



Red Cell Distribution Width and Mortality in Older Adults: A Meta-analysis

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Background. Red cell distribution width (RDW) is a quantitative measure of variability in the size of circulating erythrocytes with higher values reflecting greater heterogeneity in cell sizes. Recent studies have shown that higher RDW is associated with increased mortality risk in patients with clinically significant cardiovascular disease (CVD). Whether RDW is prognostic in more representative community-based populations is unclear.

Methods. Seven relevant community-based studies of older adults with RDW measurement and mortality ascertainment were identified. Cox proportional hazards regression and meta-analysis on individual participant data were performed.

Results. Median RDW values varied across studies from 13.2% to 14.6%. During 68,822 person-years of follow-up of 11,827 older adults with RDW measured, there was a graded increased risk of death associated with higher RDW values ($p < .001$). For every 1% increment in RDW, total mortality risk increased by 14% (adjusted hazard ratio [HR]: 1.14; 95% confidence interval [CI]: 1.11–1.17). In addition, RDW was strongly associated with deaths from CVD (adjusted HR: 1.15; 95% CI: 1.12–1.25), cancer (adjusted HR: 1.13; 95% CI: 1.07–1.20), and other causes (adjusted HR: 1.13; 95% CI: 1.07–1.18). Furthermore, the RDW–mortality association occurred in all major demographic, disease, and nutritional risk factor subgroups examined. Among the subset of 1,603 older adults without major age-associated diseases, RDW remained strongly associated with total mortality (adjusted HR: 1.32; 95% CI: 1.21–1.44).

Conclusions. RDW is a routinely reported test that is a powerful predictor of mortality in community-dwelling older adults with and without age-associated diseases. The biologic mechanisms underlying this association merit investigation.

Key Words: Aging—Erythrocyte Indices—Mortality—Risk Factors.

THE red cell distribution width (RDW) is a quantitative measure of variability in the size of circulating erythrocytes with higher values reflecting greater heterogeneity in cell sizes. Although RDW is routinely reported to physicians in clinical practice as part of the automated complete blood count (CBC), it is currently mainly used as an auxiliary index in the differential diagnosis of microcytic anemia. Iron deficiency anemia is associated with a high RDW, whereas thalassemia syndromes produce red blood cells (RBCs) of more homogenous size.

A few studies recently showed that higher RDW, even within the normal reference range, was strongly associated with increased risk of death and cardiovascular disease

(CVD) events in middle-aged and older adults (1–7). Although the exact mechanisms are unclear, this association is provocative because it is independent of numerous factors, including nutritional status, anemia, inflammation, and age-associated diseases (5). Furthermore, RDW significantly improved mortality risk prediction beyond established risk factors, as assessed by several indices of model calibration and discrimination (5). Given that higher RDW is associated with advancing age and higher disease burden (5), it is possible that RDW is a novel biomarker that reflects multiple physiological impairments related to aging.

Of the previous studies that examined RDW and mortality, all but one were performed in patients with clinically

significant CVD. Whether RDW is prognostic in more representative community-based populations requires further investigation. The aim of the current study was to quantify the association of RDW with total and cause-specific mortality in seven population-based studies of older adults with varied health and demographic compositions. Specifically, we characterized the dose-response relationship and assessed its consistency across the studies as well as in major subgroups of older adults.

METHODS

Study Populations and Design

Individual participant data of older adults were analyzed from six cohort studies developed in collaboration with the Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging/National Institutes of Health. In addition, publicly available data on older adults who participated in the Third National Health and Nutrition Examination Survey (NHANES III) were also analyzed. Table 1 provides a description of the studies included in the meta-analysis. (A search of the MEDLINE and EMBASE databases from 1974 to June 2009 using red cell distribution width or RDW and mortality as search terms did not identify additional community-based studies for inclusion in this analysis.) In all seven studies, RDW was measured as part of the automated CBC and participants were subsequently followed for mortality. Although each study cohort was composed of community-dwelling older adults, the goals of the studies varied and therefore the sampling procedures and target populations differed accordingly. The Women's Health and Aging Study I (WHAS I), for instance, sampled moderately to severely disabled women aged 65 years and older, whereas the Health, Aging, and Body Composition Study (Health ABC Study) recruited well-functioning men and women aged 70–79 years from a Medicare sample within selected zip codes. The InCHIANTI (“Invecchiare in Chianti,” aging in Chianti area) Study, NHANES III, and the New Haven site of the Established Populations for the Epidemiologic Studies of the Elderly (EPESE) used probabilistic methods to sample men and women aged 65 years and older regardless of functional status, whereas the East Boston and Iowa EPESE sites recruited all older persons in their geographical areas. CBCs were collected at the baseline visit in the InCHIANTI Study, NHANES III, and WHAS I; 2 years after baseline in the Health ABC Study; and 6 years after baseline in the East Boston, Iowa, and New Haven sites of the EPESE.

