Health Education and General Practitioner Training in Hypertension Management: Long-Term Effects on Kidney Function

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Abstract
Background and objectives In the Control of Blood Pressure and Risk Attenuation trial, a 2×2 factorial design study (2004–2007), the combined home health education and trained general practitioner intervention delivered over 2 years was more effective than no intervention (usual care) in lowering systolic BP among adults with hypertension in urban Pakistan. We aimed to assess the effectiveness of the interventions on kidney function.

Design, participants, settings, & methods In 2012–2013, we conducted extended follow-up of a total of 1271 individuals aged ≥40 years with hypertension (systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or receipt of antihypertensive treatment) and serum creatinine measurements with 2 years in-trial and 5 years of post-trial period in 12 randomly selected low-income communities in Karachi, Pakistan. The change in eGFR from baseline to 7 years was assessed among randomized groups using a generalized estimating equation method with multiple imputation of missing values.

Results At 7 years of follow-up, adjusted mean eGFR remained unchanged, with a change of −0.3 (95% confidence interval [95% CI], −3.5 to 2.9) ml/min per 1.73 m² among adults randomly assigned to the combined home health education plus trained general practitioner intervention compared with a significant decline of −3.6 (95% CI, −5.7 to −2.0) ml/min per 1.73 m² in those assigned to usual care (P=0.01, modified intention-to-treat analysis). The risk for the combined intervention of death from kidney failure or >20% decline in eGFR relative to usual care was significantly reduced (risk ratio, 0.47; 95% CI, 0.25 to 0.89).

Conclusions The combined home health education plus trained general practitioner intervention is beneficial in preserving kidney function among adults with hypertension in communities in Karachi. These findings highlight the importance of scaling up simple strategies for renal risk reduction in low- and middle-income countries.


Introduction
CKD is ranked as the 18th leading (and rising) cause of death by the Global Burden of Disease Study 2010 (1). About one in five adults in South Asia has CKD (2,3). However, evidence to inform prevention strategies for CKD is scarce, especially in low- and middle-income countries (LMICs).

GFR is an excellent marker of kidney function. Decline in GFR is a strong predictor of progression to advanced stages of CKD and thus a valid subclinical marker in observational studies and clinical trials (4,5). We previously reported 2-year outcomes of the Control of Blood Pressure and Risk Attenuation (COBRA) trial (2004–2007) in Karachi, Pakistan (6). The main trial was designed to assess the effect of family-based home health education (HHE) delivered every 3 months to households in randomized clusters, with a second approach of training general practitioners (GPs) to optimally manage hypertension. We found that the combined strategy (HHE plus trained GPs) was the most beneficial for lowering BP in people with hypertension at 2 years, with a reduction of 5 mmHg in systolic BP compared with no intervention (usual care) (6). At 7 years, the benefit of intervention on BP was attenuated to 2.1 mmHg but still evident (7). However, it remains unclear whether the benefit translates into preservation of kidney function among individuals with hypertension.

We therefore conducted a 7-year follow-up of all the COBRA trial participants, inclusive of the 2-year in-trial and 5-year postintervention period, to determine the effect of trial interventions on change in eGFR among adults with hypertension in Karachi, Pakistan.

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GP intervention would exhibit a slower decline in eGFR than those assigned to a single intervention (GP only or HHE only) or no intervention.

Materials and Methods
The Ethics Review Committee at the Aga Khan University approved the main trial and the postintervention follow-up. All participants provided informed consent.

COBRA Trial Description
As previously described, the COBRA trial was a 2×2 factorial design, cluster randomized controlled trial to determine the effect of family-based HHE and/or special training of GPs on the BP of adults with hypertension (registration number NCT00327574, ClinicalTrials.gov) (6). Briefly, 12 communities (with about 250 households each) were randomly selected using multistage sampling from middle- to low-income areas in Karachi. Patients eligible for study enrollment were residents of the selected clusters who were aged ≥40 years and had known hypertension or consistently elevated BP on two separate visits (mean of last two of three measurements of systolic BP ≥140 mmHg or mean diastolic BP ≥90 mmHg). Computer-generated codes were used to randomly assign the 12 clusters to four groups of three clusters each: HHE only, trained GPs only, HHE plus trained GPs, and no intervention (usual care). A total of 1341 adults from the 12 randomly selected clusters were included in the trial (6).

