Heart Online First, published on April 23, 2014 as 10.1136/heartjnl-2013-305028

ORIGINAL ARTICLE

Red cell distribution width in relation to incidence of coronary events and case fatality rates: a population-based cohort study

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Received 3 October 2013
Revised 24 March 2014
Accepted 29 March 2014

ABSTRACT

Aims High red cell distribution width (RDW) is a strong prognostic factor in patients with cardiovascular disease. We investigated the association between RDW and incidence of acute coronary events (CEs) and fatal outcome in subjects who subsequently experienced a first CE.

Methods and results RDW was measured in 26 820 subjects (aged 45–73 years, 61.6% women), without history of myocardial infarction or stroke, who participated in the Malmö Diet and Cancer study during 1991–1996. Cox proportional hazards model was used to analyse the association between RDW and CE. During a mean follow-up of 14 years, 1995 subjects had a first CE, of which 415 subjects died on the same day as the CE (fatal on day 1), another 86 died within 28 days (fatal in 28 days) and 1494 were non-fatal (survived >28 days). After adjustment for risk factors, baseline RDW was significantly associated with incidence of fatal CE (HR 1.82, CI 1.35 to 2.44) but not with non-fatal CE (HR 0.96, CI 0.82 to 1.12). Among all subjects with a CE during follow-up, the proportion who died on day 1 was 13.7%, 18.2%, 22.5% and 26.7%, respectively, for first, second, third and fourth quartiles of RDW.

Conclusions In this population-based study of subjects without history of CE or stroke, high RDW was associated with increased incidence of fatal CE. No relationship was observed for incidence of non-fatal CE.

INTRODUCTION

Red cell distribution width (RDW) is a measure of anisocytosis, that is, the variability of the volumes of circulating erythrocytes. RDW is part of routine haematology laboratory tests and has been a useful diagnostic tool for differentiation and classification of anaemia.[1] Recently, studies have reported associations between elevated RDW and adverse prognosis in patients with heart failure and myocardial infarction (MI).[2–5] High RDW has been associated with increased incidence of heart failure[6] and atrial fibrillation[7] and has been shown as a strong independent predictor of death and cardiovascular events in coronary artery disease patients.[3] Another study found that increased RDW was associated with mortality after acute MI.[2] The causal link between RDW and cardiovascular disease mortality is unclear.

Approximately 25%–30% of individuals who experience a first acute coronary event (CE) die within the first day, and most of them die suddenly without reaching the hospital. To identify individuals with high risk and prevent the out-of-hospital deaths is a major challenge for healthcare. Previous studies have shown that the patterns of risk factors are different for fatal and non-fatal CE,[8] and certain risk factors, for example, hypertension and inflammation, particularly increase the risk of CEs with fatal outcome.[9 10] High RDW has been associated with worse prognosis in subjects with clinically manifest coronary artery disease, but there are limited data from population-based studies of incidence and case fatality, including subjects who died out-of-hospital.

Thus, the purpose of the present study was to explore whether RDW is associated with incidence of CEs and with fatal outcome in subjects who subsequently experienced a first CE.

METHODS

Study population

The Malmö Diet and Cancer study, a prospective cohort study from the city of Malmö in southern Sweden, was used.[6 11] Between 1991 and 1996, all men, 46–73-years-old, and all women, 45–73-years-old, resident in Malmö were invited to the baseline examination. A total of 28 449 individuals (11 246 men and 17 203 women) participated (41% of all eligible subjects). Participants underwent sampling of peripheral venous blood, a physical examination and filled out a self-administered questionnaire. Information on RDW was available in 28 363 subjects. Subjects with history of MI or stroke (n=872) at the baseline examination were excluded. In addition, 671 subjects were excluded due to missing information on cardiovascular risk factors (ie, leucocyte counts, mean corpuscular volume (MCV), haemoglobin, smoking habits, alcohol consumption, blood pressure, use of blood pressure-lowering or lipid-lowering medications, diabetes mellitus, waist circumference, physical activity, education level, marital status, immigrant status or diet). Thus, the final study population in the analysis consisted of 26 820 subjects (aged 45–73 years, 61.6% women).

