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The Impacts of Albuminuria and Low eGFR on the Risk of Cardiovascular Death, All-Cause Mortality, and Renal Events in Diabetic Patients: Meta-Analysis

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Abstract

Background: Precise effects of albuminuria and low estimated glomerular filtration rate (eGFR) on cardiovascular mortality, all-cause mortality, and renal events in diabetic patients are uncertain.

Materials and Methods: A systematic review was conducted of the literature through MEDLINE, EMBASE, and CINHAL from 1950 to December 2010. Cohort studies of diabetic patients providing adjusted relative risk (RR) of albuminuria and eGFR for risks of cardiovascular mortality, all-cause mortality, and renal events were selected. Two reviewers screened abstracts and full papers of each study using standardized protocol.

Results: We identified 31 studies fulfilling the criteria from 6546 abstracts. With regard to the risk of cardiovascular mortality, microalbuminuria (RR 1.76, 95%CI 1.38–2.25) and macroalbuminuria (RR 2.96 95%CI 2.44–3.60) were significant risk factors compared to normoalbuminuria. The same trends were seen in microalbuminuria (RR 1.60, 95%CI 1.42–1.81), and macroalbuminuria (RR 2.64, 95%CI 2.13–3.27) for the risk of all-cause mortality, and also in microalbuminuria (RR 3.21, 95%CI 2.05–5.02) and macroalbuminuria (RR 11.63, 95%CI 5.68–23.83) for the risk of renal events. The magnitudes of relative risks associated with low eGFR along with albuminuria were almost equal to multiplying each risk rate of low eGFR and albuminuria. No significant factors were found by investigating potential sources of heterogeneity using subgroup analysis.

Conclusions: High albuminuria and low eGFR are relevant risk factors in diabetic patients. Albuminuria and low eGFR may be independent of each other. To evaluate the effects of low eGFR, intervention, or race, appropriately designed studies are needed.

Introduction

The prevalence of diabetes is increasing globally, and management of diabetic complications is particularly important. [1,2,3] Diabetic nephropathy, resulting in end-stage renal events requiring renal replacement therapy, is one of the most common complications. Furthermore, in the course of diabetic nephropathy, patients have higher rates of mortality from cardiovascular disease. [4] Albuminuria is an early marker of diabetic nephropathy, and previous reports described the association between albuminuria and risks of adverse cardiovascular and kidney events. [5,6] Albuminuria is often used as a surrogate marker for the risk of fatal and non-fatal events in clinical trials of antihyperglycemic medications or in antihypertensive therapy. [7,8,9] Similarly, low eGFR, which is a common manifestation of progressed diabetic nephropathy, has also been demonstrated to be an independent risk factor for cardiovascular events and death. [10,11] Recent evidence suggests that both high albuminuria and low eGFR are independent risk factors for progressive kidney failure and cardiovascular disease. [10] In addition, the magnitudes of risk for progressive kidney failure, cardiovascular disease, and all-cause mortality were different between studies, and the unevenness may have been due to differences in study design or characteristics of participants. It is important to clarify these problems to apply this evidence to individuals.

To manage diabetic nephropathy, it is necessary to clarify the precise magnitude of the risks for cardiovascular mortality, all-cause mortality, and renal events according to the status of the patient. These observations may be useful for the screening of high-risk patients or considering interventions. Therefore, we conducted a systematic review and meta-analysis of published
studies on diabetic nephropathy to provide an accurate estimation of the influence of albuminuria and low eGFR.

**Methods**

**Data Sources and Searches**

We conducted a systematic review of disease prognosis. A systematic review of the available literature according to MOOSE (meta-analysis of observational studies on epidemiology) guidelines was conducted. MEDLINE (http://ovidsp.ovid.com/), EMBASE (http://www.embase.com/), and CINHAL (http://www.ebscohost.com/cinahl/) from 1950 until December 2010 were searched, and the related literature were identified. Search strategies consisted of medical subject headings and text words, including all spellings of proteinuria, albuminuria, microalbuminuria, macroalbuminuria, and glomerular filtration rate combined with cardiovascular diseases, mortality, renal events (Table 1), and limited to cohort studies of diabetic patients. References from identified studies were also screened manually.

**Study Selection**

Studies were included if they were cohort studies on diabetic patients that estimated the relative risk (RR) and 95% confidence intervals (CIs) of albuminuria or low eGFR on cardiovascular mortality, all-cause mortality, or renal events (Table 1), and limited to cohort studies of diabetic patients. References from identified studies were also screened manually.

**Data Extraction and Quality Assessment**

The literature search and screening were performed by two of the authors (TT and MS). Authors independently judged the contents of abstracts and full papers in duplicate using standardized data collection form. Additional data were not collected from authors of literature. To eliminate the potential influences of specific disease, studies were excluded if their cohorts included patients with specific complications. Studies were also excluded if they reported estimates of influences without any information about standard error, and if they did not yield an estimate that was not adjusted at least by age.