HHE
Trained community health workers visited households and delivered healthy lifestyle messages (reduce dietary sodium and total and saturated fat consumption; increase fruit, vegetable, and low-fat dairy product intake; stop smoking; maintain a normal body weight; and increase physical activity) using a behavior change communication strategy. In addition, they underscored the importance of adherence to antihypertensive medications. Home visits were made every 3 months for 2 years (i.e., the duration of the trial).

GP Education
In the six study areas assigned to this intervention, all GPs were invited for training. The training curriculum was based on the seventh report of the Joint National Committee and the Fourth Working Party of the British Hypertension Society guidelines (8,9). Target BP was <140/90 mmHg for all individuals.

Screening and Recruitment
Trained research staff visited all households in each of the 12 clusters and screened all eligible adults aged ≥40 years for hypertension after obtaining informed consent. Those with an elevated BP or known hypertension were invited to participate and advised to consult a local GP. The baseline measurements were conducted over 1 year (2004–2005).

A routine physical examination was performed and a fasting blood specimen collected in the morning after an overnight fast. First-morning urine sample was collected and concentrations of albumin and creatinine were measured.

Serum creatinine measurements were calibrated at the Cleveland Clinic laboratory (reference laboratory), where serum creatinine levels were measured again using the Roche enzymatic creatinine assay (in duplicate); this is traceable to the National Institute of Standards and Technology creatinine reference measurement (10). The eGFR was computed using the CKD-Epidemiology Collaboration (CKD-EPI) equation, validated for the Pakistani population (10).

In-Trial Follow-up during 2 Years of Intervention
Hypertensive adults were evaluated by trained field staff in all four groups, masked to randomization status, at 4-monthly intervals over the 2 years of intervention, during which three consecutive BP readings were taken. Blood and urine measurements were not collected at 2 years.

Postintervention Follow-up
Trained outcomes assessors masked to randomization status visited the homes of the participants 7 years after randomization (2012–2013) to establish contact and track vital status. Informed consent was obtained for participation in the study. BP was measured. Fasting blood and urine samples were collected using the same protocol as during baseline.

For individuals who had reportedly died, a dedicated field team contacted the next of kin or nearest relative to verify mortality. Efforts were made to obtain information on the cause and date of death, and death certificates were tracked from the hospital and/or the graveyard, as well as the district mortality registers.

Analysis
No power calculations were done as this was a post-trial follow-up.

Primary Outcome. The primary outcome for the analysis was change in CKD-EPI eGFR from baseline to 7-year post-trial follow-up visit.

Secondary Outcomes. The secondary outcomes were: (1) >20% decline in eGFR from baseline to 7-year follow-up, (2) mortality from kidney failure, (3) composite of >20% decline in eGFR from baseline to 7-year follow-up visit or all-cause mortality, and (4) composite of >20% decline in eGFR from baseline to 7-year follow-up visit or death from kidney failure. In addition, we also evaluated change in urine albumin-to-creatinine ratio (ACR) from baseline to end of 7-year follow-up.

Statistical Analyses
Analyses were performed using Stata software, version 12 (Stata Corp., College Station, TX), and SAS software, version 9.13 (SAS Institute, Inc., Cary, NC). Extreme outliers (change in eGFR±31 ml/min per 1.73 m² during 7 years, defined as three times the interquartile range of change in eGFR) corresponding to 90th or 10th percentile cluster-specific values, were truncated (11). Main analyses were performed on all participants with baseline eGFR measurements under a modified intention-to-treat (ITT) principle—modified ITT because not all randomly assigned patients (n=1341) were entered into the.
final analysis as those without baseline eGFR were excluded \( (n=70) \) from all analyses.

The multiple regression was adjusted for clustering and known predictors of CKD, including age at baseline, sex, baseline systolic and diastolic BP, body mass index, baseline eGFR, baseline ACR, and presence of diabetes \((12-14)\). At the 2-year postintervention follow-up, an analysis that used a conventional main effect and interaction model for a \( 2 \times 2 \) factorial design showed a statistically significant interaction between the HHE and the trained GP study intervention factors. Consequently, at the 7-year follow-up, the standard factorial analysis was abandoned in favor of a more interpretable one-way layout approach comparing treatment means among the four groups. This was the same approach used previously for the 2-year analysis \((6,15)\). For consistency and comparability among reported results, we have used the four-group one-way layout approach in the present analysis.

