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Unexplained decline in the prevalence of anemia among US children and women between 1988–1994 and 1999–2002[1–3]

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ABSTRACT

Background: The current anemia burden among US preschool children and women of childbearing age has not been documented.

Objective: We used data from National Health and Nutrition Examination Surveys 1988–1994 and 1999–2002 to examine recent anemia changes.

Design: We calculated the prevalence of anemia (hemoglobin < 11.0 g/dL at <24 mo, <11.1 g/dL at 24–59 mo, and <12.0 g/dL for women), iron deficiency anemia (anemia plus abnormal value ≥2: serum ferritin, transferrin saturation, and erythrocyte protoporphyrin), and high blood lead (≥10 μg/dL) with anemia among children 12–59 mo and women 20–49 y in both surveys. Among women, we also calculated the prevalence of folate deficiency (erythrocyte folate < 317.2 nmol/L) with anemia and high C-reactive protein (>10 mg/L) with anemia. Multiple logistic regression was used to compare anemia prevalence between surveys, with control for race and age.

Results: Anemia declined significantly in children (from 8.0% to 3.6%; OR: 0.4; 95% CI: 0.3, 0.7) and women (10.8% to 6.9%; OR: 0.6; CI: 0.4, 0.7), but the prevalence of iron deficiency anemia did not change significantly in children (1.5% compared with 1.2%; OR: 0.7; 95% CI: 0.4, 1.5) or women (4.9% compared with 4.1%; OR: 0.8; 95% CI: 0.6, 1.1). Folate deficiency with anemia declined significantly in women (from 4.1% to 0.5%; OR: 0.1; 95% CI: 0.1, 0.2), but logistic regression models and standardization indicated that none of the known possible anemia causes could account for the decline in total anemia in children or women.

Conclusions: The prevalence of anemia declined significantly among US women and children between 1988–1994 and 1999–2002, but this decline was not associated with changes in iron or folate deficiency, inflammation, or high blood lead. *Am J Clin Nutr* 2008;88:1611–7.

INTRODUCTION

Anemia is a condition in which the number of red blood cells or their oxygen-carrying capacity is not adequate to meet normal physiologic demands (1). Iron deficiency is believed to be the most common cause of anemia worldwide (2), but deficiencies of other vitamins, inflammation, infections, and inherited hemoglobin disorders can also cause anemia (3–5).

Depending on the cause of anemia, the consequences of the condition are potentially serious and long-lasting. The consequences of iron deficiency anemia—including impaired cognitive and motor development (6–9) and increased susceptibility to lead poisoning (10, 11) in young children and impaired aerobic capacity and reduced work productivity (12, 13) in adults—have been widely reported, but anemia resulting from other nutritional deficiencies or inflammation can also reflect harmful health conditions. Among other possible causes of nutritional anemia, folate deficiency is associated with an increased risk of neural tube defects and may also be associated with adverse pregnancy outcomes, cardiovascular disease, depression, and dementia, whereas vitamin B-12 deficiency may be associated with an increased risk of heart disease and neuropathy (14–18). Anemia resulting from vitamin A deficiency may be linked with impaired immunity, growth, and vision (19). Anemia can also indicate inflammation caused by a variety of conditions, including infection, or it may occur in chronic illnesses such as chronic renal disease or endocrine disorders that can result in decreased erythropoiesis (4, 20).

Earlier data indicated that the prevalence of anemia declined in the 1970s and 1980s in US preschool children, but not among women of childbearing age (21, 22). The current burden of anemia in these 2 high-risk groups in the United States is unclear. In the present study, we used data from 2 recent National Health and Nutrition Examination Surveys (NHANES 1988–1994 and 1999–2002) to examine recent changes in total anemia prevalence. We also investigated between-survey changes in the prevalence of several types of anemia, including anemia associated with iron deficiency, folate deficiency, vitamin B-12 deficiency, vitamin A deficiency, high blood lead, and inflammation to assess whether these factors played a role in any observed changes

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in total anemia. Identification of a likely cause for changes in anemia could highlight existing public health interventions that have been successful or could identify new interventions that might be considered.