Adjustment Variables

A standard set of variables that might confound the association of RDW with mortality was available in each study. This included information on demographic and health behavior-related factors (age, sex, race, education level,

Table 1. Study Characteristics

Study	Sample	RDW Measurement Dates	Sample Size With RDW (N = 11,827)	Follow-up, Median (IQR), y	Total Person-years of Follow-Up (N = 68,822)	Number of Deaths (N = 3,985)	Mortality Rate per 1,000 Person-years (95% CI)
East Boston EPESE	Population-based cohort of adults, aged ≥ 71 y in East Boston, MA	1988–1989	1,152	4.9 (4.6–5.2)	5,104	265	51.9 (46.0–58.6)
Iowa EPESE	Population-based cohort of adults, aged ≥ 71 y in Iowa and Washington Counties, IA	1988	1,550	5.8 (5.6–5.9)	8,032	405	50.4 (45.7–55.6)
New Haven EPESE	Population-based cohort of adults, aged ≥ 71 y in New Haven, CT	1988–1989	866	4.3 (3.8–4.5)	3,278	246	75.0 (66.2–85.0)
NHANES III	Population-based cohort of adults, aged ≥ 65 y, USA	1988–1994	4,198	7.2 (4.9–9.2)	28,747	1,976	54.5 (51.2–58.0)
WHAS I	Population-based cohort of disabled women, aged ≥ 65 y in Baltimore, MD	1993–1995	742	4.8 (3.4–5.0)	2,983	229	76.8 (67.5–87.4)
InCHIANTI Study	Population-based cohort of adults, aged ≥ 65 y in Tuscany, Italy	1998–2000	1,036	6.0 (5.7–6.2)	5,620	265	47.2 (41.8–53.2)
Health ABC Study	Population-based cohort of well-functioning adults, aged 71–82 y in Memphis, TN and Pittsburgh, PA	1999–2000	2,283	7.3 (6.9–7.4)	15,058	599	39.8 (36.7–43.1)

Note: CI = confidence interval; EPESE = Established Populations for the Epidemiologic Studies of the Elderly; Health ABC Study = Health, Aging, and Body Composition Study; IQR = interquartile range; NHANES III = Third National Health and Nutrition Examination Survey; RDW = red cell distribution width; WHAS I = Women's Health and Aging Study I.

