American Journal of Epidemiology
Vol. 171, No. 2
DOI: 10.1093/aje/kwp360
Advance Access publication:
December 14, 2009

Original Contribution

Red Blood Cell Distribution Width and Risk of Cardiovascular Events and Mortality in a Community Cohort in Taiwan

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Initially submitted June 22, 2009; accepted for publication October 6, 2009.

The authors investigated whether red blood cell distribution width (RDW) was associated with the development of cardiovascular disease (CVD) events and mortality in a community cohort in Taiwan. The influence of anemia on the association was also assessed. RDW levels were measured in 3,226 participants aged 35 years or older who reported no CVD or cancer at baseline in 1990. During a median follow-up period of 15.9 years (1990–2007), 358 participants experienced stroke and/or coronary heart disease, and 810 participants died. The multivariate-adjusted hazard ratio for subjects in the highest RDW quartile as compared with the lowest quartile was 1.46 for both all-cause mortality (95% confidence interval: 1.17, 1.81) and non-CVD mortality (95% confidence interval: 1.13, 1.88) (P for trend < 0.01 for both) but was not significant for CVD morbidity and mortality. Further analyses showed that in comparison with participants with low RDW and no anemia, persons with high RDW but no anemia had elevated risks of all-cause mortality and non-CVD mortality. The authors conclude that elevated RDW values are associated with increased risk of mortality but not the development of CVD in the general population. RDW may precede anemia in predicting the risk of non-CVD death.

anemia; blood cell count; cardiovascular diseases; cohort studies; erythrocyte indices; erythrocytes; mortality

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RDW, red blood cell distribution width.

Red blood cell distribution width (RDW), which measures the variation in erythrocyte size, is routinely tested during complete blood cell counts (1). RDW is generally used, in combination with mean corpuscle volume, as an indicator of the differential diagnosis of anemia (2). Two studies have shown that high RDW values may increase adverse cardiovascular outcomes and mortality among people with heart failure or coronary disease (3, 4). The risk occurs even in patients with RDW values in the clinically normal range and remains significant after adjusting for mean corpuscle volume and hemoglobin. Elevated RDW might indicate impaired production or increased destruction of red blood cells, reflecting unfavorable physiologic conditions that may lead to adverse clinical outcomes (2, 3, 5). However, information on general populations has not been well documented. Particularly, data on the incidence of cardiovascular disease (CVD) in relation to RDW are not available. We investigated whether RDW was independently associated with the risk of developing CVD events and mortality in a general population that had been followed for a median of 15.9 years in a community in Taiwan. We also assessed whether anemia influenced this association.

MATERIALS AND METHODS

Study design and participants

Details on the design of this cohort study and the validity of the data collected have been reported elsewhere (6, 7). Briefly, the Chin-Shan Community Cardiovascular Cohort Study is a prospective study of CVD risk in adults residing in a suburban township north of Taipei City, Taiwan, where the population is of homogenous Chinese ethnicity. At the baseline survey in 1990 and 1991, 3,602 noninstitutionalized residents aged 35 years or more who were able to come

to a clinic for a health checkup consented to participate in the study (a response rate of 82.8%). The institutional review board at National Taiwan University Hospital approved the study. The present study included 3,226 participants with available RDW data who reported no history of stroke, coronary heart disease, or cancer at enrollment. Comparing subjects with RDW data with those without RDW data, those who did not have RDW data were more likely to be male, to smoke, and to drink alcohol, but clinical characteristics did not differ between the 2 groups.

At baseline and follow-up visits conducted approximately every other year, information regarding sociodemographic characteristics, lifestyle factors, personal medical history, and family health history was collected by in-person questionnaire interview. Each participant also received a health checkup, including anthropometric measures, electrocardiography, echocardiography, fundoscopic examination, and serial biochemical examinations of blood and urine specimens for assessment of health status.

Study outcomes

In follow-up visits that took place through 2007, information about CVD events and deaths was obtained from annual review of medical records, death certificates, and the biennial follow-up checkups. Cardiologists and physicians who were blind to the medical status of the study participants reviewed these data and verified the events and causes of death (7). The completeness of follow-up of 3,226 study subjects into 2007 was 92%. Subjects who were and were not lost to follow-up did not differ in terms of clinical characteristics at baseline, except that persons in the lost group were younger and more likely to be female.