SUBJECTS AND METHODS

The NHANES are multistage, nationally representative surveys of the US civilian, noninstitutionalized population (23, 24). Each participant is interviewed at home, and most participants also undergo a physical evaluation in a mobile examination center. We began with all children aged 12–59 mo and women aged 20–49 y in NHANES 1988–1994 and 1999–2002 who had a physical exam (1988–1994: $n = 4812$ children, $n = 5104$ women; 1999–2002: $n = 1978$ children, $n = 2782$ women). We excluded pregnant women and women whose pregnancy status could not be ascertained (1988–1994: $n = 338$; 1999–2002: $n = 701$), any woman with a missing value for red blood cell folate or C-reactive protein (CRP), and any participant with a missing value for hemoglobin, serum ferritin, erythrocyte protoporphyrin, transferrin saturation, or blood lead. We were unable to include red blood cell folate or CRP in the children's analyses because they were assessed only in children ≥4 y during 1988–1994 and in children ≥3 y during 1999–2002. Total exclusions for missing laboratory data were as follows: $n = 2026$ children and $n = 374$ women for 1988–1994 and $n = 776$ children and $n = 112$ women for 1999–2002. After the exclusions, the final sample size for each survey was as follows: $n = 2786$ children and $n = 4392$ women for 1988–1994 and $n = 1202$ children and $n = 1969$ women for 1999–2002.

Phlebotomy refusal was the primary reason for missing laboratory data among children in both surveys (AC Looker, personal communication) (25). We compared the race/ethnicity distribution and income status of children excluded for having missing laboratory values with those of included children and found that whereas the race/ethnicity distribution was not significantly different in either survey, excluded children in both surveys were less likely to be of low income (family income ≤130% of the US poverty threshold) than were included children (1988–1994: 31% compared with 40%, chi-square test $P < 0.01$; 1999–2002: 34% compared with 44%, chi-square test $P = 0.01$).

In contrast, women excluded in 1999–2002 for having missing laboratory data were more likely to be of low income than were their included counterparts (39% compared with 25%, chi-square test $P = 0.02$). Excluded women were also more likely to be of non-Hispanic black race/ethnicity than were their included counterparts in both surveys (1988–1994: 21% compared with 12%, chi-square test $P = 0.01$; 1999–2002: 23% compared with 12%, chi-square test $P < 0.01$).

Finally, because serum vitamin B-12 and retinol were not measured for the entirety of both surveys, we constructed a subsample of women in each survey who also had data for serum vitamin B-12 (1991–1994: $n = 2506$; 1999–2002: $n = 1968$) and serum retinol (1988–1994: $n = 4378$; 1999–2000: $n = 903$). This subanalysis was not possible for children because both indicators were assessed only in children ≥4 y during 1988–1994 and in children ≥3 y during 1999–2002.

Laboratory methods

In both surveys, blood was collected from study participants ≥1 y by venipuncture. Hemoglobin was measured as part of a complete blood count done with a Coulter S-plus Jr in 1988–1994 and with a Coulter MAXM in 1999–2002 (both from Coulter Electronics, Hialeah, FL). The laboratory methods for other indicators were described in detail elsewhere (26–28). Briefly, serum ferritin was measured by using the Bio-Rad QuantImune Ferritin immunoradiometric assay (Bio-Rad Laboratories, Hercules, CA), whereas transferrin saturation was calculated as serum iron divided by total-iron-binding capacity, as measured by a Centers for Disease Control and Prevention modification of the automated Technicon AAII-25 ferrozine colorimetric method (Alpkem TFA analyzer; Alpkem, Clackamas, OR). Free erythrocyte protoporphyrin was measured in whole blood by fluorescence extraction by using a modification of the Sassa method. Red blood cell folate was measured with the QuantaPhase-I Folate Radioassay Kit (Bio-Rad Laboratories) from 1988 to 1991 and with the QuantaPhase-II kit from 1991 to 1994 and from 1999 to 2001. The QuantaPhase-II kit reflected recalibration of the assay for which appropriate adjustments were made to the 1988–1991 values to make them comparable with the 1991–2001 values before public release. The QuantaPhase II assay also measured serum vitamin B-12. During both surveys, serum CRP was measured by latex-enhanced nephelometry (lower limit of detection: 0.2 mg/L). Blood lead was measured by atomic absorption spectroscopy, and serum retinol was measured by HPLC.

