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Comparison of Anemia Screening Methods Using Paired Venous Samples in Women of Reproductive Age in Southern India

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Abstract

Background: Anemia is an important public health problem, and accurate estimates may inform policy and programs. Although hemoglobin (Hb) assessment of venous blood via automated hematology analyzers (AHAs) is recommended, most population-based surveys estimate anemia prevalence based on analysis of capillary blood via portable hemoglobinometers.

Objectives: We aimed to evaluate screening methods for hemoglobin and anemia assessment using paired venous samples.

Methods: Participants were women 15–40 y who were not pregnant or lactating. Paired venous whole blood samples (n = 896) were analyzed for hemoglobin (Hb) via portable hemoglobinometer (HemoCue 301) and Coulter Counter AHA. Anemia and severe anemia were defined as Hb <12.0g/dL and <8.0 g/dL, respectively. Bland–Altman methods were used to assess the level of agreement for Hb results (mean difference, SD of differences, limits of agreement). Diagnostic accuracy parameters (sensitivity, specificity, positive predictive value, negative predictive value, accuracy) were calculated to evaluate HemoCue performance compared to the AHA reference, overall and by sociodemographic, nutritional, and metabolic characteristics.

Results: The estimated anemia prevalence was significantly lower via HemoCue vs. AHA (36.3% compared with 41.6%; P value < 0.0001). The HemoCue had 84.4% accuracy for anemia screening and 98.8% for severe anemia, compared to the AHA reference. The HemoCue had

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Supplemental Tables 1–3 and Supplemental Figures 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

Data Availability

Data will be made available upon request to the corresponding author.

74.8% sensitivity and 91.2% specificity, compared to AHA. HemoCue sensitivity was higher in women with iron deficiency [serum ferritin (SF) <15.0 μg/L: 81.6% compared with SF ≥15.0 μg/L: 41.3%], and lower in women with metabolic risk factors, including overweight [BMI ≥25.0 kg/m^2: 63.9% vs. BMI <25.0 kg/m^2 : 78.8%], or elevated CRP (>1.0 mg/L: 67.2% vs. ≤1.0 mg/L: 82.9%), trunk fat (>35%: 62.7% vs. ≤35%: 80.1%), or whole-body fat (>35%: 63.9% vs. ≤35%: 80.3%).

Conclusions: Findings suggest that women with anemia may be incorrectly identified as not anemic via portable hemoglobinometer, and anemia prevalence may be underestimated at the population level. This study was registered at clinicaltrials.gov as NCT04048330.

Keywords

anemia; hemoglobin; screening; women of reproductive age; India; iron

Introduction

Anemia is an important public health problem affecting over 1.8 billion people worldwide (1, 2). Women of reproductive age are a high-risk population for anemia, due in part to menstrual blood losses, increased iron requirements during pregnancy, and inadequate intake or bioavailability of other nutrients, such as folate and vitamin B-12 (3–5). Anemia has been associated with cognitive impairment and reduced work productivity (1, 4, 5); and during pregnancy, it has been associated with increased risk of maternal and infant mortality, low birth weight, and preterm birth (6–12). Anemia affects ~30% of women of reproductive age and ~37% of pregnant women globally (2). The burden of anemia in India is estimated to be among the highest globally, affecting over half of women 15–49 y [pregnant: 52.2%; nonpregnant: 57.2%; as assessed by HemoCue 201+; NFHS-5, 2019–2020] (13).

The WHO recommends evaluating hemoglobin (Hb) at the population level to monitor anemia prevalence. Anemia is defined as low Hb concentrations (e.g., <12.0 g/dL in nonpregnant women) (14). The cyanmethemoglobin method (CMH) is the gold-standard method for Hb assessment, and has been used to validate other methods, including automated hematology analyzers (AHAs) (15). The WHO recommends Hb assessment of venous blood analyzed via AHA when available (5). However, most national (population-based) surveys are based on capillary blood analysis via portable hemoglobinometers (e.g., HemoCue), because of the reduced availability, associated costs, need for trained personnel, and infrastructure required of AHAs (16–18). Differences in methods for Hb assessment (e.g., HemoCue compared with AHA, capillary compared with venous blood samples) and differences in instrument performance (e.g., attributable to temperature and humidity), particularly in field settings (16), constrain direct comparison of anemia estimates across studies (16, 18).

The WHO recently initiated a technical consultation to review guidelines for Hb assessment and anemia thresholds— and highlighted factors that may influence Hb screening at the individual and population levels including assessment method and type of blood sample (19–24). Recent systematic reviews have also highlighted biological differences between venous and capillary blood, methodological differences (e.g., AHA compared with portable

hemoglobinometer) (16, 18), variation in instruments (e.g., different models of portable hemoglobinometers) (16), and analytic factors (e.g., postural effect, environmental factors, intertechnician variability, laboratory personnel expertise) that may influence the accuracy of screening methods for Hb assessment. A number of studies have examined paired venous samples (25–31); however, most studies to date evaluating anemia screening methods have compared portable hemoglobinometer (HemoCue) analysis of capillary blood samples to AHA analysis of venous blood samples, which limits the ability to differentiate between biological as opposed to methodological differences (16, 18). Few studies to date have evaluated diagnostic accuracy parameters of anemia screening methods (e.g., sensitivity), or examined factors associated with diagnostic accuracy (16). Accurate estimates of anemia prevalence can aid in informing recommendations and policy.

The objective of this analysis was to use paired venous samples to compare anemia screening via portable hemoglobinometer (HemoCue 301; HemoCue) and the AHA (Coulter Counter HMX) reference, to evaluate diagnostic accuracy parameters (i.e., sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), accuracy) of HemoCue compared to the AHA, and to examine variation in these parameters by sociodemographic, nutritional, and metabolic characteristics as part of a population-based biomarker survey in southern India (32, 33).

Subjects and Methods

Study population

Participants were women aged 15–40 y who were not pregnant or lactating and participated in a population-based biomarker survey in Chittoor, Andhra Pradesh, in southern India. The study design has been previously described (NCT04048330) (32, 33). Briefly, a total of 4124 households (n=3124 rural , n=1000 urban) were selected for the biomarker survey, which was designed to be population representative for women of reproductive age in this setting. Women were eligible for inclusion in this analysis if they had paired venous samples analyzed by HemoCue (HemoCue 301) and AHA (Coulter Counter HMX). Programmatically, Hb analysis via HemoCue was implemented after the start of data collection; as a result, Hb data for paired venous samples were available for 896 of the total 980 participants in the biomarker survey.

Ethics

The study protocol for the biomarker survey was approved by the Institutional Review Board at Cornell University, and the Institutional Ethics Committees at Arogyavaram Medical Centre and St. John’s Research Institute (32, 33). The protocol was reviewed in accordance with CDC human research protection procedures and determined to be a nonresearch, routine surveillance activity. A nondisclosure agreement for personally identifiable information and data sharing agreement for de-identified data were established. This study received clearance from the Indian Council of Medical Research Health Ministry Screening Committee. Written informed consent (≥18 y) or assent (15 to <18 y) was obtained from all participants before the start of data collection. Women who had severe anemia (Hb <8.0 g/dL) were referred to a local clinic for follow-up per standard of care (33).

Data collection

All data were collected at Arogyavaram Medical Centre by trained nurse enumerators via interviewer-administered questionnaires on electronic tablets (34). Data collection procedures (32, 33) included sociodemographic, anthropometric (e.g., weight, height; midupper arm, hip, and waist circumferences), dietary (e.g., 24-hour recall), health (e.g., signs, symptoms), and reproductive history data; and biological specimens (i.e., blood, saliva, urine). BIA (BC-148 MA; Tanita Corporation) was conducted among adults (≥18 y).

