Review Article

Impact of microalbuminuria on incident coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis of prospective studies

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Abstract: This study is to investigate the magnitude of relationship between microalbuminuria and incident coronary heart disease (CHD) and mortality in the general population by conducting a meta-analysis. A comprehensive literature search in Pubmed and Embase database was performed prior to March 2014. Only prospective studies investigating the presence of microalbuminuria and incident CHD, cardiovascular disease (CVD), and mortality and were selected. Pooled risk ratio (RR) and 95% confidence interval (CI) were calculated by the presence of microalbuminuria versus without microalbuminuria. Finally, we identified 8 prospective studies involving 114,105 individuals. Participants with microalbuminuria were associated with 69% greater risk of CVD (RR=1.69; 95% CI 1.41-2.02) and 41% greater risk of CHD (RR=1.41; 95% CI 1.17-1.69). Participants with microalbuminuria were also associated with 57% greater risk of cardiovascular mortality (RR=1.57; 95% CI 1.20-2.06) and 65% greater risk of all-cause mortality (RR=1.65; 95% CI 1.45-1.88). Microalbuminuria is an independent predictor for CHD, CVD, and all-cause mortality in the general population. Early detection of microalbuminuria in the general population is likely to identify patients at increased risk of CVD and mortality.

Keywords: Microalbuminuria, cardiovascular disease, coronary heart disease, mortality, meta-analysis

Introduction

Microalbuminuria is generally defined as an albumin excretion rate of 30 to 300 mg/day or an albumin: creatinine ratio of 2.5 to 25 mg/mmol in men and 3.5 to 25 mg/mmol in women [1]. Microalbuminuria is used by clinicians as both a screening and diagnostic diabetic nephropathy. Apart from microalbuminuria as a marker of early kidney disease, it also has been used as a predictor for development coronary heart disease (CHD) and mortality. However, whether impaired renal function confounds the association remains controversial.

The available evidences indicate that microalbuminuria is associated with the development and progression of CHD [2-5], and cardiovascular disease (CVD) [6-11]. Moreover, microalbuminuria are also recognized as predictor of cardiovascular and all-cause mortality in the general populations [6, 8, 10, 12] and type 2 diabetic persons [13-15]. A gender specific association with cardiovascular mortality was found for women in one study [11], while another study [8] indicated that microalbuminuria could not predict the development of cardiovascular mortality. These discrepancies may have arisen from differences in the ethnic groups and the wide range of age cross the studies. Therefore, whether microalbuminuria is an independent risk factor for cardiovascular or all-cause mortality remains controversial.

