Altitude and the risk of cardiovascular events in incident US dialysis patients

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Abstract

Background. Altitude is associated with all-cause mortality in US dialysis patients, but its association with cardiovascular outcomes has not been assessed. We hypothesized that higher altitude would be associated with lower rates of cardiovascular events due to an altered physiological response of dialysis patients to altitude induced hypoxia.

Methods. We studied 984,265 patients who initiated dialysis from 1995 to 2006. Patients were stratified by the mean elevation of their residential zip codes and were followed from the start of dialysis to the occurrence of several validated cardiovascular endpoints: myocardial infarction, stroke, cardiovascular death and a composite of these endpoints. Incidence rate ratios across altitude strata were estimated using proportional hazards regression.

Results. All outcomes occurred less frequently among patients living at higher altitude compared with patients living at or near sea level, and the association appeared monotonic for all outcomes except for stroke, which was most incident in the 250–1999 ft group. Compared with otherwise similar patients residing at or near sea level, patients living at ≥6000 ft had 31% [95% confidence interval (CI): 21–41%] lower rates of myocardial infarction, 27% (95% CI: 15–37%) lower rates of stroke and 19% (95% CI: 14–24%) lower rates of cardiovascular death. Additional adjustment for biometric information did not materially change these findings. Effect modification between race and altitude was only consistently significant for Native Americans. Altitude did not significantly alter the rates of non-cardiovascular death.

Conclusion. We conclude that dialysis patients at higher altitude experience lower rates of cardiovascular events compared to otherwise similar patients at lower altitude.

Keywords: elevation; end-stage renal disease; hypoxia; hypoxia-inducible factor; USRDS

Introduction

We recently reported an inverse association between residential altitude and all-cause mortality in US dialysis patients and the general population. The relative mortality reductions of dialysis patients residing at altitudes >6000 ft compared with those at or near sea level were twice as pronounced as the corresponding mortality reductions observed in the general population [1]. One of the hypothesized mechanisms for this difference in observed mortality rates is the persistent activation of hypoxia-inducible factor-1 (HIF-1) in dialysis patients who live at higher elevation. This hypothesis is motivated by earlier work in hemodialysis patients describing a more efficient response to erythropoiesis-stimulating agents at higher altitude [2]. We confirmed this association by evaluating the relocation patterns of dialysis patients from low altitudes to similar versus higher altitudes as a natural experiment [3]. Compatible with these observations is HIF-1 activation, one of several physiological adaptations to hypoxic conditions at high altitude, which stimulates erythropoietin production and increases intestinal absorption of iron and its subsequent availability to the bone marrow.

These previous studies raised the possibility that persistent HIF-1 activation, as it correlates with altitude, could also be especially protective against cardiovascular outcomes in the dialysis population given the molecule’s central role as a mediator of cardiovascular response to ischemic conditions. We hypothesized that there would be an inverse relationship between altitude and fatal and non-fatal cardiovascular events among incident dialysis patients in the USA and that this relationship would be larger than that previously observed for all-cause mortality.

Materials and methods

The data source and assembly of the study cohort correspond to our previous report on altitude and all-cause mortality [1]; for the present study, two additional years of data were available (2005 and 06).
Data sources
We used the United States Renal Data System (USRDS) and the US Geological Survey (USGS). The USRDS contains detailed data on all patients in Medicare’s ESRD program. The Medical Evidence Form contains demographic data, the likely cause of end-stage renal disease (ESRD), various clinical baseline data such as weight and height and certain laboratory measurements such as serum albumin and hematocrit concentrations. Certain comorbid conditions reported in this form have previously been validated [4]. In addition, the USRDS contains all Medicare Part A and B claims that include information on diagnoses and procedures recorded for all hospitalizations and outpatient visits. We used data from the USGS and each patient’s residential zip code to approximate the altitude of each study patient’s residence. The Institutional Review Boards of Brigham and Women’s Hospital and Stanford University School of Medicine approved this research.

Patient selection
From USRDS files, we selected all adult patients (≥18 years) who initiated hemodialysis treatment between 1 January 1995 and 31 December 2006. We excluded all patients who underwent preemptive kidney transplantation as primary ESRD treatment. Patients whose age, gender or race was missing or implausible were also dropped from the study. Follow-up began at the first reported date of renal replacement therapy.