The study was approved by the ethical committee at Lund University, Lund, Sweden (LU 51/90). All participants provided written informed consent.

Measurements and definitions

Waist circumference (in centimetres) was measured midway between the lowest rib margin and iliac crest. A mercury-column sphygmomanometer was used to measure blood pressure in the supine position after 10 min of rest. Information on current

To cite: Borné Y, Smith JG, Melander O, *et al*. *Heart* Published Online First: [*please include* Day Month Year] doi:10.1136/heartjnl-2013-305028

use of antidiabetic, blood pressure-lowering or lipid-lowering medications was assessed in a questionnaire. Smoking habits, alcohol consumption, leisure-time physical activity, education level, marital and immigrant status and medical history (history of cancer or asthma/chronic bronchitis) were also obtained from the questionnaire. History of diabetes mellitus at baseline was defined as self-reported physician's diagnosis of diabetes, use of antidiabetic medications or fasting whole blood glucose greater than 109 mg/dL (ie, 6.0 mmol/L). Subjects were categorised into current smokers (ie, those who smoked regularly or occasionally) or non-smokers (ie, former smokers and never smokers). The items 'How much do you smoke?' (in cigarettes per day) and 'How many years have you been smoking regularly?' were used to assess tobacco consumption in smokers. High alcohol consumption was defined as >40 g alcohol per day for men and >30 g per day for women. Low level of physical activity was defined as the lowest tertile of a score based on 18 questions covering a range of activities in the four seasons.[12] Educational level was categorised into <9, 9–12 and >12 years of education.[13] Marital status was defined as married or not.[13] Immigrant status was grouped as Swedish-born and foreign-born.

RDW, MCV, haemoglobin and leucocyte concentrations were analysed in fresh blood. Erythrocyte diameter was measured using a fully automated assay (SYSMEX K1000). RDW was calculated as the width of the erythrocyte volume distribution curve at a relative height of 20% above the baseline.[14] Reference values were 35.1–43.9 fL in men and 36.4–46.3 fL in women.

The dietary intake of folic acid, B_{12} and iron was assessed in an interview-based, modified diet history method. The methods and the validity of the nutrient data have been described elsewhere.[15 16] The intake of nutrients was log-transformed and adjusted for total energy intake[15] and method version of the diet assessment,[16] when used as covariates in the multivariate models.

Follow-up and ascertainment of CEs

All subjects were followed from the baseline examination until a first CE event, emigration, death or 30 June 2009, whichever came first. A CE was defined as a hospital diagnosis of acute MI (International Classification of Diseases code 410 or I21, for the 9th and 10th versions, respectively) or death due to ischaemic heart disease (410–414 or I20–I25). The Swedish Hospital Discharge Register (SHDR) and Swedish Cause of Death register were used for case retrieval. A validation study reported high validity of a primary diagnosis of MI in the SHDR.[17] Case fatality rates during the first day include those who died outside hospital or inhospital on the day of the CE. Case fatality rates within 28 days include out-of-hospital deaths and deaths within 28 days after hospitalisation.

Statistical analysis

The sample was categorised into sex-specific quartiles of RDW, that is, four groups with equal proportions of men and women in each quartile. To assess cross-sectional relationships between RDW quartiles and cardiovascular risk factors, linear regression was used for continuous variables and logistic regression for dichotomous variables. P-values for trends across quartiles were calculated. Cox proportional hazards regression was used to examine the incidence of CE. Time axis was follow-up time until death, emigration, incident CE or 30 June 2009. HRs with 95% CIs were calculated. The basic model included age and sex as covariates. In the final model, we also adjusted for established cardiovascular risk factors. Possible interactions between RDW and the other risk factors on incidence of CE were studied by introducing interaction terms in the multivariate model. The Kaplan–Meier estimator and log-rank test were used to study incidence of CE across quartiles of RDW. The proportional hazards assumption was confirmed by plotting incidence rates over time. Since follow-up time for case-fatality rate was limited to 28 days and most cases died on the first day, a binary outcome (fatal vs non-fatal) was explored in a logistic regression model, which does not require proportionality over time. All analyses were performed using IBM SPSS Statistics V.20 (IBM Sweden AB, Stockholm, Sweden).