Table 2. Baseline Participant Characteristics for Each Cohort

Characteristics	East Boston EPESE (N = 1,152)	Iowa EPESE (N = 1,550)	New Haven EPESE (N = 866)	NHANES III (N = 4,198)*	WHAS I (N = 742)	InCHIANTI Study (N = 1,036)	Health ABC Study (N = 2,283)
RDW%, median [IQR]	14.1 [13.5–15.0]	14.5 [13.7–15.8]	14.6 [13.8–15.9]	13.2 [12.7–13.8]	14.0 [13.4–14.9]	13.5 [13.1–14.1]	13.3 [12.8–14.0]
Age, <i>M</i> (<i>SD</i>), y	77.9 (5.1)	78.4 (5.4)	79.1 (6.0)	73.6 (0.2)	77.6 (7.8)	75.1 (7.4)	75.6 (2.9)
Women, <i>n</i> (%)	734 (63.7)	996 (64.3)	551 (63.6)	2,191 (57.3)	742 (100.0)	580 (56.0)	1,190 (52.1)
Black race, <i>n</i> (%)	0 (0)	0 (0)	187 (21.6)	740 (7.8)	204 (27.5)	0 (0)	876 (38.4)
Education, <i>M</i> (<i>SD</i>), y	8.9 (3.3)	10.9 (3.0)	9.3 (3.8)	10.9 (0.1)	9.7 (3.7)	5.3 (3.3)	13.1 (3.2)
Smoking history, <i>n</i> (%)							
Never	654 (56.8)	1,122 (72.8)	459 (53.0)	2,075 (46.8)	394 (53.1)	612 (59.1)	1,048 (47.4)
Former	388 (33.7)	351 (22.8)	295 (34.1)	1,606 (40.4)	262 (35.3)	281 (27.1)	993 (44.9)
Current	110 (9.6)	68 (4.4)	112 (12.9)	517 (12.8)	86 (11.6)	143 (13.8)	172 (7.8)
Body mass index, <i>M</i> (<i>SD</i>), kg/m ²	26.8 (4.8)	26.7 (4.6)	25.2 (4.7)	26.7 (0.1)	28.9 (9.3)	27.5 (4.1)	27.3 (4.8)
Cancer, <i>n</i> (%)	250 (21.7)	326 (21.0)	182 (21.0)	403 (10.2)	87 (11.7)	66 (6.4)	474 (20.8)
Diabetes, <i>n</i> (%)	249 (21.6)	210 (13.6)	153 (17.7)	661 (12.7)	125 (16.9)	133 (12.8)	456 (20.0)
Heart attack, <i>n</i> (%)	168 (14.6)	212 (13.7)	151 (17.4)	523 (12.3)	153 (20.6)	79 (7.6)	439 (19.2)
Hypertension, <i>n</i> (%)	728 (63.2)	1,008 (65.0)	567 (65.5)	2,852 (65.5)	530 (71.4)	639 (61.7)	1,464 (64.1)
Stroke, <i>n</i> (%)	81 (7.0)	134 (8.7)	87 (10.1)	385 (7.8)	40 (5.4)	79 (7.6)	191 (8.4)
eGFR, <i>M</i> (<i>SD</i>), mL/min/1.73 m ²	56.1 (15.3)	55.4 (15.1)	57.8 (21.4)	72.1 (0.4)	58.8 (16.0)	75.5 (17.5)	73.0 (15.9)
Hemoglobin, <i>M</i> (<i>SD</i>), g/L	134 (15)	141 (15)	134 (16)	139 (0.4)	129 (14)	137 (14)	136 (14)
Mean corpuscular volume, <i>M</i> (<i>SD</i>), fL	91.5 (6.5)	93.9 (5.3)	92.1 (6.0)	91.2 (0.2)	93.3 (6.6)	90.6 (4.9)	91.0 (17.8)
Albumin, <i>M</i> (<i>SD</i>), g/L	40.7 (10.8)	41.2 (2.8)	40.2 (3.2)	40.2 (0.2)	40.4 (3.0)	41.8 (3.1)	39.9 (3.1)
Nutritional status, <i>n</i> (%)							
Iron deficient	n/a	n/a	n/a	135 (5.6)	19 (2.6)	61 (6.1)	n/a
Folate deficient	n/a	n/a	n/a	163 (6.4)	7 (1.0)	188 (18.2)	n/a
Vitamin B ₁₂ deficient	n/a	n/a	n/a	110 (5.4)	48 (6.6)	117 (11.7)	n/a

Notes: eGFR = estimated glomerular filtration rate; EPESE = Established Populations for the Epidemiologic Studies of the Elderly; Health ABC Study = Health, Aging, and Body Composition Study; n/a = not available; IQR = interquartile range; NHANES III = Third National Health and Nutrition Examination Survey; RDW = red cell distribution width; WHAS I = Women's Health and Aging Study I.

* Observed *n* (weighted percent) or weighted *M* (*SE*).

smoking history, and body mass index [BMI]) as well as age-associated medical conditions (cancer, diabetes, heart attack, hypertension, and stroke). Self-reported data on race were included because of known differences in the distribution of some CBC parameters by race, including RDW (5), and the differential effect of hemoglobin concentration on mortality by race (8). Laboratory measures included serum creatinine, serum albumin, hemoglobin concentration, and mean corpuscular volume (MCV). The four-variable abbreviated Modification of Diet in Renal Disease Study formula was used to calculate estimated glomerular filtration rate (eGFR) (9). For subgroup analysis, chronic kidney disease was defined as eGFR less than 60 mL/min/1.73 m² and anemia was defined as hemoglobin concentration less than 13 and less than 12 g/dL in men and women, respectively. In addition, deficiencies in iron, folate, and vitamin B₁₂ were determined in the InCHIANTI Study, NHANES III, and WHAS I using previously established criteria (10–13).

