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Original Article

ORIGINAL ARTICLE

Prevalence of anaemia in adults with chronic kidney disease in a representative sample of the United States population: analysis of the 1999–2018 National Health and Nutrition Examination Survey

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ABSTRACT

Background. Population-based estimates of anaemia prevalence in patients with chronic kidney disease (CKD) vary, and data on the prevalence of severe anaemia of CKD are limited. This study examined the prevalence of anaemia and anaemia eligible for erythropoiesis-stimulating agent (ESA) treatment in patients with CKD in the USA.

Methods. National Health and Nutrition Examination Survey (NHANES) data from 1999–2000 to 2017–18 were used to determine the prevalence of diagnosed anaemia (haemoglobin <12 g/dL in women; <13 g/dL in men) and anaemia eligible for ESA treatment (haemoglobin <10 g/dL) in survey participants aged ≥18 years with stage 3–5 non-dialysis-dependent CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2). The study objectives were to (i) obtain a more recent estimate of anaemia prevalence in patients with non-dialysis-dependent CKD and (ii) examine the characteristics of individuals with CKD and haemoglobin <10 g/dL.

Results. Of 51 163 eligible NHANES participants, 2926 (5.7%) with stage 3–5 CKD were included. In all participants, the weighted prevalences of anaemia and haemoglobin <10 g/dL were 25.3% and 1.9%, respectively. Mean haemoglobin levels decreased numerically between 1999 and 2012 and remained stable thereafter. The prevalence of anaemia and haemoglobin <10 g/dL increased with advancing CKD stage. The odds of haemoglobin <10 g/dL were significantly higher in stage ≥3B versus 3A and in non-Hispanic Blacks versus other races.

Conclusions. In our analysis, approximately 25% of individuals with stage 3–5 CKD in the USA had anaemia and approximately 2% had anaemia eligible for ESA treatment.

LAY SUMMARY

We used National Health and Nutritional Examination Survey (NHANES) data from 1999 to 2018 to determine how many adults (age ≥18 years) with non-dialysis-dependent chronic kidney disease (CKD) have anaemia (haemoglobin <12 g/dL for women; <13 g/dL for men) and severe anaemia (haemoglobin <10 g/dL). People with severe anaemia may be eligible for treatment with erythropoiesis-stimulating agents (ESAs), which stimulate the bone marrow to produce red blood cells.

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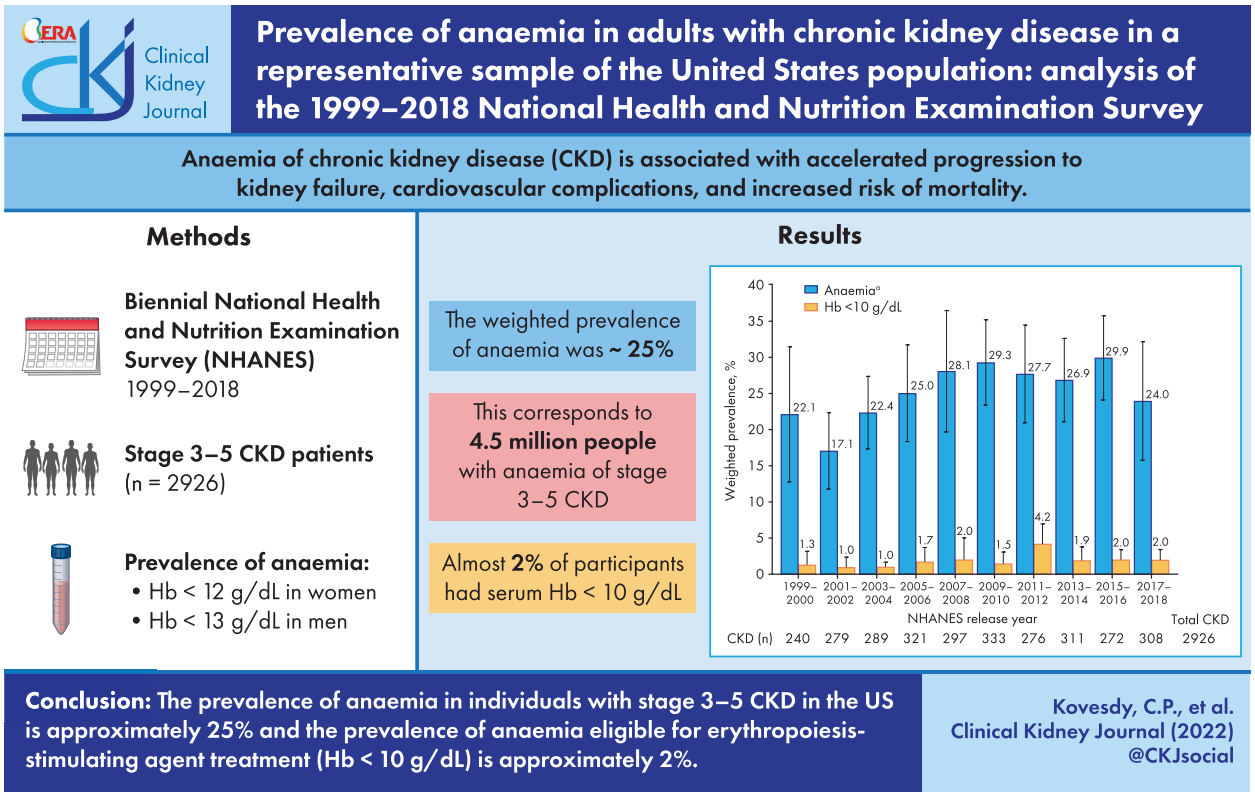
Among 51 163 eligible NHANES participants, 2926 (5.7%) had stage 3–5 CKD. Of these, 25.3% had anaemia and 1.9% had severe anaemia. The odds of severe anaemia were greater for participants with CKD stage ≥3B (more severe) versus stage 3A (less severe) and for non-Hispanic Black participants than those of other races or ethnicities.
Our study found that one-quarter of people with stage 3–5 CKD in the USA have anaemia and ∼2% may be eligible for ESA treatment.