**Data Synthesis and Analysis**

Random-effects model were used to obtain summary estimates of RR and 95% CI. Summary estimates were obtained separately according to the level of albuminuria (microalbuminuria, macroalbuminuria, any level of albuminuria). If only subgroups of the estimate were reported (e.g., by gender), these were pooled by fixed-effects model as a within-study summary estimate. We also investigated studies providing RR associated with low eGFR according to the level of albuminuria. If the study population was representative of a particular level of eGFR (e.g., eGFR >60), it was handled as stratified. To evaluate the influences of albuminuria and low eGFR, compare the relative risks pooled by fixed-effects model according to stratified category of albuminuria (micro- and macroalbuminuria), low eGFR (< 60 mL/min/}

### Table 1. Search Strategies.

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:</td>
<td>diabetes mellitus AND (proteinuria OR albuminuria OR microalbuminuria OR macroalbuminuria)</td>
</tr>
<tr>
<td>2:</td>
<td>(diabetic nephropathy)</td>
</tr>
<tr>
<td>3:</td>
<td>(kidney failure, chronic) OR (glomerular filtration rate)</td>
</tr>
<tr>
<td>4:</td>
<td>(cardiovascular diseases) OR (cerebrovascular disorders)</td>
</tr>
<tr>
<td>5:</td>
<td>mortality OR death</td>
</tr>
<tr>
<td>6:</td>
<td>(cohort studies) OR (case-control studies)</td>
</tr>
<tr>
<td>(1 or 2) and (3 or 4 or 5) and 6</td>
<td>Terms associated with Medical Subject Headings.</td>
</tr>
</tbody>
</table>

**Table 2. Definitions of Albuminuria.**

<table>
<thead>
<tr>
<th>Measurement Method</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
<th>Any level of albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hour urine collection</td>
<td>30–300 mg/day or 20–200 µg/min</td>
<td>&gt;300 mg/day or &gt;200 µg/min</td>
<td>&gt;30 mg/day or &gt;20 µg/min</td>
</tr>
<tr>
<td>(proteinuria)</td>
<td>N/A</td>
<td>&gt;0.3–0.5 g/day</td>
<td>N/A</td>
</tr>
<tr>
<td>Spot urine albumin creatinine ratio</td>
<td>30–300 mg/g or 3.4–34 mg/mmol</td>
<td>&gt;300 mg/g or &gt;34 mg/mmol</td>
<td>&gt;30 mg/g or &gt;3.4 mg/mmol</td>
</tr>
<tr>
<td>(proteinuria)</td>
<td>N/A</td>
<td>&gt;0.3–0.5 g/g</td>
<td>N/A</td>
</tr>
<tr>
<td>Spot urine albumin concentration</td>
<td>3–30 mg/dl</td>
<td>&gt;30 mg/dl</td>
<td>&gt;3 mg/dl</td>
</tr>
<tr>
<td>(proteinuria)</td>
<td>N/A</td>
<td>&gt;0.3–0.5 g/l</td>
<td>N/A</td>
</tr>
<tr>
<td>Spot urine dipstick</td>
<td>Specific microalbuminuria dipstick positive</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Abbreviation:** N/A, not available. Based on Sarnak et al. [12].

**doi:**10.1371/journal.pone.0071810.t002
1.73 m$^2$) and normal eGFR (≥ 60 mL/min/1.73 m$^2$) regardless of the reference category of eGFR. Heterogeneity between studies was assessed using Cochran Q test and $I^2$ value. Potential sources of heterogeneity were examined by subgroup analysis comparing summary estimates from subset of studies categorized by characters of participants or study design. Univariate meta-regression was used to compare the subgroups. Begg’s test [13] and Egger’s test [14] were used to evaluate possible publication bias (where $P<0.05$ was taken to indicate statistical significance). To evaluate an influence of a single study, sensitivity analysis is performed to examine the exclusion of any single study altered the magnitude of relative risk or test for heterogeneity. All analyses were performed using Stata (release 11.2; Stata Corporation, College Station, TX). For all tests, a two-sided $p$-value below 0.05 was considered significant.

**Results**

**Literature Search and Characteristics of Studies**

The systematic database search yielded 6546 studies, of which 326 papers were reviewed in full (Figure 1). Finally, 31 studies that fulfilled the criteria were included in the analysis, including information for 148350 participants. The crude incidence rates were 19.1 deaths from cardiovascular disease, 35.7 deaths, and 11.7 renal events (per 1000 person-years, respectively). The process of study identification is shown in the flow chart, and the study characteristics are listed in Table 3 and Table 4. Studies consisted of four studies of type 1 diabetic patients, 23 studies of type 2 diabetic patients, one study of type 1 and type 2 diabetic patients, and 3 studies of unknown type of diabetic patients. The study size was in the range of 146 to 94934, and the average follow-up period was in the range of 3 to 19 years. Regarding cardiovascular mortality, Asian population study was not included according to the criteria. We pooled the risk of two studies [15,16] reporting only subgroups of the estimate.