Statistical Analysis

Descriptive statistics were used to examine the baseline characteristics of each study sample (Table 2). To assess the shape of the RDW-to-mortality relationship, hazard ratios (HRs) for RDW divided into nine categories were obtained

with data combined from all studies using a Cox proportional hazards model that adjusted for age, sex, and study (Figure 1). The proportional hazards assumption was confirmed by examining plots of Schoenfeld residuals. Test of trend was performed by entering RDW as an ordinal variable. HRs for RDW as a continuous variable were then obtained from each study separately using Cox models adjusted for age, sex, education, race, smoking status, BMI, eGFR, hemoglobin concentration, MCV, serum albumin, and medical conditions (cancer, diabetes, heart attack, hypertension, and stroke). (A Cox model fitted with a penalized spline for RDW as a continuous variable confirmed a linear association with mortality.) As per established meta-analysis methods (14,15), a random-effects model was then used to pool these HRs and determine the overall effect of RDW on total mortality and assess the consistency of effect across studies (Figure 2). These analyses were repeated to separately examine cause-specific mortality outcomes, including CVD, cancer, and other deaths (Figure 3). Finally, Cox models were estimated with the pooled data to determine whether RDW predicted mortality in various subgroups adjusting for age, sex, and study (Figure 4). Statistical interactions were tested to determine whether the effect of RDW on mortality varied by subgroups. Analyses were completed using Stata/SE version 10.1 (StataCorp,

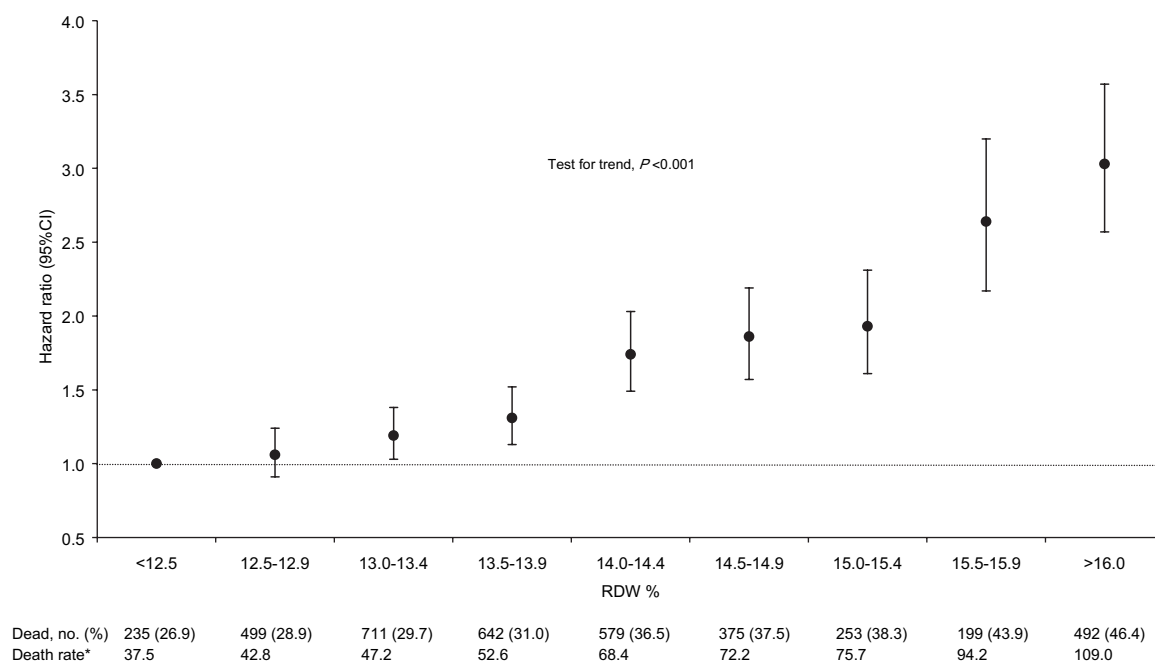


Figure 1. Hazard ratios for total mortality according to red cell distribution width (RDW) level for all studies combined adjusting for age, sex, and study ($N = 11,827$).

Note: *death rate per 1,000 person-years.

College Station, TX) and R Foundation for Statistical Computing (Vienna, Austria). Associations with p values $< .05$ were considered statistically significant.

RESULTS

The characteristics of the studies included in the meta-analysis are reported in Table 1. Among the 11,827 older adults with RDW measured, there were a total of 3,985 deaths that occurred during the 68,822 person-years of follow-up. Table 2 shows the baseline participant characteristics for each cohort

study. Median RDW values varied across studies from 13.2% to 14.6% and were generally higher in the older cohorts (Table 2). The mean ages in the studies ranged from 73.6 to 79.1 years; women comprised the majority in each of the studies. Racial/ethnic minorities were included in four of the studies with the proportion of blacks ranging from 7.8% to 38.4%.

