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

Fang Xia1*, Guanghua Liu2*, Yifu Shi1, Yan Zhang1

1Department of Cardiology, Dahua Hospital, Xuhui District, Shanghai 200237, China; 2Department of Interventional Radiology, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200092, China. *Equal contributors.

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

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

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.
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 each study. Heterogeneity across the studies was evaluated with Cochrane Q test and the I² statistic. We regarded P>0.10 or I²<50% as indicators of no heterogeneity using a fixed-effect model. Otherwise, P≤0.10 or I²>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.
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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...
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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].
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 target-
ed specifically at reducing microalbuminuria could improve CHD outcomes.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yan Zhang, Department of Cardiology, Dahua Hospital, No. 901 Old Humin Road, Xuhui District, Shanghai 200237, China. Tel: +86-021-64535555-8218; Fax: +86-021-64555854; E-mail: zhangyanshh@126.com

References

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