Original Report:
Cardiovascular Disease
and Risk Factors

Sex and Race-Ethnicity Secular Trends in Mean and Elevated Red Blood Cell Distribution Width Among Adults in the United States, 1999-2012

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Objective: Red blood cell distribution width (RDW) has been shown to associate with increased risk of cardiovascular and non-cardiovascular death. To our knowledge, no study has examined secular trends in RDW over the last decade.

Design: Serial cross-sectional design.

Setting: Data from the National Health and Nutrition Examination Survey (NHANES), 1999-2012, were used.

Patients: 34,171 adults.

Main Outcome Measure: RDW was assessed from a blood sample derived from the coefficient of variation of the red cell volume distribution histogram and reported as a percent. Elevated RDW was defined as an RDW > 14.6%.

Results: The overall age-adjusted mean RDW increased progressively and significantly (P<.05) from 12.59% in 1999-2000 to 12.89% in 2011-2012. The overall age-adjusted prevalence of elevated RDW increased progressively and significantly (P<.05) from 4.01% in 1999-2000 to 6.25% in 2011-2012. Statistically significant increases over this time period also occurred among non-Hispanic White women, non-Hispanic Black men and women, and Mexican American men and women. Across all sex and race-ethnicity combinations, women, compared with men, had higher RDW and larger increases over time in mean and elevated RDW.

Conclusion: Mean and elevated RDW has progressively increased from 1999-2012 among adults in the United States, with increases observed among non-Hispanic Whites, Blacks, and Mexican Americans.

Introduction

Red blood cells are an important component of the complete blood count and play a principal role in delivering oxygen (via hemoglobin) throughout the circulatory system. Abnormal red blood cell levels, which are interpreted in the context of other diagnostic results, may be indicative of various medical conditions, such as anemia (low red blood cell levels) or polycythemia (high red blood cell levels). Red blood cell distribution width (RDW) is also an important component of the complete blood count that is routinely measured during clinical assessments and provides a measure of the heterogeneity of the erythrocyte volume. A high degree of variability (eg, >14.6%) in the volume of red blood cells (ie, high RDW) may be indicative of different types of anemia and other medical conditions, providing valuable inexpensive prognostic information related to cardiovascular disease and premature mortality.[1-4]

Although inconclusive, the pathophysiology linking RDW with morbidity and mortality may be a result of inflammation-induced anisocytosis and/or disordered iron homeostasis,[5-8] or possibly a result of cytokine-induced erythropoietin resistance.[9] There is also some evidence to suggest that sex may moderate the relationship between RDW and mortality,[10] with the need of future research examining potential ethnic effects. Although RDW is associated with increased morbidity and mortality,[1] its trend over time is unknown. Therefore, the objective of this brief study was to examine trends

Future research is needed to describe the determinants and implications of this RDW rise, as well as explanations for why a greater RDW change has occurred among women. *Ethn Dis*.2016;26(1):45-50; doi:10.18865/ed.26.1.45

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in mean RDW and prevalence of elevated RDW among adults in the United States from 1999-2012, with a particular focus on trends across sex and race-ethnicity combinations.

The objective of this brief study was to examine trends in mean RDW and prevalence of elevated RDW among adults in the United States from 1999-2012, with a particular focus on trends across gender and race-ethnicity combinations.

Methods

Design

Data from seven 2-year cycles of the National Health and Nutrition Examination Survey (NHANES) were used, starting in 1999-2000 and concluding in 2011-2012 (latest available cycle). The NHANES is an ongoing survey conducted by the Centers for Disease Control and Prevention that uses a representative sample of non-institutionalized United States civilians selected by a complex, multistage, stratified, clustered probability design. Examination response rates across the survey cycles ranged from 69.5% to 79.6%. Participants provided consent to participate, with the study procedures approved by the National Center for Health Statistics ethics committee.

Measurement of Red Blood Cell Distribution Width

The complete blood count was from a blood sample using the Beckman Coulter MAXM analyzer. Red cell distribution width was derived from the coefficient of variation of the red cell volume distribution histogram and reported as a percent. Elevated RDW was defined as an RDW >14.6%.[11]

Analysis

All analyses, conducted in Stata (v. 12), took into account the complex sampling design of the surveys; sample weights (adjusted based on the combined cycles used), primary sampling units and clustering parameters were used to adjust for non-response, non-compliance and render nationally representative estimates. Mean RDW and prevalence of elevated RDW across the seven 2-year cycles was determined. Because unadjusted and age-adjusted results were similar, only the latter are reported. Age adjustments were performed using the direct method using the projected year 2000 US population aged >20 years. Tests for linear trend were conducted using linear-specific orthogonal polynomial coefficients. A two-sided $P<.05$ was considered statistically significant.

