Low Hemoglobin, Chronic Kidney Disease, and Risk for Coronary Heart Disease–Related Death: The Blue Mountains Eye Study

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A recent report found that chronic kidney disease (CKD) increased the risk for coronary heart disease (CHD) events in people with anemia but not in those without anemia. This study aimed to verify these findings in the Blue Mountains Eye Study cohort, a prospective Australian population-based study of 3654 residents aged 49 to 97 yr. Fasting blood samples were obtained at baseline and confirmed CHD-related deaths over 9 yr with the Australian National Death Index. "Low hemoglobin" was defined as levels in the lowest quintile of the cohort. Body surface area–adjusted GFR was estimated using a variety of methods (Cockcroft-Gault, abbreviated Modification of Diet in Renal Disease, and Bjornsson equations). People with CKD (GFR <60 ml/min per 1.73 m^2 as estimated using the Cockcroft-Gault equation) and low hemoglobin (mean 13.2 g/dl; range 7.6 to 14.6 g/dl) had an increased risk for CHD-related death (multivariable-adjusted hazard risk ratio 1.49; 95% confidence interval 1.08 to 2.06) compared with people with CKD but in higher hemoglobin quintiles. This effect was not evident in people without CKD. The interaction between GFR and hemoglobin was significant ($P = 0.05$) when GFR was estimated using either the Cockcroft-Gault or Bjornsson equations or when serum creatinine instead of GFR was used in the analyses but not when GFR was estimated using the abbreviated Modification of Diet in Renal Disease equation. In conclusion, this study found that low hemoglobin, even within the normal range, together with CKD increased the risk for CHD-related death.

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End-stage renal failure is a strong independent predictor of cardiovascular mortality (1). Whether chronic kidney disease (CKD) also predicts cardiovascular mortality independent of traditional risk factors is less clear, with some studies showing an association (2–4) and others not (5,6). Recently, the Atherosclerosis Risk In Communities (ARIC) Study demonstrated a near tripling of the risk for coronary heart disease (CHD) events in people with anemia and concomitant CKD when compared with people with anemia but without CKD (7). An earlier report from the same study found that anemia was a modest but independent risk factor for cardiovascular disease (8), and CKD slightly increased the risk for cardiovascular events (9). The effect that was observed in people with both CKD and anemia, however, was larger than the sum of the two risk factors alone, suggesting a possible interaction between CKD and anemia (7).

We sought to verify these findings in the Blue Mountains Eye Study (BMES) population-based cohort. We looked for evidence that low hemoglobin levels modified the effect of CKD on CHD mortality, an outcome that was not reported separately in the ARIC study (7).

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Materials and Methods

The BMES is a population-based cohort study of a predominantly white Australian population. The initial aim of the study was to report on the prevalence and the incidence of eye-related health outcomes, and the study later was expanded to include other systemic health outcomes. Details of recruitment methods are given elsewhere (10,11). In brief, in 1992, after a door-to-door census of two postcode regions in the Blue Mountains area, west of Sydney, all permanent residents who were born before January 1, 1943, were invited to attend a local clinic for a detailed interview and physical examination. People who lived in nursing homes were excluded. Baseline participants ($n = 3654$, aged 49 to 97 yr) represented 82.4% of eligible people who were identified in the census. This study was conducted according to the recommendations of the Declaration of Helsinki and was approved by the Western Sydney Area Human Ethics Committee. Written, informed consent was obtained from all participants.

At the baseline examination that was conducted during 1992 to 1994, we measured participants' height, weight, and BP. We measured systolic (SBP) and diastolic BP (DBP) once using a single mercury sphygmomanometer with appropriate adult cuff size, after the participants were seated for at least 10 min. Fasting blood samples were collected from 3222 (88%) of the 3654 participants (12). The Institute of Clinical Pathology and Medical Research at Westmead Hospital performed laboratory tests within 4 h of blood collection. Hemoglobin was mea-