To the best of our knowledge, there were no meta-analysis assessing the relationship between microalbuminuria and CHD, CVD, or mortality risk. The objective of this study was to determine the magnitude of relationship between microalbuminuria and CHD, CVD, cardiovascular and all-cause mortality in the general population by conducting a meta-analysis based on prospective studies.
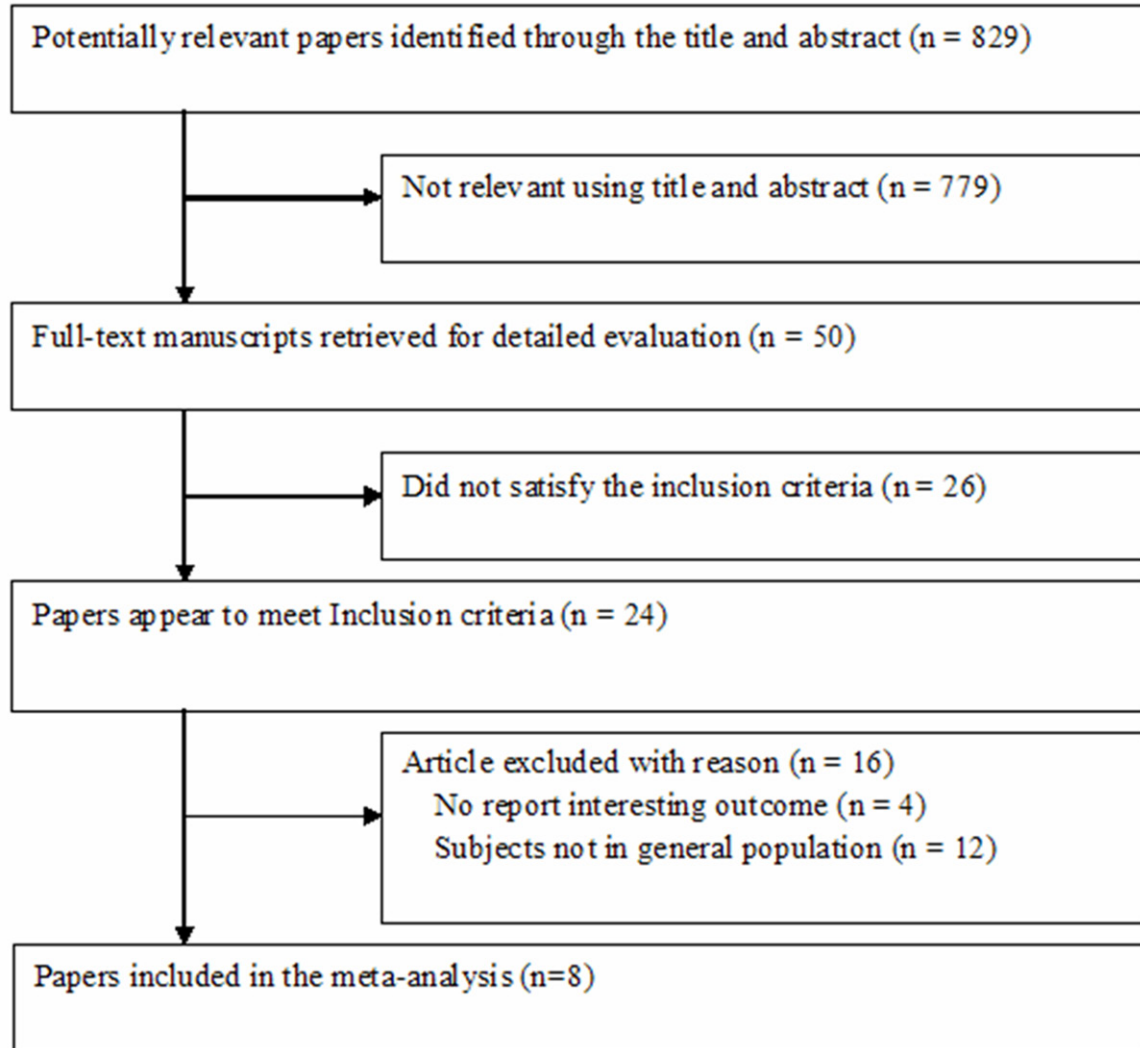
Figure 1. Flow chart of study selection process for meta-analysis.

Materials and methods

Search strategy

The meta-analysis was conducted according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology [16]. A systemic search of the electronic literature using Pubmed and Embase was performed to identify relevant papers published prior to March 2014. There were no language restrictions. Potentially relevant studies were identified by MeSH of the following key words: microalbuminuria, albuminuria, urine albumin excretion; cardiovascular mortality, mortality, death, heart death, coronary heart disease, cardiovascular disease; observational studies, prospective studies, and follow-up. In addition, we manual searched the reference list of the selected papers to identify possible additional studies.

Study selection

Studies meeting the following criteria were included: (i) prospective design; (ii) general population; (iii) using an exposure of microalbuminuria (microalbuminuria is defined as an albumin excretion rate of 30 to 300 mg/day or an albumin: creatinine ratio of 2.5 to 25 mg/mmol or nearest equivalent interval); (iv) description of risk estimates for the association between microalbuminuria and incident CHD, CVD, cardiovascular or all-cause mortality; and (v) providing at least age-adjusted risk