The outcomes in this study included the development of stroke and coronary heart disease and all-cause death. Coronary heart disease was defined as nonfatal myocardial infarction, hospitalization for percutaneous coronary intervention or coronary artery bypass surgery, or fatal coronary heart disease (8, 9). Fatal coronary heart disease was considered to have been present if a fatal myocardial infarction was confirmed from a review of medical records, if the death certificate stated it as the cause, underlying cause, or most plausible cause of death, or if evidence of previous coronary heart disease was available. Stroke was defined as a sudden neurologic deficit of vascular origin persisting for more than 24 hours and supported by imaging data. Transient ischemic attacks were not included. Causes of death were identified from official certificates and further verified by household visits. All causes of death were further classified into CVD or non-CVD causes for data analysis.

Laboratory measurements

Overnight-fasted venous blood samples obtained from the participants during the baseline study were transported in an ice bath to the laboratory at National Taiwan University Hospital within 6 hours. RDW and other blood counts were immediately determined using an F-800 Hematology Analyzer (Sysmex Company, Kobe, Japan). Serum or plasma samples were then obtained by centrifugation at $3{,}000 \times g$ for 10 minutes at 4°C and stored at −70°C pending biochemical measurements. Serum lipid levels and plasma uric acid concentrations were determined as described elsewhere (7, 8). Estimated glomerular filtration rate (mL/minute), a measure of kidney function, was calculated using the Cockcroft-Gault equation as follows: [(140 − age in years) × weight in kg/72 × serum creatinine in mg/dL] × (0.85 if female) (10). All measurements were performed at the hospital's central laboratory. Serum albumin and creatinine levels were measured at the same laboratory using the Dimension Clinical Chemistry System (E. I. du Pont de Nemours and Company, Wilmington, Delaware).

Statistical analysis

We classified the participants into 4 groups using the RDW quartile values. Differences in baseline clinical characteristics among groups were examined by 1-way analysis of variance for continuous variables and χ^2 test for categorical variables.

We calculated the incidence rate of events or mortality in each RDW quartile by dividing the number of cases by the number of person-years of follow-up in each category. We used 4 Cox proportional hazards models to assess the associations between the baseline RDW quartiles and subsequent risks of CVD events and mortality. These models estimated the hazard ratios and 95% confidence intervals for each RDW quartile using the lowest quartile as the reference group. Model 1 estimated the crude association with RDW quartiles. Model 2 included adjustment for age (years) and sex (men vs. women). We then added several other potential confounders as covariates in model 3, including body mass index (weight (kg)/height $(m)^2$), smoking (yes vs. no), histories of diabetes and hypertension (yes vs. no), total cholesterol (mg/dL), triglycerides (log-transformed; mg/dL), albumin (g/dL), and estimated glomerular filtration rate (mL/minute). Levels of low density and high density lipoprotein cholesterol (mg/dL) were also included for adjustment in the model for CVD. To evaluate the effect of RDW independent of other hematologic parameters, we further added blood count parameters to model 3 to create model 4.

Hematocrit (%) and mean corpuscle volume (μm^3) were included in the model of CVD incidence, and red blood cell count (10^6 cells/μL), mean corpuscle volume (μm^3), and hemoglobin (g/dL) were included in mortality models. All analyses were repeated using RDW as a continuous variable. Covariates selected for these models were based on previous experience with the study cohort and variables with a P value of 0.05 or less in the univariate analysis. We examined the linear trends across RDW categories by defining a median RDW value in each quartile. In addition, we performed joint analyses to assess the influence of anemia, defined by World Health Organization criteria (11), on the association of RDW with CVD events and mortality using the fully adjusted models. The highest RDW quartile was used as the cutoff point, and anemia was defined as a hemoglobin

Table 1. Baseline Characteristics[a] of Participants by Quartile of Red Blood Cell Distribution Width, Chin-Shan Community Cardiovascular Cohort Study, Taiwan, 1990–2007