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sured on a Technician H2 hematology analyzer (Bayer Technicon, Germany), and creatinine was measured with a Hitachi 747 biochemistry analyzer (Hitachi, Japan). Anemia was defined as hemoglobin <12 g/dl in women and <13 g/dl in men (13). We calculated hemoglobin quintiles for men and women separately and defined "low hemoglobin" for the whole population as the sum of men and women with the lowest quintile of hemoglobin. We used the National Kidney Foundation (NKF) (14) definition of CKD and classified people with GFR <60 ml/min per 1.73 m^2 (body surface area) as having CKD. We used three different methods of estimating GFR: Cockcroft-Gault (CG) equation (15), abbreviated Modification of Diet in Renal Disease (MDRD) equation (16), and Bjornsson equation (17). NKF guidelines recommend estimating GFR using either the Cockcroft-Gault or MDRD equations, and we decided also to use the Bjornsson equation because it has been reported to be one of the most accurate in people with CKD and normal levels of serum creatinine (18). We corrected the CG and Bjornsson equations for body surface area according to the Mosteller formula (19,20) to obtain GFR in ml/min per 1.73 m^2. As the equations that are used to estimate GFR have varying degrees of accuracy (18) and may lead to misclassification of CKD, we also classified people as having high or low serum creatinine. We specified high serum creatinine as levels ≥1.46 mg/dl for men and ≥1.26 mg/dl for women because these values correspond to the 90th percentile of serum creatinine in men and women in our population. These cutoffs approximate those used in the ARIC study (7), the results of which we were seeking to confirm (1.5 mg/dl for men and 1.2 mg/dl for women in the ARIC study). They are also close to the values that were found to correspond to an inulin clearance of 60 ml/min per 1.73 m^2 (1.55 mg/dl for men, 1.18 mg/dl for women) (21).

CG:

$$\frac{(140 - age) \times weight}{72 \times serum\ creatinine} (\times 0.85\ if\ female)$$

Abbreviated MDRD:

$$186 \times serum\ creatinine^{-1.154} \times age^{-0.203} \times (1.212\ if\ black) \times (0.742\ if\ female)$$

Bjornsson:

$$\text{Male:} \quad \frac{[27 - (0.173 \times age)] \times weight \times 0.07}{serum\ creatinine}$$

$$\text{Female:} \quad \frac{[25 - (0.175 \times age)] \times weight \times 0.07}{serum\ creatinine}$$

Diabetes was defined as a physician diagnosis of diabetes or a fasting blood sugar of ≥7 mmol/L, mean arterial BP was defined as two thirds of DBP plus one third of SBP and body mass index was calculated from height and weight. We defined alcohol consumption from history as none (0 standard drinks/wk), low (1 to 6 standard drinks/wk), moderate (7 to 27 standard drinks/wk), and heavy (≥28 standard drinks/wk). We followed the 2003 World Health Organization/International Society of Hypertension guidelines (22) to define severe hypertension as World Health Organization/International Society of Hypertension category grade 2 or 3, *i.e.*, SBP ≥ 160 mmHg or DBP ≥ 100 mmHg at examination. If the participant previously had a diagnosis of hypertension and currently using antihypertensive medications, then we could not accurately assess these participants' BP level; therefore, we assumed that they were at least grade 2.

Deaths that occurred during the period between the baseline examinations to December 31, 2001, were confirmed by cross-matching demographic information of the 3654 participants with Australian National Death Index (NDI) data using probabilistic record linkage (23,24). Cause of death was collected from death certificates by NDI and defined using *International Classification of Diseases, Ninth Revision* (ICD-9) and ICD-10. CHD-related deaths were defined according to codes from ICD-9—3949, 4029, 4109, 4119, 4140, 4148, 4149, 4151, 4240, 4241, 4254, 4269, 4273, 4274, 4275, 4278, 4280, 4281, 4289, 4290, 4291, 4410, 4411, 4413, 4414, 4415, 4439—and ICD-10—I059, I10, I132, I219, I249, I251, I255, I259, I269, I271, I350, I352, I358, I429, I469, I48, I500, I514, I515, I516, I709, I711. The sensitivity and the specificity of Australian NDI data have been estimated to be 93.7 and 100%, respectively, for all deaths and 92.5 and 89.6%, respectively, for cardiovascular deaths (23,24).

We used SAS (SAS Institute, Cary, NC) for statistical analysis. Baseline characteristics of participants in the lowest hemoglobin quintile were compared with those of participants in other hemoglobin quintiles using t test for means and χ^2 test for proportions. We applied Cox regression models to assess the association between low hemoglobin and CKD at baseline and the risk for CHD-related death, after adjusting for age, gender, pre-existing CHD, mean arterial BP, smoking, self-rated health, total cholesterol, fibrinogen levels, body mass index, and diabetes. We tested for statistical interaction by adding the cross product term GFR × hemoglobin (both continuous variables) to multivariate adjusted models. Rate of CHD events was calculated per 1000 person-years of follow-up. Hazard risk ratios (HR) and 95% confidence intervals (CI) are presented.

