Pregnant women	42 pica 67 non-pica	Hb, Hct, Zn
Lopez et al.	2012	Buenos Aires, Argentina	Pregnant women	235 pica 779 non-pica	Hb
Bryant et al.	2013	Bethesda, MD, USA	Blood donors	152 pica 1484 non-pica	Anemia

* Hematocrit (%): Hct, Hemoglobin (g/dL): Hb, Serum Zinc (g/dL): Zn

** For children, anemia was defined as Hb <10.5 g/dL in children age 6 months-3 years, <12 g/dL in boys age 4 to 12 years and girls age 4 years and older, and <13g/dL in boys age 12 years and older. One study used a definition of anemia in children age 1–14 years as Hb <2 standard deviations below the mean, serum iron <9 ng/mL, or transferrin saturation under 12% (Ece et al. 1998). In pregnant women, anemia was defined as Hb <12.5 g/dL, with most studies using a cutoff of <10 or 11 g/dL, or as Hct <33%. One study defined anemia in pregnant women as Hct or Hb in the 5th percentile (Rainville 1996). Two studies had no specific definition of anemia (Kirsch 1990, Cavdar et al. 1983).

*** Children aged 0.5–3 and aged 4–15 were grouped separately in this analysis