GRAPHICAL ABSTRACT



Keywords: anaemia, chronic kidney disease, National Health and Nutrition Examination Survey, prevalence

INTRODUCTION

Patients with chronic kidney disease (CKD) often develop anaemia as kidney function declines due to erythropoietin deficiency as well as decreased red blood cell survival, increased blood loss, impaired absorption of dietary iron, iron deficiency, inflammation and decreased utilization of iron stores [1, 2]. According to the World Health Organization (WHO), anaemia is defined as a serum haemoglobin (Hb) level of <12 g/dL in women and <13 g/dL in men [3].

Anaemia of CKD presents a considerable healthcare burden because of the increased costs associated with disease management [4] and its negative impact on patient health-related quality of life [5]. In addition, anaemia of CKD is associated with accelerated progression to kidney failure, cardiovascular complications (particularly in patients with increased age, type 2 diabetes, hypertension and dyslipidaemia), and higher mortality rates [6–9]. Anaemia may also be associated with sleep disturbances [10] and cognitive impairment [11, 12], although there is conflicting evidence for both of these complications.

According to 2007–10 data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of anaemia among patients with CKD in the USA was previously estimated to be 15.4% [13]. This corresponds to approximately 4.8 million people with anaemia of CKD [13]. Population-based estimates of anaemia in US patients with CKD may have changed over time because of increased monitoring of Hb in patients with earlier CKD stages [14] and improved awareness of the potential complications of CKD [15]. Furthermore, data on the prevalence of anaemia eligible for erythropoiesis-stimulating agent (ESA) treatment (i.e. Hb <10 g/dL) in patients with CKD are limited [2].

The current analysis used the most recently available NHANES data (1999–2018) to examine the prevalence of anaemia and Hb <10 g/dL in patients in the USA with CKD. The objectives of this analysis were to (i) obtain a more recent update of anaemia prevalence among patients with non-dialysis-dependent (NDD)-CKD of different stages and (ii) examine the characteristics of patients with CKD and Hb <10 g/dL in further detail to inform thresholds for future management of patients with anaemia of CKD.