Cutoffs and definitions

Hemoglobin cutoffs used to define anemia and cutoffs used for defining abnormal values for indicators of iron status, blood lead, red blood cell folate, CRP, retinol, and vitamin B-12 are presented in **Table 1**. We defined iron deficiency as having an abnormal value for ≥2 of the 3 following indicators: serum ferritin, transferrin saturation, and erythrocyte protoporphyrin (29). We defined iron deficiency anemia as iron deficiency plus anemia.

Statistical analysis

All analyses were conducted with SAS 8.2 with SUDAAN (SAS Institute Inc, Cary, NC) and used sample weights to account for differential probabilities of selection and complex sampling design. For children and women in each survey, we first calculated the prevalence of total anemia. Among children, we then calculated the prevalence of iron deficiency anemia, the prevalence of high blood lead with anemia, and the prevalence of the coexistence of iron deficiency, high blood lead, and anemia. Among women, we calculated the prevalence of iron deficiency anemia, folate deficiency with anemia, high CRP with anemia, high blood lead with anemia, and the coexistence of ≥2 of these conditions with anemia. We also calculated the prevalence of vitamin B-12 deficiency with anemia and the prevalence of vitamin A with anemia among women in the sub-sample.

We then used multiple logistic regression to compare overall anemia prevalence and type-specific anemia prevalence between the surveys for children and women, controlling for race/ethnicity, sex (in the children's models), and age. We further adjusted the children's overall anemia model for iron deficiency and high blood lead and the women's overall anemia model for iron deficiency, high blood lead, folate deficiency, and high CRP to assess the role of these potential causes of anemia in any observed change in anemia prevalence.

TABLE 1
Cutoffs for defining abnormal values of biochemical indicators used in the study[1]

Indicator	Age	Cutoff value	Reference
Hemoglobin	12-23 mo	<11.0 g/dL	CDC 1998 (29)
	24-59 mo	<11.1 g/dL	
	20-49 y (women)	<12.0 g/dL	
Serum ferritin	12-59 mo	<10 μg/L	Looker et al 1997 (30)
	20-49 y	<12 μg/L	
Erythrocyte protoporphyrin	12-35 mo	>1.42 μmol/L RBC	Looker et al 1997 (30)
	36-59 mo	>1.24 μmol/L RBC	
	20-49 y	>1.24 μmol/L RBC	
Transferrin saturation	12-35 mo	<10%	Looker et al 1997 (30)
	36-59 mo	<12%	
	20-49 y	<15%	
Blood lead	All ages	≥10 μg/dL	CDC 2005 (31)
Red blood cell folate	All ages	<317.2 nmol/L RBC	Institute of Medicine 1998 (32)
C-reactive protein	All ages	>10 mg/L	Ford et al 2001 (33)
Serum retinol	All ages	<20 μg/dL	de Pee and Dary 2002 (34)
Serum vitamin B-12	All ages	<148 pmol/L	Miller et al 2006 (35)

[1] CDC, Centers for Disease Control and Prevention; RBC, red blood cell.

Because preliminary analyses and recently published data (36) indicated that the prevalence of folate deficiency declined significantly among women of childbearing age between the surveys, we used direct standardization to examine the possible effect this decline had on the prevalence of anemia between the surveys (37).