Laboratory analyses and sample processing

Venous blood samples were collected in 3 vacutainers (i.e., red-top, purple-top dipotassium EDTA (K2EDTA), and blue-top metal-free K2EDTA) by a trained phlebotomist (MPR) using standardized protocols (33). Blood samples (nonfasted) were collected from the antecubital vein from participants in the supine position. Venous whole blood samples collected via K2EDTA vacutainers were analyzed for Hb in real time, using both a HemoCue 301 (HemoCue) and an AHA (Coulter Counter HMX) as reference. HbA1c was assessed via nephelometry (Agappe Diagnostics). Plasma, serum, and RBCs were processed and stored at ≤ −80°C until batch analysis after the end of data collection. Blood samples were stored in a portable freezer unit (set to 4–6°C) immediately after collection until they were processed (≤4 h). After being allowed to reach room temperature, the K2EDTA vacutainers were remixed by inversion (10 times) and then aliquots were taken for analysis via both the AHA (700–800 μL) and the HemoCue device (1 drop, ~30 μL). A single drop of blood was taken from the K2EDTA vacutainer with a pipette and then placed on a glass slide. The microcuvettes were filled (10 μL) from the glass slide in 1 continuous process, and excess blood was wiped off. Microcuvettes were analyzed within 40 s of preparation.

Serum ferritin (SF) concentrations were measured by electrochemiluminescence (E411, Roche Diagnostics). Serum soluble transferin receptor (sTfR), C-reactive protein (CRP), and α−1 acid glycoprotein (AGP) concentrations were analyzed via the Roche COBAS Integra 400 plus analyzer (Roche Diagnostics). Red blood cell (RBC) folate and serum folate concentrations were measured using the WHO-recommended microbiologic assay (Bangalore, India). Serum total vitamin B-12 concentrations were assessed via chemiluminescence (E411, Roche Diagnostics). Plasma methylmalonic acid (MMA) and homocysteine (Hcy) were assessed by GC-MS (5975, Agilent Technologies).

Instrument calibration and quality control

One HemoCue device (i.e., HemoCue 301) was used for all sample analyses. The same HemoCue and AHA instruments were used for the duration of the study, and standardized protocols recommended by the instrument manufacturer were followed for instrument calibration and performance maintenance. Quality controls were performed each month for the HemoCue (Eurotrol Hb 301 controls Low/normal/high) and AHA. Protocols for repeating controls and adjusting as needed were in place if any controls registered outside of the acceptable range. No control results were outside of the acceptable range for the HemoCue or AHA during the study.

HemoCue.—The HemoCue cuvette holder was cleaned daily at the end of sample processing with alcohol (or mild detergent) in accordance with the operating manual, and the optical unit on the analyzer was cleaned on the first day of each month. Disposable microcuvettes for the HemoCue were stored in a temperature- and humidity-controlled room, examined to verify their expiration date before use, used once, and discarded. Before analysis, the microcuvette was examined to ensure it was completely filled and void of air bubbles. If the microcuvette had insufficient sample or visible air bubbles, it was discarded and a new microcuvette was used. The same laboratory technicians analyzed 91.1% of the blood samples using the HemoCue (MPR) and 100% of the blood samples using the AHA (SY).

Definitions of variables

Iron status.—Anemia was defined as Hb <12.0 g/dL and severe anemia as Hb <8.0 g/dL (14). Iron deficiency (ID) was defined as SF <15.0 μg/L; iron insufficiency was defined as SF <20.0 μg/L (35). Body iron index was estimated using an equation proposed by Cook et al. (36) after converting the Roche sTfR data from this study to data equivalent to the original Flowers ELISA assay (37) used in the development of the body iron model via the equation Flowers sTfR = 1.5*Roche sTfR + 0.35 mg/L (38). Elevated inflammatory biomarkers were defined as CRP >5.0 mg/L or AGP >1.0 g/L (39); additional definitions of CRP >3.0 mg/L and >1.0 mg/L (40, 41) were also considered.

Folate and vitamin B-12 status.—Folate deficiency was defined as RBC folate <305 nmol/L (i.e., risk of macrocytic anemia), and folate insufficiency was defined as RBC folate <748 nmol/L (i.e., the recommended calibrator-adjusted equivalent of the threshold for optimal neural tube defect prevention) (42–44). Vitamin B-12 deficiency and vitamin B-12 insufficiency were defined as total serum vitamin B-12 <148 pmol/L and <221 pmol/L, respectively (45, 46). Elevated MMA was defined as MMA >0.26 μmol/L and MMA >0.37 μmol/L (46, 47), and impaired vitamin B-12 status was defined as total vitamin B-12 <148 pmol/L and MMA >0.26 μmol/L (or vitamin B-12 <148 pmol/L and MMA >0.37 μmol/L). Elevated Hcy was defined as Hcy >15.0 μmol/L and >10.0 μmol/L (43).

Metabolic and anthropometric characteristics.—BMI was calculated as weight (kg) divided by height (m) squared and categorized using WHO criteria (i.e., BMI <18.5, 18.5 to <25.0, 25.0 to <30.0, ≥ 30.0 kg/m^2) and using cutoffs identified in Asian populations as being associated with increased health risks (i.e., BMI <18.5, 18.5 to <23.0, 23.0 to <27.5, and ≥27.5 kg/m^2) (48). Additional anthropometric measurements (e.g., elevated waist circumference and elevated waist-hip ratio (WHR)) were defined using WHO criteria (49), and elevated whole-body fat and trunk fat percentages were defined based on criteria suggested by the American Association of Clinical Endocrinology (50). HbA1c concentrations were categorized as <5.7% (normal), ≥5.7% to <6.5% (prediabetes), and ≥6.5% (diabetes) using WHO and American Diabetes Association criteria (51, 52); HbA1c ≥5.7% (compared with <5.7%) was also considered in analyses.

Statistical analyses

Hb concentrations were adjusted for self-reported smoking status, as recommended by the WHO (14). Continuous biomarker variables were ln-transformed before analyses. Biomarker results outside the assay limits of detection (LOD) were set to half the LOD (if below the LOD) or 2 times the LOD (if above the LOD). SF concentrations were adjusted for inflammation, using Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) methods (53, 54). Geometric means (GMs) and 95% CIs were calculated to facilitate statistical inference.

Diagnostic accuracy parameters, including sensitivity, specificity, NPV, PPV, and accuracy, were calculated to evaluate the performance of HemoCue compared to the AHA reference. HemoCue diagnostic accuracy was examined using receiver operating characteristic curves.

Bland–Altman methods (i.e., mean difference, SD of differences (SDd), limits of agreement (mean difference ± 2 SDd)) (55) were used to evaluate the agreement between Hb concentrations measured via HemoCue and the AHA reference. Schuirmann's two 1-sided tests method was used to evaluate equivalency between Hb concentrations assessed via HemoCue and AHA. A ± 7% threshold (16, 56) was used to examine differences in paired Hb results and differences in the overall mean, evaluated by HemoCue and AHA. Additional threshold differences of 0.5 g/dL and 1.0 g/dL were also considered.

Sensitivity analyses were performed by restricting the sample to HemoCue analyses conducted by the main laboratory technician. Analyses were also conducted within subsets of participants including stratification by rural residence, self-reported smoking status, Hb ≥8.0 g/dL (via AHA), and age (≥18 y, <18 y). Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc.). Analyses were reproduced by Cornell Results Reproduction (R^2) at the Cornell Institute for Social and Economic Research.

Results

Table 1 presents characteristics of study participants, and Figure 1 presents a flowchart of study participants. Women with paired Hb data included in the analyses (n = 896; paired venous samples analyzed for Hb via HemoCue and AHA) were similar to women who provided a blood sample in the overall population-based biomarker survey (n = 979) in terms of most sociodemographic, nutritional, and anthropometric characteristics (Tables 1–3). Most participants lived in rural households (78.6%), were currently married (80.6%), and had some formal education (83.2%) although few reported finishing secondary school (11.0%). Among adults (≥18 y old), 19.3% were underweight (BMI <18.5 kg/m^2), 27.3% were overweight (BMI: 23.0 to <27.5 kg/m^2), and 20.3% had obesity (BMI ≥ 27.5 kg/m^2).