	Quartile of RDW								*P* Value
	1 (*n* = 951)		2 (*n* = 705)		3 (*n* = 764)		4 (*n* = 806)		
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	
RDW	≤12.7		>12.7–13.1		>13.1–13.7		>13.7		
Age, years		52.5 (11.5)		53.7 (11.8)		55.7 (12.2)		56.9 (13.1)	<0.001
Female sex	54.5		52.5		51.2		51.2		0.021
Educational level ≥9 years	7.1		5.5		6.5		4.7		0.182
Current smoking	28.8		36.2		38.1		41.1		<0.001
Current alcohol drinking	28.8		27.8		30.6		30.5		0.559
Hypertension	27.8		26.0		31.8		30.0		0.073
Diabetes mellitus	16.6		11.7		12.1		9.7		<0.001
Family history of cardiovascular disease	42.3		37.9		39.1		35.6		0.036
Body mass index[b]		23.7 (3.2)		23.7 (3.5)		23.3 (3.3)		23.2 (3.7)	0.004
Cholesterol, mg/dL									
Total cholesterol		203.4 (44.7)		198.9 (45.1)		197.7 (45.4)		189.8 (44.0)	<0.001
Low density lipoprotein cholesterol		144.0 (43.6)		138.8 (43.7)		136.7 (44.3)		129.4 (41.7)	<0.001
High density lipoprotein cholesterol		46.9 (11.8)		47.1 (11.6)		48.8 (13.30)		48.2 (13.7)	0.010
Triglycerides, mg/dL		137.0 (109.6)		126.7 (91.6)		121.9 (91.2)		113.2 (81.4)	<0.001
Uric acid, mg/dL		5.63 (1.66)		5.58 (1.67)		5.71 (1.68)		5.67 (1.80)	0.518
Creatinine, mg/dL		0.86 (0.26)		0.87 (0.56)		0.83 (0.25)		0.85 (0.31)	0.120
Estimated glomerular filtration rate, mL/minute		83.2 (31.2)		86.1 (33.7)		84.1 (33.9)		81.3 (33.7)	0.040
Albumin, g/dL		4.84 (0.54)		4.67 (0.52)		4.64 (0.48)		4.56 (0.52)	<0.001
Hematocrit, %		43.7 (4.7)		43.4 (5.6)		43.6 (5.2)		42.2 (6.4)	<0.001
Red blood cell count, 10^6 cells/μL		4.6 (0.5)		4.6 (0.6)		4.7 (0.6)		4.9 (0.8)	<0.001
Hemoglobin, g/dL		14.3 (1.5)		14.1 (1.6)		14.1 (1.6)		13.1 (2.1)	<0.001
Mean corpuscle volume, μm^3		94.4 (4.4)		93.6 (4.9)		93.6 (5.1)		87.6 (11.9)	<0.001

Abbreviations: RDW, red blood cell distribution width; SD, standard deviation.

[a] Conversion factors for International Units: To convert total cholesterol, low density lipoprotein cholesterol, and high density lipoprotein cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert uric acid values to μmol/L, multiply by 59.485; to convert creatinine values to μmol/L, multiply by 88.4; to convert albumin values to g/L, multiply by 10; to convert hematocrit values to proportion of 1.0, multiply by 0.01; to convert red blood cell count to 10^{12} cells/L, multiply by 10^6; and to convert hemoglobin values to g/L, multiply by 10.

[b] Weight (kg)/height $(m)^2$.

level less than 13 g/dL in men and less than 12 g/dL in women. We tested for an interaction effect by comparing likelihood ratio statistics from models that included a term for the interaction between RDW category and anemia status and models that did not.

All analyses were performed using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina), and STATA, version SE9 (Stata Corporation, College Station, Texas). A 2-sided *P* value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of participants

The median RDW level among the 3,226 participants was 13.1%, with an interquartile range of 12.7%–13.7% (Table 1). Persons in the highest RDW quartile were more likely to be older, male, and smokers, to have a lower prevalence of histories of diabetes and family CVD, and to have a lower body mass index with favorable lipid levels.