The generalized estimating equations (GEE) approach was used in the main analysis of eGFR and secondary end points with adjustment for clustering. Multiple imputation was employed to handle bias due to missing 7-year eGFR \((50.4\%)\) follow-up values. All F-tests comparing eGFR among intervention groups were GEE based and constructed from multiple imputation samples, with the exception of the per-protocol sensitivity analysis on those with eGFR available at 7 years \((n=630)\).

Variables were included in the eGFR multiple imputation model if they were risk factors for progression of kidney disease. Therefore, the multiple imputation model included baseline age, sex, baseline body mass index, history of diabetes, systolic and diastolic BP at baseline, eGFR at baseline, and urine albumin excretion at baseline. The resultant dataset allowed us to use data from all 1271 individuals randomly assigned. Ten imputed datasets were generated using the fully conditional specification method and predictive mean matching of continuous variables under the missing-at-random assumption. After imputation, each dataset was analyzed separately using the GEE method, with F-tests constructed from the pooled imputed samples.

We considered \( P \leq 0.05 \) to represent statistically significant differences for the omnibus tests and comparisons among group means; \( P \leq 0.10 \) was considered to indicate significant differences for interactions. We report marginal adjusted means and 95% confidence intervals (95% CIs) for treatment effects adjusted for the other variables in the model.

Logistic regression used to obtain 7-year follow-up risk ratios (RRs) and 95% CIs for the intervention groups relative to usual care as the reference group \((16)\). The Miettinen doubling-of-cases approach was used to estimate RRs through use of a linear mixed model for a cluster sample design with logit link, binary error distribution, maximum likelihood parameter estimation, and sandwich method (robust) variance-covariance estimation. Calculations were performed using SAS PROC GLIMMIX with the EMPIRICAL variance estimation option \((17)\).

To evaluate factors influenced by intervention that could potentially mediate the primary outcome, we accounted for change in systolic BP from baseline at 7-year follow up in the main analysis on change in eGFR \((7)\).

**Results**

The Consolidated Standards of Reporting Trials diagram is shown in Figure 1, and baseline characteristics of clusters and participants are presented in Table 1. Baseline characteristics of participants alive at the post-trial visit are summarized in Supplemental Table 1.

**Response Rate during Post-Trial Follow-up**

At the 7-year follow up, 283 \((22.3\%)\) members of the original cohort with a baseline eGFR measurement had reportedly died. An eGFR measurement was available for 630 \((64\%)\) of the total remaining cohort with baseline eGFR targeted for recruitment at follow up \((n=988)\). Urine ACR was available for 648 participants at follow-up. However, comparison of characteristics between participants alive at the post-trial follow up with an eGFR \((n=630)\) measurement versus those without an eGFR measurement \((n=358)\) revealed no significant differences in baseline characteristics (Supplemental Table 1).

**Change in eGFR**

By the end of the 7-year follow-up period, mean follow-up eGFR \((89.3 \text{ ml/min per 1.73 m}^2)\) was higher in the combined intervention group than in the single-intervention group \((86.8 \text{ and } 82.7 \text{ ml/min per 1.73 m}^2)\) and no-intervention (usual care) group \((84.9 \text{ ml/min per 1.73 m}^2)\) groups \((P\leq0.002)\) (Table 2). The unadjusted change from baseline eGFR showed nonsignificant increase in the combined HHE plus GP group compared with a decline in individuals assigned to single or no intervention (usual care) \((P\leq0.01)\) (Table 2). Model-based, adjusted mean changes in eGFR differed significantly among the four intervention groups \((P\leq0.01)\). Of particular interest is that eGFR showed a nonsignificant change of \(-0.3 \text{ (95\% CI, } -3.5 \text{ to } -2.9) \text{ ml/min per 1.73 m}^2\) in the HHE plus GP group compared with a significant change of \(-3.6 \text{ (95\% CI, } -5.7 \text{ to } -2.0) \text{ ml/min per 1.73 m}^2\) in the no-intervention group \((P=0.01 \text{ difference among groups and } P=0.04 \text{ difference between groups})\) (Table 2). As shown in Figure 2, the histogram of the model-based, individual predicted changes in eGFR for individuals receiving the combined HHE plus trained GP intervention demonstrated a positive shift, indicating an increase in eGFR compared with reductions in eGFR for the usual care and single-intervention groups. The model residual diagnostics are shown in Supplemental Figures 1 and 2. The intraclass coefficient for change in eGFR was 0.03.