Hemoglobin

Table 4 presents Hb screening results analyzed via HemoCue and AHA methods, and Figure 2 presents the distributions of the Hb concentrations by method. The same laboratory technician (MPR) conducted most of the analyses via HemoCue (91.1%; data not shown). Hb concentrations evaluated by HemoCue were higher compared to AHA (n = 896; HemoCue: GM: 12.1 g/dL; 95% CI: 12.0, 12.2 g/dL compared with AHA: GM: 11.9 g/dL;

95% CI: 11.7, 12.0 g/dL; two 1-sided tests: not equivalent) (Table 4), with an overall mean difference (HemoCue – AHA) of 0.21 g/dL (Figure 2, Table 4). The mean difference in paired Hb results ranged from −5.6 to +4.1 g/dL. The limits of agreement were −1.8 to 2.3 g/dL, and the magnitude of the differences appeared to increase at higher Hb concentrations (Table 4, Figure 3). Although 65.8% of paired samples were within the recommended ±7% threshold, 27.7% of results differed by a magnitude of ≥1.0 g/dL and 56.5% differed by ≥0.5 g/dL (Table 4). Findings from sensitivity analyses were similar to those of the overall analyses (Supplemental Tables 1–3).

Anemia

Table 4 also presents anemia screening results analyzed via HemoCue and AHA methods. The prevalence of anemia (Hb <12.0 g/dL) as evaluated by HemoCue was significantly lower than the AHA reference (36.3% compared with 41.6%; P <0.001). The prevalence of severe anemia (Hb <8.0 g/dL) as evaluated by HemoCue was not significantly different from the AHA reference (2.3% compared with 2.9%; P = 0.13) (Table 4).

Diagnostic accuracy parameters of anemia screening methods

Table 5 presents diagnostic accuracy parameters for anemia screening for HemoCue compared to the AHA reference. The HemoCue had 74.8% sensitivity, 91.2% specificity, 85.8% PPV, 83.5% NPV, and 84.4% accuracy for anemia screening, compared to the AHA reference (Supplemental Figures 1–3). When assessed via receiver operating characteristic curves (sensitivity plotted against 1 − specificity), the AUC was 0.893 for anemia and 0.997 for severe anemia (Supplemental Figure 4).

Diagnostic accuracy parameters by nutritional biomarkers.—Table 6 presents diagnostic accuracy parameters of the anemia screening methods by nutritional biomarkers.

Iron status.: HemoCue sensitivity and PPV were higher in individuals with ID (SF <15.0 compared with ≥15.0 μg/L) or low body iron index (body iron index <0.0 compared with ≥0.0 mg/kg). In contrast, HemoCue specificity and NPV were lower in WRA with ID or low body iron index (Table 6). Results were similar before adjusting SF for inflammation (data not shown).

Inflammation.: HemoCue sensitivity and accuracy were lower in WRA with CRP >1.0 mg/L (compared with ≤1.0 mg/L) or CRP >3.0 mg/L (compared with ≤3.0 mg/L). HemoCue PPV was lower in WRA with CRP >3.0 mg/L (compared with ≤3.0 mg/L). Diagnostic accuracy parameters did not differ by CRP > 5.0 mg/L or other inflammatory biomarkers (Table 6).

Vitamin B-12 and folate status.: HemoCue sensitivity, PPV, and accuracy were lower in WRA with elevated MMA (MMA >0.37 μmol/L compared with ≤0.37 μmol/L). HemoCue PPV was also lower in WRA with MMA >0.26 μmol/L (compared with ≤0.26 μmol/L) and HemoCue NPV was higher among WRA with RBC folate insufficiency (RBC folate <748 nmol/L compared with ≥748 nmol/L). Diagnostic accuracy parameters did not differ by other biomarkers of vitamin B-12 status or folate status (Table 6).

Diagnostic accuracy parameters by metabolic risk factors.—Table 7 presents diagnostic accuracy parameters of the anemia screening methods by metabolic risk factors. The sensitivity of the HemoCue was lower in WRA with overweight based on WHO criteria (BMI ≥25.0 compared with <25.0 kg/m^2) or cutoffs for South Asian populations (BMI ≥23.0 compared with <23.0 kg/m^2). HemoCue sensitivity was also lower among WRA with elevated whole-body fat (>35% compared with ≤35%) or trunk fat (>35% compared with ≤35%). The HemoCue PPV was lower in WRA with elevated WHR (≥0.85 compared with <0.85). HemoCue accuracy was lower in WRA with overweight based on cutoffs for South Asian populations but did not differ by WHO criteria. Diagnostic accuracy parameters did not differ by elevated HbA1c or other metabolic risk factors (Table 7).

Discussion

In this population-based analysis of paired venous blood samples from WRA, the estimated prevalence of anemia was significantly lower (36.3% compared with 41.6%) when evaluated via portable hemoglobinometer (HemoCue 301) than via the AHA reference. A total of 84.4% of anemia and 98.8% of severe anemia screening results were concordant. The HemoCue sensitivity was higher in WRA with ID, and lower in WRA with metabolic risk factors, including overweight, CRP >1.0 or >3.0 mg/L, or elevated trunk or whole-body fat.

Hemoglobin

In this study, Hb concentrations assessed via HemoCue were significantly higher than those via the AHA reference. Although the overall mean difference was small (i.e., 0.2 g/dL), it ranged from −5.6 to +4.1 g/dL and this difference was ≥1.0 g/dL in 27.7% of paired samples. Findings are consistent with previous studies comparing screening methods of paired venous samples that reported higher Hb concentrations via HemoCue 301 than via the AHA reference (25–31), including studies in India in blood donors in Uttarakhand (n = 115) (27), women not accepted for blood donations in Mumbai (n = 147, 21–54 y) (25), and adults in a community-based study in Puducherry and Kolkata (n = 680, 18–60 y) (28); as well as in routine hematology analyses of whole blood samples in South Africa (n = 60) (26), and studies in children in Laos (n = 129, 15–32 mo) (29), pregnant women (n = 499, 18–45 y) (30) and children in the Gambia (n = 371, 6–24 mo) (30), and a refugee population in the United States (n = 299, 10 mo–60 y) (31). These studies reported higher Hb concentrations when evaluated by HemoCue 301 than by the AHA reference, although some did not report significance testing (25–28, 30) or magnitude of differences (57).

Anemia

In the current study, the estimated prevalence of anemia via HemoCue 301 was significantly lower than that via the AHA reference (i.e., 36.3% compared with 41.6%). On an individual level, women with anemia may be incorrectly classified as not anemic (false negative) by portable hemoglobinometer and this has implications for follow-up. From a public health perspective, the prevalence of anemia may be underestimated at the population level. The estimated prevalence of anemia in this population is consistent with previous population-based studies in WRA in India when assessed by CMH or AHA (28–58.7%) (58, 59), but lower than recent state-level NFHS data for nonpregnant WRA (15–49 y;

HemoCue 201+; NFHS-5 2019–2020: 59%; NFHS-4 2015–2016: 60.2%) (13). The lower estimated anemia prevalence via HemoCue observed here is consistent with previous studies evaluating venous blood via HemoCue 301 in comparison to the AHA reference, including whole blood samples submitted for routine laboratory analyses in South Africa (Hb <12.0 g/dL; HemoCue compared with AHA: 44% compared with 49%) (26), children in Laos (Hb <11.0g/dL; 36.4% compared with 65.9%) (29), pregnant women (Hb <11.0 g/dL; 37.1% compared with 54.5%) and children (Hb <11.0 g/dL; 63.9% compared with 84.4%) from the Gambia (30), and a refugee population in the United States (8.7% compared with 12.5%) (31); although significance testing was not reported in some studies (26, 30, 31).

Studies to date evaluating paired venous blood samples using the HemoCue 301 have consistently reported higher Hb concentrations and lower estimated anemia prevalence via HemoCue than via the AHA reference (25–31). In contrast, findings from studies evaluating paired venous samples on other HemoCue models (e.g., HemoCue B-Hb, HemoCue 201+, HemoCue 801, HB Donor Checker, or unspecified HemoCue model) have been heterogeneous, including higher (31, 60–68), lower (27, 68, 69), or not significantly different (60, 67, 68) Hb concentrations via HemoCue compared to the AHA and lower (31, 61), similar (60, 69), or higher estimated prevalence of anemia via HemoCue compared to the AHA, although statistical significance was not reported in some studies (27, 31, 60, 61, 63, 64, 69). A laboratory study of paired venous samples analyzed on the HemoCue 201+ compared with the HemoCue 301 found higher (2.6%) Hb concentrations on the HemoCue 301 than on the HemoCue 201+ (70). Methodological differences in Hb assessment between HemoCue models, such as measuring Hb absorbance in whole blood as opposed to lysed RBCs—which relies on cuvettes that are more susceptible to temperature and humidity (70, 71)—constrain the comparability of findings across studies using different HemoCue models (71).