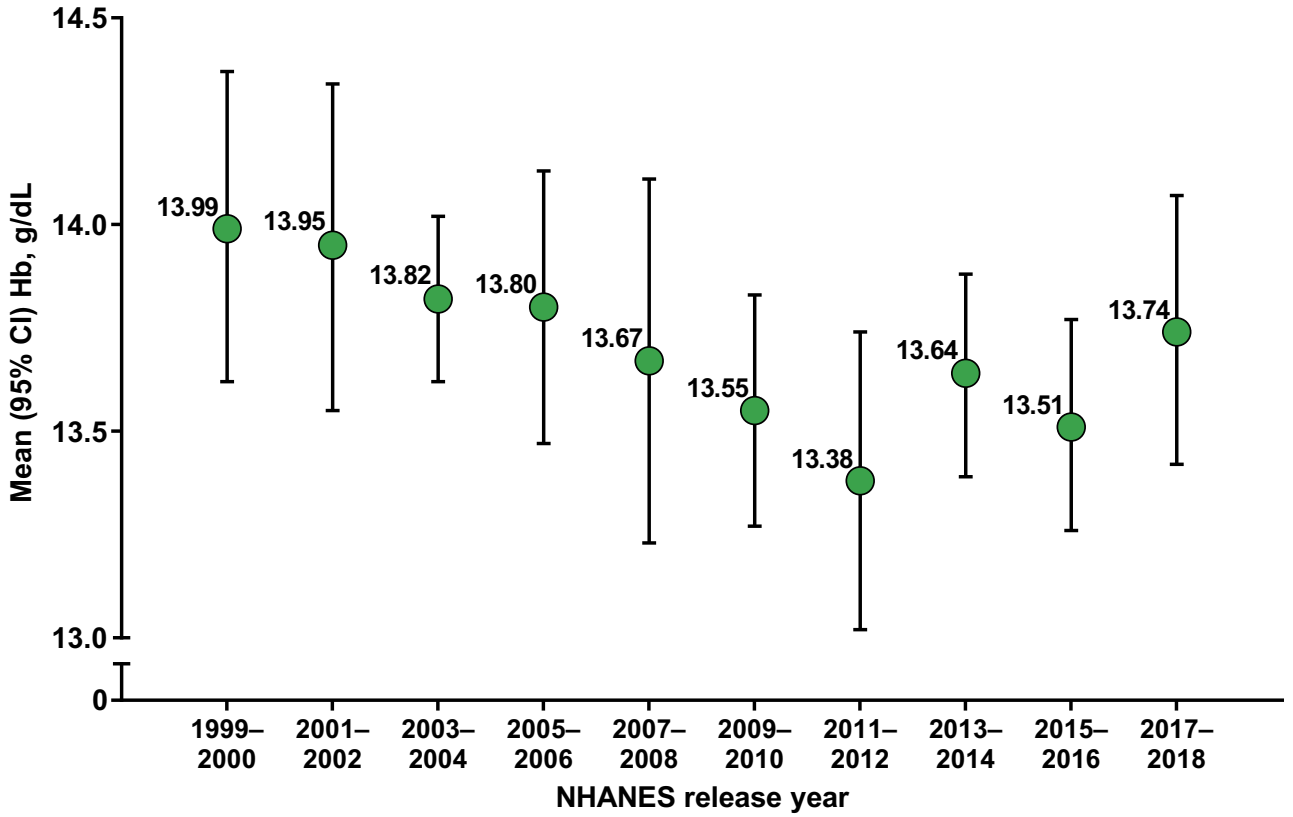


Figure 1: Mean (95% CI) Hb levels in participants with stage 3–5 CKD by NHANES release year from 1999–2018.

MATERIALS AND METHODS

Study design

This cross-sectional study used biennial NHANES data from 1999–2000 to 2017–18 to examine the prevalence of anaemia in US patients with CKD. The NHANES database is part of a series of health-related programs run by the US Centers for Disease Control and Prevention's National Center for Health Statistics, whose Research Ethics Review Board reviewed and approved each NHANES cycle [16], and all NHANES participants provided written informed consent. NHANES examines yearly a nationally representative sample of approximately 5000 civilian non-institutionalized adults and children residing in all 50 US states and Washington, DC [16]. NHANES uses a complex, multistage probability design to assure that the sample is nationally representative. To produce reliable statistics, NHANES over-samples persons aged 60 years and older and African American, Asian American and Hispanic populations [16]. The survey comprises home-based questionnaires followed by standardized health examination [16].

Study population

This analysis included data from male and female survey participants aged ≥18 years with documented stage 3–5 CKD [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2] who were not on dialysis. Exclusion criteria included an eGFR of ≥60 mL/min/1.73 m^2, dialysis in the previous 12 months, and a lack of documented Hb or serum creatinine levels. Pregnant women were also excluded from the analysis. All study participants provided informed consent at the time of the survey.

Study definitions

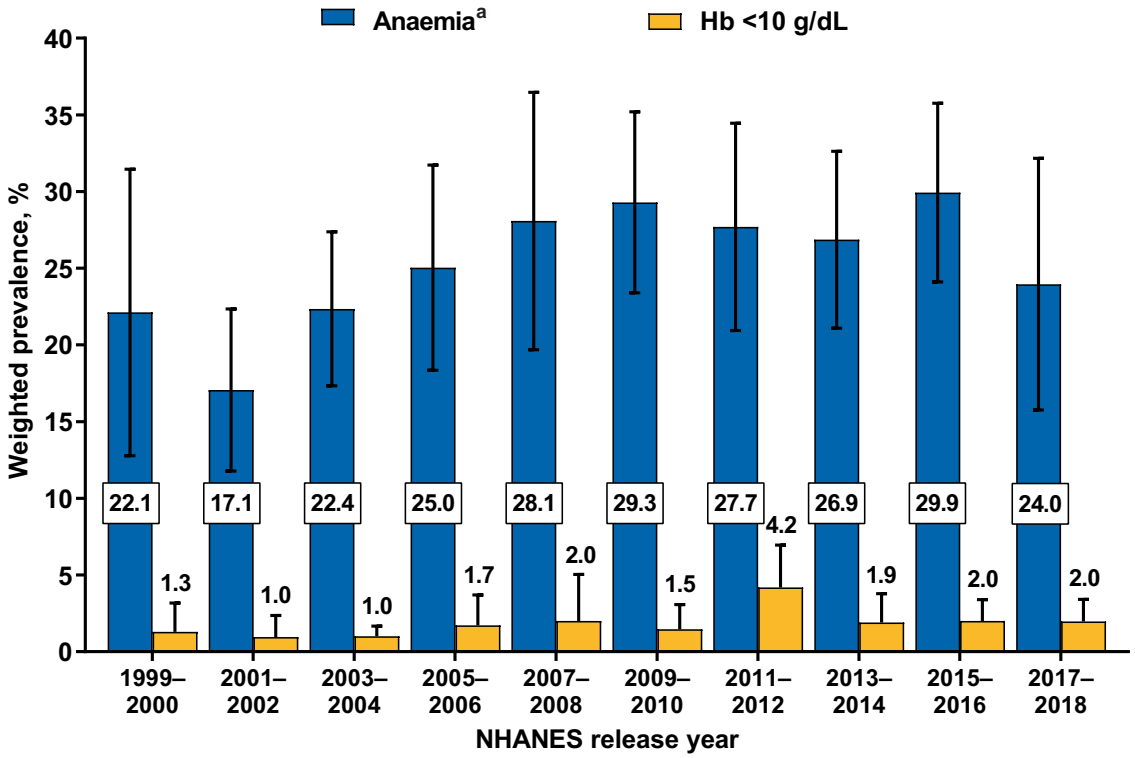
We calculated the eGFR using the CKD Epidemiology Collaboration equation and staged CKD using the eGFR-based Kidney Disease: Improving Global Outcomes (KDIGO) classification into CKD stages 3A (eGFR 45–59 mL/min/1.73 m^2), 3B (eGFR 30–44 mL/min/1.73 m^2), 4 (eGFR 15–29 mL/min/1.73 m^2) or 5 (eGFR <15 mL/min/1.73 m^2) [17].