Results

We excluded 580 (15.9%) people from analyses because of incomplete or missing information. Most of those excluded (n = 432; 11.8%) did not have blood profiles taken. Of those excluded, 43.9% were male, the average age was 67.9 yr, 44.8% had severe hypertension, 6.5% had diabetes, 19.9% had pre-existing CHD, and 15.3% experienced CHD-related death. Among those who were included in our analyses, 43.2% were male, the average age was 65.9 yr, 45.5% had severe hypertension, 8.0% had diabetes, 15.5% had pre-existing CHD, and 7.3% experienced CHD-related death.

Baseline characteristics of the 3074 people with data available on GFR, stratified by GFR and hemoglobin quintiles, are shown in Table 1. People with CKD as estimated using the CG equation (n = 1639; 53.3%) were in general older (mean age 71.5 *versus* 59.4 yr) and more likely to have severe hypertension (53.4 *versus* 36.4%) and pre-existing CHD (19.8 *versus* 10.5%) than people without CKD. The mean GFR in people with CKD was 48.3 ml/min per 1.73 m^2, whereas the GFR in people without CKD was 70.2 ml/min per 1.73 m^2. Because of the small number of people with anemia (n = 67), we used the lowest quintile of hemoglobin (n = 632) for analyses instead. The mean hemoglobin of people in the lowest quintile of hemoglobin was 13.2 g/dl, with a median of 13.3 g/dl and a range from 7.6 to 14.6 g/dl. The mean follow-up period was 8.2 yr for the study population.

Table 1. Baseline characteristics, by CKD and hemoglobin quintiles[a]

Baseline Characteristics	CKD[b] (GFR <60 ml/min per 1.73 m^2; Range 11.9 to 59.97)			No CKD[b] (GFR ≥60 ml/min per 1.73 m^2; Range 60.0 to 129.8)		
	Lowest Hemoglobin Quintile (n = 352; mean 13.1 g/dl)[c]	Other Hemoglobin Quintiles (n = 1287; mean 15.2 g/dl)[c]	P Value	Lowest Hemoglobin Quintile (n = 258; mean 13.4 g/dl)[c]	Other Hemoglobin Quintiles (n = 1177; mean 15.3 g/dl)[c]	P Value
Age (yr; mean [SE])	73.9 (0.46)	70.8 (0.22)	0.0001	59.6 (0.42)	59.4 (0.18)	0.63
Mean arterial BP (mmHg; mean [SE])	105.2 (0.74)	105.1 (0.35)	0.93	101.4 (0.69)	103.6 (0.34)	0.005
Total serum cholesterol (mmol/L; mean [SE])	5.9 (0.06)	6.1 (0.03)	0.0002	5.8 (0.06)	6.0 (0.03)	0.0002
Fibrinogen (mg/dl; mean [SE])	4.6 (0.07)	4.1 (0.03)	<0.0001	4.0 (0.06)	3.9 (0.04)	0.027
Body mass index (kg/m^2; mean [SE])	25.0 (0.21)	25.0 (0.11)	0.77	26.5 (0.27)	27.7 (0.13)	0.0002
Mean hemoglobin (g/dl; mean [SE])	13.1 (0.05)	15.2 (0.03)	<0.0001	13.5 (0.05)	15.3 (0.03)	<0.0001
Mean GFR (ml/min per 1.73 m^2; mean [SE])	44.7 (0.56)	49.2 (0.23)	<0.0001	70.3 (0.60)	70.2 (0.24)	0.85
Mean alcohol consumption, standard drinks per week (mean [SE])	4.3 (0.52)	5.8 (0.27)	0.01	7.7 (0.91)	8.1 (0.41)	0.72
Male (n [%])	131 (37.2)	519 (40.3)	0.29	115 (44.6)	563 (47.8)	0.34
Severe hypertension[d] (n [%])	200 (56.8)	675 (52.5)	0.15	82 (31.8)	441 (37.5)	0.09
Diabetes (n [%])	25 (7.1)	114 (8.9)	0.29	17 (6.6)	91 (7.7)	0.53
Anemia (n [%])	50 (14.2)	0	<0.0001	17 (6.6)	0	<0.0001
Pre-existing CHD (n [%])	67 (19.0)	258 (20.1)	0.67	20 (7.8)	130 (11.1)	0.12
Current smoker (n [%])	23 (6.5)	181 (14.1)	0.0001	24 (9.3)	221 (18.8)	0.0002