Table 2. Adjusted Hazard Ratio for Cardiovascular Disease Incidence According to Quartile of Red Blood Cell Distribution Width at Baseline, Chin-Shan Community Cardiovascular Cohort Study, Taiwan, 1990–2007[a]

Cardiovascular Disease Outcome and RDW Quartile	Person-Years at Risk	No. of Events	Model 1		Model 2		Model 3		Model 4	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Stroke and/or coronary heart disease										
1 (≤12.7%)	13,951	96	1.00		1.00		1.00		1.00	
2 (>12.7%–13.1%)	9,961	81	1.19	0.88, 1.59	1.11	0.83, 1.50	1.05	0.77, 1.43	1.06	0.78, 1.45
3 (>13.1%–13.7%)	10,506	90	1.26	0.95, 1.68	0.99	0.74, 1.32	1.05	0.78, 1.41	1.05	0.78, 1.42
4 (>13.7%)	10,431	91	1.29	0.97, 1,71	0.97	0.72, 1.29	1.09	0.80, 1.41	1.14	0.83, 1.57
P for trend			0.09		0.68		0.60		0.42	
Per %			1.04	0.97, 1.11	1.00	0.94, 1.07	1.02	0.94, 1.11	1.05	0.95, 1.15
Stroke										
1 (≤12.7%)	14,132	55	1.00		1.00		1.00		1.00	
2 (>12.7%–13.1%)	10,043	49	1.25	0.85, 1.84	1.20	0.82, 1.77	1.14	0.76, 1.70	1.15	0.77, 1.72
3 (>13.1%–13.7%)	10,573	59	1.44	1.00, 2.08	1.13	0.78, 1.64	1.16	0.79, 1.70	1.17	0.80, 1.81
4 (>13.7%)	10,565	55	1.35	0.93, 1.96	1.02	0.70, 1.49	1.16	0.78, 1.72	1.20	0.80, 1.81
P for trend			0.12		0.93		0.50		0.41	
Per %			1.04	0.95, 1.14	1.01	0.92, 1.10	1.03	0.93, 1.15	1.05	0.94, 1.18
Coronary heart disease										
1 (≤12.7%)	14,128	46	1.00		1.00		1.00		1.00	
2 (>12.7%–13.1%)	10,092	33	1.02	0.65, 1.59	0.92	0.59, 1.45	0.91	0.57, 1.45	0.93	0.58, 1.48
3 (>13.1%–13.7%)	10,724	33	0.97	0.62, 1.52	0.77	0.49, 1.20	0.87	0.55, 1.39	0.88	0.56, 1.40
4 (>13.7%)	10,587	39	1.16	0.76, 1.78	0.87	0.57, 1.35	0.98	0.62, 1.55	1.05	0.65, 1.68
P for trend			0.50		0.51		0.97		0.83	
Per %			1.02	0.92, 1.14	0.99	0.89, 1.10	1.01	0.88, 1.15	1.04	0.90, 1.20

Abbreviations: CI, confidence interval; HR, hazard ratio; RDW, red blood cell distribution width.

[a] Models included the following baseline variables: model 1, RDW; model 2, all model 1 variables plus age and sex; model 3, all model 2 variables plus body mass index, smoking, history of diabetes, history of hypertension, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides (log-transformed), albumin, and estimated glomerular filtration rate; and model 4, all model 3 variables plus hematocrit and mean corpuscle volume.

A higher RDW level was also associated with lower albumin, estimated glomerular filtration rate, hematocrit, hemoglobin, and mean corpuscle volume but was associated with higher red blood cell counts.

Association between RDW values and CVD incidence

During a median follow-up period of 15.9 years, 358 participants experienced a first stroke, coronary heart disease, or both. The incidence rate of stroke and/or coronary heart disease rose from 6.9 per 1,000 person-years for the lowest quartile to 8.7 per 1,000 person-years for the highest RDW quartile (Table 2). However, the hazard ratio for higher RDW values did not increase appreciably in either unadjusted or multivariate-adjusted regression models.

Association between RDW values and mortality

During the follow-up period, 810 people died. The rates of all-cause mortality from the lowest RDW quartile to the highest were 12.1, 15.9, 19.5, and 24.5 per 1,000 person-years, respectively (Table 3). Compared with subjects in the lowest RDW quartile in unadjusted models, subjects in the highest RDW quartile had a hazard ratio of 2.06 (95% confidence interval (CI): 1.70, 2.49) for all-cause death, 2.14 (95% CI: 1.46, 3.12) for CVD death, and 2.03 (95% CI: 1.63, 2.54) for non-CVD death (for trend across quartiles, $P < 0.001$ in all 3 models). The corresponding hazard ratios for all-cause death (95% CI: 1.17, 1.81) and non-CVD death (95% CI: 1.13, 1.88) were both attenuated to 1.46 after age, sex, and other potentially confounding factors were added to the unadjusted model, but they remained significant (*P* values for trend were <0.001 and 0.003, respectively; Table 3, model 4). However, the association between RDW and CVD death was weakened to a marginally significant level after adjustment for age and sex.