Finally, to investigate the possibility of a systematic difference in hemoglobin measurement between the surveys, we constructed mean-difference plots for hemoglobin among women by subtracting hemoglobin values at each percentile in 1988–1994 from hemoglobin values at the corresponding percentile in 1999–2002 and plotting this difference on the *y* axis, with hemoglobin in the first survey on the *x* axis (38).

RESULTS

The racial distribution and income status for children and women were similar between the 2 surveys, although women in 1999–2002 tended to have a higher prevalence of family income ≤130% of the Federal Poverty Threshold than did women in 1988–1994 ($P = 0.05$; **Table 2**).

Among children, the prevalence of all-cause anemia decreased significantly between the 2 surveys, falling from 8.0% to 3.6%, with a corresponding adjusted odds ratio (OR) of 0.4 (95% CI: 0.3, 0.7; **Table 3**). However, the prevalence of iron deficiency anemia was low (< 2%) and did not change significantly between the surveys (OR: 0.7; 95% CI: 0.4, 1.5). The prevalence of high blood lead with anemia declined significantly, but was <1% in either survey. Coexisting iron deficiency, high blood lead and anemia was rare in either survey.

The prevalence of all-cause anemia also declined significantly among women, falling 4 percentage points from 10.8% to 6.9% (OR: 0.6; 95% CI: 0.4, 0.7; Table 3). Iron deficiency anemia was the predominant known type of anemia among women in both surveys, but its prevalence did not change significantly (OR: 0.8; 95% CI: 0.6, 1.1). The prevalence of folate deficiency with anemia, however, declined significantly by almost 4 percentage points (from 4.1% to 0.5%; OR: 0.1; 95% CI: 0.1, 0.2), and the proportion of women with ≥2 types of anemia declined by more than a percentage point. Further analysis showed that >70% of the women in 1988–1994 who had 2 types of anemia had concurrent iron and folate deficiency (data not shown). High blood lead, inflammation, vitamin A deficiency, and vitamin B-12 deficiency concurrent with anemia were rare among women in both surveys (<1%; subsample data not shown).

Type-specific anemia patterns remained when we stratified by race/ethnicity category (**Table 4**). The prevalence of anemia

TABLE 2
Sample demographics, by survey[1]

	NHANES 1988–1994	NHANES 1999–2002	*P*[2]
Children aged 12-59 mo			
n	2786	1202	
Sex			
Male	50.9 (48, 54)[3]	54.5 (50, 59)	0.18
Race/ethnicity			
White	58.8 (54, 63)	57.6 (51, 64)	0.21
Black	17.3 (15, 20)	14.3 (11, 19)	
Mexican American	10.9 (9, 13)	16.0 (12, 21)	
Other	13.0 (9, 18)	12.1 (8, 17)	
Poverty income ratio ≤130%[4]	40.2 (36, 45)	42.4 (38, 47)	0.23
Women aged 20–49 y			
n	4392	1969	
Race/ethnicity			
White	72.7 (70, 76)	67.8 (63, 72)	0.13
Black	12.4 (11, 14)	12.0 (9, 15)	
Mexican American	5.6 (5, 7)	8.0 (6, 10)	
Other	8.3 (6, 11)	10.8 (8, 14)	
Poverty income ratio ≤130%	20.4 (18, 23)	24.9 (22, 29)	0.05

[1] Data are for nonpregnant study participants with complete laboratory data as described in Subjects and Methods. NHANES, National Health and Nutrition Examination Survey.

[2] *P* value from chi-square test comparing proportions between surveys.

[3] Weighted percentage; 95% CI in parentheses (all such values).

[4] Family income ≤130% of US poverty threshold for the years of the survey. Sample size for family income data: $n = 2597$ children and $n = 4041$ women for 1988-1994 and $n = 1106$ children and $n = 1802$ women for 1999-2002. US poverty threshold for a family of 4 was approximately $14 000 in 1990 and $18 000 in 2000.