Table 1. Summary of clinical studies included in meta-analysis

Study/year	Country	Sample size (% women)	Age (range)	Definition of microal-buminuria (number)	Follow-up (years)	Outcome assessment	Outcomes (number) Risk estimate and 95% confidence interval	Adjustment for covariates
Muntner et al [8] 2002	USA	14,407 (53.1)	30-74	Urine albumin excretion 30-299 mg/dl (196)	16	CVD is defined as ICD-9 390-459. National Death Index	CVD death (1,215): 1.57 (0.99-2.48) Total death (1,876): 1.64 (1.23-2.18)	Age, race, gender, SBP, TC, BMI, DB, history of MI or stroke, current smoking, physical inactivity, and education level
Hillege et al [9] 2002	The Neth-erlands	40, 548 (54.3)	28-75	Urine albumin excretion 20-200 mg/L (4,541)	3	Central Bureau of Statistics	CVD death (178): 1.29 (1.18-1.40)	Use of antihypertensive and lipid-lowering drugs, smoking, sex, age, DB, family history of CVD, previous MI, and previ-ous stroke.
Romundstad et al [12] 2003	Norway	2,089 (53.5)	>20	ACR (<265.2 μg/mg [30 mg/mmol]) (85)	4.4	Death Registry at Statistics Norway	Total death (46): 7.0 (1.7-28.8) men 6.3 (1.6-25.6) women	Age, BMI, DB, HDL, smoking.
Yuyun et al [2] 2004	UK	22,368 (54.6)	40-79	ACR 2.5-25 mg/mmol. (2,572)	6.4	CHD is defined as ICD-9: 410-414; CVD is defined as ICD-9 390-459 or ICD-10 I00-I99	1.36 (1.12-1.64) CHD (800)1.38 (1.07-1.75) men; 1.36 (1.02-1.84) women Total death (934): 1.48 (1.20-1.79) CVD death (313): 2.03 (1.55-2.67)	For CHD: Age, sex, smoking, SBP, TC, DB, and BMI. For death: Age, sex, smoking, SBP, TC, DB, BMI, and family history of CVD
Wang et al [3] 2005	Australia	870 (49.2)	20-74	ACR 2.5-25 mg/mmol. (265)	9.2	CHD is defined as ICD-9: 410-414; ICD-10: I20-I25	CHD (89): 2.4 (1.2-5.5)	Age, gender, BMI, blood pres-sure, TC, DB, smoking, and alcohol consumption.
Cao et al [6] 2008	USA	3,112 (61.9)	68-102	Urine albumin excretion 30-300 mg/24 h (459)	5.4	CVD is defined as incident or recurrent MI and stroke, and cardiovascular death. Death certificates	CVD (753): 2.4 (1.4-3.9) 68-74 year; 1.4 (1.0-1.8) 75-84 year; 2.4 (1.4-4.1) >85 year Total death (634): 2.1 (1.2-3.6) 68-74 year; 1.7 (1.3-2.2) 75-84 year; 1.7 (1.1-2.6) >85 year.	Age, gender, race, BMI, smok-ing, SBP, DBP, hypertension, DB, fasting glucose levels, triglycerides, HDL, serum cre-atinine, and C-reactive protein
Jassal et al [11] 2008	USA	1,444 (60)	40-96	ACR 30-300 mg/g (151)	8	CVD is defined as ICD-9: 410-414, 426-428, 430-438, 440-448. Death certificates.	CVD death (180) 2.17 (1.36-3.46) women 1.04 (0.58-1.86) men	Prevalent CVD & Metabolic Syndrome
Scheven et al [7] 2013	The Neth-erlands	8,356 (50.2)	28-75	Urine albumin excre-tion30-300 mg/24 h (300)	12	CVD is defined as ICD-9 410, 411, 430-434.	1.37 (1.00-1.90) CVD (1,206)	Age, gender, cardiovascular risk factors

Abbreviations: BMI, body mass index; ACR, albumin to creatinine ratio; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; CHD, coronary heart disease; DB, diabetes mellitus; MI, myocardial infarction; ICD, International Statistical Classification of Diseases.

Table 2. Quality assessment of studies included in meta-analysis

Study/Year	Clear inclusion and exclusion criteria	Document the loss to follow up rate	Clear definition of outcome	Sufficient duration follow-up (>5 years)	Control of confounding	Appropriate statistics	Total points
Muntner et al [8] 2002	Yes	Yes	Yes	Yes	Yes	Yes	6
Hillege et al [9] 2002	Yes	Yes	No	No	Yes	Yes	4
Romundstad et al [12] 2003	Yes	Yes	Yes	No	Yes	Yes	5
Yuyun et al [2] 2004	Yes	unclear	Yes	Yes	Yes	Yes	5
Wang et al [3] 2005	Yes	Yes	Yes	Yes	Yes	Yes	6
Cao et al [6] 2008	Yes	unclear	Yes	Yes	Yes	Yes	5
Jassal et al [11] 2008	Yes	Yes	Yes	Yes	No	Yes	6
Scheven et al [7] 2013	Yes	Yes	Yes	Yes	Yes	Yes	6

ratio (RR) or hazard ratio (HR) and 95% confidence interval (CI). The following kinds of studies were excluded if (i) case-control, cross-sectional, or retrospective cohort design; (ii) unadjusted RR or HR; and (iii) subjects in a high selected group, such as diabetes, hypertension, etc.

