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Original Investigation

Impact of Educational Attainment on Health Outcomes in Moderate to Severe CKD

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Background: The inverse association between educational attainment and mortality is well established, but its relevance to vascular events and renal progression in a population with chronic kidney disease (CKD) is less clear. This study aims to determine the association between highest educational attainment and risk of vascular events, cause-specific mortality, and CKD progression.

Study Design: Prospective epidemiologic analysis among participants in the Study of Heart and Renal Protection (SHARP), a randomized controlled trial.

Setting & Participants: 9,270 adults with moderate to severe CKD (6,245 not receiving dialysis at baseline) and no history of myocardial infarction or coronary revascularization recruited in Europe, North America, Asia, Australia, and New Zealand.

Predictor: Highest educational attainment measured at study entry using 6 levels that ranged from "no formal education" to "tertiary education."

Outcomes: Any vascular event (any fatal or nonfatal cardiac, cerebrovascular, or peripheral vascular event), cause-specific mortality, and CKD progression during 4.9 years' median follow-up.

Results: There was a significant trend ($P < 0.001$) toward increased vascular risk with decreasing levels of education. Participants with no formal education were at a 46% higher risk of vascular events (relative risk [RR], 1.46; 95% CI, 1.14-1.86) compared with participants with tertiary education. The trend for mortality across education levels was also significant ($P < 0.001$): all-cause mortality was twice as high among those with no formal education compared with tertiary-educated individuals (RR, 2.05; 95% CI, 1.62-2.58), and significant increases were seen for both vascular (RR, 1.84; 95% CI, 1.21-2.81) and nonvascular (RR, 2.15; 95% CI, 1.60-2.89) deaths. Lifestyle factors and prior disease explain most of the excess mortality risk. Among 6,245 participants not receiving dialysis at baseline, education level was not significantly associated with progression to end-stage renal disease or doubling of creatinine level (P for trend = 0.4).

Limitations: No data for employment or health insurance coverage.

Conclusions: Lower educational attainment is associated with increased risk of adverse health outcomes in individuals with CKD.

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INDEX WORDS: Chronic kidney failure; chronic kidney disease (CKD); education; educational attainment; disease progression; end-stage renal disease (ESRD); vascular event; mortality; health behavior; risk factor; socioeconomic factors; inequalities; renal dialysis; Study of Heart and Renal Protection (SHARP).

Editorial, p. 1

The inverse association between education and health outcomes is well established in the general population, with a gradient in health across levels of educational attainment.[1] Two general mechanisms, lifestyle factors (or behaviors) and access to effective health care, are believed to contribute to this gradient.[1-5] Previous work has shown that health behaviors explain some of the observed changes in the education-mortality gradient over time across the population,[6] with lower

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levels of smoking and better control of hypertension associated with lower age-adjusted mortality, and increased obesity associated with higher mortality risk.[6]

However, studies of the relevance of educational attainment to health outcomes in chronic kidney disease (CKD) are sparse.[7] Two small studies of patients on dialysis therapy have shown that poor health literacy (defined as the ability to obtain, process, and understand basic health information to make decisions regarding one's health and medical care) is associated with 54% (hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.01-2.35) higher risk of death,[8] and tertiary education compared with primary school education only is associated with 46% (HR, 0.54; 95% CI, 0.32-0.91) lower cardiovascular mortality.[9]

We used data from 9,270 participants with moderate to severe CKD in the Study of Heart and Renal Protection (SHARP) to: (1) assess associations between highest educational attainment (ie, level of schooling, vocational, or tertiary education obtained early in life) and particular health outcomes (vascular morbidity, cause-specific mortality, and kidney disease progression) and (2) determine whether there are gradients in health outcomes by educational attainment in moderate to severe CKD. With more than 2,300 vascular events, more than 2,200 deaths, and more than 2,400 participants doubling their creatinine levels or progressing to end-stage renal disease (ESRD) during a median 4.9 years' follow-up, the study provides an opportunity to investigate associations between educational attainment and health outcomes in a large and carefully phenotyped population with CKD.