Diagnostic accuracy parameters of anemia screening methods

In the current study, HemoCue sensitivity was 74.8% and specificity was 91.2%. To date, 13 studies (25, 26, 28, 31, 60, 64, 68, 69, 72–76) have evaluated diagnostic accuracy parameters of anemia screening methods, of which 8 used a HemoCue 301 (25, 26, 28, 31, 64, 72, 75, 76) and 4 (25, 26, 28, 31) analyzed paired venous blood samples using the HemoCue 301 compared to the AHA reference, with which our results are directly comparable. In studies in populations in India, South Africa, and the United States, the reported sensitivity (85.3%–99%) (25, 26, 28) and specificity (97.6%–100%) (26, 28, 31) of the HemoCue 301 were higher than observed here; in contrast, reported sensitivity (54.7%) (31), and specificity (52%) (25) were lower in studies in a refugee population in the United States (31) and in women not accepted for blood donations in India (25).

Diagnostic accuracy parameters of anemia screening methods by nutritional status.—In the current study, HemoCue sensitivity for anemia was higher in WRA with ID (defined as SF <15.0 μg/L, body iron index <0.0 mg/kg) than in WRA without ID (81.6% compared with 41.3%); whereas specificity was lower in WRA with ID (86.4% compared with 95.1%). In contrast, findings did not vary by other nutritional biomarkers, including RBC folate or vitamin B-12 deficiency. Few studies have been conducted to date to examine

factors associated with HemoCue performance. In a survey in Uttar Pradesh, India (n = 977 nonpregnant women, ~52% ID), anemia classification did not differ by iron status, although sensitivity and specificity were not reported (18), and methodological differences (venous compared with capillary Hb; HemoCue 201+) constrain the comparability of findings.

Diagnostic accuracy parameters of anemia screening methods by metabolic risk factors.—In the current study, HemoCue sensitivity was lower in WRA with overweight (BMI ≥25.0 or ≥23.0 kg/m^2), CRP >1.0 or >3.0 mg/L, and elevated trunk or whole-body fat, although HemoCue specificity was similar across these categories. Few studies to date have examined metabolic factors associated with HemoCue performance. In 1 study in the United Kingdom comparing paired venous samples analyzed via HemoCue 301 or the AHA (57), it was noted that increased bilirubin (>100.0 μmol/L) and/or elevated CRP (>20.0 mg/L) appeared to influence HemoCue Hb assessment, but no consistent trend was identified.

Strengths

This analysis of paired venous samples from a population-based biomarker survey in WRA is among the largest of its kind, in a population at high risk of anemia. To our knowledge, this is among the first studies to date to evaluate diagnostic accuracy parameters of the HemoCue 301 by nutritional and metabolic characteristics of importance for WRA. This study leverages a well-characterized population with gold-standard biomarker assessment and comprehensive assessment of nutritional and metabolic characteristics. The use of paired venous samples, quality control measures, and analyses by the same laboratory instruments (e.g., the same HemoCue 301 device) and technician minimized variability between samples.

Limitations

This study has several limitations. The cross-sectional study design does not enable evaluation of effects of nutritional or metabolic characteristics on anemia assessment. The WHO defines WRA as women aged 15–49 y; the current study focuses on a subset of this age range: women aged 15–40 y who were not currently pregnant or lactating. This in an important study limitation that may constrain comparability with other studies with heterogeneous definitions of WRA. The low prevalence of severe anemia (2.9%) limited the evaluation of HemoCue performance for severe anemia. The observed differences in variability between HemoCue and AHA at lower and higher Hb concentrations could not be fully investigated, owing to the small number of participants at the lower end of the Hb distributions, and this is an important study limitation. Analysis of both capillary and paired venous samples, inclusion of RBC morphology (microcytosis, macrocytosis), additional replicates of sample analyses prospectively by different methods, and evaluation in populations with wider variation in Hb concentrations would improve generalizability.

Conclusion

In summary, in this analysis of paired venous samples from a population-based biomarker survey in WRA in southern India, the estimated anemia prevalence via portable hemoglobinometer (HemoCue 301) was lower than via the AHA reference and may

underestimate the prevalence of anemia at the population level. HemoCue sensitivity for anemia was higher in WRA with ID and lower in WRA with metabolic risk factors. The substantial burden of anemia and ID in WRA in this population and the variation in anemia assessment by screening method suggest an opportunity for prospective evaluation of screening methods and interventions for prevention of anemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors' responsibilities were as follows—JLF: designed the research and had primary responsibility for the final content; AF: wrote the initial draft manuscript and conducted the statistical analyses; JLF and KSC: revised the manuscript; WB, CBJ, and AF: supervised the data collection and field activities; BB and MPR: conducted the laboratory analyses; and all authors: contributed to the development of the manuscript, provided feedback, and read and approved the final manuscript.

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Abbreviations used:

AGP	α−1 acid glycoprotein
AHA	automated hematology analyzer
CMH	cyanmethemoglobin method
GM	geometric mean
Hb	hemoglobin
Hcy	homocysteine
ID	iron deficiency
LOD	limits of detection
MMA	methylmalonic acid
NFHS	National Family Health Survey
NPV	negative predictive value
PPV	positive predictive value
SDd	SD of differences

sTfR	soluble transferrin receptor
WHR	waist-hip ratio
WRA	women of reproductive age

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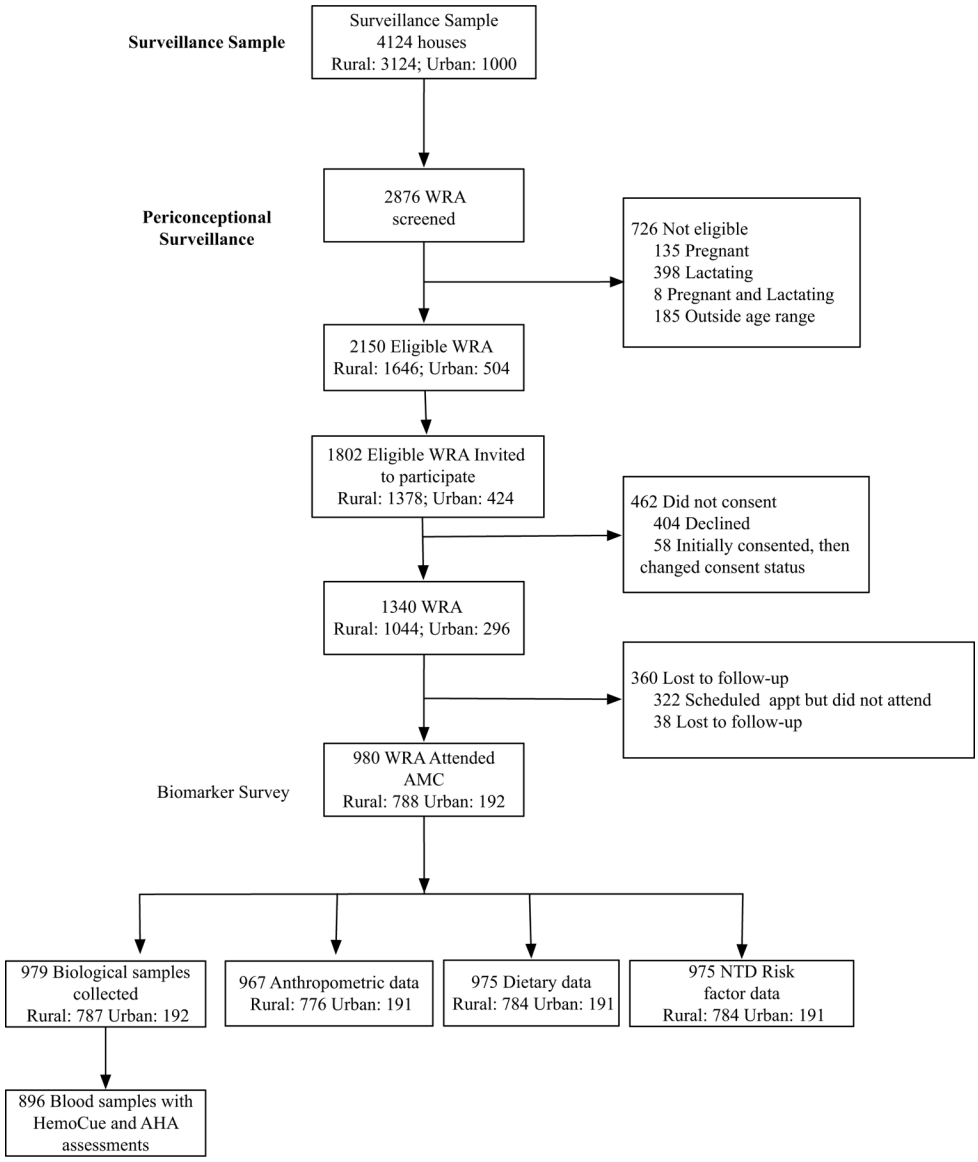

FIGURE 1.