Outcome measures and data extraction

The included studies had at least one of the following outcome measures: CHD, CVD, cardiovascular or all-cause mortality. Mortality outcomes were ascertained according to the death certificate with an underlying cause of death coded according to the International Classification of Diseases Ninth Revision (ICD-9). Cardiovascular mortality included the following subgroups according to ICD-9: 390-459 or ICD-10 I0-I15, I30-I41, I44-I49, I51.0, I51.4, I51.8, I51.9, I70-I74.

All data were extracted by two authors (F Xia and GH Liu) independently. For each study, the following data were extracted: authors, year of publication, region of the study conducted, follow-up time, sample sizes, gender, age, number of incident, the most fully adjusted RR or HR and 95% CI, and statistical adjustments for confounding factors. Any disagreement was resolved by discussion.

Quality assessment

Quality assessment was done according to the meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [16]. All items had the following answer options: yes/no/unclear. When a criterion was fulfilled, a score of 1 was given, 0 if a criterion was unclear, and -1 if a criterion was not achieved. High-

quality studies had ≥5 points and medium- or low-quality studies <5 points.

Data analyses

All analyses were performed with STATA statistical software (version 12.0). Meta-analysis was performed using multi-adjusted RR or HR and 95% CI. If the publications reported separate RR for gender or age, we pooled the separate RR for the different items and compared the microalbuminuria to the normal subjects from the each study. Heterogeneity across the studies was evaluated with Cochrane Q test and the I^2 statistic. We regarded P>0.10 or I^2<50% as indicators of no heterogeneity using a fixed-effect model. Otherwise, P≤0.10 or I^2>50% were regarded as indicators of heterogeneity using a random effect model [17]. Begg's rank correlation test [18] and Egger's linear regression test [19] were used to assess the publication bias. Sensitivity analysis was performed to evaluate the stability of the results by sequentially omitting one study at each turn with the metaninf algorithm in STATA. *P*<0.05 was considered to be statistically significant.

Results

Search results and study characteristics

The preliminary literature search yielded 829 references. After screening and reviewing the abstracts or titles, 779 studies were excluded. After reading the full manuscripts, eight prospective studies [2, 3, 6-8, 10-12] involving 114,105 subjects were included in the meta-analysis. A detailed description of the studies selection is presented in **Figure 1**. The characteristics of the individual studies are listed in the **Table 1**. The qualities of the individual studies are listed in supplement **Table 2**.
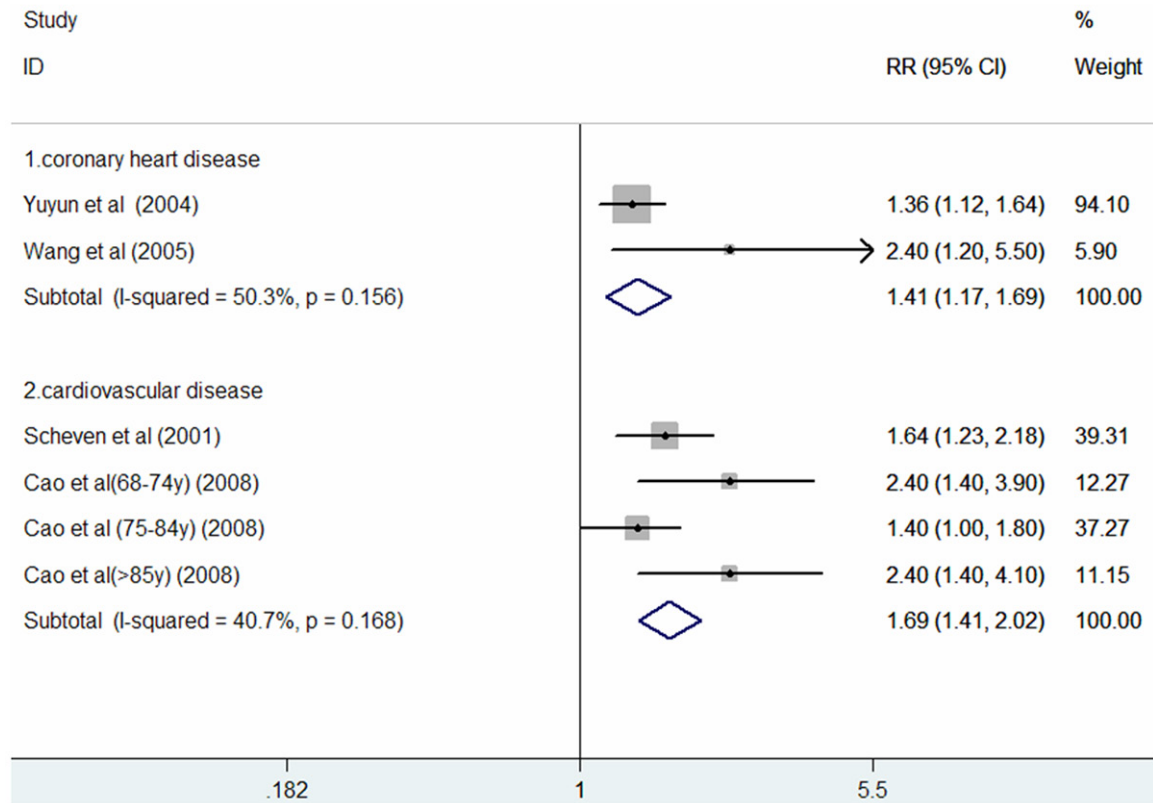
Figure 2. RR and 95% CI from the eligible studies of coronary heart disease and cardiovascular disease comparing the microalbuminuria to without microalbuminuria in a random effect model.