Micro- and macroalbuminuria were defined as risk factors in 25 studies. Any level of albuminuria (i.e., micro- or macroalbuminuria) was defined as a risk factor in 7 studies. In these studies, various means of expression of albuminuria were adopted. The magnitude of microalbuminuria was expressed as urinary albumin excretion rate ($n^{12}$), urinary albumin-creatinine ratio on spot urine samples ($n^{10}$), spot urinary albumin concentration ($n^{6}$), qualitative test of albuminuria ($n^{2}$), or urinary protein excretion rate ($n^{2}$). Almost all of the estimates were adjusted for multiple risk factors including age. In one study [17], the estimate was not adjusted for age because age was not a statistically significant risk.

**Association of Albuminuria with Risk of Cardiovascular Mortality**

Microalbuminuria was associated with 1.76 (95% confidence interval [CI] 1.38–2.25) times greater risk of cardiovascular mortality as compared with normoalbuminuria (Figure 2), with strong heterogeneity among studies ($I^2 = 66\%$, $p = 0.003$ for heterogeneity). We found no significant evidence of publication bias. Subgroup analysis did not determine the suspected source of heterogeneity (Figure S1). Age stratified analysis showed no trends neither micro- nor macroalbuminuria (Figure S2). Macroalbuminuria was associated with about 2.96 (95%CI 2.44–3.60) times greater risk of cardiovascular mortality compared with normoal-