Participant flowchart. AHA, automated hematology analyzer; AMC, Arogyavaram Medical Center; NTD, neural tube defect; WRA, women of reproductive age.

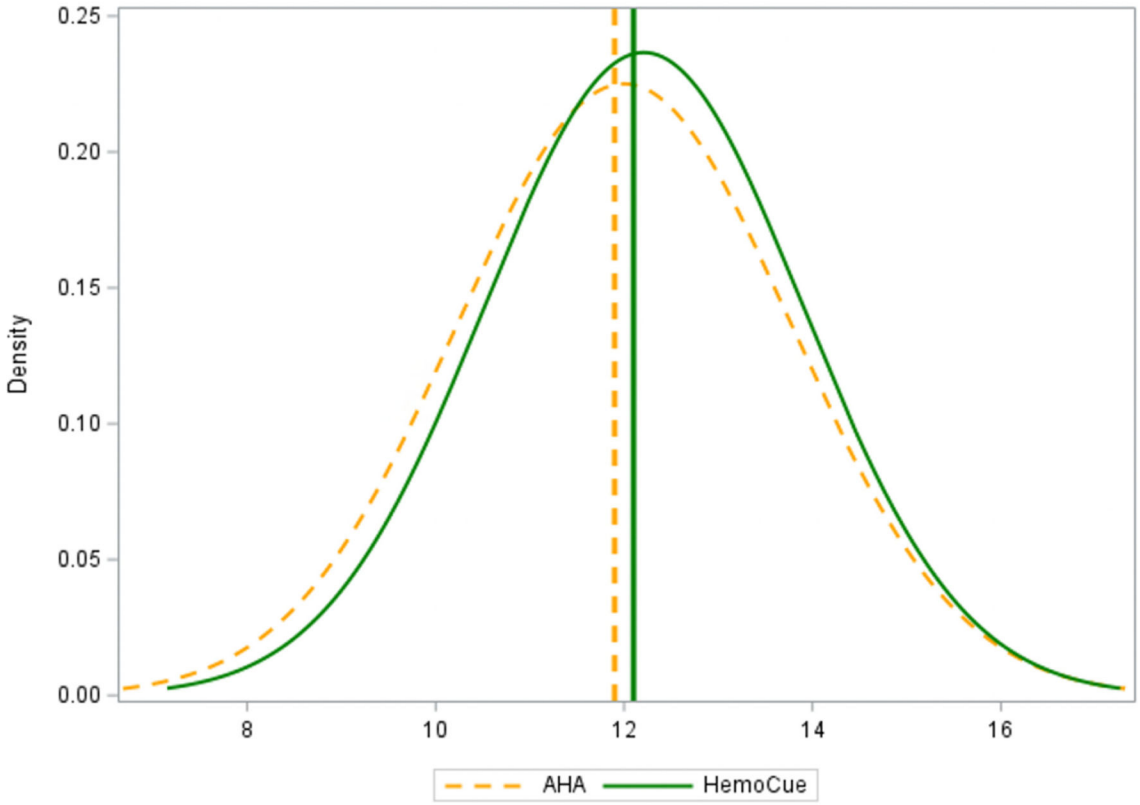

FIGURE 2.
Distribution of hemoglobin concentrations (g/dL) assessed via HemoCue and AHA. AHA, automated hematology analyzer.

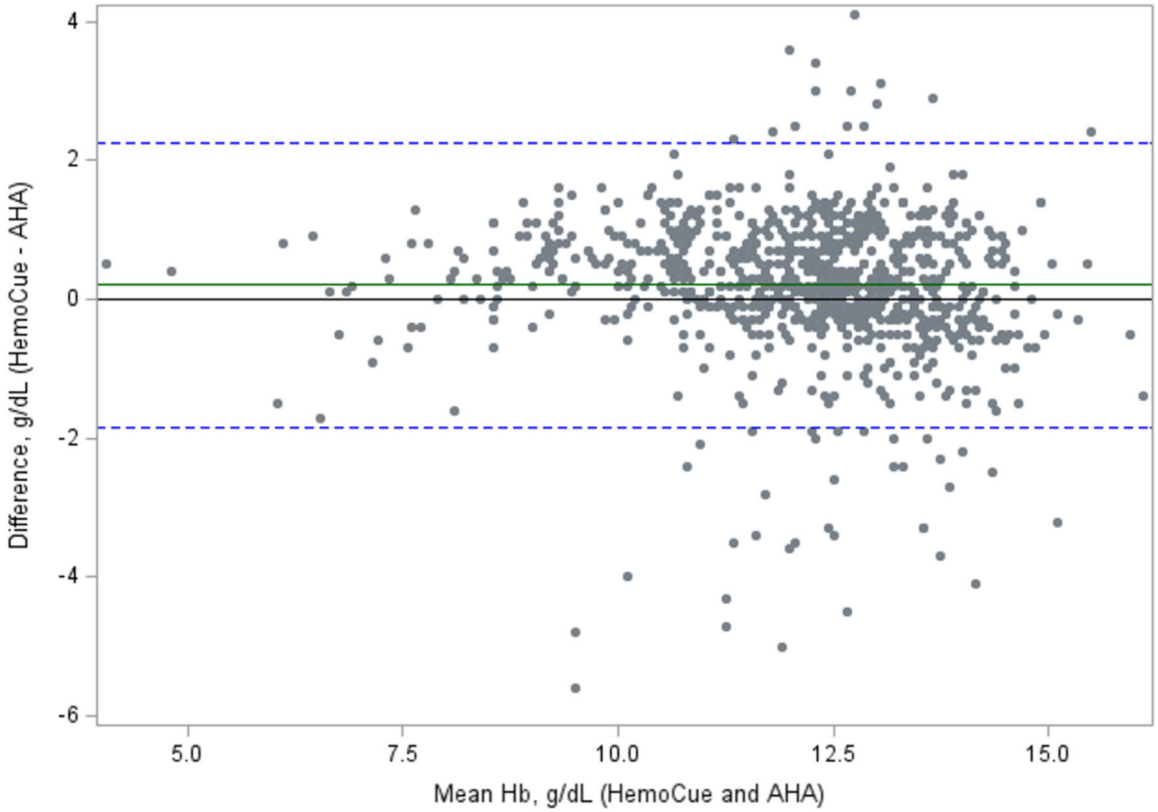

FIGURE 3.

Bland–Altman plot of differences in Hb concentrations as evaluated by HemoCue and AHA methods (HemoCue – AHA) compared with the mean Hb concentrations. The solid line represents the mean difference (HemoCue – AHA; 0.2 g/dL) and dashed lines represent the limits of agreement (±2 SD of the difference: −1.8, 2.3 g/dL). AHA, automated hematology analyzer; Hb, hemoglobin.