Results

Data from 34,171 adults (≥ 20 yrs) were analyzed. The weighted mean (SE, standard error) age across the entire sample (1999-2012) was 46.7 years; the weighted proportion (SE) of women across the entire sample was 52.0%; and the weighted proportion (SE) of Whites, Blacks and Mexican Americans across the entire sample, respectively, were 70.5%, 10.7% and 7.8%. As noted in the footnote of the Tables, age, sex and race-ethnicity estimates were similar across each individual cycle.

Participants were not excluded from the analyses based on any known presence of disease. Among the analyzed 34,171 adults, 3,025 self-reported a physician diagnosis of cancer; of these 3,025 participants, the unweighted proportion (SE) across the 7 two-year cycles, respectively, were 7.1 (.3), 8.9 (.4), 9.2 (.4), 8.2 (.4), 9.5 (.4), 9.8 (.3) and 8.4 (.3). Among the analyzed 34,171 adults, 1,165 self-reported a physician diagnosis of liver disease; of these 1,165 participants, the unweighted proportion (SE) across the 7 two-year cycles, respectively, were 3.0 (.2), 3.0 (.2), 3.4 (.2), 3.4 (.2), 3.8 (.2), 3.0 (.2) and 3.9 (.2). Lastly, among the 34,171 participants, 3,217 had some evidence of anemia, which we defined as a hemoglobin level < 12 g/dL for women and < 13 g/dL for men; the unweighted proportion (SE) of anemia across the respective cycles were 8.4 (.4), 9.0 (.4), 7.8 (.4), 9.4 (.4), 8.9 (.3), 9.4 (.3) and 12.3 (.4).

The overall age-adjusted mean RDW increased progressively and significantly from 12.59% in 1999-2000 to 12.89% in 2011-2012 (Table 1; Figure 1). Statistically significant increases in mean RDW over this time period were also

Table 1. Age-adjusted [a] mean red blood cell distribution width among adults in the National Health and Nutrition Examination Survey, 1999-2012 (N=34,171)

	Mean Red Blood Cell Distribution Width (95% CI), %								
	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	%Change [b]	P [c]
Overall Sample	12.59 (12.54-12.64)	12.65 (12.60-12.69)	12.66 (12.61-12.71)	12.73 (12.67-12.78)	12.74 (12.68-12.80)	12.79 (12.73-12.86)	12.89 (12.80-12.97)	.3	<.001
Overall – Men	12.56 (12.50-12.62)	12.56 (12.51-12.60)	12.59 (12.53-12.64)	12.62 (12.56-12.67)	12.61 (12.55-12.66)	12.67 (12.60-12.73)	12.76 (12.69-12.83)	.2	<.001
Overall - Women	12.63 (12.56-12.70)	12.74 (12.67-12.81)	12.74 (12.68-12.80)	12.83 (12.77-12.89)	12.87 (12.79-12.94)	12.92 (12.83-13.00)	13.01 (12.91-13.12)	.38	<.001
Non-Hispanic White									
Men	12.49 (12.42-12.56)	12.5 (12.45-12.55)	12.52 (12.45-12.59)	12.53 (12.49-12.57)	12.56 (12.49-12.62)	12.6 (12.52-12.68)	12.68 (12.60-12.77)	.19	<.001
Women	12.47 (12.37-12.57)	12.6 (12.52-12.68)	12.57 (12.52-12.62)	12.67 (12.61-12.73)	12.73 (12.64-12.82)	12.74 (12.64-12.82)	12.83 (12.71-12.96)	.36	<.001
Non-Hispanic Black									
Men	13 (12.87-13.13)	13.03 (12.92-13.14)	13.02 (12.93-13.10)	13.16 (13.07-13.25)	13.1 (12.98-13.21)	13.2 (13.05-13.36)	13.2 (13.08-13.31)	.2	.001
Women	13.24 (13.13-13.35)	13.5 (13.33-13.67)	13.56 (13.41-13.71)	13.7 (13.54-13.87)	13.55 (13.41-13.69)	13.8 (13.65-13.96)	13.64 (13.46-13.82)	.4	<.001
Mexican American									
Men	12.5 (13.43-12.56)	12.48 (12.41-12.55)	12.54 (12.45-12.63)	12.51 (12.46-12.57)	12.54 (12.46-12.63)	12.64 (12.51-12.77)	12.76 (12.66-12.86)	.26	<.001
Women	12.77 (12.73-12.82)	12.91 (12.72-13.10)	12.93 (12.80-13.07)	12.97 (12.75-13.19)	12.95 (12.84-13.05)	13.01 (12.87-13.15)	13.32 (13.10-13.54)	.55	<.001