Anaemia was defined according to the WHO criteria as serum Hb <12 g/dL in women or <13 g/dL in men [3]. Anaemia eligible for ESA treatment was defined as serum Hb <10 g/dL.

With regard to comorbidities, uncontrolled hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg (with or without the use of antihypertensive medications), and diabetes was defined as a confirmed diagnosis from a healthcare professional or glycated Hb levels of ≥6.5%.

Statistical analysis

Descriptive statistics were used to analyse the data. Analysis of longitudinal trends in mean Hb between 1999 and 2018 were conducted using SAS® PROC SURVEYREG (SAS, Cary, NC, USA), employing the relevant stratum, cluster and weighting variables. Weighted statistics were used to calculate the prevalence of anaemia, with weight factors used to take into consideration confounding variables and the complex survey sampling scheme that is conducted with NHANES. The 20-year weight was calculated starting with the 4-year NHANES weights provided for 1999–2002 and then combining the weights for each 2-year period between 2003 and 2018. Weighted prevalence values were



CKD, n	240	279	289	321	297	333	276	311	272	308	Total CKD 2926

Figure 2: Weighted prevalence (95% CI) of anaemia and Hb <10 g/dL in participants with stage 3–5 CKD by NHANES release year from 1999–2018. [a]Defined as Hb <12 g/dL in women and <13 g/dL in men.

converted to estimates of the corresponding numbers in the US population using 2015–18 US census data.

Regression analysis was used to examine the association between the mean Hb levels across all study participants or the weighted prevalence of anaemia or Hb <10 g/dL and CKD stage, age, sex, race, body mass index, smoking status, and the presence of concurrent diabetes or uncontrolled hypertension.

RESULTS

Patient population

In total, data from 51 163 individual NHANES participants were eligible for inclusion in the analysis. Of this population, 2926 individuals (5.7%) had stage 3–5 CKD and were included in this analysis (Supplementary data, Fig. S1). This corresponded to an estimated 17.7 million people in the US with stage 3–5 CKD. The demographics and characteristics of the study participants are summarized in the Supplementary data, Table S1; the majority were aged ≥75 years, male, non-Hispanic white, and had stage 3A CKD and no concurrent diabetes or uncontrolled hypertension.

Change in mean haemoglobin over time

Mean [95% confidence interval (CI)] Hb levels ranged from 13.38 (13.02–13.74) g/dL to 13.99 (13.62–14.37) g/dL across all survey releases. Numeric decreases over time were observed between 1999 and 2012, after which the levels remained relatively stable (Fig. 1). In 2017–18, mean (95% CI) Hb levels were 13.74 (13.42–14.07) g/dL.