TABLE 1

Sociodemographic characteristics of the study population[1]

Sociodemographic variables	*n*	Total (*n* = 979) GM (95% CI) or *n* (%)	Paired Hb sample (*n* = 896) GM (95% CI) or *n* (%)
Rural	979	787 (80.4)	704 (78.6)
Age, y	979	28.8 (28.4, 29.3)	29.0 (28.5, 29.5)
15 to <18		49 (5.0)	44 (4.9)
18 to <26		229 (23.4)	198 (22.1)
26 to <36		453 (46.3)	421 (47.0)
36–40		248 (25.3)	233 (26.0)
Current smoker	974	49 (5.0)	46 (5.2)
Highest level of education completed	974		
No formal schooling		158 (16.2)	150 (16.8)
Grades 1–5		173 (17.8)	167 (18.7)
Grades 6–8		177 (18.2)	162 (18.2)
Grades 9–10		207 (21.3)	192 (21.5)
Grades 11–12		106 (10.9)	98 (11.0)
College or graduate degree		153 (15.7)	122 (13.7)
Marital status	974		
Currently married		774 (79.5)	718 (80.6)
Widowed, divorced, separated		35 (3.6)	34 (3.8)
Never married		165 (16.9)	139 (15.6)
Parity	974		
Nulliparous		230 (23.6)	195 (21.9)
Primiparous		90 (9.2)	86 (9.7)
Multiparous		654 (67.1)	610 (68.5)
Dietary preference[2]	973		
Vegan		3 (0.3)	3 (0.3)
Vegetarian		64 (6.6)	57 (6.4)
Vegan or vegetarian		67 (6.9)	60 (6.7)
Nonvegetarian		906 (93.1)	830 (93.3)

[1] GM, geometric mean; Hb, hemoglobin.

[2] Vegetarian: consumed milk and/or eggs; nonvegetarian: consumed poultry, meat, and/or fish.

TABLE 2

Nutritional biomarkers in the study population[1]

Variables	*n*	Total (*n* = 979) GM (95% CI) or *n* (%)	Paired Hb sample (*n* = 896) GM (95% CI) or *n* (%)
SF, μg/L	978	16.8 (15.8, 17.9)	17.2 (16.1, 18.3)
<15.0		453 (46.3)	406 (45.3)
<20.0		538 (55.0)	485 (54.1)
Serum sTfR, mg/L	976	5.4 (5.3, 5.6)	5.4 (5.3, 5.6)
>5.3		443 (45.4)	407 (45.5)
Body iron index,[2] mg/kg	976	1.0 (0.7, 1.3)	1.1 (0.7, 1.4)
<0.0		397 (40.7)	358 (40.0)
Serum CRP, mg/L	978	1.2 (1.1, 1.4)	1.3 (1.1, 1.4)
>1.0		553 (56.5)	513 (57.3)
>3.0		292 (29.9)	271 (30.2)
>5.0		169 (17.3)	157 (17.5)
Serum AGP, g/L	976	0.8 (0.8, 0.8)	0.8 (0.8, 0.8)
>1.0		217 (22.2)	199 (22.3)
SF,[3] μg/L	976	10.5 (9.9, 11.2)	10.7 (10.1, 11.4)
<15.0		600 (61.5)	544 (60.9)
<20.0		710 (72.7)	645 (72.1)
Body iron index,[2,3] mg/kg	976	− 0.7 (−1.0, −0.4)	− 0.6 (−1.0, −0.3)
<0.0		507 (51.9)	456 (51.0)
RBC folate,[4] nmol/L	977	540.5 (526.2, 555.1)	545.7 (530.7, 561.1)
<305		74 (7.6)	65 (7.3)
<748		775 (79.3)	706 (78.9)
Serum folate,[4] nmol/L	977	16.5 (16.0, 17.0)	16.4 (15.8, 16.9)
<7.0		34 (3.5)	32 (3.6)
Plasma homocysteine, μmol/L	979	6.6 (6.4, 6.8)	6.6 (6.4, 6.8)
>10.0		157 (16.0)	139 (15.5)
>15.0		65 (6.6)	61 (6.8)

Variables	*n*	Total (*n* = 979) GM (95% CI) or *n* (%)	Paired Hb sample (*n* = 896) GM (95% CI) or *n* (%)
Serum vitamin B-12, pmol/L	978	156.0 (150.3, 162.0)	157.4 (151.3, 163.6)
<148		472 (48.3)	428 (47.8)
<221		727 (74.3)	660 (73.7)
Plasma methylmalonic acid (MMA), μmol/L	979	0.3 (0.3, 0.3)	0.3 (0.3, 0.4)
>0.26		593 (60.6)	537 (59.9)
>0.37		433 (44.2)	400 (44.6)
Impaired vitamin B-12 status	978		
Vitamin B-12 <148 pmol/L and MMA >0.26 μmol/L		370 (37.8)	332 (37.1)
Vitamin B-12 <148 pmol/L and MMA >0.37 μmol/L		286 (29.2)	263 (29.4)

[1] Results outside the assay LOD were set to 0.50∗LOD (if below the LOD) or 2∗LOD (if above the LOD). Results outside assay LODs: sTfR (*n* = 4 above the upper LOD of 20 mg/L), CRP (*n* = 7 below the lower LOD of 1.0 mg/L), serum folate (*n* = 1 below the lower LOD of 1.7 nmol/L), vitamin B-12 (*n* = 4 below the lower LOD of 36.9 pmol/L, *n* = 6 above the upper LOD of 1475.6 pmol/L). AGP, α−1 acid glycoprotein; GM, geometric mean; Hb, hemoglobin; LOD, limits of detection; SF, serum ferritin; sTfR, soluble transferrin receptor.

[2] Body iron index (mg/kg) was estimated using Cook et al.'s equation (36) (–{$\log_{10}$ [sTfR(Ramco; mg/L) × 1000/SF(μg/L)] – 2.8229}/0.1207) after converting sTfR to Flowers Ramco equivalents [Ramco = (1.5∗Roche) +0.35] (38).

[3] SF adjusted for inflammation via Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) methods (53).

[4] Assessed via microbiologic assay.

TABLE 3

Anthropometric characteristics of the study population[1]

Variables	*n*	Total (*n* = 979) GM (95% CI) or *n* (%)	Paired Hb sample (*n* = 896) GM (95% CI) or *n* (%)
Weight, kg	968	53.0 (52.2, 53.8)	53.0 (52.2, 53.8)
Height, cm	968	153.3 (152.9, 153.6)	153.2 (152.8, 153.6)
BMI, kg/m^2	968	22.6 (22.3, 22.9)	22.6 (22.3, 22.9)
BMI[2,3]	919		
<18.5		176 (19.2)	162 (19.3)
18.5 to <25.0		440 (47.9)	399 (47.4)
25.0 to <30.0		215 (23.4)	194 (23.1)
≥30.0		88 (9.6)	86 (10.2)
<25.0		616 (67.0)	561 (66.7)
≥25.0		303 (33.0)	280 (33.3)
BMI[2,4]	919		
<18.5		176 (19.2)	162 (19.3)
18.5 to <23.0		308 (33.5)	278 (33.1)
23.0 to <27.5		253 (27.5)	230 (27.3)
≥27.5		182 (19.8)	171 (20.3)
<23.0		484 (52.7)	440 (52.3)
≥23.0		435 (47.3)	401 (47.7)
Midupper arm circumference, cm	968	26.7 (26.5, 27.0)	26.8 (26.5, 27.1)
Waist circumference, cm	968	74.6 (73.9, 75.4)	74.8 (74.0, 75.5)
>88.9[2]	919	123 (13.4)	115 (13.7)
>80.0[2]	919	329 (35.8)	309 (36.7)
Waist-hip ratio[2,5]	919	0.8 (0.8, 0.8)	0.8 (0.8, 0.8)
≥0.80		443 (48.2)	408 (48.5)
≥0.85		191 (20.8)	173 (20.6)
Whole-body fat mass,[2,5] %	921	30.6 (30.0, 31.3)	30.6 (30.0, 31.3)
>35		362 (39.3)	333 (39.5)

Variables	*n*	Total (*n* = 979) GM (95% CI) or *n* (%)	Paired Hb sample (*n* = 896) GM (95% CI) or *n* (%)
Trunk fat mass,[2,5] %	921	27.8 (27.0, 28.7)	27.8 (26.9, 28.7)
>35		334 (36.3)	307 (36.4)
HbA1c,[6] %		5.4 (5.4, 5.5)	5.4 (5.4, 5.5)
<5.7	979	734 (75.0)	671 (74.9)
≥5.7 to <6.5		196 (20.0)	182 (20.3)
≥6.5		49 (5.0)	43 (4.8)

[1] GM, geometric mean; Hb, hemoglobin.