[a]CKD, chronic kidney disease; CHD, coronary heart disease.
[b]CKD is defined according to National Kidney Foundation criteria of GFR <60 ml/min per 1.73 m^2, with GFR estimated using the Cockcroft-Gault equation.
[c]Mean hemoglobin for men and women combined. For women, hemoglobin in the lowest quintile ranged from 8.4 to 13.5 g/dl, whereas hemoglobin in other quintiles ranged from 13.6 to 22.4 g/dl. For men, hemoglobin in the lowest quintile ranged from 7.6 to 14.6 g/dl, whereas hemoglobin in other quintiles ranged from 14.7 to 19.3 g/dl.
[d]Severe hypertension is defined according to World Health Organization/International Society of Hypertension category grade 2 or 3, *i.e.*, a previous diagnosis of hypertension and current use of antihypertensive medication, or systolic BP ≥ 160 mmHg, or diastolic BP ≥ 100 mmHg at baseline examination.

Table 2 shows the relationship between low hemoglobin (*i.e.*, hemoglobin in the lowest quintile) and CHD in people with and without CKD. We estimated GFR by three different methods and present results for analyses using serum creatinine as well. When GFR was estimated using the CG equation, low hemoglobin was associated with CHD deaths only in people with CKD (HR 1.49; 95% CI 1.08 to 2.06) but not in people without CKD (HR 0.55; 95% CI 0.18 to 1.62). The interaction between GFR and hemoglobin was marginally significant (P = 0.05). When we estimated GFR using the abbreviated MDRD equation, a lower number of people were classified as having CKD (n = 1427; 46.4%) compared with the number classified using the CG equation. With the abbreviated MDRD classification, low hemoglobin was not significantly associated with CHD deaths in either the group with CKD (HR 1.36; 95% CI 0.95 to 1.94) or the group without CKD (HR 1.21; 95% CI 0.66 to 2.20), and the interaction between GFR and hemoglobin was NS (P = 0.61). Using the Bjornsson equation to estimate GFR, 1258 (40.9%) people were classified as having CKD, and similar results to the CG equation were obtained, *i.e.*, low hemoglobin was associated with increased CHD deaths only in people with CKD (HR 1.57; 95% CI 1.12 to 2.19) and not in people without CKD (HR 0.51; 95% CI 0.20 to 1.31). The interaction between GFR and hemoglobin was marginally NS (P = 0.08). When we used serum creatinine rather than GFR for analyses, we found that 294 (9.6%) people had high serum creatinine, and the association between low hemoglobin and CHD deaths again was present only in people with high serum creatinine (HR 1.80; 95% CI 1.02 to 3.18) and not in those with normal serum creatinine (HR 1.09; 95% CI 0.75 to 1.58). The interaction between serum creatinine and GFR was significant (P = 0.04).

For sensitivity analyses, we repeated our calculations with GFR cutoffs at 45, 50, 55, 65, 70, and 75 ml/min per 1.73 m^2 (as estimated using the CG equation) and obtained essentially the same results, *i.e.*, low hemoglobin was related to higher CHD deaths only in people with GFR below all of these cutoffs from 45 up to and including 75 ml/min per 1.73 m^2.

We also explored the interaction using the lowest quintiles of both hemoglobin and GFR (as estimated using the CG equation) for the entire population and for men and women separately (Table 3). GFR in the lowest quintile ranged from 11.9 to 48.2 ml/min per 1.73 m^2, with a mean of 38.6 ml/min per 1.73 m^2. People in the lowest quintile of hemoglobin alone at baseline did not have an increased risk for CHD death (multivariate adjusted HR 0.95; 95% CI 0.56 to 1.62); neither did people in the lowest quintile of GFR alone at baseline (HR 1.33; 95% CI 0.89

Table 2. Hemoglobin quintiles and CHD-related deaths, by different methods of estimating GFR[a]