The influence of anemia

Compared with participants with no anemia and RDW values in the 3 lower quartiles, those with anemia and with RDW in the highest quartile had an increased risk of all-cause mortality (hazard ratio (HR) = 1.41, 95% CI: 1.06, 1.88; Figure 1). Increased risks were also observed for persons with anemia alone (HR = 1.36, 95% CI: 1.02, 1.82) and persons with high RDW alone (HR = 1.30, 95%

Table 3. Adjusted Hazard Ratio for Mortality According to Quartile of Red Blood Cell Distribution Width at Baseline, Chin-Shan Community Cardiovascular Cohort Study, Taiwan, 1990–2007[a]

Mortality Outcome and RDW Quartile	Person-Years at Risk	No. of Events	Model 1		Model 2		Model 3		Model 4	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-cause death										
1 (≤12.7%)	14,326	174	1.00		1.00		1.00		1.00	
2 (>12.7%–13.1%)	10,180	162	1.32	1.07, 1.64	1.24	1.00, 1.54	1.17	0.94, 1.46	1.19	0.95, 1.48
3 (>13.1%–13.7%)	10,796	211	1.64	1.34, 2.01	1.25	1.02, 1.53	1.21	0.98, 1.48	1.22	0.99, 1.50
4 (>13.7%)	10,727	263	2.06	1.70, 2.49	1.44	1.18, 1.75	1.37	1.12, 1.67	1.46	1.17, 1.81
P for trend			<0.001		<0.001		0.003		<0.001	
Per %			1.13	1.08, 1.17	1.08	1.03, 1.13	1.07	1.02, 1.12	1.10	1.04, 1.17
CVD death										
1 (≤12.7%)		44	1.00		1.00		1.00		1.00	
2 (>12.7%–13.1%)		48	1.55	1.03, 2.34	1.46	0.97, 2.21	1.26	0.83, 1.91	1.26	0.83, 1.91
3 (>13.1%–13.7%)		55	1.70	1.15, 2.53	1.28	0.86, 1.90	1.18	0.79, 1.76	1.17	0.78, 1.75
4 (>13.7%)		69	2.14	1.46, 3.12	1.45	0.99, 2.13	1.43	0.96, 2.12	1.45	0.95, 2.21
P for trend			<0.001		0.115		0.092		0.108	
Per %			1.11	1.02, 1.21	1.06	0.97, 1.15	1.07	0.97, 1.19	1.09	0.96, 1.23
Non-CVD death										
1 (≤12.7%)		130	1.00		1.00		1.00		1.00	
2 (>12.7%–13.1%)		114	1.24	0.97, 1.60	1.17	0.91,1.50	1.14	0.88, 1.47	1.15	0.89, 1.50
3 (>13.1%–13.7%)		156	1.62	1.29, 2.05	1.24	0.99, 1.57	1.21	0.95, 1.54	1.24	0.97, 1.57
4 (>13.7%)		194	2.03	1.63, 2.54	1.43	1.14, 1.80	1.34	1.06, 1.70	1.46	1.13, 1.88
P for trend			<0.001		0.002		0.014		0.003	
Per %			1.13	1.08, 1.19	1.08	1.03, 1.14	1.07	1.01, 1.12	1.11	1.03, 1.18

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RDW, red blood cell distribution width.

[a] Models included the following baseline variables: model 1, RDW; model 2, all model 1 variables plus age and sex; model 3, all model 2 variables plus body mass index, smoking, history of diabetes, history of hypertension, total cholesterol, triglycerides (log-transformed), albumin, and estimated glomerular filtration rate; and model 4, all model 3 variables plus red blood cell count, hemoglobin level, and mean corpuscle volume.