[2] Among participants ≥18 y old (*n* = 852).

[3] BMI categories as defined by the WHO (77).

[4] BMI categories for Asian populations (48).

[5] Anthropometric and bioelectrical impedance cutoffs from WHO and NHLBI criteria (49, 78, 79).

[6] HbA1c cutoffs per the American Diabetes Association (51).

TABLE 4

Hb and anemia screening results via HemoCue and AHA methods[1]

Variables	GM (95% CI) or *n* (%)
Hb concentrations, g/dL	
HemoCue	12.1 (12.0, 12.2)
AHA	11.9 (11.7, 12.0)
Difference between Hb concentrations via screening methods (HemoCue – AHA), g/dL	0.21 (0.14, 0.28)[2]
Difference ≥ 0.5 g/dL	506 (56.5)
Difference ≥ 1.0 g/dL	248 (27.7)
Difference > 7%	306 (34.2)
Anemia (Hb <12.0 g/dL)	
HemoCue	325 (36.3)
AHA	373 (41.6)
Concordant	756 (84.4)[3]
Severe anemia (Hb <8.0 g/dL)	
HemoCue	21 (2.3)
AHA	26 (2.9)
Concordant	885 (98.8)[3]

[1] $n = 896$. Hb concentrations adjusted for smoking status (14). AHA, automated hematology analyzer; Hb, hemoglobin.

[2] Range of differences: −5.6 to 4.1 g/dL (SD of differences: 1.02); limits of agreement (±2SD): −1.8, 2.3 g/dL; Schuirmann's two 1-sided tests method was used to compare Hb means between assessment methods: not equivalent.

[3] McNemar's tests were used to evaluate differences in overall anemia ($P < 0.0001$) and severe anemia ($P = 0.13$).

TABLE 5

Diagnostic accuracy parameters of anemia screening methods[1]

Diagnostic accuracy parameters	% (95% CI)
Anemia (Hb <12.0 g/dL)	
Sensitivity	74.8 (70.4, 79.2)
Specificity	91.2 (88.8, 93.6)
PPV	85.8 (82.1, 89.6)
NPV	83.5 (80.5, 86.6)
Accuracy	84.4 (82.0, 86.8)
Severe anemia (Hb <8.0g/dL)	
Sensitivity	69.2 (51.5, 87.0)
Specificity	99.7 (99.3, 100.0)
PPV	85.7 (70.7, 100.0)
NPV	99.1 (98.5, 99.7)
Accuracy	98.8 (98.1, 99.5)

[1]HemoCue compared with automated hematology analyzer reference; Hb adjusted for smoking status (14). Hb, hemoglobin; NPV, negative predictive value; PPV, positive predictive value.

TABLE 6

Diagnostic accuracy parameters of anemia screening methods by nutritional biomarkers[1]

Diagnostic accuracy parameter		
SF,[2] μg/L	<15.0	≥15.0
Sensitivity	81.6 (77.2, 85.9)	41.3 (29.1, 53.4)
Specificity	86.4 (82.0, 90.8)	95.1 (92.6, 97.6)
PPV	88.7 (85.1, 92.4)	65.0 (50.2, 79.8)
NPV	78.1 (73.0, 83.1)	88.1 (84.5, 91.7)
Accuracy	83.6 (80.5, 86.7)	85.4 (81.7, 89.1)
Body iron index,[2,3] mg/kg	<0.0	≥0.0
Sensitivity	84.7 (80.6, 88.9)	40.5 (30.0, 51.0)
Specificity	85.1 (79.7, 90.5)	94.1 (91.6, 96.5)
PPV	90.7 (87.2, 94.2)	61.8 (49.0, 74.7)
NPV	76.5 (70.4, 82.6)	86.9 (83.6, 90.3)
Accuracy	84.9 (81.6, 88.2)	83.8 (80.3, 87.2)
CRP, mg/L	>1.0	≤1.0
Sensitivity	67.2 (60.5, 73.8)	82.9 (77.4, 88.4)
Specificity	91.3 (88.2, 94.4)	91.1 (87.2, 95.0)
PPV	82.2 (76.2, 88.2)	89.3 (84.6, 94.0)
NPV	82.3 (78.3, 86.3)	85.6 (80.9, 90.3)
Accuracy	82.3 (79.0, 85.6)	87.2 (83.9, 90.6)
CRP	>3.0	≤3.0
Sensitivity	62.2 (52.6, 71.8)	79.3 (74.5, 84.1)
Specificity	90.2 (85.7, 94.6)	91.7 (88.8, 94.6)
PPV	78.2 (69.0, 87.4)	88.3 (84.2, 92.3)
NPV	80.8 (75.3, 86.4)	84.9 (81.3, 88.5)
Accuracy	80.1 (75.3, 84.8)	86.2 (83.5, 88.9)
CRP	>5.0	≤5.0
Sensitivity	64.3 (51.7, 76.8)	76.7 (72.0, 81.3)
Specificity	91.1 (85.5, 96.6)	91.2 (88.5, 93.9)
PPV	80.0 (68.3, 91.7)	86.8 (82.8, 90.8)

Diagnostic accuracy parameter		
NPV	82.1 (75.0, 89.2)	83.9 (80.5, 87.2)
Accuracy	81.5 (75.5, 87.6)	85.0 (82.4, 87.6)
α−1-Acid glycoprotein, g/L	>1.0	≤1.0
Sensitivity	75.0 (65.0, 85.0)	74.7 (69.7, 79.6)
Specificity	92.1 (87.4, 96.8)	90.9 (88.0, 93.7)
PPV	84.4 (75.5, 93.3)	86.2 (82.0, 90.4)
NPV	86.7 (80.9, 92.4)	82.5 (79.0, 86.1)
Accuracy	85.9 (81.1, 90.8)	83.9 (81.2, 86.6)
Vitamin B-12, pmol/L	<148	≥148
Sensitivity	73.0 (66.2, 79.8)	76.2 (70.4, 82.0)
Specificity	91.3 (87.9, 94.7)	91.1 (87.6, 94.6)
PPV	83.8 (77.7, 89.9)	87.4 (82.6, 92.2)
NPV	84.6 (80.4, 88.8)	82.5 (78.0, 86.9)
Accuracy	84.3 (80.9, 87.8)	84.4 (81.1, 87.7)
Vitamin B-12, pmol/L	<221	≥221
Sensitivity	74.7 (69.5, 79.9)	75.0 (66.7, 83.3)
Specificity	91.3 (88.5, 94.1)	90.9 (86.0, 95.8)
PPV	85.5 (81.0, 90.0)	86.7 (79.6, 93.7)
NPV	84.0 (80.5, 87.5)	82.2 (76.0, 88.4)
Accuracy	84.5 (81.8, 87.3)	83.9 (79.2, 88.6)
MMA, μmol/L	>0.26	≤0.26
Sensitivity	72.9 (66.9, 79.0)	77.1 (70.7, 83.5)
Specificity	90.0 (86.8, 93.2)	93.3 (89.7, 96.8)
PPV	82.1 (76.5, 87.6)	90.8 (86.0, 95.6)
NPV	84.1 (80.3, 87.9)	82.6 (77.5, 87.6)
Accuracy	83.4 (80.3, 86.6)	85.8 (82.2, 89.4)
MMA	>0.37	≤0.37
Sensitivity	69.3 (62.0, 76.6)	78.6 (73.2, 84.1)
Specificity	89.1 (85.2, 93.0)	93.1 (90.1, 96.1)
PPV	79.7 (72.9, 86.5)	90.1 (85.9, 94.3)
NPV	82.4 (77.8, 87.0)	84.5 (80.5, 88.6)