METHODS

Study Overview

SHARP was a randomized placebo-controlled trial investigating the effects of lowering low-density lipoprotein cholesterol levels for an average of 5 years with simvastatin, 20 mg, plus ezetimibe, 10 mg, daily on major vascular and kidney disease outcomes. The study enrolled 9,270 participants with CKD (6,245 [67%] not receiving and 3,025 [33%] receiving dialysis at baseline) in 18 countries.[10] Study procedures and clinical results from the randomized comparisons have been published previously.[10,11] Procedures for the current analyses followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines[12] and are summarized next.

Study Participants and Baseline Assessment

Individuals with CKD who were 40 years or older were eligible to participate if they had more than one previous measurement of serum or plasma creatinine of at least 1.7 mg/dL (150 μmol/L) in men or 1.5 mg/dL (130 μmol/L) in women. Individuals with prior myocardial infarction or coronary revascularization and those with a medical history that might limit their ability to participate or take study treatments for the duration of the study (eg, severe respiratory disease, history of cancer other than nonmelanoma skin cancer, or recent history of alcohol or substance misuse) were excluded. A 6-week run-in period was undertaken to identify and exclude from randomization participants who were unlikely to adhere to the study medication for the duration of the study. For the purpose of the current analyses, baseline information refers to information that was recorded at or shortly before a participant's random assignment to simvastatin plus ezetimibe versus placebo. Recorded baseline information included sociodemographic characteristics (such as age, sex, and ethnicity), blood pressure, blood and urine test results, anthropometric measurements to calculate body mass index (BMI), previous disease history, current medications, cigarette smoking, and alcohol consumption. To facilitate the planned analysis of the impact of educational attainment on health outcomes, the participant's highest educational level completed was recorded at trial entry according to the relevant description in each country: postgraduate tertiary education, undergraduate tertiary education, high school, vocational studies, lower high school, primary school, or no formal education (see separate country-specific classifications in Table S1, available as online supplementary material). In addition, participants without recorded education data were categorized as "unrecorded." Due to the small number of participants with postgraduate tertiary education, the top 2 education categories were combined to make one tertiary education level. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[13]

Follow-up Procedures and Study Outcomes

Participants were to be seen in person at 2, 6, and 12 months and every 6 months thereafter for at least 4 years. At each visit, information for all serious adverse events (including vascular events, revascularization procedures, and initiation of renal replacement therapy), adherence to study medication, and use of concomitant medication was collected; further information was also sought from hospital and other health records. Trained clinicians at the international coordinating center adjudicated major study outcomes, including cause-specific mortality, using standardized definitions and procedures.

For current analyses, the main vascular outcome of interest is "any vascular event" during the study, defined as nonfatal myocardial infarction, coronary death, hemorrhagic and nonhemorrhagic stroke, arterial revascularization, noncoronary cardiac death; atherosclerotic other coronary, other cerebrovascular, other peripheral arterial disease events; and nonfatal nonischemic heart failure, arrhythmias, or valvular heart disease (see Item S1). Mortality was subdivided into vascular and nonvascular (ie, renal, cancer, respiratory, or other nonvascular) causes. To further understand the possible relevance of educational attainment to respiratory and cancer deaths, exploratory analyses of cancer incidence and nonfatal respiratory events were undertaken. Among participants not receiving dialysis at baseline, the main kidney disease outcomes in this analysis included 2 composite end points: (1) progression to ESRD (defined as kidney transplantation or initiation of maintenance dialysis therapy) or doubling of creatinine level and (2) progression to ESRD or death. In addition, the availability of serial creatinine measurements allowed for estimation of each individual's annual rate of change in eGFR over time.[14]

Statistical Analysis

The relevance of highest educational attainment to first occurrence of disease outcomes of interest was estimated using Cox proportional hazards models stratified by country of recruitment. The proportional hazard assumption was tested through examination of the time-dependency of the Schoenfeld residuals.[15] The gradient in health outcomes across all education levels, before and after adjustment for potential mediators (see text that follows), was estimated using Wald χ^2 tests for trend after excluding participants for whom education was unrecorded. The χ^2 statistics allow for a quantitative assessment of both the extent to which the mediators explain any education gradients and the residual (ie, unexplained) relevance of education to risk after adjustment for the recorded mediators.