No significant interactions were detected between intervention and baseline characteristics, including age, baseline systolic BP, baseline eGFR, or urine albumin excretion \((interaction P>0.15 \text{ for each})\).

In addition to the baseline variables, upon accounting for change in systolic BP from baseline to 7 year, the significant difference in change in eGFR among randomized group persisted \((P\leq0.02)\); however, the level of significance between the HHE plus trained GP group versus the usual care group was attenuated \((P=0.07)\) (Supplemental Table 2) \((7)\).

**A >20% Decline in Baseline eGFR**

Table 3 shows that the percentage of individuals with a >20% decline in baseline eGFR was lower for the
combined intervention (5.6%) than usual care (10.3%) ($P=0.06$). The adjusted RR for a $>20\%$ decline in baseline eGFR for the combined intervention relative to usual care was 0.53 (95% CI, 0.29 to 0.96) (Table 4).

All-Cause Mortality and Death from Kidney Failure
A total of 283 of 1271 (22.3%) participants died during the 7 years of follow-up. The differences in all-cause mortality or death from kidney failure were not statistically significant. However, the adjusted RR for the composite outcome of death from kidney failure or $>20\%$ decline in baseline eGFR was significantly reduced to 0.47 (95% CI, 0.25 to 0.89) for the combined intervention versus usual care (Table 4).

Sensitivity and Subgroup Analysis
The per-protocol analysis yielded results consistent in direction of change in eGFR among the randomized groups.
with eGFR showed a nonsignificant increase of 1.3 (95% CI, −2.0 to 4.6) ml/min per 1.73 m² in the HHE plus trained GP group compared with a significant change of −4.1 (95% CI, −4.8 to −3.4) ml/min per 1.73 m² in the no-intervention group (P=0.3 difference among groups and P=0.002 difference between groups) (Supplemental Table 3).

Analysis restricted to individuals with available information at follow-up showed improved adherence to Table 1. Baseline characteristics of study participants by intervention group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HHE and GP (n=317)</th>
<th>HHE Only (n=327)</th>
<th>GP Only (n=315)</th>
<th>Usual Care (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of clusters</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age, yr</td>
<td>53.4±0.6</td>
<td>52.8±0.6</td>
<td>55.1±0.6</td>
<td>53.4±0.6</td>
</tr>
<tr>
<td>Men</td>
<td>107 (33.8)</td>
<td>130 (39.8)</td>
<td>134 (42.5)</td>
<td>116 (37.2)</td>
</tr>
<tr>
<td>Literacy</td>
<td>196 (61.8)</td>
<td>189 (57.8)</td>
<td>214 (67.9)</td>
<td>160 (51.3)</td>
</tr>
<tr>
<td>Current tobacco users</td>
<td>91 (28.7)</td>
<td>92 (28.1)</td>
<td>92 (29.2)</td>
<td>144 (46.2)</td>
</tr>
<tr>
<td>Physical activity (METs≥840)</td>
<td>91 (28.7)</td>
<td>112 (34.3)</td>
<td>92 (29.2)</td>
<td>144 (46.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>76 (24.0)</td>
<td>214 (67.9)</td>
<td>49 (15.6)</td>
<td>49 (15.7)</td>
</tr>
<tr>
<td>History of heart disease</td>
<td>39 (12.3)</td>
<td>35 (10.7)</td>
<td>49 (15.6)</td>
<td>49 (15.7)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>20 (6.3)</td>
<td>16 (4.9)</td>
<td>17 (5.4)</td>
<td>20 (6.4)</td>
</tr>
<tr>
<td>Sought ambulatory care last 2 wk</td>
<td>109 (32.8)</td>
<td>113 (32.5)</td>
<td>94 (28.1)</td>
<td>105 (32.1)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.7±0.3</td>
<td>26.3±0.3</td>
<td>25.9±0.3</td>
<td>27.1±0.3</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>148.1±1.4</td>
<td>151.6±1.4</td>
<td>153.4±1.4</td>
<td>153.8±1.4</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>91.1±0.7</td>
<td>93.9±0.7</td>
<td>93.0±0.7</td>
<td>95.7±0.7</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>121.0±2.07</td>
<td>117.8±2.0</td>
<td>117.2±1.9</td>
<td>123.4±2.4</td>
</tr>
<tr>
<td>ACR² mg/g</td>
<td>6.2 (3.9, 16.0)</td>
<td>6.4 (3.9, 13.2)</td>
<td>6.9 (4.5, 14.9)</td>
<td>6.6 (4.4, 15.3)</td>
</tr>
<tr>
<td>eGFR=90 ml/min per 1.73 m²</td>
<td>155 (46.6)</td>
<td>191 (54.9)</td>
<td>141 (42.1)</td>
<td>165 (50.6)</td>
</tr>
<tr>
<td>eGFR=60–89 ml/min per 1.73 m²</td>
<td>114 (34.3)</td>
<td>114 (32.7)</td>
<td>135 (40.3)</td>
<td>122 (37.4)</td>
</tr>
<tr>
<td>eGFR&lt;60 ml/min per 1.73 m²</td>
<td>41 (12.3)</td>
<td>43 (12.3)</td>
<td>59 (17.6)</td>
<td>39 (11.9)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or number (percentage) of patients. HHE, home health education; GP, general practitioner; METs, metabolic equivalents; ACR, albumin-to-creatinine ratio.