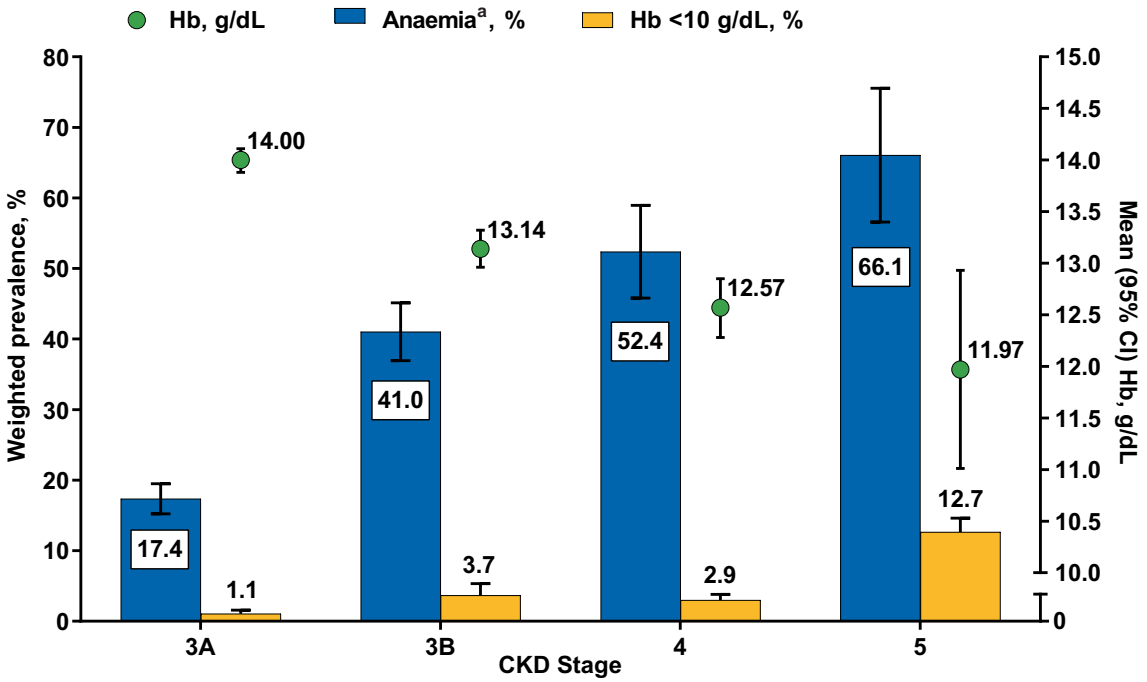
Prevalence of anaemia

Overall, the weighted prevalences of anaemia and Hb <10 g/dL in all participants with CKD were 25.3% and 1.9%, respectively. These corresponded to an estimated 4.5 million people with anaemia of stage 3–5 CKD (excluding dialysis) and 324 000 people with Hb <10 g/dL in the USA. The weighted anaemia prevalence increased numerically over time between 2001 and 2010 and stabilized thereafter (Fig. 2). In 2017–18, the weighted prevalence of anaemia in participants with CKD was 24.0% (95% CI 15.7%–32.2%).

The weighted prevalence of Hb <10 g/dL remained relatively stable over time between 1999 and 2018 (Fig. 2) and was 2.0% (95% CI 0.5%–3.4%) in 2017–18.

Mean haemoglobin and anaemia prevalence by chronic kidney disease stage

According to pooled NHANES data from 1999 to 2018, the Hb levels decreased as the CKD stage increased from a mean (95% CI) of 14.00 (13.88–14.11) g/dL in participants with stage 3A CKD to 11.97 (11.01–12.93) g/dL in those with stage 5 CKD (Fig. 3). The weighted prevalences of anaemia and Hb <10 g/dL also increased with advancing CKD stage, from 17.1% and 1.1%,



CKD stage, n	1930	730	218	48	Total CKD 2926

Figure 3: Weighted prevalence (95% CI) of anaemia and Hb <10 g/dL (left y-axis) and mean (95% CI) Hb levels (right y-axis) by CKD stage using pooled NHANES data from 1999–2018. [a]Defined as Hb <12 g/dL in women and <13 g/dL in men.

respectively, in stage 3A CKD to 66.1% and 12.7%, respectively, in stage 5 CKD (Fig. 3).

Regression analyses

In univariate and multivariate linear regression analyses by participant baseline demographics and characteristics, least-squares mean Hb levels were significantly lower in participants aged ≥75 years (vs younger participants), females (vs males), those of non-Hispanic Black race (vs non-Hispanic white, Hispanic or other races), with stage 3B–5 CKD (vs stage 3A) or diabetes (vs non-diabetics) (Table 1).

In univariate logistic regression analyses, the odds of participants developing anaemia or Hb <10 g/dL were higher in females (vs males), non-Hispanic Blacks (vs non-Hispanic whites) and participants with stage 3B–5 CKD (vs stage 3A CKD; Table 2). The odds of anaemia development were also higher in participants with diabetes or uncontrolled hypertension (vs those without these comorbidities).

In multivariate logistic regression analyses, the odds of anaemia development were higher in participants aged ≥75 years (vs those aged 18–44 years), females (vs males), non-Hispanic Blacks (vs non-Hispanic whites), participants with stage 3B–5 CKD (vs stage 3A CKD), and participants with diabetes (vs non-diabetics; Fig. 4A). The odds of Hb <10 g/dL were higher in participants with stage 3B–5 CKD (vs stage 3A CKD) and non-Hispanic Blacks (vs non-Hispanic whites; Fig. 4B).

DISCUSSION

In our analysis of NHANES data from 1999 to 2018, the estimated prevalence of anaemia among individuals with stage 3–5 NDD CKD was 25.3% (corresponding to an estimated 4.5 million people in the USA) and of anaemia eligible for ESA treatment (Hb <10 g/dL) was 1.9% (approximately 324 000 people in the USA).

The prevalence of anaemia in our analysis was slightly higher than those of previous studies [13, 18]. However, in these previous studies, the analysis included a wider range of patients with CKD than our study (i.e. stage 1–2 CKD) but did not evaluate the prevalence of Hb <10 g/dL [13] or were conducted without the use of weighted statistics [18]. In the previous analysis of NHANES 2007–10 data, the estimated weighted prevalence of anaemia was 15.4% among US patients with stage 1–5 CKD [13]. In a US Veterans Administration study of patients with NDD CKD (eGFR <60 mL/min/1.73 m^2), the unweighted prevalences of Hb <12 g/dL, Hb >8 to <10 g/dL and Hb <8 g/dL were 20.6%, 3.6% and 0.55%, respectively [18].