RESULTS

Baseline characteristics

Median RDW (IQR) was 40.1 (36.8–44.4) in men and 40.6 (37.3–44.5) in women. Cardiovascular risk factors at the baseline examination in relation to the sex-specific quartiles of RDW are presented in table 1. Erythrocytes, haemoglobin, MCV, leucocytes and platelet count were significantly associated with RDW. Age, waist circumference, use of blood pressure-lowering medication, current smoking, high alcohol consumption and being unmarried were positively associated and diabetes was inversely associated with RDW (table 1).

Incidence of first CE in relation to RDW and known cardiovascular risk factors

A total of 1995 individuals (1252 men and 743 women) had a first CE during a mean follow-up of 14±3.5 years (range 0–18 years). Of these, 501 (335 men and 166 women) died within 28 days after the CE; most of them (n=415) died on the first day of the CE. In cases with CE, the mean time between the baseline examination and the CE was 8.5 years.

Subjects in the top compared with the bottom quartile of RDW had a significantly higher risk for any CE (ie, fatal or non-fatal) (HR 1.20, 95% CI 1.06 to 1.37) in the model adjusted for age and sex (table 2 and figure 1). However, this was completely explained by an increased incidence of fatal events and no relationship was seen for non-fatal CE. RDW was associated with fatal CEs (within 28 days) (HR 2.00; CI 1.52 to 2.62 for Q4 vs Q1) in the model adjusted for age and sex; the risk for fatal CEs remained adjusting for all covariates (HR 1.82; CI 1.35 to 2.44) (table 2).

In the final model age (HR per year: 1.10; CI 1.08 to 1.11), male sex (HR 2.53; CI 2.00 to 3.18), systolic blood pressure (HR per mm Hg: 1.02; CI 1.01 to 1.02), use of blood pressure-lowering medication (HR 1.25; CI 1.02 to 1.54), diabetes (HR 2.94; CI 2.18 to 3.95), waist circumference (HR per cm: 1.02; CI 1.01 to 1.03), leucocyte count (HR per 10^9/L: 1.02; CI 1.01 to 1.03), high iron intake (HR 1.14; 1.04–1.24), smoking (HR 2.22; CI 1.82 to 2.71), low physical activity (HR 1.37; CI 1.13 to 1.66), being unmarried (HR 1.80; CI 1.50 to 2.16) and history of asthma/chronic bronchitis (HR 1.52; CI 1.13 to 2.05) were independently associated with an increased risk for fatal CE.

A significant positive interaction was observed between RDW and smoking (p=0.007). Separate analyses of smokers and non-smokers were performed. Among non-smokers, the adjusted HR for fatal CE was 1.48 (CI 1.04 to 2.10) comparing fourth and first quartile of RDW. The corresponding HR in smokers was 3.93 (CI 2.83 to 5.46). With additional adjustment for number of cigarettes and years of smoking among smokers, the HR was reduced but remained significant (HR 2.47; CI 1.20 to 5.08).

Additional analysis was performed after excluding 826 subjects with anaemia (haemoglobin <120 g/L in women

Table 1 Baseline characteristics for Malmö Diet and Cancer (MDC) cohort in relation to quartiles (Q1–Q4) of RDW