CI: 1.08, 1.56). However, an increased risk of CVD death was observed only in people with anemia; the risk was slightly greater in those with lower RDW values (HR = 1.95, 95% CI: 1.14, 3.35) than in those with high RDW values in the highest quartile (HR = 1.75, 95% CI: 1.01, 3.04). In contrast, persons with high RDW alone without coexisting anemia incurred a greater risk of 1.30 (95% CI: 1.05, 1.61) for non-CVD death, but the risk associated with anemia was not significant. The test for interaction between RDW quartile and anemia, determined by the likelihood ratio statistic, showed no significant interaction effect in any multivariate model.

DISCUSSION

In this middle-aged general population, a high RDW value was a predictor of increased all-cause, non-CVD, and CVD mortality during the 15.9-year follow-up period. However, the association with CVD mortality was sex- and age- dependent. Our observations showed no significant association between RDW and the development of CVD. Furthermore, the association between high RDW values and non-CVD death was significant only in subjects without anemia.

RDW has been shown to be a strong prognostic factor for all-cause mortality and CVD events in patients with histories of heart disease or chronic heart failure (3, 4). A recent study by Patel et al. (12), using data extended to a general population, also reported a positive association between RDW and mortality from CVD and other causes. However, our findings in this community population showed that higher RDW values are more likely to be associated with increased risk of non-CVD death than with CVD mortality and morbidity. In contrast to findings in the general population (12), our observations showed that the relation between RDW and CVD death was appreciably weakened by adjustment for age and sex. Possible explanations for the inconsistency between studies may include racial differences and/or other variance in population characteristics. Further studies in other populations may help clarify the issue.

A population-based study has shown an inverse relation between RDW and lung function (13). Another study found RDW to be a sensitive predictor of colon cancer (14). The potential explanation given by the authors for these findings was linked to deficiencies in nutrients such as iron, vitamin B_{12}, and folate, in which the RDW levels rise. We had no direct knowledge of the nutritional status of our study participants. Irrespective of other risk factors, this study