In our analysis, mean Hb levels showed numeric decreases over time from 1999 to 2012, after which they remained relatively stable. The weighted prevalence of anaemia increased between 2001 and 2010 and stabilized thereafter, whereas the weighted prevalence of Hb <10 g/dL remained relatively stable from 1999 to 2018.

Consistent with previous studies [13, 19, 20], our analysis showed that the prevalences of anaemia and Hb <10 g/dL increased as the CKD stage increased, with anaemia observed in >50% of study participants with stage 4 or 5 CKD. This observation may be explained by the reduction in erythropoiesis and increase in inflammation, functional iron deficiency and erythropoietin deficiency that occurs with the progressive loss of kidney function in patients with advanced-stage CKD [2].

In our linear regression analyses, increased age (≥75 years), female sex, Black race, CKD stage ≥3B, and concurrent diabetes were significantly associated with lower least-squares mean

Table 1: Estimated difference in least-squares mean Hb levels by CKD participant demographics and characteristics using pooled NHANES data from 1999 to 2018.

		Univariate analysis		Multivariate analysis	
		Difference in LSM Hb (95% CI), g/dL	P-value	Difference in LSM Hb (95% CI), g/dL	P-value
Age category, years					
18–44	vs 45–64	–0.054 (–0.707, 0.599)	.8704	–0.131 (–0.630, 0.367)	.6041
	vs 65–74	0.281 (–0.353, 0.914)	.3829	0.092 (–0.415, 0.599)	.7212
	vs ≥75	0.713 (0.099, 1.327)	.0231	0.427 (–0.082, 0.936)	.0994
45–64	vs 65–74	0.335 (0.054, 0.616)	.0199	0.223 (–0.040, 0.486)	.0963
	vs ≥75	0.767 (0.521, 1.013)	<.0001	0.558 (0.305, 0.811)	<.0001
65–74	vs ≥75	0.432 (0.237, 0.628)	<.0001	0.335 (0.159, 0.511)	.0002
Sex					
Female	vs Male	–1.594 (–1.739, –1.449)	<.0001	–1.421 (–1.582, –1.260)	<.0001
Race					
Hispanic	vs NH-Black	1.204 (0.773, 1.635)	<.0001	0.967 (0.546, 1.388)	<.0001
	vs NH-white	–0.001 (–0.400, 0.398)	.9955	0.007 (–0.401, 0.415)	.9737
	vs Other	0.364 (–0.076, 0.804)	.1040	0.152 (–0.260, 0.565)	.4669
NH-Black	vs NH-white	–1.205 (–1.401, –1.010)	<.0001	–0.960 (–1.173, –0.747)	<.0001
	vs Other	–0.840 (–1.143, –0.537)	<.0001	–0.815 (–1.083, –0.546)	<.0001
NH-white	vs Other	0.365 (0.112, 0.619)	.0051	0.146 (–0.093, 0.384)	.2291
BMI category, kg/m^2					
<25	vs 25 to <30	0.024 (–0.141, 0.190)	.7714	–0.1073 (–0.248, 0.033)	.1342
	vs ≥30	0.054 (–0.147, 0.256)	.5947	0.021 (–0.171, 0.212)	.8309
25 to <30	vs ≥30	0.030 (–0.190, 0.250)	.7879	0.128 (–0.052, 0.309)	.1628
Smoking status					
Current	vs Former	0.246 (–0.105, 0.597)	.1684	0.378 (0.101, 0.654)	.0077
	vs Non-smoker	0.432 (0.083, 0.780)	.0155	0.322 (0.030, 0.614)	.0311
Former	vs Non-smoker	0.186 (0.004, 0.368)	.0453	–0.056 (–0.210, 0.098)	.4724
CKD stage					
Stage 3A	vs 3B	0.852 (0.655, 1.049)	<.0001	0.580 (0.391, 0.768)	<.0001
	vs 4	1.427 (1.133, 1.721)	<.0001	1.2372 (0.995, 1.480)	<.0001
	vs 5	2.027 (1.066, 2.988)	<.0001	1.936 (0.870, 3.002)	.0004
Stage 3B	vs 4	0.575 (0.245, 0.905)	.0008	0.658 (0.374, 0.942)	<.0001
	vs 5	1.175 (0.231, 2.119)	.0151	1.357 (0.305, 2.408)	.0118
Stage 4	vs 5	0.600 (–0.351, 1.550)	.2144	0.699 (–0.351, 1.749)	.1904
Diabetes					
No	vs Yes	0.640 (0.462, 0.819)	<.0001	0.478 (0.330, 0.625)	<.0001
Hypertension (uncontrolled[a])					
No	vs Yes	0.335 (0.162, 0.508)	.0002	–0.048 (–0.210, 0.113)	.5550

[a]Defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (with or without the use of antihypertensive medications)
BMI, body mass index; LSM, least squares mean; NH, non-Hispanic.