	Quartiles of RDW				
MDC (N=26 820)	Q1 (N=6 690)	Q2 (N=6 721)	Q3 (N=6 787)	Q4 (N=6 622)	p Value for trend
RDW range, men (fL)	<38.2	38.2–40.1	40.2–42.5	42.6–72.9	
RDW range, women (fL)	<38.5	38.5–40.5	40.6–42.7	42.8–67.9	
Age (years)	56.8±7.0	57.8±7.4	58.5±7.8	59.1±7.9	<0.001
Male sex (%)	38.5	39.0	38.6	37.6	
Waist circumference (cm)	84.7±12.7	84.3±12.8	83.7±12.7	82.5±13.1	<0.001
Systolic blood pressure (mm Hg)	141±20	141±20	141±20	141±20	0.475
Blood pressure-lowering medication (%)	17.3	16.9	16.3	16.0	0.038
Lipid-lowering medication (%)	2.7	2.2	2.5	2.2	0.131
Diabetes (%)	4.5	3.0	2.0	1.9	<0.001
Current smoker (%)	14.3	21.6	29.9	47.3	<0.001
High alcohol consumption (%)	3.2	3.5	4.3	6.4	<0.001
Low physical activity (%)	25.3	24.3	24.2	26.3	0.195
Married (%)	69.0	66.0	64.4	61.2	<0.001
Low education (%)	42.6	40.7	41.2	41.3	0.228
Foreign-born (%)	14.4	12.0	10.6	10.5	<0.001
Erythrocytes (10^{12}/L)	4.8±0.4	4.7±0.5	4.6±0.5	4.5±0.6	<0.001
Haemoglobin (g/L)	139.6±26.2	140.8±20.8	140.9±17.7	140.5±18.6	0.007
Mean corpuscular volume (fL)	84.6±16.6	87.8±8.7	89.9±7.6	93.1±4.7	<0.001
Platelet count (10^9/L)	227.5±56.5	229.3±58.0	230.9±57.0	234.5±66.2	<0.001
Leucocytes (10^9/L)	6.1±1.5	6.3±2.0	6.4±1.8	6.8±3.7	0.028
History of cancer (%)	7.1	7.0	8.1	8.6	<0.001
History of asthma/chronic bronchitis (%)	6.4	6.3	7.7	8.6	<0.001

All values are mean±SD, unless otherwise stated.
RDW, red cell distribution width.

and <130 g/L in men).[18] After exclusions, the analysis included 489 fatal CEs and 1459 non-fatal CEs. The association between RDW and fatal CEs (within 28 days) changed marginally (HR 1.81; CI 1.35 to 2.45 for Q4 vs Q1) in the final model. We also performed a sensitivity analysis after excluding 16 individuals with extremely low RDW values (<25.0 fL). The results were virtually identical as in the main analysis.

Quartiles of RDW and case fatality rate

Of the 1995 incident cases of CE, 415 (20.8%, 283 men and 132 women) died on the day of the CE, another 86 (4.3%, 52 men and 34 women) subjects died within 28 days. Of the 415 patients who died within the first day, cause of death was based on autopsy in 280 patients (67.5%).

Case fatality rate (within 1 day or within 28 days) was significantly associated with high RDW. The proportion who died within 1 day was 13.7%, 18.2%, 22.5% and 26.7%, respectively, for cases with RDW in quartiles 1–4, respectively. After adjustments for sex, age at CE and year of CE, the OR (95% CI) for fatal outcome (first day) was 1.00 (reference), 1.34 (0.93 to 1.93), 1.76 (1.24 to 2.48) and 2.24 (1.61 to 3.12), respectively, for RDW in quartiles 1–4 (p<0.001). Results were similar for deaths within 28 days (figure 2).