Diagnostic accuracy parameter		
Accuracy	81.5 (77.7, 85.3)	86.7 (83.7, 89.7)
Vitamin B-12 <148 pmol/L and MMA >0.26 μmol/L	Yes	No
Sensitivity	69.7 (61.5, 78.0)	77.2 (72.0, 82.3)
Specificity	89.7 (85.6, 93.8)	92.3 (89.3, 95.2)
PPV	79.0 (71.3, 86.8)	89.1 (85.0, 93.2)
NPV	84.1 (79.4, 88.9)	83.1 (79.2, 87.1)
Accuracy	82.5 (78.4, 86.6)	85.5 (82.6, 88.4)
Vitamin B-12 <148 pmol/L and MMA >0.37 μmol/L	Yes	No
Sensitivity	66.7 (57.1, 76.2)	77.5 (72.6, 82.4)
Specificity	88.8 (84.1, 93.6)	92.4 (89.6, 95.1)
PPV	76.5 (67.3, 85.8)	88.9 (85.0, 92.9)
NPV	83.0 (77.5, 88.4)	83.8 (80.1, 87.5)
Accuracy	81.0 (76.2, 85.7)	85.8 (83.1, 88.5)
RBC folate,[4] nmol/L	<305	≥305
Sensitivity	75.0 (56.0, 94.0)	74.8 (70.3, 79.3)
Specificity	88.9 (79.7, 98.1)	91.6 (89.1, 94.1)
PPV	75.0 (56.0, 94.0)	86.8 (83.0, 90.6)
NPV	88.9 (79.7, 98.1)	83.1 (79.9, 86.3)
Accuracy	84.6 (75.8, 93.4)	84.5 (82.0, 86.9)
RBC folate[4]	<748	≥748
Sensitivity	75.2 (70.0, 80.4)	73.9 (65.7, 82.0)
Specificity	91.7 (89.1, 94.2)	89.7 (83.0, 96.5)
PPV	84.2 (79.5, 88.9)	91.1 (85.2, 97.0)
NPV	86.2 (83.1, 89.3)	70.7 (61.7, 79.7)
Accuracy	85.6 (83.0, 88.1)	80.4 (74.8, 86.1)
Serum folate,[4] nmol/L	<7.0	≥7.0
Sensitivity	69.2 (44.1, 94.3)	75.0 (70.5, 79.5)
Specificity	89.5 (75.7, 100.0)	91.5 (89.0, 93.9)
PPV	81.8 (59.0, 100.0)	86.3 (82.4, 90.1)
NPV	81.0 (64.2, 97.7)	83.6 (80.5, 86.7)

Diagnostic accuracy parameter		
Accuracy	81.2 (67.7, 94.8)	84.6 (82.2, 87.0)
Homocysteine, μmol/L	>10.0	≤10.0
Sensitivity	72.9 (61.5, 84.2)	75.2 (70.4, 79.9)
Specificity	90.0 (83.4, 96.6)	91.4 (88.8, 94.0)
PPV	84.3 (74.3, 94.3)	86.1 (82.0, 90.2)
NPV	81.8 (73.8, 89.9)	83.9 (80.6, 87.1)
Accuracy	82.7 (76.5, 89.0)	84.7 (82.1, 87.2)

[1] Values are percentages (95% CIs). Hb adjusted for smoking status (14). Results outside the assay LOD were set to 0.50∗LOD (if below the LOD) or 2∗LOD (if above the LOD). Results outside assay LODs: sTfR (n = 4 above the LOD), CRP (n = 6 below the LOD), serum folate (n = 1 below the LOD), vitamin B-12 (n = 4 below the LOD, n = 6 above the LOD). LOD, limits of detection; MMA, methylmalonic acid; NPV, negative predictive value; PPV, positive predictive value; SF, serum ferritin; sTfR, soluble transferrin receptor.

[2] SF adjusted for inflammation via Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) methods (53).

[3] Body iron index (mg/kg) was estimated using Cook et al.'s equation (36) ($-\{\log_{10}$ [sTfR(Ramco; mg/L) × 1000/SF(μg/L)] – 2.8229}/0.1207) after converting sTfR to Flowers Ramco equivalents (Ramco = 1.5∗Roche + 0.35) (38).

[4] Assessed via microbiologic assay.

TABLE 7

Diagnostic accuracy parameters of anemia screening methods by metabolic risk factors[1]

Diagnostic accuracy parameter		
BMI,[2] kg/m^2	≥25.0	<25.0
Sensitivity	63.9 (54.4, 73.5)	78.8 (73.8, 83.8)
Specificity	92.3 (88.5, 96.2)	90.5 (87.2, 93.8)
PPV	81.6 (72.9, 90.3)	87.4 (83.1, 91.7)
NPV	82.8 (77.7, 88.0)	83.7 (79.7, 87.7)
Accuracy	82.5 (78.0, 87.0)	85.2 (82.3, 88.1)
BMI	≥23.0	<23.0
Sensitivity	63.6 (56.0, 71.2)	83.3 (78.1, 88.5)
Specificity	92.3 (89.0, 95.6)	90.1 (86.3, 93.8)
PPV	83.8 (77.1, 90.4)	87.3 (82.6, 92.0)
NPV	80.3 (75.7, 84.9)	86.9 (82.7, 91.0)
Accuracy	81.3 (77.5, 85.1)	87.0 (83.9, 90.2)
WHR[2]	≥0.80	<0.80
Sensitivity	70.7 (63.8, 77.7)	78.2 (72.3, 84.1)
Specificity	89.8 (85.9, 93.6)	92.7 (89.4, 95.9)
PPV	82.3 (76.0, 88.6)	89.1 (84.3, 93.8)
NPV	82.0 (77.4, 86.6)	84.7 (80.4, 89.0)
Accuracy	82.1 (78.4, 85.8)	86.4 (83.1, 89.6)
WHR	≥0.85	<0.85
Sensitivity	64.4 (52.2, 76.6)	76.8 (72.0, 81.6)
Specificity	88.6 (82.8, 94.4)	92.0 (89.3, 94.7)
PPV	74.5 (62.5, 86.5)	88.2 (84.3, 92.2)
NPV	82.8 (76.1, 89.5)	83.5 (80.0, 87.1)
Accuracy	80.3 (74.4, 86.3)	85.3 (82.6, 88.0)
Waist circumference, cm	>88.9	≤88.9
Sensitivity	64.1 (49.0, 79.2)	76.0 (71.3, 80.8)
Specificity	92.1 (86.0, 98.2)	91.0 (88.3, 93.8)
PPV	80.6 (66.7, 94.6)	86.5 (82.5, 90.6)

Diagnostic accuracy parameter		
NPV	83.3 (75.4, 91.3)	83.4 (79.9, 86.8)
Accuracy	82.6 (75.7, 89.5)	84.6 (81.9, 87.2)
Whole-body fat,[2] %	>35	≤35
Sensitivity	63.9 (55.4, 72.5)	80.3 (75.2, 85.5)
Specificity	93.4 (90.0, 96.7)	89.7 (86.1, 93.2)
PPV	84.8 (77.4, 92.1)	86.4 (81.8, 91.0)
NPV	81.7 (76.9, 86.6)	84.8 (80.8, 88.9)
Accuracy	82.6 (78.5, 86.7)	85.5 (82.4, 88.5)
Trunk fat,[2] %	>35	≤35
Sensitivity	62.7 (53.7, 71.8)	80.1 (75.0, 85.1)
Specificity	93.4 (89.9, 96.9)	89.8 (86.4, 93.3)
PPV	84.1 (76.2, 92.1)	86.5 (82.1, 91.0)
NPV	81.8 (76.7, 86.8)	84.7 (80.7, 88.7)
Accuracy	82.4 (78.2, 86.7)	85.4 (82.5, 88.4)
HbA1c, %	≥5.7	<5.7
Sensitivity	68.7 (59.6, 77.8)	77.0 (72.0, 82.0)
Specificity	91.3 (86.3, 96.2)	91.2 (88.4, 94.0)
PPV	86.1 (78.4, 93.7)	85.8 (81.4, 90.1)
NPV	78.8 (72.1, 85.4)	85.2 (81.8, 88.6)
Accuracy	81.3 (76.2, 86.4)	85.4 (82.7, 88.1)

[1]Values are percentages (95% CIs). Hb adjusted for smoking status (14). NPV, negative predictive value; PPV, positive predictive value; WHR, waist-hip ratio.

[2]Among adults only; anthropometric and bioelectrical impedance cutoffs from WHO and NHLBI criteria (49, 78, 79).

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