Hb levels. Similarly, our multivariate logistic regression analysis showed that anaemia was significantly more likely to occur in participants aged ≥75 years, females, Blacks, those with CKD stage ≥3B and those with concurrent diabetes. In this analysis, the odds of Hb <10 g/dL were significantly higher in Blacks and participants with CKD stage ≥3B. These findings can be explained by the known impact of increased age, female sex and Black race on erythropoiesis and anaemia prevalence [21–26] and suggest that enhanced anaemia surveillance may be warranted for some patients in these groups.

The results of this analysis may have practical implications, as these data may assist in optimizing the screening of anaemia by identifying high-risk patients with CKD who require treatment.

One of the strengths of this study is its inclusion of recent, contemporary data that have been stratified by CKD stage and anaemia severity. In comparison, the previous 2007–10 NHANES analysis reported on overall anaemia prevalence in all participants with CKD (stages 1–5) [13]. Therefore, our analysis confirms the findings of similar studies in patients with NDD CKD regarding trends and risk factors for anaemia and is applicable to the entire adult non-institutionalized US population with stage 3A–5 NDD CKD.

The limitations of this analysis include the lack of data regarding the treatment of anaemia in the study participants. Therefore, our analysis may have underestimated anaemia prevalence, particularly anaemia eligible for ESA treatment, and overestimated mean Hb levels, especially in patients with advanced-stage CKD who are more likely to be receiving ESA therapy. Furthermore, the NHANES data include a limited number of individuals with advanced-stage CKD. Conversely, one general limitation of NHANES data is the inability to confirm abnormal laboratory findings or rule out alternative aetiologies of anaemia; therefore, the prevalence of anaemia of CKD may have been overestimated. In particular, transferrin saturation was not evaluated, and therefore the potential contribution of iron deficiency to the anemia incidences reported herein cannot be determined. Additionally, the data do not provide explanations for differences in anaemia prevalence observed among groups. For example, regarding the increased anaemia

Table 2: Univariate logistic regression analysis of patient characteristics associated with the prevalences of anaemia and anaemia eligible for ESA treatment (Hb <10 g/dL) using pooled NHANES data from 1999 to 2018.

	Anaemia[a]		Hb <10 g/dL	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years				
18–44	Ref	<.0001	Ref	.0649
45–64	0.800 (0.409–1.566)		0.748 (0.164–3.420)	
65–74	1.049 (0.549–2.005)		0.312 (0.082–1.192)	
≥75	1.477 (0.793–2.751)		0.702 (0.181–2.722)	
Sex				
Male	Ref	<.0001	Ref	.0063
Female	1.968 (1.609–2.406)		2.243 (1.261–3.990)	
Race				
NH-White	Ref	<.0001	Ref	<.0001
NH-Black	3.331 (2.642–4.198)		5.564 (2.896–10.691)	
Hispanic	1.080 (0.707–1.651)		1.494 (0.503–4.433)	
Other	1.524 (1.135–2.047)		1.185 (0.491–2.858)	
BMI, kg/m^2				
<25	Ref	.3634	Ref	.1940
25 to < 30	1.067 (0.850–1.338)		0.402 (0.150–1.079)	
≥30	1.201 (0.926–1.559)		0.858 (0.416–1.769)	
Smoking status				
Non-smoker	Ref	.4208	Ref	.2093
Current	0.772 (0.524–1.136)		0.789 (0.332–1.874)	
Former	0.958 (0.778–1.179)		0.553 (0.286–1.070)	
CKD stage				
3A	Ref	<.0001	Ref	<.0001
3B	3.311 (2.651–4.136)		3.582 (1.716–7.476)	
4	5.233 (3.709–7.383)		2.890 (1.084–7.701)	
5	9.262 (3.515–24.404)		13.596 (4.480–41.267)	
Diabetes				
No	Ref	<.0001	Ref	.2384
Yes	1.836 (1.496–2.253)		1.436 (0.785–2.626)	
Hypertension (uncontrolled[b])				
No	Ref	<.001	Ref	.1897
Yes	1.481 (1.224–1.793)		1.496 (0.818–2.736)	

[a]Defined as Hb <12 g/dL in women and <13 g/dL in men.
[b]Defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (with or without the use of antihypertensive medications).
BMI, body mass index; NH, non-Hispanic; OR, odds ratio; Ref, reference.

prevalence and increased prevalence of Hb <10 g/dL among Black NHANES participants with CKD, NHANES is unable to address the potential contributions of disparities in access to healthcare [27] or biological differences such as increased incidence of thalassaemia [25]. Other limitations include potential misclassification of CKD stage due to a single eGFR measurement that is not compliant with KDIGO guidelines [17], the fact that a formal diagnosis of CKD is not documented in NHANES, and the cross-sectional design of NHANES that lacks follow-up.