Table 2. Mean eGFR and change in eGFR at 7-year follow up

<table>
<thead>
<tr>
<th>Variable</th>
<th>HHE and GP, n=317 (95% CI)</th>
<th>HHE Only, n=327 (95% CI)</th>
<th>GP Only, n=315 (95% CI)</th>
<th>Usual Care, n=312 (95% CI)</th>
<th>P value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean eGFR at baseline¹</td>
<td>88 (87.2 to 88.8)</td>
<td>88.5 (87.6 to 89.4)</td>
<td>83.9 (81.4 to 86.3)</td>
<td>87.5 (85.7 to 89.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean eGFR at 7-Year Follow-Up¹</td>
<td>89.3 (86.8 to 91.7)</td>
<td>86.8 (83.9 to 89.6)</td>
<td>82.7 (79.1 to 86.4)</td>
<td>84.9 (82.5 to 87.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean (LS) Change in eGFR¹</td>
<td>1.2 (−1.6 to 4.0)</td>
<td>−1.77 (−4.0 to 0.5)</td>
<td>−1.29 (−3.4 to 0.9)</td>
<td>−2.69 (−4.4 to −1.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted (LS) Mean Change in eGFR¹</td>
<td>−0.3 (−3.5 to 2.9)</td>
<td>−3.0 (−5.6 to −0.5)</td>
<td>−2.6 (−4.9 to −0.3)</td>
<td>−3.6 (−5.7 to −2.0)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Pakistan equation with eGFR units in ml/min per 1.73m². Change in eGFR is the difference from baseline to last follow up with negative values indicating a decrease from baseline in follow-up eGFR. HHE, home health education; GP, general practitioner; 95% CI, 95% confidence interval; LS, least squares; GEE, generalized estimating equations.

¹P-value, post-hoc comparison to usual care.

²F-test p-value from GEE analysis using multiple imputation.

References:

1. Model 1: Univariate GEE analysis with multiple imputation; exchangeable working covariance matrix structure; clinics are clusters nested in treatment groups.

2. Model 2: Multivariate GEE analysis with multiple imputation - Model 1 + fixed effects for age, sex, baseline eGFR, baseline systolic and diastolic BP, diabetes, BMI and baseline urine albumin excretion.
antihypertensive therapy with blockers of the renin-angiotensin system in the combined HHE plus GP group (26.1%) relative to usual care (18.2%), but this difference was not statistically significant \((P=0.31)\) (Supplemental Table 4).

**Change in ACR**

In the per-protocol analysis, mean urine ACR (mg/g) increased in all four groups, with nonsignificant differences among groups \((P=0.6)\). Adjusted mean increase was lowest for the combined HHE plus trained GP intervention at 10.3 (95% CI, 8.8 to 11.8) mg/g, followed by GP only at 10.2 (95% CI, 8.1 to 16.2) mg/g, HHE only at 25.8 (95% CI, 9.1 to 42.5) mg/g, and usual care at 13.4 (95% CI, 5.4 to 21.5) mg/g.