Hemoglobin Quintile	Method of Estimating GFR	CKD (GFR <60 ml/min per 1.73 m^2)				No CKD (GFR 60 ml/min per 1.73 m^2)				
		No. at Risk	No. of Deaths	Rate[b]	Multivariate-Adjusted HR (95% CI)[c]	No. at Risk	No. of Deaths	Rate[b]	Multivariate-Adjusted HR (95% CI)[c]	*P* Interaction[d]
Lowest quintile	Cockcroft-Gault[f]	352	64	25.0	1.49 (1.08 to 2.06)	258	4	1.8	0.55 (0.18 to 1.62)	0.05
Other quintiles		1287	115	11.2	Reference	1177	41	4.0	Reference	
Lowest quintile	Abbreviated MDRD	312	53	23.1	1.36 (0.95 to 1.94)	298	15	6.1	1.21 (0.66 to 2.20)	0.61
Other quintiles		1115	95	10.5	Reference	1349	61	5.3	Reference	
Lowest quintile	Bjornsson[f]	299	63	29.9	1.57 (1.12 to 2.19)	311	5	1.9	0.51 (0.20 to 1.31)	0.08
Other quintiles		959	102	13.6	Reference	1505	54	4.1	Reference	
		High SCr[e]				Low SCr[e]				
Lowest quintile	Serum Creatinine (SCr)	99	28	47.3	1.80 (1.02 to 3.18)	511	40	9.6	1.09 (0.75 to 1.58)	0.04
Other quintiles		195	31	21.8	Reference	2269	125	6.5	Reference	

[a]MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; HR, hazard ratio; CI, confidence interval.
[b]Rate per 1000 person-years of follow-up.
[c]Cox regression model adjusting for age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, body mass index, diabetes, and self-reported health status.
[d]*P* value for interaction terms GFR × hemoglobin (or SCr × hemoglobin) in the multivariate adjusted model. GFR, SCr, and hemoglobin are treated as continuous variables for assessing interaction.
[e]High SCr is SCr ≥ 1.46 mg/dl (for men) and SCr ≥ 1.26 mg/dl (for women); low SCr is SCr < 1.46 mg/dl (for men) and SCr < 1.26 mg/dl (for women).
[f]Corrected for body surface area.

to 1.99). People in the lowest quintiles of both hemoglobin and GFR had an increased risk for CHD death (HR 2.07; 95% CI 1.33 to 3.22) compared with people in other hemoglobin and GFR quintiles. The age-adjusted HR of CHD death in women with the lowest quintile of both hemoglobin and GFR was significant (HR 2.34; 95% CI 1.18 to 4.65), but this effect attenuated and became NS after adjustment for other risk factors (HR 1.82; 95% CI 0.88 to 3.78). Additional adjustment for hormone replacement therapy use did not change these results (HR 1.78; 95% CI 0.86 to 3.71). The age-adjusted HR of CHD death in men with the lowest quintile of both hemoglobin and GFR was 2.20 (95% CI 1.24 to 3.89), and this strengthened slightly after multivariate adjustment (HR 2.32; 95% CI 1.29 to 4.17). When we tested for interaction between GFR and hemoglobin in men and women separately, the interaction was marginally NS in men ($P = 0.08$) and NS in women ($P = 0.38$).

Discussion

In an older Australian population, we found that low hemoglobin and low GFR interact to increase the risk for CHD-related death ($P = 0.05$ using the CG equation to estimate GFR). In people with CKD, hemoglobin in the lowest quintile was associated with an increased risk for CHD-related death (HR 1.49; 95% CI 1.08 to 2.06), whereas in people without CKD, this association was not evident (HR 0.55; 95% CI 0.18 to 1.62). This interaction was observed when GFR was estimated using the CG and Bjornsson equations and with serum creatinine but not when the abbreviated MDRD equation was used.

The ARIC study (7) recently reported an interaction between anemia and high serum creatinine that increased the risk for CHD events in people with both anemia and high serum creatinine. In our study population, we found that people with both CKD and the lowest quintile of hemoglobin experienced an increased risk for CHD death despite that most (86%) were not yet anemic. Our findings confirm and extend the ARIC Study finding of a possible interaction between low hemoglobin and CKD, which increased the risk for CHD events, even when hemoglobin was within the normal range. These findings and their clinical implications in terms of management of CKD warrant further investigation.