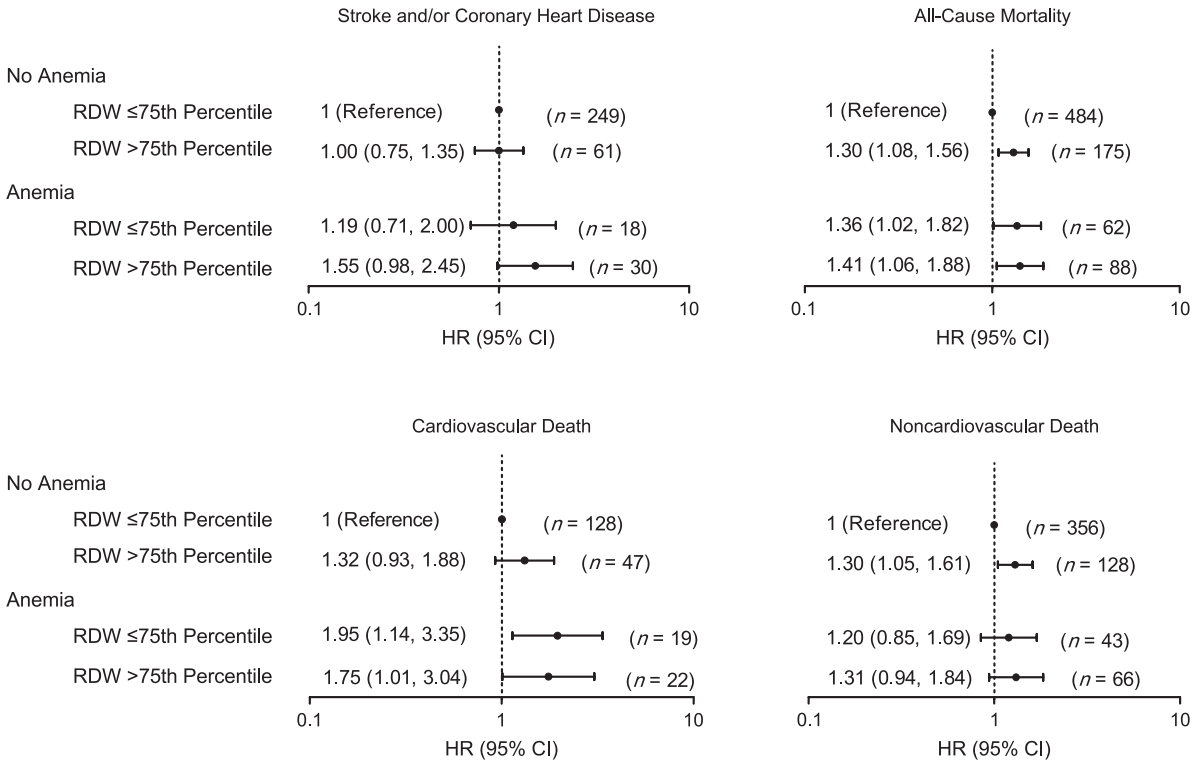

Figure 1. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) (plotted on a log scale) for the joint effect of anemia and red blood cell distribution width (RDW) on cardiovascular disease (CVD) events and mortality, Chin-Shan Community Cardiovascular Cohort Study, Taiwan, 1990–2007. Variables included for adjustment are listed in Table 2 for CVD incidence and in Table 3 (model 4) for mortality, except for hemoglobin in mortality models. Numbers of subjects in each category are shown in parentheses. One participant who died from a non-CVD cause was excluded from analyses of all-cause and non-CVD mortality because of unknown anemia status.

showed a long-term and linear relation between RDW and mortality. Although the cause and mechanism are not yet clear, this finding suggests that RDW may contribute to physiologic changes leading to clinical consequences as a marker for underlying pathologic effects.

In previous studies on the association between RDW and heart disease, investigators adjusted for hemoglobin and mean corpuscle volume in the data analyses (3, 4) but did not evaluate the effect of interaction between RDW and blood count on CVD events and mortality. Anemia and hemoglobin levels have been considered strong predictors for the development of CVD and mortality in different populations (15–17). Our data revealed that an elevated RDW was significantly associated with all-cause mortality in persons without anemia. The mortality risks for both high and low RDW values were similar in subjects with anemia. These findings suggest that the association between RDW and mortality may be more pronounced among persons without anemia. Further analyses of the effect of interaction between RDW categories and anemia status on mortality in univariate models produced significant results, but the effect disappeared after multivariate adjustment. In addition, we found that high RDW values alone increased the risk of non-CVD death. Previous studies have shown evidence that the development of iron deficiency may subsequently raise RDW, followed by other abnormal blood counts and finally the development of anemia (13, 18, 19). RDW may precede anemia in predicting the risk of non-CVD death.

Some limitations of this study merit consideration. First, in the analyses stratified by anemia status, relatively few cases met the anemia criteria, which resulted in fairly wide confidence intervals. This analysis may have had insufficient statistical power for detecting a mild risk difference and interaction effect. Second, we did not report data on specific causes of non-CVD death—including deaths from cancer, deaths from diseases of the lung, liver, kidney, and gastrointestinal tract, and deaths from infections, accidents, etc.—owing to the small numbers of subjects who died from each of these causes, although the multivariate analyses using RDW as a continuous variable showed a strong association between RDW and death from liver diseases (21 events; HR = 1.46, 95% CI: 1.17, 1.83). We observed no association with death from colon cancer (26 events), for which RDW has been suggested as an early indicator for high-risk groups (14). Third, we measured the RDW values once. The observed association might have been underestimated owing to intraindividual variation.

We performed additional analyses, with the follow-up duration stratified, to observe whether a high RDW level measured at baseline was associated with increased

mortality over a long period. The results revealed that mortality in the highest RDW quartile was slightly lower than that in the third quartile after 10 years of follow-up but was appreciably greater than that in the other 2 lower quartiles (data not shown). Overall, the positive association between a high RDW level and mortality was observed throughout the follow-up period. In addition, the median latency time to death was shorter in subjects in the highest RDW quartile than in those in the lowest quartile (8 years vs. 11 years, $P < 0.001$; data not shown), indicating that persons in the highest RDW quartile died earlier.

In conclusion, we found that a high RDW was independently associated with increased risk of all-cause mortality but not the development of CVD in a middle-aged community population. The association between RDW and mortality was primarily attributable to non-CVD deaths. Persons with high RDW values but without anemia have increased risks of all-cause and non-CVD death. Further investigation is needed to explain the increased mortality associated with high RDW values.

ACKNOWLEDGMENTS

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This work was funded by the National Science Council, Executive Yuan, Taiwan (grant NSC 96-2314-B-039-016-MY2 to F. C. S. and Y. T. L.).

Conflict of interest: none declared.

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