Coronary heart disease and cardiovascular disease

Two studies [2, 3] reported the relative risk of developing CHD. The total number of participants included in this meta-analysis was 23,238, which included 889 cases of CHD. A total of 2,837 (12.2%) had microalbuminuria at baseline. As shown in **Figure 2**, the pooled RR for CHD was 1.41 (95% CI 1.17-1.69) in a fixed-effect model. No significant heterogeneity between studies was observed (I^2=50.3%; P=0.156). Two studies [6, 7] reported the risk estimates of developing cardiovascular disease. The total number of participants included in this meta-analysis was 11,468, which included 1,959 cases of CVD. A total of 759 (6.62%) had microalbuminuria at baseline. As shown in **Figure 2**, the pooled RR for cardiovascular disease was 1.69 (95% CI 1.41-2.02) in a fixed-effect model. No significant heterogeneity between studies was observed (I^2=40.7%; P=0.168).

Cardiovascular mortality and all-cause mortality

Four studies [8-11] reported the relative risk of developing cardiovascular mortality. The total number of participants included in this meta-analysis was 73,310, which included 1,886 cases of cardiovascular mortality. A total of 7,224 (9.85%) had microalbuminuria at baseline. As shown in **Figure 3**, the pooled RR for cardiovascular mortality was 1.57 (95% CI 1.20-2.06), with evidence of significant heterogeneity (I^2=73%; P=0.005).