Table 2 Incidence of CEs in relation to quartiles of red cell distribution width

	Quartiles of red cell distribution width					
	Q1 (n=6690)	Q2 (n=6721)	Q3 (n=6787)	Q4 (n=6622)	p Trend	HR per SD (3.57 fL)
All CE, n, per 1000 p-y	437 (4.5)	461 (4.8)	516 (5.5)	581 (6.5)		
HR (CI), model 1	1.00	0.97 (0.85 to 1.11)	1.03 (0.91 to 1.17)	1.20 (1.06 to 1.37)	<0.001	1.08 (1.04 to 1.12)
HR (CI), model 2	1.00	0.98 (0.86 to 1.11)	1.04 (0.91 to 1.19)	1.12 (0.97 to 1.28)	*	1.06 (1.01 to 1.10)
Fatal CE<28 d, n, per 1000 p-y	76 (0.8)	105 (1.1)	139 (1.5)	181 (2.0)		
HR (CI), model 1	1.00	1.23 (0.91 to 1.65)	1.51 (1.14 to 2.00)	2.00 (1.52 to 2.62)	<0.001	1.17 (1.12 to 1.22)
HR (CI), model 2	1.00	1.24 (0.92 to 1.67)	1.53 (1.14 to 2.05)	1.82 (1.35 to 2.44)	<0.001	1.19 (1.11 to 1.27)
Non-fatal CE, n, per 1000 p-y	361 (3.7)	356 (3.1)	377 (4.0)	400 (4.5)		
HR (CI), model 1	1.00	0.92 (0.79 to 1.06)	0.93 (0.80 to 1.08)	1.03 (0.89 to 1.19)	*	1.01 (0.96 to 1.06)
HR (CI), model 2	1.00	0.92 (0.79 to 1.07)	0.94 (0.80 to 1.09)	0.96 (0.82 to 1.12)	*	0.99 (0.94 to 1.04)

HR model 1 adjusted for age and sex.
HR model 2 adjusted for age, sex, systolic blood pressure, use of blood pressure-lowering medications, use of lipids-lowering medications, diabetes mellitus, haemoglobin, mean corpuscular volume, intake of iron, B_{12} and folate, leucocyte count, waist circumference, smoking habits, high alcohol consumption, low physical activity, education level, marital and immigrant status, history of cancer, and history of asthma/chronic bronchitis.
*p>0.05.
CE, coronary events; p-y, person-year.

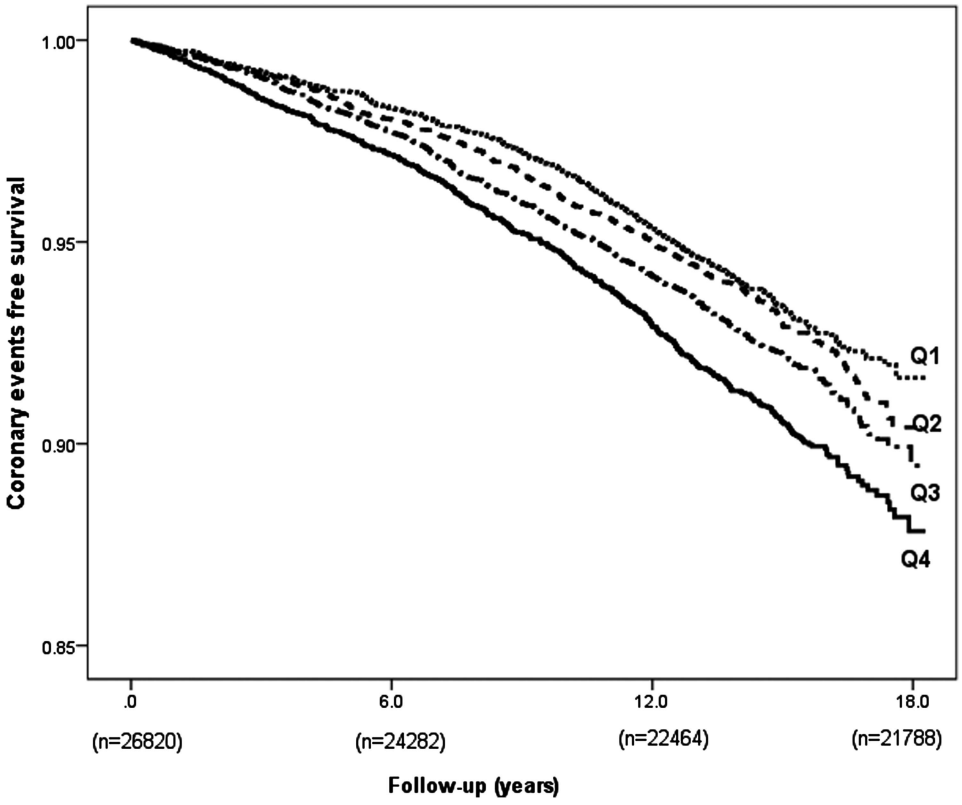

Figure 1 Incidence of first coronary events in relation to quartiles (Q1–Q4) of red cell distribution width at the baseline examination.