We found that women with the lowest quintile of both hemoglobin and GFR had a higher age-adjusted risk for CHD death, but this effect disappeared after multivariate adjustment for other cardiovascular risk factors. In men with the lowest quintile of both hemoglobin and GFR, age- and multivariate-adjusted risk for CHD death remained significant after multivariate adjustment. These findings are different from the ARIC study (7), which found that anemia and high serum creatinine increased risk for CHD events in women but not in men. The discrepancy could be due to random-sample variation arising from small numbers or also could be related to our generally older sample and the different ethnic mix—the ARIC population comprised a substantial number of black individuals, whereas our population was 98% white. These gender-based differences warrant further investigation in other populations.

We are not certain how low hemoglobin may interact with CKD or low GFR to lead to an increase in CHD death. Low hemoglobin can be a marker for the severity of kidney disease (5). However, in people with CKD, the mean GFR of those with low hemoglobin was 44.7 ml/min per 1.73 m^2, compared with

Table 3. Hemoglobin, GFR quintiles, and CHD-related deaths[a]

Quintiles of Hemoglobin and GFR[b]	CHD-Related Deaths				
	No. at Risk	No. of CHD-Related Deaths	Rate[c]	Age- and Gender-Adjusted HR (95% CI)[d]	Multivariate-Adjusted HR (95% CI)[d]
All participants, lowest quintile of					
neither	2033	82	4.7	Reference	Reference
hemoglobin only	434	17	4.7	0.90 (0.54 to 1.53)	0.95 (0.56 to 1.62)
GFR only	431	74	23.7	1.39 (0.94 to 2.06)	1.33 (0.89 to 1.99)
both hemoglobin and GFR	176	51	45.3	2.32 (1.51 to 3.57)	2.07 (1.33 to 3.22)
Women, lowest quintile of					
neither	1130	26	2.6	Reference	Reference
hemoglobin only	272	11	4.7	1.37 (0.67 to 2.81)	1.26 (0.61 to 2.61)
GFR only	252	38	20.2	1.49 (0.80 to 2.76)	1.23 (0.64 to 2.35)
both hemoglobin and GFR	92	25	40.8	2.34 (1.18 to 4.65)	1.82 (0.88 to 3.78)
Men, lowest quintile of					
neither	903	56	7.4	Reference	Reference
hemoglobin only	162	6	4.6	0.57 (0.25 to 1.32)	0.68 (0.29 to 1.59)
GFR only	179	36	29.0	1.33 (0.80 to 2.24)	1.51 (0.88 to 2.59)
both hemoglobin and GFR	84	26	50.7	2.20 (1.24 to 3.89)	2.32 (1.29 to 4.17)

[a]HR, hazard risk ratio.
[b]GFR as estimated using the Cockcroft-Gault equation.
[c]Rate per 1000 person-years of follow-up.
[d]Cox regression model adjusted for age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total serum cholesterol, fibrinogen, body mass index, diabetes, and self-reported health.

a mean GFR of 49.2 ml/min per 1.73 m^2 in people with higher hemoglobin. We cannot exclude the possibility of a synergistic effect of low hemoglobin and low GFR on CHD death, as it is unlikely that the small difference in mean GFR could totally account for the differences in CHD mortality.

This study has several strengths, including a large population-based sample, well-documented data on confounding risk factors, and ascertainment of CHD events using validated NDI data. The most important limitation is potential misclassification of CKD, as we did not measure GFR directly but rather estimated it from serum creatinine and other measured variables. We examined the robustness of our findings by estimating GFR using different methods. When we estimated GFR using the CG and Bjornsson equations, we obtained similar findings. When we used the abbreviated MDRD equation to estimate GFR, however, the interaction was not evident. The CG and Bjornsson equations have been reported to be the most accurate for estimating GFR in people with CKD and normal levels of serum creatinine (18), whereas the MDRD equation has been reported to have significant bias in the general population and in the elderly (25). As our sample comprised mainly community-dwelling older people, the MDRD equation may have misclassified substantial numbers of them and hence masked the interaction. This possibility is supported by our analyses using serum creatinine (rather than GFR), which also found that low hemoglobin increased the risk for CHD death only in people with high serum creatinine.