Four studies [6, 8, 10, 12] reported the relative risk of developing all-cause mortality. The total number of participants included in this meta-analysis was 40,519, which included 3609 cases of all-cause mortality. A total of 3,076 (7.59%) had microalbuminuria at baseline. As shown in **Figure 4**, the pooled RR for all-cause mortality was 1.65 (95% CI 1.45-1.88) in a fixed-effect model. No significant heterogeneity
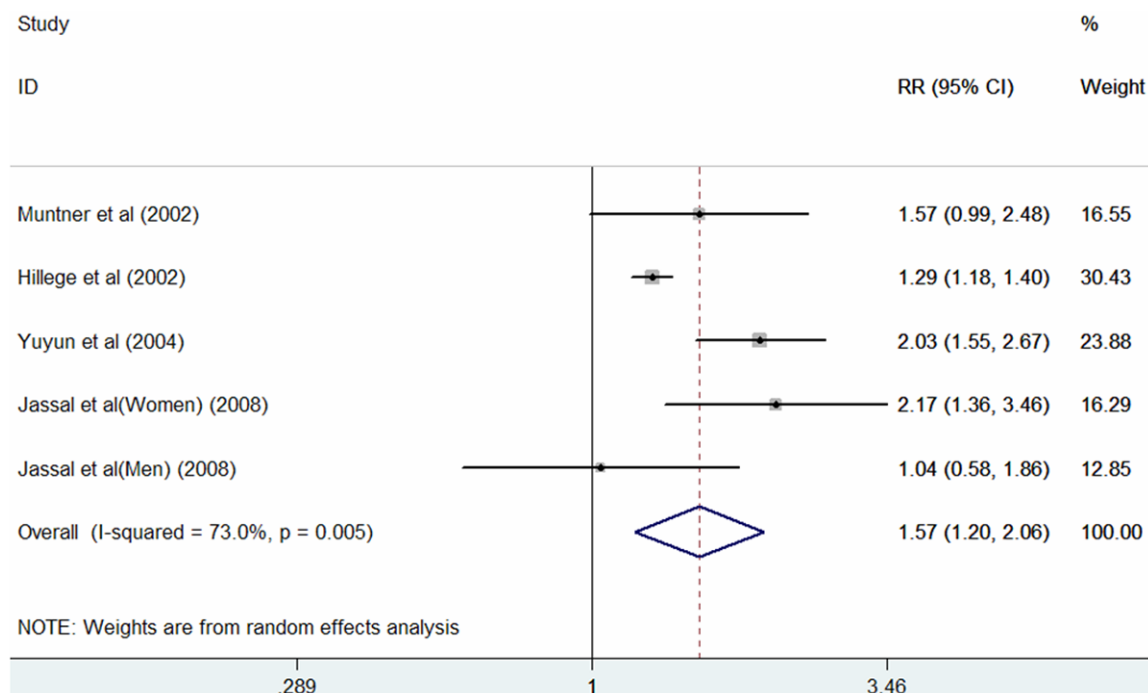
Figure 3. RR and 95% CI from the eligible studies of cardiovascular mortality comparing the microalbuminuria to without microalbuminuria in a random effect model.

between studies was observed (I^2=37.1%; P=0.145).

Sensitivity analysis

Sensitivity analysis was performed based on cardiovascular mortality and all-cause mortality and the results demonstrated robustness of analysis (Data not shown).

Discussion

This meta-analysis suggests that microalbuminuria is a strong predictor of CHD, cardiovascular and all-cause mortality. Microalbuminuria led to 41% greater risk of CHD, 57% greater risk of cardiovascular mortality, and 65% greater risk of all-cause mortality. The excess mortality risk was more attributable to death from cardiovascular causes than to death from other causes. These findings indicated that microalbuminuria might be used as CHD or mortality risk stratification in the general people.

Microalbuminuria appeared to significantly increase the risk of CHD in women. The possible explanation for the observed differences might be related to different microalbuminuria levels between men and women. A previous

study [20] found a significant association between microalbuminuria and cardiovascular mortality only in women (RR=6.10; 95% CI, 2.62-15.19) but not in men (RR=1.77; 95% CI, 0.91-3.44). The reasons for the gender difference in the ability of microalbuminuria to predict CHD and mortality are largely unknown. Age is an important predictor of microalbuminuria and the age-related decline results in a relative higher albumin excretion rate in older people [21].