DISCUSSION

The present study showed a graded association between elevated RDW and risk of fatal CEs among middle-aged subjects. The relationship persisted after adjustment for established cardiovascular risk factors. The proportion dying on the first day of the CE was 13.7% and 26.7%, respectively, for subjects with prior RDW values in the first and fourth quartiles. There was no relationship between RDW and non-fatal CE.

Even though fatal and non-fatal CEs obviously share many risk factors, the predisposing factors also show differences

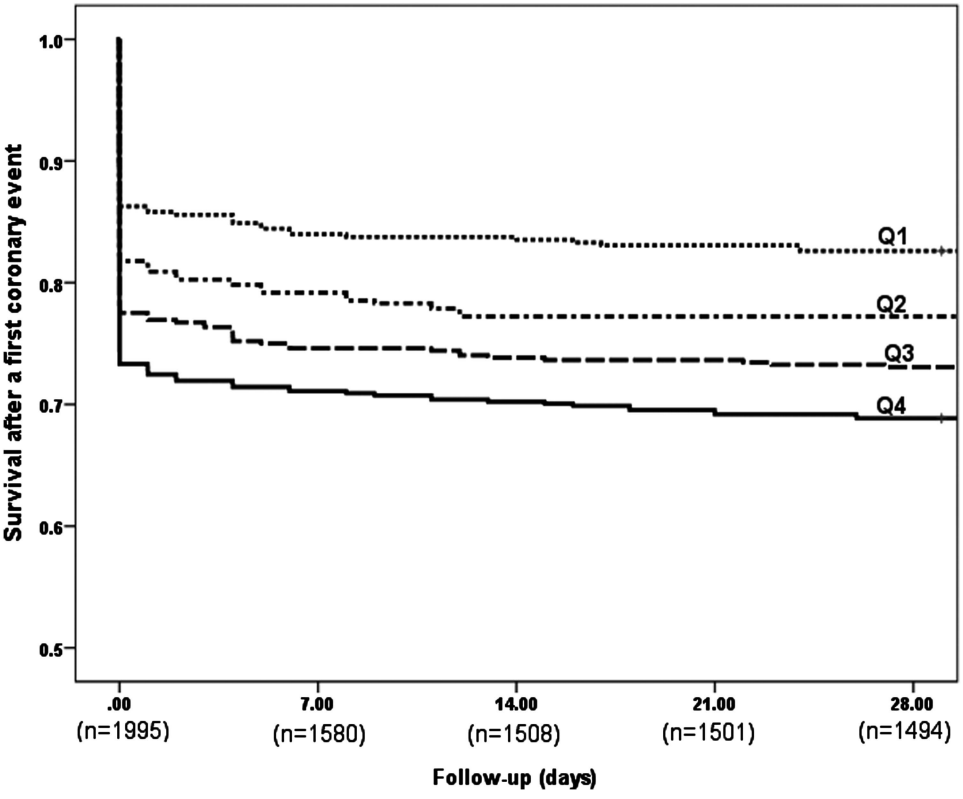

Figure 2 Survival during the first 28 days after a first coronary event in relation to quartiles (Q1–Q4) of red cell distribution width at the baseline examination.

between these outcomes. Several population-based studies have reported increased case-fatality in individuals with a history of hypertension.[9 10 19] Low grade inflammation[9 20 21] and diabetes[22 23] are other cardiovascular risk factors which have been associated with increased case-fatality in population studies. According to the present results, RDW is another factor which is associated with fatal CE. However, the results should be replicated in other population-based studies before making recommendations about the clinical benefits of measuring RDW.

The mechanism underlying the relationship between RDW and fatal CEs is unclear. A study of patients with heart failure reported that heart rate variability was substantially reduced in patients with high RDW, suggesting a relationship between RDW and autonomic dysfunction.[24] Low heart rate variability has been associated with incidence of CE and mortality post-MI.[25 26] Cardiac arrhythmia is considered to be an important contributing factor or the underlying cause in incidence of MI and mortality.[27 28] Therefore, it seems possible that the increased case-fatality rates in subjects with high RDW could be related to autonomic dysfunction.