Figure 1 shows that mortality risk increased steadily with higher levels of RDW (p for trend $< .001$) adjusting for age, sex, and study. Compared with a reference RDW less than 12.5%, the HRs were significantly increased for RDW greater than 12.9%. Mortality risk was nearly doubled in participants

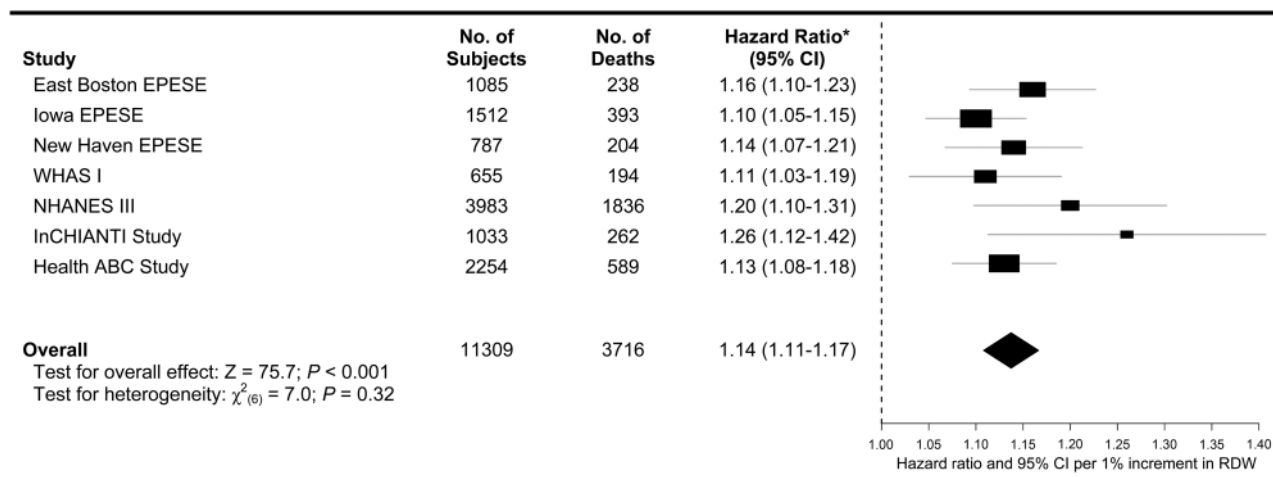


Figure 2. Hazard ratios (HRs) for total mortality per 1% increment in red cell distribution width (RDW). Note: *HRs were adjusted for age, sex, race, education, smoking status, body mass index, cancer, diabetes, heart attack, hypertension, stroke, estimated glomerular filtration rate, hemoglobin concentration, mean corpuscular volume, and serum albumin.

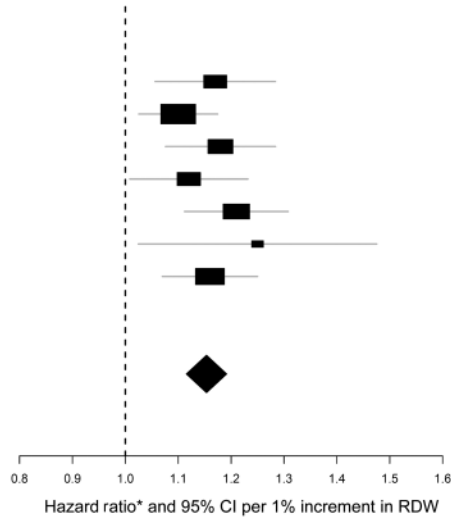
A. Cardiovascular Disease Mortality

Study

East Boston EPESE
Iowa EPESE
New Haven EPESE
WHAS I
NHANES III
InCHIANTI Study
Health ABC Study

Overall

Hazard ratio* (95% CI): 1.15 (1.12-1.25)
Test for overall effect: $Z = 58.8$; $P < 0.001$
Test for heterogeneity: $\chi^2_{(6)} = 4.7$; $P = 0.59$