CONCLUSIONS

This analysis of NHANES data from 1999 to 2018 shows that the prevalence of anaemia in individuals with stage 3–5 CKD in the USA is approximately 25% and the prevalence of anaemia eligible for ESA treatment (Hb <10 g/dL) in this population is approximately 2%.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study design, read and edited various drafts of the manuscript, approved the final submission, and take full responsibility for the integrity of the work as a whole. J.R.D. contributed to the study design and interpretation of the results, and I.D. performed the data analyses.

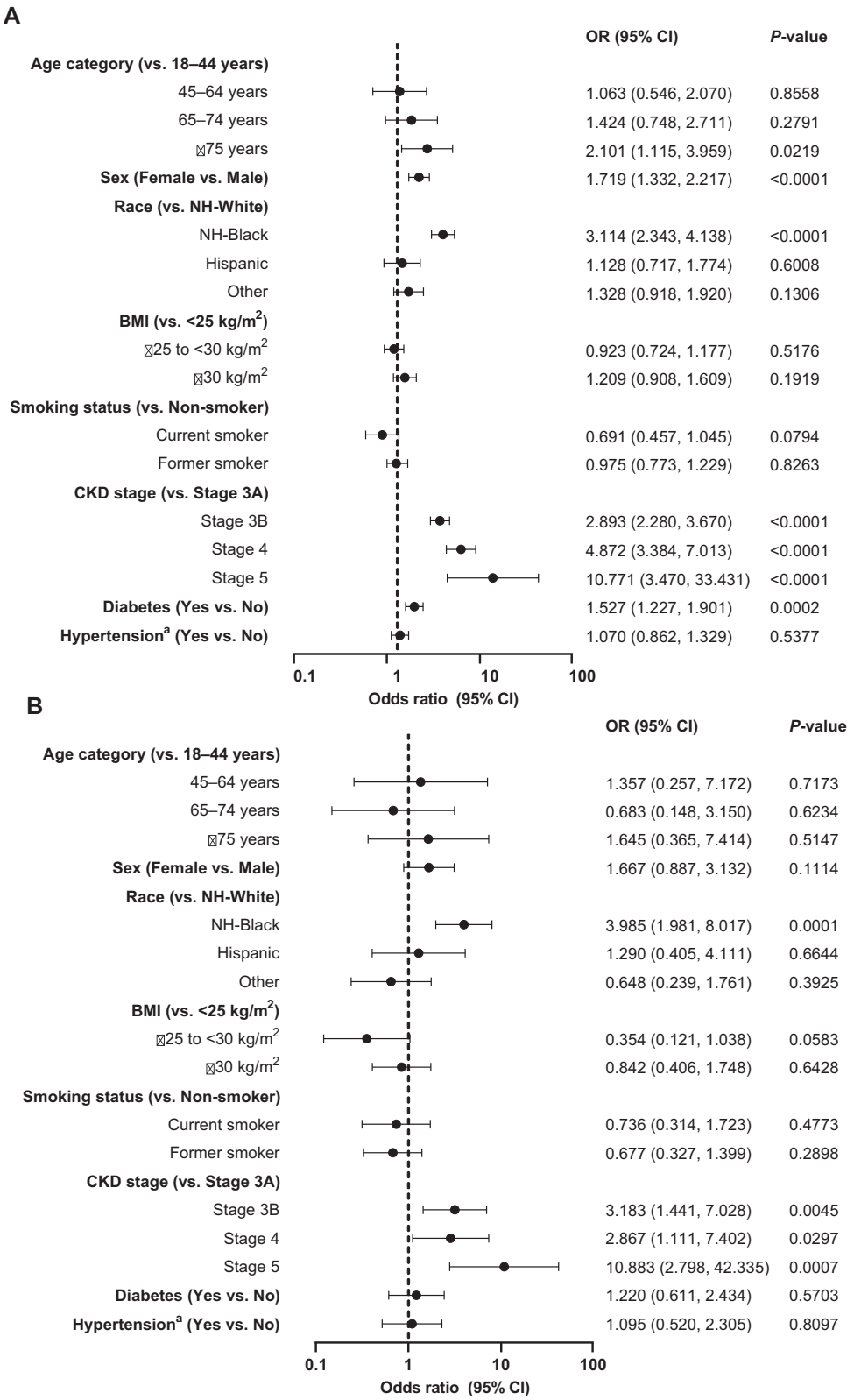

Figure 4: Multivariate logistic regression analysis of patient characteristics associated with prevalence of (**A**) anaemia (defined as Hb <12 g/dL in women and <13 g/dL in men) and (**B**) Hb <10 g/dL in participants with stage 3–5 CKD using pooled NHANES data from 1999 to 2018. [a]Uncontrolled hypertension; defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (with or without the use of antihypertensive medications). BMI, body mass index; NH, non-Hispanic; OR, odds ratio.

DATA AVAILABILITY STATEMENT

The data underlying this article are available from https://www.cdc.gov/nchs/nhanes/index.htm.

CONFLICT OF INTEREST STATEMENT

C.P.K. has served as consultant for Akebia, Ardelyx, AstraZeneca, Bayer, Cara Therapeutics and Tricida, Inc. I.D. and D.J.L. are employees of AstraZeneca. J.R.D. was an employee of AstraZeneca at the time of the study and manuscript development.

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