![Figure 1. Process for identification of eligible studies Abbreviation: N/A, not available. doi:10.1371/journal.pone.0071810.g001](#)
Table 3. Characteristic of Studies Reporting on the Association between Albuminuria or low eGFR and Subsequent Risk of Adverse Outcomes.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study size</th>
<th>%male</th>
<th>%white</th>
<th>Endpointsa</th>
<th>No. of CV mortality</th>
<th>No. of all-cause mortality</th>
<th>No. of renal events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jager[15]</td>
<td>2010</td>
<td>Netherlands</td>
<td>173</td>
<td>48.0</td>
<td>N/A</td>
<td>CV mortality</td>
<td>16</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O’Hare[16]</td>
<td>2010</td>
<td>US</td>
<td>94,934</td>
<td>98.0</td>
<td>87.0</td>
<td>All-cause mortality</td>
<td>25481</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Grauslund[17]</td>
<td>2010</td>
<td>Denmark</td>
<td>389</td>
<td>55.0</td>
<td>N/A</td>
<td>CV mortality</td>
<td>N/A</td>
<td>117</td>
<td>N/A</td>
</tr>
<tr>
<td>Molitch[18]</td>
<td>2010</td>
<td>US</td>
<td>1,439</td>
<td>52.5</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>N/A</td>
<td>89</td>
<td>N/A</td>
</tr>
<tr>
<td>Ninomiya[10]</td>
<td>2009</td>
<td>Multicountries</td>
<td>10,640</td>
<td>57.0</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>432</td>
<td>817</td>
<td>107</td>
</tr>
<tr>
<td>Groop[19]</td>
<td>2009</td>
<td>Finland</td>
<td>4,201</td>
<td>51.8</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>N/A</td>
<td>291</td>
<td>N/A</td>
</tr>
<tr>
<td>de Boer[20]</td>
<td>2009</td>
<td>US</td>
<td>691</td>
<td>42.1</td>
<td>80.6</td>
<td>CV mortality</td>
<td>N/A</td>
<td>169</td>
<td>378</td>
</tr>
<tr>
<td>Vlie[6]</td>
<td>2008</td>
<td>Netherlands</td>
<td>759</td>
<td>76.5</td>
<td>N/A</td>
<td>CV mortality</td>
<td>N/A</td>
<td>49</td>
<td>82</td>
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<tr>
<td>Luk[21]</td>
<td>2008</td>
<td>China</td>
<td>5,829</td>
<td>49.8</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>N/A</td>
<td>741</td>
<td>N/A</td>
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<tr>
<td>Tong[22]</td>
<td>2007</td>
<td>China</td>
<td>4,416</td>
<td>42.9</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>N/A</td>
<td>110</td>
<td>221</td>
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<tr>
<td>Bruno[23]</td>
<td>2007</td>
<td>Italy</td>
<td>1,538</td>
<td>43.4</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>331</td>
<td>670</td>
<td>N/A</td>
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<tr>
<td>Roy[24]</td>
<td>2006</td>
<td>US</td>
<td>725</td>
<td>41.7</td>
<td>0.0</td>
<td>All-cause mortality</td>
<td>N/A</td>
<td>131</td>
<td>N/A</td>
</tr>
<tr>
<td>So[25]</td>
<td>2006</td>
<td>Hong Kong</td>
<td>4,421</td>
<td>43.2</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>N/A</td>
<td>212</td>
<td>N/A</td>
</tr>
<tr>
<td>Retnakaran[26]</td>
<td>2006</td>
<td>UK</td>
<td>5,032</td>
<td>59.0</td>
<td>81.0</td>
<td>Renal events</td>
<td>N/A</td>
<td>584</td>
<td>N/A</td>
</tr>
<tr>
<td>Xu[27]</td>
<td>2005</td>
<td>USA</td>
<td>1,953</td>
<td>37.6</td>
<td>N/A</td>
<td>CV mortality</td>
<td>223</td>
<td>627</td>
<td>N/A</td>
</tr>
<tr>
<td>Yuyun[28]</td>
<td>2003</td>
<td>UK</td>
<td>427</td>
<td>62.1</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>N/A</td>
<td>56</td>
<td>N/A</td>
</tr>
<tr>
<td>Bruno[29]</td>
<td>2003</td>
<td>Italy</td>
<td>1,408</td>
<td>43.6</td>
<td>N/A</td>
<td>Renal events</td>
<td>N/A</td>
<td>82</td>
<td>N/A</td>
</tr>
<tr>
<td>Jude[30]</td>
<td>2002</td>
<td>UK</td>
<td>340</td>
<td>66.5</td>
<td>66.8</td>
<td>CV mortality</td>
<td>N/A</td>
<td>44</td>
<td>63</td>
</tr>
<tr>
<td>Ostgren[31]</td>
<td>2002</td>
<td>Sweden</td>
<td>400</td>
<td>50.5</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>131</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Stehouwe[32]</td>
<td>2002</td>
<td>Netherlands</td>
<td>328</td>
<td>61.6</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>113</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gerstein[33]</td>
<td>2001</td>
<td>North and South America and Europe</td>
<td>3,498</td>
<td>62.9</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>431</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>de Grauw[34]</td>
<td>2001</td>
<td>Netherlands</td>
<td>262</td>
<td>39.0</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>57</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Florkowsk[35]</td>
<td>2001</td>
<td>New Zealand</td>
<td>447</td>
<td>46.5</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>187</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Casiglia[36]</td>
<td>2000</td>
<td>Italy</td>
<td>683</td>
<td>50.2</td>
<td>N/A</td>
<td>CV mortality</td>
<td>68</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Valmadr[37]</td>
<td>2000</td>
<td>US</td>
<td>840</td>
<td>45.0</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>364</td>
<td>529</td>
<td>N/A</td>