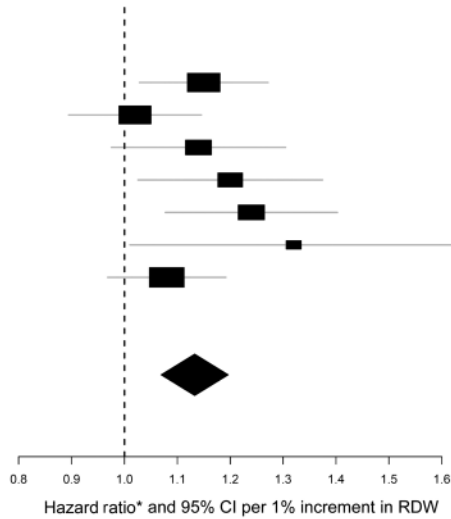
B. Cancer Mortality

Study

East Boston EPESE
Iowa EPESE
New Haven EPESE
WHAS I
NHANES III
InCHIANTI Study
Health ABC Study

Overall

Hazard ratio* (95% CI): 1.13 (1.07-1.20)
Test for overall effect: $Z = 34.8$; $P < 0.001$
Test for heterogeneity: $\chi^2_{(6)} = 7.7$; $P = 0.26$



C. Other Mortality

Study

East Boston EPESE
Iowa EPESE
New Haven EPESE
WHAS I
NHANES III
InCHIANTI Study
Health ABC Study

Overall

Hazard ratio* (95% CI): 1.13 (1.07-1.18)
Test for overall effect: $Z = 38.4$; $P < 0.001$
Test for heterogeneity: $\chi^2_{(6)} = 7.9$; $P = 0.25$

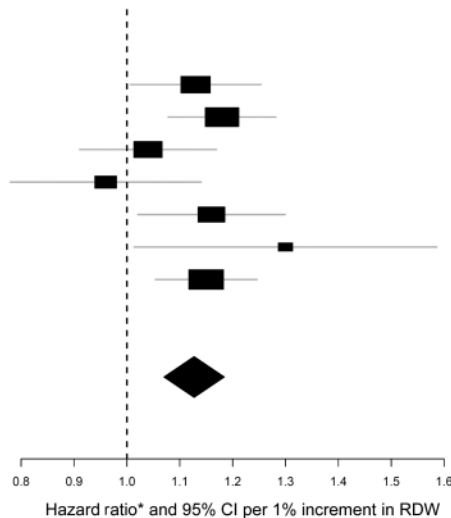


Figure 3. Hazard ratios (HRs) for cause-specific mortality per 1% increment in RDW. Note: *HRs were adjusted for age, sex, race, education, smoking status, body mass index, cancer, diabetes, heart attack, hypertension, stroke, estimated glomerular filtration rate, hemoglobin concentration, mean corpuscular volume, and serum albumin. (A) Cardiovascular disease mortality, (B) cancer mortality, and (C) other mortality.