The robustness of our findings is also supported by our sensitivity analyses using different cutoffs of GFR (as estimated using the CG equation), with the same findings when we took low GFR as GFR <45, 50, 55, 65, 70, or 75 ml/min per 1.73 m^2. Second, the prevalence of CKD (53.3%), as defined using NKF criteria and the CG equation, is somewhat high but similar to that reported for older people in a previous Australian survey (54.8% in people aged ≥65 yr) (26). This high prevalence may be related to our considerably older population with high prevalence of hypertension and to possible calibration differences in serum creatinine assays, as they were performed before the introduction of international standards. As the focus of our study was to document the interaction effect on CHD death between low GFR and low hemoglobin rather than establish the prevalence of CKD, we believe that nondifferential misclassification arising from the estimating equations would not alter our main findings. We used serum fibrinogen to control for systemic inflammation, but this may not have controlled adequately for the effects of inflammation. Finally, we excluded 15.9% of the original sampled population because of missing data, which might have introduced selection bias into the study findings. Participants who were excluded were similar to the study population in terms of gender, age, and presence of severe hypertension and diabetes and differed in having more pre-existing CHD and hence had higher rates of CHD deaths.

In summary, we confirmed the ARIC study (7) findings that low hemoglobin together with low GFR increased the risk for CHD death. We found that low hemoglobin, even within the normal range, increased the risk for CHD death in people with CKD but not in people without CKD. This interaction was observed when GFR was estimated using the CG and Bjornsson

equations and with serum creatinine but not when the abbreviated MDRD equation was used.

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References

1. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32[Suppl 3]: S112–S119, 1998
2. Muntner P, He J, Hamm L, Loria C, Whelton PK: Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 13: 745–753, 2002
3. Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, Kuller LH, Newman AB: Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 41: 1364–1372, 2003
4. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108: 2154–2169, 2003
5. Garg AX, Clark WF, Haynes RB, House AA: Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. *Kidney Int* 61: 1486–1494, 2002
6. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56: 2214–2219, 1999
7. Jurkovitz CT, Abramson JL, Vaccarino LV, Weintraub WS, McClellan WM: Association of high serum creatinine and anemia increases the risk of coronary events: Results from the prospective community-based Atherosclerosis Risk in Communities (ARIC) study. *J Am Soc Nephrol* 14: 2919–2925, 2003
8. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, Levey AS: Anemia as a risk factor for cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol* 40: 27–33, 2002
9. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ: Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 41: 47–55, 2003
10. Mitchell P, Smith W, Attebo K, Wang JJ: Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* 102: 1450–1460, 1995
11. Cumming RG, Mitchell P, Leeder SR: Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 337: 8–14, 1997
12. Cumming RG, Mitchell P, Craig JC, Knight JF: Renal impairment and anaemia in a population-based study of older people. *Intern Med J* 34: 20–23, 2004
13. *Methods of Assessing Iron Status. Iron Deficiency Anaemia: Assessment, Prevention and Control. A Guide for Programme Managers*, Geneva, United Nations Children's Fund, United Nations University, World Health Organization, 2001, pp 33–45
14. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39: S1–S266, 2002
15. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
16. Levey AS, Greene T, Kusek JW, Beck GJ, MDRD Study Group: A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. *J Am Soc Nephrol* 11: A0828, 2000
17. Bjornsson TD: Use of serum creatinine concentrations to determine renal function. *Clin Pharmacokinet* 4: 200–222, 1979
18. Bostom AG, Kronenberg F, Ritz E: Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol* 13: 2140–2144, 2002
19. Mosteller RD: Simplified calculation of body-surface area. *N Engl J Med* 317: 1098, 1987
20. Lam TK, Leung DT: More on simplified calculation of body-surface area. *N Engl J Med* 318: 1130, 1988
21. Couchoud C, Pozet N, Labeeuw M, Pouteil-Noble C: Screening early renal failure: Cut-off values for serum creatinine as an indicator of renal impairment. *Kidney Int* 55: 1878–1884, 1999
22. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 21: 1983–1992, 2003
23. Powers J, Ball J, Adamson L, Dobson A: Effectiveness of the National Death Index for establishing the vital status of older women in the Australian Longitudinal Study on Women's Health. *Aust N Z J Public Health* 24: 526–528, 2000
24. Magliano D, Liew D, Pater H, Kirby A, Hunt D, Simes J, Sundararajan V, Tonkin A: Accuracy of the Australian National Death Index: Comparison with adjudicated fatal outcomes among Australian participants in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study. *Aust N Z J Public Health* 27: 649–653, 2003
25. Jones GRD, Lim E: The National Kidney Foundation guideline on estimation of the glomerular filtration rate. *Clin Biochem Rev* 24: 95–98, 2003
26. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC: Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol* 14[Suppl 2]: S131–S138, 2003