TABLE 3
Prevalence and change in total anemia and type-specific anemia in 1988-1994 and 1999–2002[1]

	Children aged 12–59 mo			Women aged 20–49 y		
	1988–1994	1999–2002	OR[2] (95% CI)	1988–1994	1999–2002	OR[2] (95% CI)
n	2786	1202	—	4392	1969	—
Total anemia (%)[3]	8.0	3.6	0.4	10.8	6.9	0.6
	(6.5, 9.8)[4]	(2.5, 5.1)	(0.3, 0.7)	(9.2, 12.7)	(5.6, 8.5)	(0.4, 0.7)
Iron deficiency anemia (%)	1.5	1.2	0.7	4.9	4.5	0.8
	(1.1, 2.2)	(0.7, 2.1)	(0.4, 1.5)	(4.1, 5.9)	(3.6, 5.6)	(0.6, 1.1)
Folate deficiency and anemia (%)[5]	—	—	—	4.1	0.5[6]	0.1
				(3.3, 5.0)	(0.3, 0.9)	(0.1, 0.2)
CRP > 10 mg/L and anemia (%)	—	—	—	0.7	0.8	1.1
				(0.5, 1.0)	(0.5, 1.2)	(0.7, 1.8)
Lead ≥ 10 μg/dL and anemia (%)	0.8[6]	0.2[6]	0.2	0.1[6]	0.1[6]	0.8
	(0.4, 1.5)	(0.1, 0.6)	(0.1, 0.8)	(0.0, 0.1)	(0.0, 0.2)	(0.2, 3.4)
≥2 of above	0.3	0.1[6]	0.4	2.0	0.8	0.4
	(0.2, 0.5)	(0.0, 0.6)	(0.1, 2.1)	(1.5, 2.7)	(0.6, 1.2)	(0.2, 0.6)

[1] Folate and CRP data were not available for the children. OR, odds ratio; CRP, C-reactive protein.
[2] ORs for 1999-2002 compared with 1988-1994 from multiple logistic regression equations adjusted for race/ethnicity, age, and sex (for children).
[3] Anemia defined as hemoglobin <11.0 g/dL (<24 mo), <11.1 g/dL (≥24 mo), and <12.0 g/dL (women).
[4] Weighted percentage; 95% CI in parentheses (all such values).
[5] Anemia plus red blood cell folate <317.2 nmol/L.
[6] Estimate is statistically unreliable. Relative SE (SE of prevalence/prevalence × 100) ≥30%.

declined significantly in each race/ethnicity group, but the prevalence of iron deficiency anemia did not change significantly in any group and remained high among both black (12%) and Mexican American (8%) women. The prevalence of folate deficiency with anemia declined significantly in each race/ethnicity group.

Multiple logistic regression showed, however, that none of the potential anemia causes fully explained the decline in anemia among children or women. When we modeled anemia among children as a function of survey (1999–2002 compared with 1988–1994), race/ethnicity, age, and sex, the OR for the survey was 0.42 (Table 3; second row). The OR remained 0.42 when iron deficiency and high blood lead were added to the model. Similarly, among women, the OR for the survey was 0.56 in the model that adjusted only for race/ethnicity and age (Table 3; second row) and was 0.46 after the model was adjusted for iron deficiency, folate deficiency, high blood lead, and high CRP.

Preliminary analyses showed that the prevalence of folate deficiency among women in our sample was 36% in 1988–1994 and 4.5% in 1999–2002. To assess further whether this decline played a role in the decline in anemia that we observed, we used direct standardization and found that if the prevalence of folate deficiency had remained 36% in both surveys, the prevalence of anemia would have declined from 11% to 8%, similar to the decline in unadjusted prevalences of 11% to 7% (Table 3). Furthermore, additional analyses showed that among nonfolate-deficient women in each survey, the prevalence of anemia also declined from 11% to 7% between the surveys.