a. Age adjustment was performed using the direct method using the projected year 2000 US Population aged ≥20 years.
b. Percent change was calculated as percent change from 1999-2000 (T1) to 2011-2012 (T2): [T2-T1].
c. Tests for linear trend were conducted using linear-specific orthogonal polynomial coefficients.
N = 34,171; 1999-2000 (n=4210), 2001-2002 (n=4775), 2003-2004 (4530), 2005-2006 (n=4508), 2007-2008 (5358), 2009-2010 (n=5753), 2011-2012 (n=5037). The weighted mean (SE, standard error) age between 1999 and 2012 was 46.7 yrs (.22). The weighted mean (SE) age across 7 two-year cycles, respectively, were 46.0 (.5), 46.3 (.5), 46.4 (.5), 46.8 (.7), 47.0 (.4), 47.0 (.4) and 47.4 (.8). The weighted proportion (SE) of women between 1999 and 2012 was 52.0 (.2). The weighted (SE) proportion of women across the 7 two-year cycles, respectively, were 52.0 (.6), 52.2 (.5), 51.9 (.7), 52.1 (.5), 52.0 (.5), 51.8 (.5) and 52.1 (.7). The weighted proportion (SE) of Whites between 1999 and 2012 was 70.5 (1.2). The weighted (SE) proportion of Whites across the 7 two-year cycles, respectively, were 69.9 (2.6), 72.9 (2.5), 72.5 (3.3), 72.4 (2.7), 70.1 (3.6), 68.7 (3.3), and 67.1 (3.8). The weighted proportion (SE) of Blacks between 1999 and 2012 was 10.7 (.6). The weighted (SE) proportion of Blacks across the 7 two-year cycles, respectively, were 10.5 (1.6), 10.0 (1.6), 10.8 (1.7), 11.1 (1.9), 10.3 (1.8), 10.8 (.8) and 10.9 (2.2). The weighted proportion (SE) of Mexican Americans between 1999 and 2012 was 7.8 (.6). The weighted (SE) proportion of Mexican Americans across the 7 two-year cycles, respectively, were 7.3 (1.5), 6.8 (.8), 7.6 (1.9), 7.9 (.9), 8.4 (1.5), 8.5 (2.1) and 7.7 (1.7).

observed for men, women, non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans.

The overall age-adjusted prevalence of elevated RDW increased from 4.01% in 1999-2000 to 6.25% in 2011-2012 (Table 2; Figure 1). Statistically significant increases in the prevalence of elevated RDW over this time period also occurred among non-Hispanic White women, non-Hispanic Black men and women, and Mexican American men and women. The largest increase in the prevalence of elevated RDW over this time period occurred among Mexican American women (4.88% increase). Notably, across all sex and race-ethnicity combinations, women, compared with men, had higher RDW and larger increases in mean and elevated RDW. Regarding men, non-Hispanic Black men had higher mean and elevated RDW across