</tr>
<tr>
<td>Hanminen[38]</td>
<td>1999</td>
<td>Finland</td>
<td>252</td>
<td>53.2</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>21</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Mattock[39]</td>
<td>1998</td>
<td>U.K.</td>
<td>146</td>
<td>56.2</td>
<td>100.0</td>
<td>CV mortality</td>
<td>20</td>
<td>36</td>
<td>N/A</td>
</tr>
<tr>
<td>Beilin[40]</td>
<td>1996</td>
<td>Australia</td>
<td>666</td>
<td>47.1</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>80</td>
<td>167</td>
<td>N/A</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Study size</td>
<td>%male</td>
<td>%white</td>
<td>Endpointsa</td>
<td>No. of CV mortality</td>
<td>No. of all-cause renal events</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>-----------</td>
<td>------------</td>
<td>-------</td>
<td>--------</td>
<td>------------</td>
<td>---------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Rossing[41]</td>
<td>1996</td>
<td>Denmark</td>
<td>939</td>
<td>52.5</td>
<td>N/A</td>
<td>CV mortality</td>
<td>74</td>
<td>207</td>
<td></td>
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<tr>
<td>Gall[42]</td>
<td>1995</td>
<td>Denmark</td>
<td>328</td>
<td>61.5</td>
<td>N/A</td>
<td>CV mortality</td>
<td>29</td>
<td></td>
<td></td>
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<tr>
<td>Neil[43]</td>
<td>1993</td>
<td>U.K.</td>
<td>246</td>
<td>50.8</td>
<td>N/A</td>
<td>All-cause mortality</td>
<td>93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-Up (years)</th>
<th>Mean age (years)</th>
<th>Type of DM</th>
<th>Duration of DM (years)</th>
<th>mean eGFR (ml/min/1.73 m²)</th>
<th>sBP (mmHg)</th>
<th>dBP (mmHg)</th>
<th>Study type</th>
<th>Use of RASS inhibitors (%)</th>
<th>Adjustment of BP or HT</th>
<th>Stratification of eGFR (ml/min/1.73 m²)</th>
<th>Level of Adjustmentd</th>
<th>Measured variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>67.8</td>
<td>T2DM</td>
<td>N/A</td>
<td>139</td>
<td>83</td>
<td>Obs</td>
<td>N/A</td>
<td>NO</td>
<td>N/A</td>
<td>E0</td>
<td>Age, sex, HT, TCHO, TG, HDL, preexistent IHD, current smoking</td>
<td></td>
</tr>
<tr>
<td>6.4</td>
<td>75.3</td>
<td>N/A</td>
<td>N/A</td>
<td>139</td>
<td>74</td>
<td>Obs</td>
<td>N/A</td>
<td>60.7</td>
<td>YES</td>
<td>≥90, 89-60, 59-45, 44-30, 29-15</td>
<td>Age, sex, BMI, sBP, dBP, race, eGFR, comorbidity, medication use</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>68.0</td>
<td>T1DM</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Obs</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<td>22.4</td>
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<td>Age, sex, sBP, dBP, LDL, vascular history, smoking</td>
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<td>Obs</td>
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<td>Renal failure: Age, waist circumference, sBP; All-cause mortality: Age, sex, BMI</td>
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<td>&gt;90/60-89/30-39/15-29</td>
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<td>Age, sex, ethnicity, Cr, smoking, waist, height, sBP, retinopathy</td>
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<td>65.7</td>
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<td>Age, sex, BMI, mean BP, duration of DM, TCHO, smoking, type of DM, baseline cardiovascular history, rate of change of albuminuria over 1 year</td>
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<td>N/A</td>
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Table 3. Cont.
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<th>Follow-Up (years)</th>
<th>Mean age (years)</th>
<th>Type of DM</th>
<th>Duration of DM (years)</th>
<th>mean eGFR (ml/min/1.73m²)</th>
<th>sBP (mmHg)</th>
<th>dBP (mmHg)</th>
<th>Study type&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Use of RASS inhibitors (%)</th>
<th>Adjustment of BP or HT</th>
<th>Stratification of eGFR (ml/min/1.73m²)</th>
<th>Level of Adjustment&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Other Abbreviations</th>
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<td>144</td>
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<td>Age, sex, HbA1c, TCHO, preexistent coronary heart disease</td>
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<td>82</td>
<td>Obs</td>
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<td>YES</td>
<td>Age, sex, DM duration, HbA1c, BMI, sBP, dBP, retinopathy, TCHOL, HDL, TG, age at diagnosis, smoking, fasting glucose, urea, loss of pinprick sensation, leg claudication, number of absent foot pulses, CHD, cerebrovascular disease</td>
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<td>86</td>
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<td>YES</td>
<td>Age, HbA1c, sBP, coronary heart disease</td>
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<td>NO</td>
<td>Age, DM duration, retinopathy, lens opacity, intermittent claudication</td>
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<sup>a</sup>Endpoints: CV mortality, cardiovascular mortality.