TABLE 4
Prevalence and change in total anemia and type-specific anemia for women aged 20-49 y by race/ethnicity in 1988-1994 and 1999-2002[1]

	White			Black			Mexican American		
	1988–1994	1999–2002	OR[2] (95% CI)	1988–1994	1999–2002	OR[2] (95% CI)	1988–1994	1999–2002	OR[2] (95% CI)
n	1393	838	—	1466	422	—	1331	533	—
Total anemia (%)	6.7	3.3	0.5	29.3	24.4	0.8	13.4	8.7	0.6
	(5.0, 8.8)[3]	(2.1, 5.0)	(0.3, 0.8)	(26.6, 32.2)	(20.9, 28.3)	(0.6, 1.0)	(11.7, 15.3)	(6.5, 11.4)	(0.4, 0.8)
Iron deficiency anemia (%)	2.8	2.6	0.9	10.9	12.2	1.1	9.2	7.6	0.8
	(2.0, 3.8)	(1.6, 4.3)	(0.5, 1.7)	(9.2, 12.8)	(9.8, 15.2)	(0.8, 1.5)	(7.9, 10.8)	(5.6, 10.1)	(0.5, 1.1)
Folate deficiency and anemia (%)	1.6	0.1[4]	0.1	16.3	3.0	0.2	4.8	0.3[4]	0.1
	(1.0, 2.7)	(0.0, 1.0)	(0.0, 0.7)	(14.6, 18.2)	(1.7, 5.0)	(0.1, 0.3)	(3.4, 6.7)	(0.0, 2.0)	(0.0, 0.4)
CRP > 10 mg/L and anemia (%)0.2[4]	0.2[4]	0.2[4]	1.0	3.2	4.6	1.4	1.2	1.2[4]	1.0
	(0.1, 0.7)	(0.0, 1.1)	(0.1, 8.2)	(2.3, 4.5)	(3.2, 6.6)	(0.9, 2.4)	(0.7, 1.8)	(0.6, 2.1)	(0.5, 2.2)
Lead ≥ 10 μg/dL and anemia (%)	0.0[4]	0.0[4]	—	0.4[4]	0.3[4]	0.5	0.2[4]	0.3[4]	1.7
				(0.1, 1.0)	(0.0, 1.7)	(0.1, 3.9)	(0.0, 0.8)	(0.1, 1.3)	(0.3, 11.3)
≥2 of above	0.6[4]	0.3	0.6	7.3	4.1	0.5	3.7	1.4	0.4
	(0.3, 1.2)	(0.3, 0.4)	(0.3, 1.3)	(5.9, 9.1)	(2.5, 6.7)	(0.3, 0.9)	(2.8, 4.9)	(0.8, 2.5)	(0.2, 0.7)

[1] OR, odds ratio; CRP, C-reactive protein.
[2] OR for 1999-2002 compared with 1988-1994 from multiple logistic regression equations adjusted for age.
[3] Weighted percentage; 95% CI in parentheses (all such values).
[4] Estimate is statistically unreliable. Relative SE (SE of prevalence/prevalence × 100) ≥30%.

To assess the possibility of a systematic error in hemoglobin measurement, we constructed mean-difference plots for hemoglobin among women by subtracting hemoglobin values at each hemoglobin percentile in 1988–1994 from the hemoglobin values at the corresponding percentile in 1999–2002 (**Figure 1**). We then plotted this difference (in g/dL) along the *y* axis with hemoglobin in 1988–1994 along the *x* axis. For example, among black women, the 10th, 50th, and 90th percentiles of hemoglobin were 11.1, 12.6, and 13.8 g/dL, respectively, in the first survey and were 11.1, 12.7, and 14.1 g/dL, respectively, in the second survey. The differences in these percentile values (1999–2002 minus 1988–1994) were 0.0, 0.1, and 0.3 g/dL, which fall along the line in the middle panel of the Figure 1. We found that the magnitude of change in hemoglobin values differed by race/ethnicity group, with a greater increase in hemoglobin observed among white (median difference: +0.34) and Mexican American (+0.37) women than among black women (+0.13).