Many studies that did not meet the inclusion criteria for the meta-analysis also found a positive association between microalbuminuria and mortality events. In a prospective population-derived cohort study [7], microalbuminuria in the absence of a CVD history, hypertension and diabetes) is associated with an increased risk for incident cardiovascular events and mortality, incident hypertension and/or diabetes mellitus. A cross-sectional study [22] found that microalbuminuria is independently associated with prevalent CVD in the general population. The prognosis of microalbuminuria for early mortality after acute MI has been demonstrated [23].
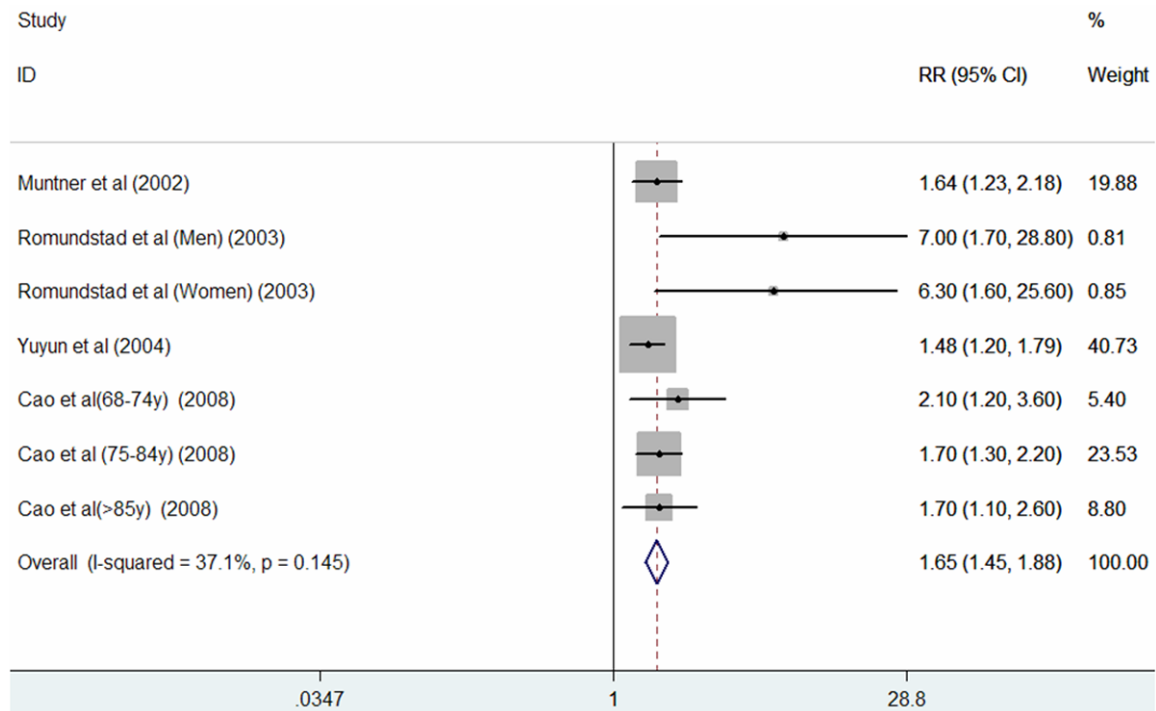
Figure 4. RR and 95% CI from the eligible studies of all-cause mortality comparing microalbuminuria to without microalbuminuria in a fixed-effect model.

Microalbuminuria is usually regarded as a marker of organ damage, reflecting the degree of cardiovascular damage induced by hypertension or diabetes mellitus. Apart from the general population, microalbuminuria is also an independent risk factor for CVD, and cardiovascular and all-cause mortality in diabetics [24, 25] and hypertensive [26]. The mechanisms underlying the association between microalbuminuria and cardiovascular disease or all-cause mortality are largely unknown but are thought to reflect endothelial dysfunction and microvascular damage [27] and possibly inflammation [28]. It seems that microalbuminuria indicates the later atherosclerotic process [29, 30].

Several limitations should be mentioned in this study. First, a major limitation was the potential misclassification of microalbuminuria. Urine albumin and creatinine were measured only once using a spot urine test, increasing the possibility of misclassification [31]; the different cut-offs of microalbuminuria between the gender might also have lead to misclassification of participants in each category. Second, possibility of the uncontrolled confounding such as renal creatinine clearance and metabolic syndrome might be existed. So we could not exclude the potential impact of these

uncontrolled confounding factors. Lack of adjustment for these important confounding factors might have resulted in a overestimation of the risk estimata. Third, race, age, and, particularly gender may affect the microalbuminuria. Due to the limited study number, we could not conduct subgroup analysis. Therefore, predictive values in different group population remain unclear; more well-designed studies in different race, age, and gender populations are need to generalize these findings.

Despite of the above limitations, our study had much strength. This meta-analysis is based on prospective studies with the large sample sizes. All the studies included in the current meta-analysis reported risk estimate adjusting for multiple confounding factors. Considering microalbuminuria are routinely and easily assayed in most clinical laboratories, screening microalbuminuria have utility to identify subjects who are at increased risk of CHD and death in the general population.

Conclusions

This meta-analysis indicates that microalbuminuria is associated with an increased risk of CHD, cardiovascular and all-cause mortality in

the general population. These results should be verified further by whether treatment targeted specifically at reducing microalbuminuria could improve CHD outcomes.

Disclosure of conflict of interest

None.

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