<sup>b</sup>Type of DM: N/A, type of DM is not documented; T1DM, population with type 1 DM; T2DM, population with type 2 DM.

<sup>c</sup>Study type: Obs, based on the cohort of observational study; Trial, based on the cohort of clinical trial.

<sup>d</sup>Level of Adjustment: ACE, angiotensin converting enzyme; Apo, apolipoprotein; BMI, body mass index; CVD, cardiovascular disease; dBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; HbA1c, glycosylated hemoglobin A1c; HDL, high-density lipoproteins; HT, hypertension; IHD, ischemic heart disease; LDL, low-density lipoproteins; PVD, peripheral vascular disease; RAAS, Renin-Angiotensin-Aldosterone System; sBP, systolic blood pressure; sCr, serum creatinine TCHO, total cholesterol; TG, triglycerides.

<sup>*</sup>Cohort of American Indians. Other abbreviations: N/A, not available; CV mortality, cardiovascular mortality; sBP, systolic blood pressure; dBP, diastolic blood pressure.

doi:10.1371/journal.pone.0071142.t003
### Table 4. Definitions of Albuminuria, eGFR categories and Outcomes.

<table>
<thead>
<tr>
<th>Author</th>
<th>Urine measurement method</th>
<th>Definition of microalbuminuria</th>
<th>Definition of macroalbuminuria</th>
<th>Definition of any level of albuminuria</th>
<th>eGFR categories</th>
<th>Criteria of renal failure</th>
<th>Criteria of CV mortality</th>
<th>Definition of CV disease&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Jager [15]</td>
<td>ACR</td>
<td>&gt;2.0 mg/mmol</td>
<td>30–299 mg/gCr</td>
<td>ICD code 390–459</td>
<td>Heart/Brain</td>
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<tr>
<td>O'Hare [16]</td>
<td>ACR</td>
<td>&gt;300 mg/gCr</td>
<td>&gt;300 mg/gCr</td>
<td>ICD-9 codes 430.0–438.9</td>
<td>ICD-10 codes I20.0–I25.9, I60.0–I60.9</td>
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<td>Grauslund [17]</td>
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<td>≥300 mg/L</td>
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<td>Molitch [18]</td>
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<td>&gt;30 mg/g/min</td>
<td>&gt;300 mg/g/min</td>
<td>Sustained eGFR&lt;60</td>
<td>Heart/Brain</td>
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<td>Ninomiya [10]</td>
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<td>≥30 mg/gCr</td>
<td>&gt;300 mg/gCr</td>
<td>Death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine to &gt;200 μmol/L</td>
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<tr>
<td>Groop [19]</td>
<td>AER</td>
<td>≥30 mg/gCr</td>
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<tr>
<td>de Boer [20]</td>
<td>ACR</td>
<td>&gt;200 μg/min</td>
<td>&gt;200 μg/min</td>
<td>Death from coronary heart disease, myocardial infarction, sudden cardiac death, or stroke</td>
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<td>Vlek [6]</td>
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<td>≥3 mg/mmol</td>
<td>≥60 mg/gCr</td>
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<td>Luk [21]</td>
<td>ACR</td>
<td>≥30 mg/mmol</td>
<td>≥60 mg/gCr</td>
<td>ICD-9 code 250.4, 585, 586 ICD-9 procedure code 39.95 (hemodialysis), 54.98 (peritoneal dialysis)</td>
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<td>Tong [22]</td>
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<td>≥25 mg/mmol</td>
<td>eGFR halving, eGFR &lt;15 ml/min/1.73 m², death as a result of renal causes or need for dialysis</td>
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<tr>
<td>Bruno [23]</td>
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<td>≥60, &lt;60</td>
<td>ICD code 390–459</td>
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<td>Roy [24]</td>
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<td>≥200 μg/min</td>
<td>≥60, &lt;60</td>
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<td>So [25]</td>
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<td>≥25 mg/mmol</td>
<td>&gt;90, 60–89, 30–59, Reduction in eGFR by 50% or progression to eGFR 15 ml/min/1.73 m² (Stage 5) or renal dialysis or death secondary to renal causes</td>
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<td>Retnakaran [26]</td>
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<td>≥25 mg/mmol</td>
<td>≥3.5 mg/mmol</td>
<td>Creatinine clearance ≤60 ml/min per 1.73 m²</td>
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<td>Xu [27]</td>
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<td>≥30, &lt;300 mg/gCr</td>
<td>≥300 mg/gCr</td>
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<td>Jude [30]</td>
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<td>Urine protein ≥0.5 g/24 h</td>
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<td>Yuyun [28]</td>
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<td>Bruno [29]</td>
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<td>≥200 μg/min</td>
<td>ESRD (need for dialysis) or chronic renal failure</td>
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<td>Yuyun [28]</td>
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<td>Heart/Brain</td>
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<td>Author</td>
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<td>Definition of macroalbuminuria</td>
<td>Definition of any level of albuminuria</td>
<td>eGFR categories</td>
<td>Criteria of renal failure</td>
<td>Criteria of CV mortality</td>
<td>Definition of CV disease</td>
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<td>Stenhouwer [32]</td>
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<td>30–299 mg/24 h</td>
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<td>exclude dipstick-positive proteinuria</td>
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<td>Hänninen [38]</td>
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<td></td>
<td>≥20 μg/min</td>
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<tr>
<td>Mattock [39]</td>
<td>AER</td>
<td>20–200 μg/min</td>
<td>UAER ≥200 μg/min</td>
<td></td>
<td></td>
<td></td>
<td>from death certificates</td>
<td>Heart</td>
</tr>
<tr>
<td>Beilin [40]</td>
<td>spot</td>
<td>30–300 mg/L</td>
<td>≥300 mg/L</td>
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<td></td>
<td></td>
<td></td>
<td>from death certificates</td>
</tr>
<tr>
<td>Rossing [41]</td>
<td>AER</td>
<td>31–299 mg/24 h</td>
<td>≥300 mg/24 h</td>
<td></td>
<td></td>
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<td>from death certificate</td>
<td>Heart/Brain</td>
</tr>
<tr>
<td>Gall [42]</td>
<td>AER</td>
<td>30–299 mg/24 h</td>
<td>AER ≥300 mg/24 h</td>
<td></td>
<td></td>
<td></td>
<td>from death certificates</td>
<td>Heart/Brain</td>
</tr>
<tr>
<td>Neil [43]</td>
<td>spot</td>
<td>40–200 mg/L</td>
<td>UAC ≥200 mg/L</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Urine measurement method: ACR, albumin creatinine ratio; AER, albumin excretion rate; PER, protein excretion rate; spot, spot urinary albumin concentration; qualitative, qualitative detection of albumin in urine.

*Definition of CV disease: Heart, ischemic heart disease; Brain, cerebrovascular disease.

doi:10.1371/journal.pone.0071810.t004
buminuria, and there was no significant evidence of heterogeneity among studies. These findings suggest that there is a dose-dependent association between albuminuria and the risk of cardiovascular mortality; the influence of macroalbuminuria was significantly higher than that of microalbuminuria ($p = 0.026$). In the three studies for which information was available, any level of albuminuria was associated with about 2.48 times (95% CI 1.57–3.91) greater risk of cardiovascular mortality compared with normoalbuminuria, without any evidence of heterogeneity in the association.

### Association of Albuminuria with Risk of All-cause Mortality

Summary estimates of the influences of microalbuminuria and macroalbuminuria on all-cause mortality were 1.60 (95% CI 1.42–1.81) and 2.64 (95% CI 2.13–3.27), respectively (Figure 2); the associations were heterogeneous among studies for both ($I^2 = 65\%$ and 84%, both $p<0.001$ for heterogeneity). There was some evidence of publication bias in microalbuminuria and macroalbuminuria (Egger’s test $P<0.014$ and $P<0.015$, respectively), which may have overestimated the strength of the association. Subgroup analysis did not determine the suspected source of heterogeneity.