DISCUSSION

The prevalence of anemia declined significantly between 1988–1994 and 1999–2002 among US preschool-aged children and women of childbearing age, but the cause of this decline was largely unexplained. The prevalence of iron deficiency anemia remained low and unchanged between the 2 surveys in both groups, and although the prevalence of folate deficiency with anemia did decline significantly among women, changes in the prevalence of folate deficiency accounted for little of the overall decline in anemia. Inflammation, high blood lead, vitamin B-12 deficiency, and vitamin A deficiency concurrent with anemia were not common in either survey.

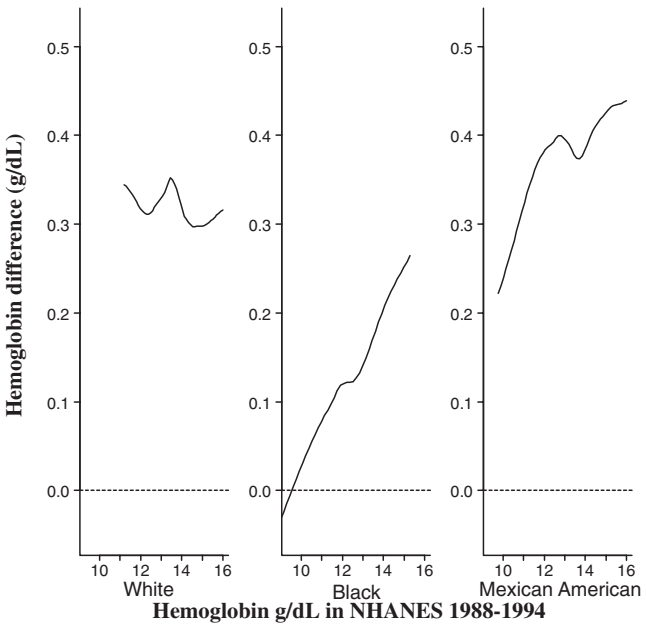

FIGURE 1. Plot of differences in hemoglobin values at various percentiles for women by race/ethnicity group. Within each race/ethnicity group, the hemoglobin values at each percentile for 1988–1994 were subtracted from hemoglobin values at the corresponding percentile in 1999–2002. The differences in each percentile (from the 1st to the 99th) were smoothed by using lowess, a nonparametric technique based on estimates of the values at each point from a weighted regression analysis of neighboring points (38).

The majority of anemia among children in both surveys was not associated with iron deficiency or high blood lead. The observed low prevalence of iron deficiency anemia among US preschool children was likely the result of concerted efforts to prevent iron deficiency anemia in this vulnerable age group, including iron fortification of infant formulas and establishment of The Special Supplemental Nutrition Program for Women, Infants, and Children in the early 1970s (21, 39–41). Blood lead concentrations have also declined significantly since the 1970s, largely because of the removal of lead from gasoline and soldered cans (42, 43).

The cause of the decline in the prevalence of anemia among children between the surveys is thus unclear, and, unfortunately, the lack of data on folate, vitamin B-12, serum retinol, and CRP among children surveyed in this age group limited our investigation of potential causes. Others have reported the importance of common infections, including upper respiratory tract infection, otitis media, and gastroenteritis as causes of anemia in preschool-aged children (20), but whether the frequency of these infections decreased sufficiently between the surveys to contribute to the decline in all-cause anemia among children is not known.

Iron deficiency anemia was the predominant type of anemia among women in both surveys and was most prevalent in black and Mexican American women. The cause of the persistently high prevalence among women in these race/ethnicity groups merits further attention, but may be due to lower socioeconomic status, lower attained education, or higher parity, all of which are associated with iron deficiency in women of childbearing age (30). Nevertheless, the prevalence of iron deficiency anemia did not change significantly between the 2 surveys among all women or in any race/ethnicity group and thus seems unlikely to explain the significant decline in the prevalence of all-cause anemia.