**Discussion**

After 7 years of follow up—5 years after cessation of intervention—adjusted mean eGFR levels remained unchanged, with a change of \(-0.3\) (95% CI, \(-3.5\) to \(-2.9\)) ml/min per 1.73 m\(^2\) among adults randomly assigned to the combined HHE plus trained GP intervention compared with a significant change of \(-3.6\) (95% CI, \(-5.7\) to \(-2.0\)) ml/min per 1.73 m\(^2\) in those assigned to usual care \((P<0.01,\) modified ITT analysis). Risks of a >20% decline in eGFR from baseline associated with combined intervention versus usual care was halved (RR, 0.53; 95% CI, 0.29 to 0.96).

The benefit of combined HHE plus trained GP intervention on preserving kidney function highlights the potential for scaling up simple strategies to reduce renal risk.

**Table 3. Comparison among intervention groups on frequency (%) of all-cause and kidney failure mortality, 20% decline in baseline eGFR, and composite causes at 7-year follow-up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HHE and GP ((n=317))</th>
<th>HHE only ((n=327))</th>
<th>GP only ((n=315))</th>
<th>Usual Care ((n=312))</th>
<th>(P) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>60 (18.9)(^b)</td>
<td>72 (22.0)</td>
<td>81 (25.7)</td>
<td>70 (22.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Death from kidney failure</td>
<td>1 (0.32)</td>
<td>4 (1.2)</td>
<td>3 (1.0)</td>
<td>7 (2.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;20% decline in baseline eGFR</td>
<td>18 (5.6)</td>
<td>19 (5.8)</td>
<td>29 (9.2)</td>
<td>32 (10.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Composite death from kidney failure or &gt;20% decline in baseline eGFR</td>
<td>19 (6.0)</td>
<td>23 (7.0)</td>
<td>32 (10.1)</td>
<td>39 (12.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Composite all-cause mortality or &gt;20% decline in baseline eGFR</td>
<td>78 (24.6)</td>
<td>91 (27.8)</td>
<td>110 (34.9)</td>
<td>102 (32.6)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

HHE, home health education; GP, general practitioner.
\(^a\)P values based on chi-squared test.
\(^b\)\%.
### Table 4. Adjusted risk ratios* on 20% decline in baseline eGFR, death from kidney failure or decline in eGFR, and all-cause mortality at 7-year follow-up (n=1271)

<table>
<thead>
<tr>
<th>Treatment Group / Baseline Characteristic</th>
<th>&gt;20% Decline in Baseline eGFR RR (95% CI) P value</th>
<th>Death from Kidney Failure or &gt;20% Decline in Baseline eGFR RR (95% CI) P value</th>
<th>All-Cause Mortality or &gt;20% Decline in Baseline eGFR RR (95% CI) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care (ref.)</td>
<td>1.00 (0.90 to 1.11)</td>
<td>1.00 (0.90 to 1.11)</td>
<td>1.00 (0.90 to 1.11)</td>
</tr>
<tr>
<td>HHE and GP</td>
<td>0.56 (0.28 to 1.11)</td>
<td>0.56 (0.28 to 1.11)</td>
<td>0.56 (0.28 to 1.11)</td>
</tr>
<tr>
<td>HHE Only</td>
<td>0.94 (0.42 to 2.13)</td>
<td>0.94 (0.42 to 2.13)</td>
<td>0.94 (0.42 to 2.13)</td>
</tr>
<tr>
<td>GP Only</td>
<td>0.98 (0.96 to 1.00)</td>
<td>0.98 (0.96 to 1.00)</td>
<td>0.98 (0.96 to 1.00)</td>
</tr>
<tr>
<td>Age (per year)c</td>
<td>1.78 (1.12 to 2.83)</td>
<td>1.78 (1.12 to 2.83)</td>
<td>1.78 (1.12 to 2.83)</td>
</tr>
<tr>
<td>Diabetes vs no diabetes</td>
<td>1.93 (1.23 to 3.04)</td>
<td>1.93 (1.23 to 3.04)</td>
<td>1.93 (1.23 to 3.04)</td>
</tr>
<tr>
<td>Systolic BP (per 10mm Hg)</td>
<td>1.10 (0.99 to 1.22)</td>
<td>1.10 (0.99 to 1.22)</td>
<td>1.10 (0.99 to 1.22)</td>
</tr>
<tr>
<td>Diastolic BP (per 10mm Hg)</td>
<td>0.88 (0.72 to 1.09)</td>
<td>0.88 (0.72 to 1.09)</td>
<td>0.88 (0.72 to 1.09)</td>
</tr>
<tr>
<td>BMI (per kg/m²)</td>
<td>1.03 (0.99 to 1.07)</td>
<td>1.03 (0.99 to 1.07)</td>
<td>1.03 (0.99 to 1.07)</td>
</tr>
<tr>
<td>eBL eGFR (per 10ml/min per 1.73m²)</td>
<td>1.12 (1.00 to 1.27)</td>
<td>1.12 (1.00 to 1.27)</td>
<td>1.12 (1.00 to 1.27)</td>
</tr>
<tr>
<td>eBL ACR (per 100mg/g)</td>
<td>1.00 (0.93 to 1.07)</td>
<td>1.00 (0.93 to 1.07)</td>
<td>1.00 (0.93 to 1.07)</td>
</tr>
</tbody>
</table>