Another possible explanation could be that the properties and functions of the red cells are suboptimal in subjects with high RDW. Patel *et al*[29] observed an inverse correlation between RDW and erythrocyte deformability in a community population. Lower erythrocyte elongation index could potentially result in impaired blood flow in the coronary microcirculation, resulting in hypoxia and increased cardiovascular risks.[29] In contrast, another study did not find any association between high RDW and erythrocyte deformability among MI patients.[30] Thus, it remains possible but unproven that high RDW could be related to impaired function of the red cells.

RDW is associated with ineffective erythropoiesis and could be part in a complex malnutrition-inflammation syndrome.[1 5 31] Inflammation may alter erythropoiesis, change iron homeostasis, the proliferation of erythroid progenitor cells, life span of red blood cell, and red cell membrane deformability, all factors that might increase anisocytosis.[32] In our study, RDW was associated with leucocyte counts, an inflammation marker which previously has been associated with incidence of CE and increased case-fatality rates. However, the increased risk of elevated levels of RDW and incident fatal CE did not change when leucocytes were taken into account. This suggests that inflammation is not the major mechanism for the increased incidence of fatal CE in this study.

Malnutrition and deficiency of vitamin B_{12} and folic acid are other factors which are associated with high RDW, because of their role in erythropoiesis. However, RDW remained significant after adjustment for iron, B_{12} and folate intake. In addition, adjustments for haemoglobin or excluding subjects with anaemia did not attenuate the association between RDW and fatal CEs.

There was a significant interaction between RDW and smoking on incidence of fatal CEs. But, even though the relationship was strongest in smokers, high RDW was significantly associated with fatal CE both in smokers and non-smokers. Thus, it is unlikely that association between RDW and fatal CEs is completely explained by smoking.

Limitations and strengths

The large numbers of subjects and events during a long follow-up period were important strengths of the present study.[11 33] The cardiovascular endpoints were retrieved from the SHDR, which has shown a 94% sensitivity and 86% positive predictive value for MI.[17] The autopsy rate was high and cause of death was based on autopsy in 67.5% of the cases that died on the first day. All subjects in this study were without history of MI at baseline examination. However, it is still possible that some individuals had a silent MI.

Another limitation is that RDW was measured once at the baseline examination and it is possible that RDW changed during the follow-up period. However, changes during follow-up would bias the relationships towards null, if anything. In a study of annual variations in haematological measures, RDW showed small annual variations and small intraindividual variability, similar to, for example, RBC and haemoglobin.[34] It is also noteworthy that RDW was associated with incidence of fatal CE over the entire follow-up period (figure 1).

In conclusion, RDW was associated with incidence of fatal CEs and increased case fatality rates. The possible mechanism underlying the association between RDW and incident CEs needs further investigation. Given the high fatality rates in subjects with high RDW, a global risk factor evaluation and intensified treatment of traditional cardiovascular risk factors could be justified in subjects with high RDW.

Key messages

What is already known on this subject?
Studies have reported associations between elevated red cell distribution width (RDW) and adverse prognosis in patients with heart failure and myocardial infarction.

What this study adds?
There are limited data from population-based studies of case fatality after acute coronary events, including subjects who die out-of-hospital. RDW is associated with increased incidence of coronary events with fatal outcome.

How might this impact on clinical practice?
Given the high fatality rates in subjects with high RDW, a global risk factor evaluation and intensified treatment of traditional cardiovascular risk factors could be justified in subjects with high RDW.

Contributors All authors were involved in: conception and design, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Funding This work was supported by grants from the Swedish Cancer Society, the Swedish Medical Research Council (2011-3891), the Swedish Heart and Lung Foundation (20130249), and funds from Skåne University Hospital and Lundströms Foundation.

Competing interests None.

Patient consent Obtained.

Ethics approval The ethical committee at Lund University, Lund, Sweden (LU 51/90).

Provenance and peer review Not commissioned; externally peer reviewed.

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