As to the racial difference, relative risks were not significantly different between Asians and non-Asians. A study in veterans

![Figure 2. Risk ratio for the association between albuminuria and cardiovascular mortality, all-cause mortality, and renal events compared with normoalbuminuria. Abbreviations: CI, confidence interval; RR, risk ratio. doi:10.1371/journal.pone.0071810.g002](image)

![Figure 3. Risk ratio for the association of low eGFR with the risk of each outcome according to the presence of albuminuria, compared with normal eGFR and normoalbuminuria. Albuminuria was defined as any level of albuminuria or pooled estimate of microalbuminuria and macroalbuminuria. Abbreviations: normoalb, normoalbuminuria; alb, albuminuria. doi:10.1371/journal.pone.0071810.g003](image)
Combined Impacts of Low eGFR on Albuminuria

A few studies [6,10,19,20] evaluated the combined influence of low eGFR on albuminuria in terms of the risk for the outcomes. As compared to those with normoalbuminuria, the risk of cardiovascular mortality tended to increase by 1.70-fold (95% CI 0.83–3.49) in subjects with microalbuminuria and eGFR of <60 mL/min/1.73 m² (Figure 3). Similarly, the presence of albuminuria was significantly associated with 2.46-fold (95% CI 1.96–3.07) increased risk of cardiovascular mortality. Furthermore, subjects with both albuminuria and eGFR <60 mL/min/1.73 m² were at 4.20 times (95% CI 3.11–5.68) higher risk of cardiovascular mortality compared to those with neither of these risk factors. However, other reports concluded that low eGFR was not always a significant risk factor for these outcomes. [6,25] Thus, the influences of albuminuria and low eGFR are not consistent among studies adjusted for each other. Further large prospective studies are needed to clarify the independent influences of albuminuria and low eGFR on the three outcomes in diabetic nephropathy.

The interaction between eGFR and albuminuria may be important in considering the possibility of albuminuria and low eGFR as independent risk factors for the three outcomes. Previous meta-analyses of general and high-risk cohorts indicated no interaction between eGFR and albuminuria on the risks of cardiovascular mortality, all-cause mortality, and renal events. [48,49] Similarly, in our results of diabetic nephropathy consisting of 4 data or less, stratified analysis demonstrated that the magnitudes of relative risks of these events with low eGFR and albuminuria were almost equivalent to those obtained by multiplying each risk rate of low eGFR and albuminuria. These results suggested that there is no interaction between eGFR and albuminuria in each adverse outcome. In our meta-analysis, only two studies evaluated the interaction between eGFR and albuminuria. [10,25] One of these studies that included stratified analysis indicated that increasing risk of cardiovascular mortality and all-cause mortality in low eGFR were significantly higher in patients with microalbuminuria but not those with normoalbuminuria. [25] Moreover, in a previous meta-analysis, one of eight general and high-risk cohorts showed significant interaction between eGFR and albuminuria for the risk of ESRD. [49] Based on these studies, the significance of the interaction between eGFR and albuminuria is still variable. Detailed analysis of cohort studies, including an unusual case of diabetic nephropathy, such as low eGFR with normoalbuminuria and high GFR with macroalbuminuria, are needed to resolve the precise interaction of them.

There was heterogeneity among studies for cardiovascular mortality, all-cause mortality, and renal events in the presence of microalbuminuria or macroalbuminuria. There are some possible causes of the heterogeneity in this study. One of the possible reasons is a large cohort with different results from the others. Another possible reason is the diversity of study design. A large study with an exceptional setting [18] may lead to heterogeneity of the outcome. The report by O’Hare et al. had the highest weight in this meta-analysis, and its relative risk was even lower than the pooled risk of all-cause mortality. [18] Therefore, this large cohort study of veterans should have some different setting from other studies. The multiplicity of study design is an unavoidable limitation of meta-analyses, which is another possible reason of heterogeneity. The entry criteria, treatment, or adjustment for confounders were different between studies, and the different settings may affect results to uneven extents. Although some other factors, such as blood pressure control or use of ACE inhibitors for renal events, are possible factors for heterogeneity, these factors were not fully evaluated in the studies included in this analysis. [50,51] Based on these results, standardization of study design is needed, including treatment strategy or adjustment of confounders.

As diabetes is a common disease with high risk of macrovascular and microvascular complications, we focused on diabetic patients. In this sense, we excluded patients without diabetes from this study. Due to this restriction of subjects, our study precisely compared the outcomes of the studies of diabetic cohorts. On the other hand, out study was not able to describe the risk of patients with diabetes compared to those without diabetes.