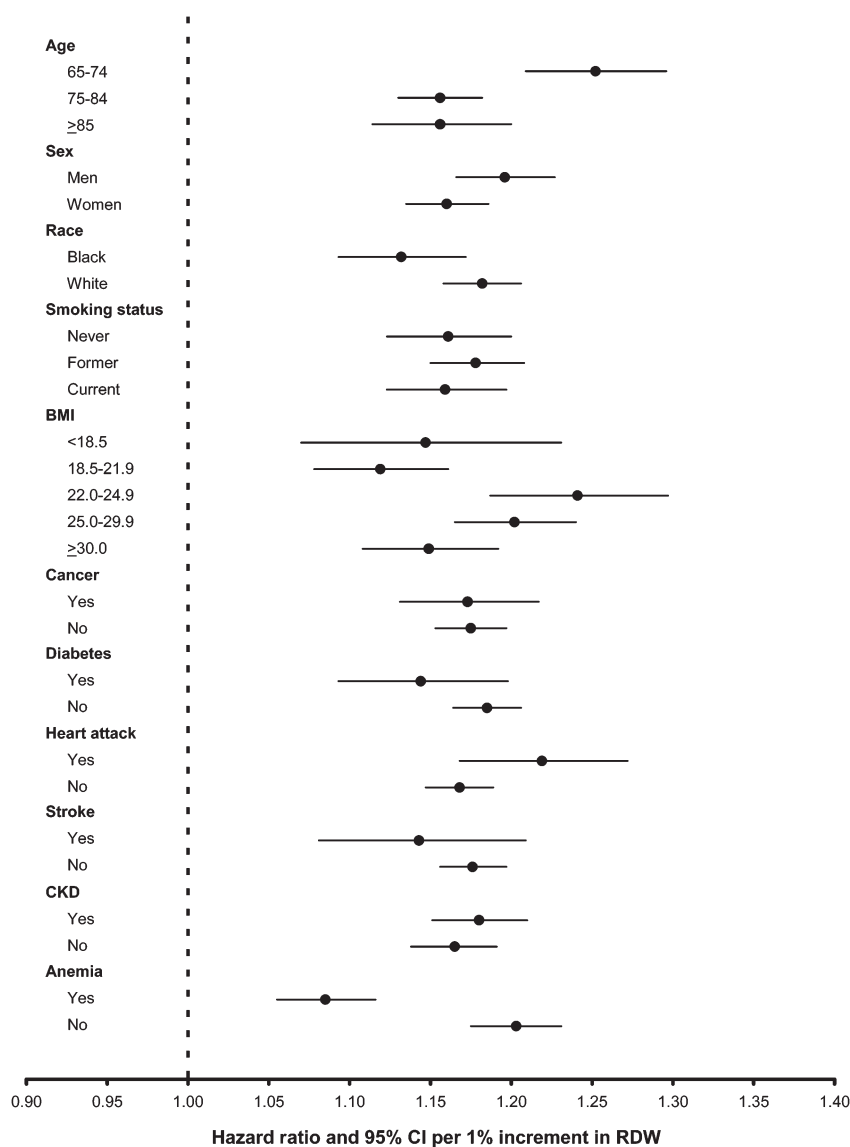


Figure 4. Hazard ratios for total mortality per 1% increment in red cell distribution width (RDW) in subgroups of older adults, adjusted for age, sex, and study.

with RDW of 14.0%–14.9% (adjusted HR = 1.77; 95% confidence interval [CI]: 1.53–2.04) and more than doubled in those with RDW greater than 14.9% (adjusted HR = 2.51; 95% CI: 2.16–2.91) relative to the reference group.

In all the studies, RDW was a significant predictor of total mortality ($p < .001$; Figure 2). Adjusting for multiple factors, mortality risk increased by 14% for every 1% increment in RDW (adjusted HR = 1.14; 95% CI: 1.11–1.17). A formal test of heterogeneity showed that this association was consistent across studies ($p = .32$). The meta-analyses also showed that RDW was significantly associated with each of the three cause-specific outcomes examined (Figure 3), although the association with CVD mortality was slightly stronger than with cancer and other causes of mortality.

In addition, RDW significantly predicted total mortality in all the major subgroups shown in Figure 4, adjusting for

age, sex, and study. Although there were significant RDW by age group interactions whereby RDW was more strongly associated with mortality in adults aged 65–74 years than in those aged 75–84 years ($p < .001$) and 85 years and older ($p < .001$), the effect of RDW on mortality was significant in each of the three age groups even adjusting for age as a continuous variable within these strata. No significant sex differences were observed in the association of RDW with mortality. The effect of RDW was weaker in blacks than in whites (p for RDW by race interaction = .011), but again, higher RDW was significantly associated with increased mortality for both racial groups. There was no significant variation in the effect of RDW on mortality across subgroups defined according to smoking status, BMI category, and individual diseases, although the association was significantly weaker in anemic than in nonanemic older adults

(p for RDW by anemia interaction $<.001$). Notably, RDW was significantly associated with mortality in the subgroups shown in Figure 4 even after further adjusting for covariates used in Figures 2 and 3 (results not shown). Furthermore, among the subset of 1,603 older adults without any of the major age-associated medical conditions (anemia, cancer, chronic kidney disease, diabetes, heart attack, hypertension, and stroke), RDW remained a strong predictor of mortality adjusting for age, sex, race, education, smoking status, BMI, eGFR, hemoglobin concentration, MCV, and serum albumin (adjusted HR for 1% increment in RDW: 1.32; 95% CI: 1.21–1.44; number of deaths = 355).

Nutritional deficiencies were determined in the InCHI-ANTI Study, NHANES III, and WHAS I. The association of RDW with mortality occurred in participants with iron, folate, and/or vitamin B₁₂ deficiencies (adjusted HR for 1% increment in RDW: 1.16; 95% CI: 1.09–1.24) as well as in those without these deficiencies (adjusted HR for 1% increment in RDW: 1.22; 95% CI: 1.18–1.27) adjusting for age, sex, and study (data not shown). There was no statistical interaction between RDW and nutritional status in predicting mortality ($p = .283$). The results remained essentially unchanged when additionally adjusting for covariates used in Figures 2 and 3.