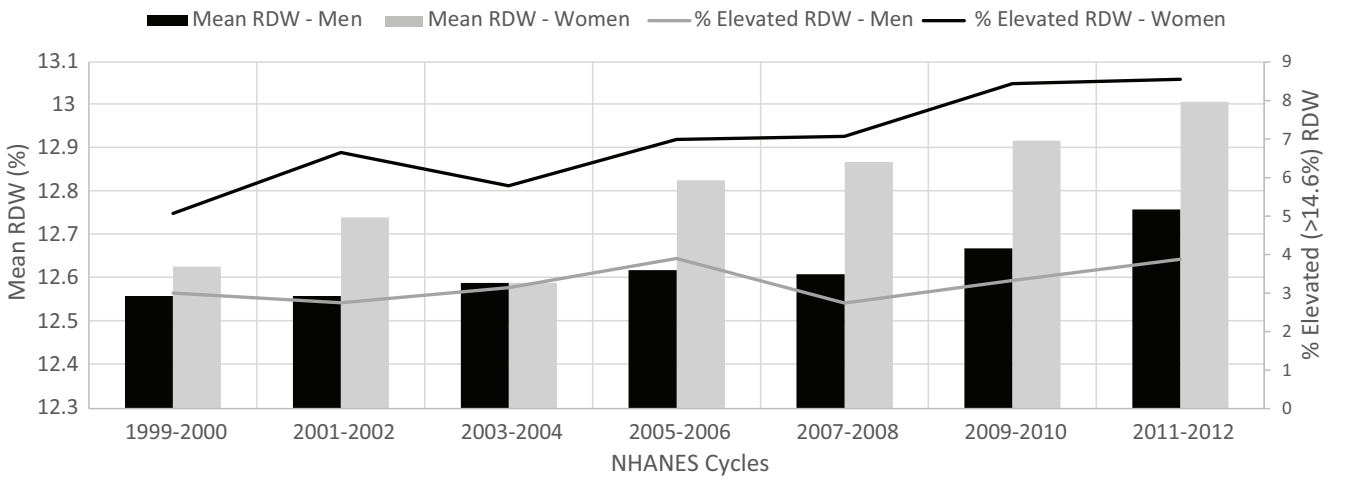

Figure 1. Mean age-adjusted RDW (left ordinate) and age-adjusted prevalence of elevated RDW (right ordinate) among men and women across the seven 2-year NHANES cycles, NHANES 1999-2012.

each time period when compared with non-Hispanic White men.

Discussion

Our study demonstrates that mean RDW levels and the prevalence of elevated RDW has progressively increased from 1999-2012, with this trend occurring across sex and race-ethnicity sub-groups. Notably, women had higher RDW levels and a steeper trajectory in RDW changes than men, with non-Hispanic Black men having higher RDW levels (and a steeper trajectory over time) when compared with non-Hispanic White men.

This progressive increase is concerning, as higher RDW is a strong predictor of various chronic diseases[12] as well as premature mortality.[1] The biological pathways underlying the association between higher RDW and morbidity and mortality are unclear at this time. Possible mechanisms linking RDW with morbidity and mortality may be a result of inflammation, disordered iron homeostasis, and/or erythropoietin resistance-induced anisocytosis.[5-9]

Conclusion

With rising health care costs, it is important to identify inexpensive biomarkers, such as RDW, which predict cardiovascular disease and premature mortality. RDW is often obtained at the time of routine physical examinations as part of the complete blood count and may provide a cost-effective way to provide incremental prognostic information. These findings support the continued routine assessment of RDW in clinical care, as well as the promotion of lifestyle factors (eg, physical activity) shown to influence RDW.[13-16] Given the progressively larger increases in RDW among women, compared with men, which is supported by other work,[17] serial monitoring of RDW changes and RDW-related morbidities among women, in particular, may be needed. Given the higher RDW levels among Black men, compared with White men, careful monitoring of RDW among Black men may be needed. Future research is needed to improve our understanding of why women have higher RDW than men (observed at each time period) and why the increased trajec-

Our study demonstrates that mean RDW levels and the prevalence of elevated RDW has progressively increased from 1999-2012, with this trend occurring across sex and race-ethnicity subgroups.

Table 2. Age-adjusted [a] prevalence of elevated (>14.6%) red blood cell distribution width among adults in the National Health and Nutrition Examination Survey, 1999-2012 (N=34,171)