*Risk ratios (RRs) and 95% confidence intervals (95% CIs) were obtained using Miettinen’s doubling-of-cases approach employing a generalized linear mixed model for a cluster sample design with logit link, binary error distribution, ML parameter estimation and robust (sandwich method) variance estimation. HHE, home health education; GP, general practitioner; BMI, body mass index; BL, baseline; ACR, albumin-to-creatinine ratio.

aAdjusted risk ratio (95% CI).

bRR for a continuous predictor is interpreted as a risk multiplier giving rate of change in RR per unit change in predictor.

cBL eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Pakistan equation. Units: eGFR = mL/min per 1.73 m².

dACR based on spot urine sample.

The combined effect of healthy lifestyle and medication could account for the finding of a greater impact of our combined (HHE plus trained GP) intervention versus either of these interventions alone compared with usual care. Results from trials on weight management and healthy diets (rich in fruit and vegetables and low in animal protein) demonstrate an increase in or preservation of eGFR (18,19). Physical activity has a beneficial effect on cardiometabolic parameters, and observational data suggest that benefit may extend to slowing progression of kidney disease (20,21). In the Look Action for Health in Diabetes trial, behavioral intervention of intensive weight loss and physical activity reduced the incidence of very high-risk CKD (eGFR<15 ml/min per 1.73 m²) among adults with type 2 diabetes (22). In terms of medication, trials of antihypertensive therapy, especially blockers of the renin-angiotensin system, demonstrate a beneficial long-term effect on reduction in progression to kidney failure—especially among individuals with CKD (23,24).

Population and health system characteristics differ between developing and developed countries. In Pakistan, as in many LMICs, diets are poor in fruit and vegetables (99% have less than one serving per day), and most individuals with hypertension have uncontrolled BP (25). Thus, the scope for improvement from interventions targeting individual and provider behavior is considerable. COBRA was designed to emphasize behavior change of the participants and the providers. We demonstrated benefit of combined intervention on BP at 2 years, which attenuated but persisted till 7 years. The latter could only partially account for the observed benefit of combined intervention on eGFR. There were indications of improvement in behavior (physical activity, tobacco use, and adherence to antihypertensive medications) at 2 years (6). There was no intended crossover during the post-trial follow-up, and the study clusters were geographically far apart (minimum distance, 10 km). Hence, it is unlikely that participants allocated to usual care would seek care from providers in the HHE and GP intervention areas. Furthermore, HHE intervention by community health workers was discontinued at 2 years. Thus, it is possible that part of the benefit of the combined intervention is derived from a legacy effect of improvement in diet, physical activity, and BP observed at 2 years, possibly acting synergistically to preserve kidney function in the long term (26).

The clinical and public health implications of a greater preservation of eGFR by 3.3 ml/min per 1.73 m² over 7 years in communities randomly assigned to the combined intervention compared with usual care can be substantial. In the population-based Coronary Artery Risk Development in Young Adults study, black patients had a 0.10 (95% CI,
In conclusion, our findings indicate that public health interventions using effective lifestyle modification approaches and training of providers in a primary care setting can yield long-term benefits for preserving kidney function. These simple strategies are implementable and should be evaluated for cost-effectiveness of prevention of CKD in LMICs.

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Disclosures

None.

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