The strength of this study is the listing of all studies allowing readers to see the inconsistency across cohorts. The limitations of this study should also be noted. First, the numbers of studies...
Impacts of Albuminuria and Low eGFR in Diabetes

regarding the associations between low eGFR and cardiovascular mortality, all-cause mortality, and renal events were small. Although low eGFR was considered as a risk factor for cardiovascular events according to the guidelines developed by KDIGO in 2002, there were few studies from this viewpoint prior to this time. [44] Second, each study had its own definition of normal eGFR as the reference category for multivariate analysis. Some studies [10,19] defined normal eGFR as > 90 mL/min/1.73 m², while others [6,20] used a definition of >60 mL/min/1.73 m². The difference in definition may have affected the magnitude of pooled risk ratio for each outcome. Third, there were differences in measurement and expression of albuminuria, such as daily excretion of albumin, or the ratio of urinary albumin to creatinine. Moreover, measurement of urinary albumin was not still standardized. [52,53,54] A standardized method for measurement of albuminuria is essential for comparing data across studies. Furthermore, collection of urine was also not standardized. Spot urine sample collection in the morning or daily collection of urine would lead to different magnitudes of risk ratio: [55] With regard to expression of urinary albumin, some guidelines [56,57,58] use albumin/creatinine ratio. However, other expressions were also used in different studies, such as 24-h excretion or concentration of urinary albumin. Fourth, there may be problems associated with reporting bias, especially for renal events. Some studies measuring serum creatinine at baseline did not report renal outcome. The outcome reporting bias may have increased the influence of renal outcome, which is a very large risk ratio compared with cardiovascular or all-cause mortality. Fifth, the numbers of studies reporting the influence of low eGFR were small. Our search strategy limited objects as “diabetes with albuminuria/proteinuria” or “diabetic nephropathy.” Therefore, studies of diabetic patients with low eGFR may not have been included in our systematic review due to our search strategy. Sixth, making the best use of information about study design or baseline characteristics, the threshold of study size was not used as a limitation in study selection. These selection criteria resulted in more than half of the selected studies consisted of less than 1000 participants.

With regard to the effects of albuminuria and eGFR in diabetic patients, the Chronic Kidney Disease Prognosis Consortium (CKDPC) reported a precise estimate of risk [59]. In addition, our study provided further information showing the inconsistency of study design or subgroup analysis, and presented pooled risk ratio by category of albuminuria and low eGFR for use in clinical care. Moreover, information about intervention or race (except Caucasian) is limited in both the report of CKDPC and this systematic review.

In summary, we conducted a systematic review and meta-analysis, including 148350 cases, and described the impacts of albuminuria and low eGFR on the risks of cardiovascular mortality, all-cause mortality, and renal events. Micro- and macroalbuminuria were significant risk factors for all three outcomes, and low eGFR and albuminuria may be independent risk factors. There was less evidence exploring the influences of low eGFR as independent risk factor on the outcomes. To evaluate the effects of low eGFR, intervention, or race, including Asian subjects, individual patient data meta-analysis or long-term prospective studies based on individual patient data are needed.

Supporting Information

Figure S1 Subgroup analysis for examination of potential sources of heterogeneity in the association between micro- or macroalbuminuria and cardiovascular mortality, all-cause mortality or renal events. (TIF)

Figure S2 Age stratified analysis for the association between albuminuria and cardiovascular mortality, all-cause mortality, and renal events compared with normoalbuminuria. (TIF)

Author Contributions

Conceived and designed the experiments: TT KF TN MS AH YI SK TW. Performed the experiments: TT TN MS. Analyzed the data: TT TN TW. Contributed reagents/materials/analysis tools: TT TN TW. Wrote the paper: TT KF TN SK TW.

References


Impacts of Albuminuria and Low eGFR in Diabetes

### Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of studies</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>2</td>
<td>1.46 (1.07 - 2.00)</td>
</tr>
<tr>
<td>50-60</td>
<td>2</td>
<td>1.51 (1.00 - 2.17)</td>
</tr>
<tr>
<td>60+</td>
<td>5</td>
<td>1.86 (1.29 - 2.69)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>2</td>
<td>2.80 (1.81 - 4.34)</td>
</tr>
<tr>
<td>50-60</td>
<td>2</td>
<td>3.49 (2.47 - 4.93)</td>
</tr>
<tr>
<td>60+</td>
<td>4</td>
<td>2.98 (1.93 - 4.61)</td>
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</table>

### All-cause Mortality

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of studies</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>3</td>
<td>2.09 (1.38 - 3.22)</td>
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<tr>
<td>50-60</td>
<td>4</td>
<td>1.43 (1.29 - 1.70)</td>
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<tr>
<td>60+</td>
<td>8</td>
<td>1.60 (1.37 - 1.88)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>3</td>
<td>3.11 (2.21 - 4.37)</td>
</tr>
<tr>
<td>50-60</td>
<td>3</td>
<td>3.13 (2.49 - 3.98)</td>
</tr>
<tr>
<td>60+</td>
<td>7</td>
<td>2.38 (1.84 - 3.08)</td>
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</table>

### Renal events

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of studies</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1</td>
<td>3.30 (1.71 - 6.07)</td>
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<tr>
<td>50-60</td>
<td>2</td>
<td>3.17 (1.41 - 7.00)</td>
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<tr>
<td>60+</td>
<td>2</td>
<td>3.28 (1.91 - 9.85)</td>
</tr>
<tr>
<td>&lt;50</td>
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<td>18.30 (8.59 - 26.28)</td>
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<td>2</td>
<td>12.49 (2.71 - 67.14)</td>
</tr>
<tr>
<td>60+</td>
<td>2</td>
<td>9.39 (3.26 - 27.00)</td>
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