We did observe a significant decline in the prevalence of concurrent folate deficiency and anemia among women, but this decline appeared to be the result of concomitant, but unrelated, declines in both folate deficiency and anemia. Several authors have reported multiple beneficial effects of the 1998 folic acid fortification of all US enriched cereal-grain products, including a reduced prevalence of neural tube disorders (44, 45) and lower concentrations of homocysteine (46, 47). No study has evaluated the effect of folic acid fortification on anemia. The timing of NHANES 1988–1994 (before fortification) and 1999–2002 (after fortification) permitted us to evaluate such an association, but regression and standardization results failed to prove a relation.

Another possible cause of the observed decline in anemia was a systematic difference in hemoglobin measurement between the surveys, introduced by the use of 2 different models of Coulter counter. A direct investigation, in which both instruments are used to measure hemoglobin on the same sera samples, was not possible because the instruments used in 1988–1994 were no longer available. We instead used an indirect approach to assess this possibility by subtracting hemoglobin values at various percentiles of the first survey from hemoglobin values at the corresponding percentiles of the second survey and then plotting this difference on the *y* axis with hemoglobin in the first survey on the *x* axis. These results suggest that a systematic difference in hemoglobin concentrations between the 2 surveys did not play a major role in the observed decline in the prevalence of anemia, because the patterns and magnitude of hemoglobin differences were different for each race/ethnicity group.

Important health trends over the past 3 decades, specifically the decline in cigarette smoking (48) and the increase in overweight and obesity (49, 50), have the potential to affect anemia rates, but likely in a direction opposite of what we observed. Among women in NHANES II, smokers had a significantly higher mean hemoglobin concentration than did nonsmokers and a lower prevalence of anemia (51), but the declining smoking rates between 1988 and 2002 (48) would be more consistent with a lower hemoglobin concentration and a higher prevalence of anemia. Similarly, overweight may be associated with an increased risk of iron deficiency (52), whereas a high prepregnancy body mass has been found to be associated with a greater risk of postpartum anemia (53), but both would be consistent with an increase, rather than with a decline, in anemia.

A limitation of our study was the possibility of selection bias introduced by the large number of children with missing laboratory data, due primarily to phlebotomy refusal. Although the race/ethnicity of children with missing laboratory data was not significantly different from included children, included children were significantly more likely to be of low income, which potentially inflated the anemia estimates. However, the relative amount of bias by income in the 2 surveys appears similar (1988–1994: 31% low income in the excluded sample compared with 40% in the included sample; 1999–2002: 34% compared with 44%). This finding suggests that the difference in prevalence between the surveys observed in our study was unlikely to be seriously affected.

Whereas a much smaller proportion of women than children were excluded because of missing laboratory values, excluded women in both surveys were more like to be of non-Hispanic black race/ethnicity than were included women, perhaps leading to an underestimation of total anemia and/or iron deficiency anemia. Again, however, the relative amount of bias by race in the 2 surveys appeared to be similar (1988–1994: 21% low income in the excluded sample compared with 12% in the included sample; 1999–2002: 23% compared with 12%). Excluded women also tended to have a higher prevalence of poverty in 1999–2002. Adjustment for poverty in multivariate models for anemia, however, did not change the OR estimates, which made it unlikely that this finding significantly affected our overall results.

Our restricted ability to assess inflammation was an additional limitation. CRP tends to peak and diminish rapidly and thus may not reflect more chronic inflammatory conditions (54). We were also unable to account for other possible causes of anemia, including hemoglobinopathies, cancer, and aplastic anemia resulting from reduced red blood cell production; however, these conditions were probably not common in the children and young adult women.

In summary, we observed a significant decline in the prevalence of all-cause anemia between 1988–1994 and 1999–2002. Whereas the explanation for the decline remains unclear, the reduced anemia burden among US children and women is notable in that anemia itself is associated with multiple adverse health outcomes, including mild-to-moderate mental retardation in children (55) and low infant birth weight and increased risk of preterm birth in pregnant women (56). Although iron deficiency anemia was not prevalent among preschool-aged children in either survey, it remains prevalent among women of childbearing age, particularly among black and Mexican American women. Further investigation of the lack of association between folate deficiency and anemia may warrant further investigation.

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