	% High (>14.6%) Red Blood Cell Distribution Width (95% CI)								
	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	% Change [b]	P-Trend [c]
Overall Sample	4.01 (3.44-4.59)	4.71 (3.67-5.76)	4.44 (3.80-5.08)	5.47 (4.74-6.21)	4.96 (4.20-5.73)	5.92 (4.95-6.89)	6.25 (5.35-7.16)	2.24	<.001
Overall – Men	3 (1.99-4.01)	2.75 (2.09-3.41)	3.14 (2.32-3.97)	3.9 (2.89-4.91)	2.74 (2.19-3.28)	3.33 (2.44-4.21)	3.88 (2.78-4.97)	.88	.07
Overall - Women	5.07 (4.26-5.88)	6.65 (4.99-8.32)	5.79 (4.89-6.69)	6.99 (6.05-7.93)	7.07 (5.82-8.32)	8.44 (6.97-9.92)	8.55 (7.12-9.98)	3.48	<.001
Non-Hispanic White									
Men	2.48 (1.43-3.53)	2.47 (1.59-3.36)	2.64 (1.46-3.83)	3.17 (2.38-3.96)	2.03 (1.52-2.54)	2.43 (1.53-3.34)	2.92 (1.98-3.86)	.44	.36
Women	2.98 (1.82-4.14)	4.53 (2.73-6.33)	3.74 (2.50-4.98)	4.71 (3.57-5.85)	4.81 (3.10-6.51)	5.91 (4.12-7.70)	5.52 (3.86-7.19)	2.54	.003
Non-Hispanic Black									
Men	5.98 (3.02-8.94)	7.21 (5.04-9.38)	6.2 (4.88-7.52)	1.76 (7.79-13.74)	9.08 (7.00-11.15)	1.4 (7.40-13.41)	9.83 (7.36-12.29)	3.85	.001
Women	14.36 (1.61-18.10)	18.41 (14.42-22.41)	16.62 (13.61-19.63)	18.04 (15.57-2.50)	18.42 (15.16-21.67)	2.95 (19.09-22.81)	18.93 (15.56-22.30)	4.57	.02
Mexican American									
Men	1.99 (1.17-2.80)	1.67 (.73-2.60)	1.74 (.87-2.62)	1.23 (.15-2.32)	2.17 (.84-3.50)	2.68 (1.18-4.17)	3.17 (1.12-5.22)	1.18	.02
Women	7.76 (6.63-8.89)	8.4 (6.10-1.69)	8.44 (4.96-11.93)	9.45 (6.05-12.85)	7.65 (5.77-9.53)	8.63 (6.66-1.60)	12.64 (8.73-16.56)	4.88	.02

a. Age adjustment was performed using the direct method using the projected year 2000 US Population aged ≥20 years.
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c. Tests for linear trend were conducted using linear-specific orthogonal polynomial coefficients.
N = 34,171; 1999-2000 (n=4210), 2001-2002 (n=4775), 2003-2004 (4530), 2005-2006 (n=4508), 2007-2008 (5358), 2009-2010 (n=5753), 2011-2012 (n=5037). The weighted mean (SE, standard error) age between 1999 and 2012 was 46.7 yrs (.22). The weighted mean (SE) age across 7 two-year cycles, respectively, were 46.0 (.5), 46.3 (.5), 46.4 (.5), 46.8 (.7), 47.0 (.4), 47.0 (.4) and 47.4 (.8). The weighted proportion (SE) of women between 1999 and 2012 was 52.0 (.2). The weighted (SE) proportion of women across the 7 two-year cycles, respectively, were 52.0 (.6), 52.2 (.5), 51.9 (.7), 52.1 (.5), 52.0 (.5), 51.8 (.5) and 52.1 (.7). The weighted proportion (SE) of Whites between 1999 and 2012 was 70.5 (1.2). The weighted (SE) proportion of Whites across the 7 two-year cycles, respectively, were 69.9 (2.6), 72.9 (2.5), 72.5 (3.3), 72.4 (2.7), 70.1 (3.6), 68.7 (3.3), and 67.1 (3.8). The weighted proportion (SE) of Blacks between 1999 and 2012 was 10.7 (.6). The weighted (SE) proportion of Blacks across the 7 two-year cycles, respectively, were 10.5 (1.6), 10.0 (1.6), 10.8 (1.7), 11.1 (1.9), 10.3 (1.8), 10.8 (.8) and 10.9 (2.2). The weighted proportion (SE) of Mexican Americans between 1999 and 2012 was 7.8 (.6). The weighted (SE) proportion of Mexican Americans across the 7 two-year cycles, respectively, were 7.3 (1.5), 6.8 (.8), 7.6 (1.9), 7.9 (.9), 8.4 (1.5), 8.5 (2.1) and 7.7 (1.7).

tory of RDW is more pronounced in women. However, future sex-specific research is needed as there is some evidence to suggest a greater magnitude of association between RDW and mortality for men compared with women.[10] Although a previous study did not observe an interaction effect of ethnicity on the RDW-mortality relationship,[10] future race-ethnicity work on this topic is warranted.

Acknowledgments

Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Loprinzi,, Loenneke, Ahmed, Blaha. Acquisition of data: Loprinzi. Data analysis and interpretation: Loprinzi, Loenneke, Ahmed, Blaha. Manuscript draft: Loprinzi, Loenneke,, Ahmed, Blaha. Statistical expertise: Loprinzi, Loenneke, Ahmed, Blaha. Supervision: Loprinzi, Loenneke, Ahmed, Blaha

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