DISCUSSION

In this collaborative analysis of 11,827 community-dwelling older adults in seven cohort studies, RDW was a remarkably consistent and strong predictor of total and cause-specific mortality. There was a clear gradient in mortality risk associated with increasing RDW values. For every 1% increment in RDW, the risk of death increased by 14%. This association was independent of several established risk factors for death in older adults, including hemoglobin concentration. Furthermore, the association occurred in all the major demographic, disease, and behavioral and nutritional risk factor subgroups examined as well as in older adults without major age-associated medical conditions. Considering that the distribution of RDW varied between cohorts and yet significantly predicted mortality in each of them indicates that greater variability in RBC volume is a risk factor for death in older adults.

The mechanisms through which RDW increases with age and is associated with mortality have not been defined; however, it is possible that oxidative stress and inflammation play a role given that both can reduce RBC survival (16,17), leading to a more mixed population of RBC volumes in the circulation. In patients with conditions characterized by increased levels of oxidative stress, such as Down syndrome (18), poor pulmonary function (19), and dialysis (20), RDW values are elevated. Analyses of the NHANES III data showed that decreased serum antioxidant levels, including carotenoids, selenium, and vitamin E, were also as-

sociated with increased RDW, although adjusting for these antioxidants did not meaningfully attenuate the RDW-to-mortality association (5). In addition to reduced RBC survival, inflammation might further influence RDW levels by disrupting erythropoiesis. Indeed, it is believed that the increased prevalence of anemia with advancing age is due, in part, to the effects of proinflammatory cytokines on inhibiting the proliferation of erythroid progenitor cells and down-regulating erythropoietin receptor expression (17,21,22). Perturbations in erythropoiesis can lead to more variation in cell sizes exiting the bone marrow and might increase RDW. Importantly, however, RDW was more strongly associated with mortality in nonanemic than in anemic older adults (Figure 4). In the NHANES III, adjustment for C-reactive protein, fibrinogen level, and white blood cell count did not substantially alter the effect of RDW on mortality, even though each of these factors was strongly related to RDW and mortality (5).

Interestingly, the association of RDW with mortality was significantly stronger in healthier older adults without major age-associated diseases than in those with disease (p for interaction $<.001$). It is conceivable that there are subclinical disease processes that cause subtle dysregulation of erythrocyte homeostasis that is expressed in RDW. Given that RDW was significantly associated with CVD mortality and cancer mortality, it might be that RDW predicts the occurrence of these diseases as well as other age-associated conditions. Further research is needed to understand the pathways through which RDW is associated with mortality.

Previous studies on RDW were mainly performed in cohorts or randomized trials of patients with significant CVD (1–4,7). Although these studies showed that RDW was strongly related to CVD events as well as all-cause mortality, data from the NHANES III showed that RDW significantly predicted deaths from CVD, cancer, chronic lower respiratory tract disease, and other causes except external ones (e.g., traffic accidents) (5,6). As RDW is associated with multiple causes of death, it is plausible that RDW is influenced by multiple diseases and is an integrative biomarker of dysfunction and impairment across physiological systems.

The clinical utility of RDW beyond its current use in the diagnosis of certain anemias needs to be evaluated. A few studies have shown that RDW might be a useful screening marker for celiac disease, colon cancer, and acute coronary syndromes in emergency department settings (23–25). In terms of mortality risk prediction, RDW significantly improved model performance in the NHANES III cohort beyond established risk factors for adults aged 45–64 years and 65 years and older (5). However, whether RDW improves risk stratification for individual conditions, such as myocardial infarction or congestive heart failure, is unknown and should be investigated.

The current study does have some limitations that should be considered. First, RDW was assessed in several different laboratories. Although almost all modern automated blood

cell counters report RDW as the coefficient of variation of red cell volume, algorithms used to eliminate artifacts and outliers vary to some extent between manufacturers, and recommendations for standardization of cell sizing have not been uniformly adopted (26–28). Nonetheless, there was no evidence of heterogeneity among studies in the association of RDW with mortality. Second, RDW was assessed on a single occasion that might be influenced by biologic variability or measurement error, although such errors are likely to attenuate the observed associations between RDW and mortality. Third, despite adjusting for multiple risk factors and prevalent diseases, it is possible that there may be residual confounding from conditions and medications not included in the analysis.

In summary, RDW is a newly recognized and powerful predictor of mortality in community-dwelling older adults with and without major age-associated diseases. The biologic mechanisms underlying this association merit investigation. Considering that RDW is an inexpensive test that is routinely reported to physicians, further research is needed to determine whether RDW is a useful risk assessment tool in different clinical settings.

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