Exposure
We classified all patients into five strata based on the average elevation above sea level of their zip code of residence: <250 ft (<76 m), 250–1999 ft (76–609 m), 2000–3999 ft (610–1218 m), 4000–5999 ft (1219–1828 m) and >6000 ft (>1828 m).

Other patient characteristics
Covariates included demographic data as reported in the Medical Evidence Form, such as age at first dialysis, gender, race (white, black, Asian, Native American, Other), and Medicaid coverage as a proxy for socioeconomic status. Comorbidities were also derived from the Medical Evidence Form and included diabetes, hypertension, heart failure, arteriosclerotic heart disease, cerebrovascular disease, peripheral arterial vascular disease, chronic obstructive pulmonary disease and cancer. We also noted whether a patient was unable to ambulate or transfer as well as whether a patient used hemodialysis or peritoneal dialysis and whether they had received erythropoietin treatment prior to initiation of dialysis. From height and weight, we calculated each patient’s body mass index (BMI). Baseline laboratory measurements included albumin, hemoglobin, estimated glomerular filtration rate (eGFR) and hematocrit.

Outcomes
Myocardial infarction was ascertained from hospitalization claims, where we required an International Classification of Diseases, 9th Revision (ICD-9) code indicating myocardial infarction (410 with any fourth digit) in primary diagnosis and a length of stay between 3 and 180 days or death within 3 days. This algorithm has been validated in Medicare data and found to have a positive predictive value of 94% [5]. Stroke was ascertained from hospitalization claims with a primary diagnosis code of 433, 434 or 436. Cause of death was ascertained from the corresponding variables in the USRDS and categorized into cardiovascular, non-cardiovascular and missing. We also studied an aggregate cardiovascular endpoint of the earliest among myocardial infarction, stroke or cardiovascular death.

Statistical analyses
We calculated means and frequencies of patient characteristics by elevation group. We built Cox proportional hazards models for the time from first dialysis to the cardiovascular event of interest, stratifying by year and censoring patients at 5 years of follow-up, end of database (31 December 2006), loss to follow-up or death; the lowest elevation group (<250 ft) served as reference category for all analyses. We tested for violations of the proportional hazards assumption and found no statistical interaction between altitude category and time. We also tested for interactions between year of incidence (continuous) and altitude group (ordinal) for all outcomes using a Bonferroni-adjusted significance threshold; however, we did not find evidence for effect modification of the reported associations with calendar year.

We explored the forces driving any possible confounding by building increasingly adjusted models: (i) unadjusted, (ii) adjusted for demographic factors and Medicaid insurance, (iii) additionally adjusted for comorbid conditions including the inability to ambulate or transfer and dialysis modality and (iv) additionally adjusted for BMI, eGFR, hemoglobin and albumin. The incidence rate ratio constituted the measure of association and was accompanied by its 95% confidence interval (CI). Statistical significance was set at α ≤ 0.05. All statistical analyses were conducted using SAS version 9.1 (The SAS Institute, Cary, NC).

Results
We studied 984 265 patients who initiated dialysis in the USA from 1995 to 2006; these patients contributed 2.71 million person-years. Almost 95% of these patients resided at <2000 ft. The highest altitude group, classified as >6000 ft, was composed of 4356 (0.4%) patients who lived mostly in the Rocky Mountains or the Sierra Nevada. Baseline characteristics of the dialysis patients, by altitude group, are shown in Table 1. Patients at higher altitude were younger, less likely to be covered by Medicaid and more likely to initiate dialysis using peritoneal dialysis. While the proportion of Native Americans on dialysis was larger at higher altitudes, the proportions of blacks and Asians were inversely correlated with altitude. Most comorbid conditions were distributed similarly across altitude groups, but patients at higher altitude had more diagnosed diabetes and hypertension, slightly less arteriosclerotic heart disease and heart failure and fewer instances of reported inability to ambulate or transfer. Although fewer patients received erythropoiesis-stimulating agents prior to initiation of dialysis, mean hemoglobin concentrations were higher at increased altitude.

The 5-year incidence rates of myocardial infarction, stroke and cardiovascular death were 22.4, 21.2 and 95.3 per 1000 person-years; counting the earliest of these events, the incidence was 125.6 per 1000 person-years. Table 2 shows the number of cardiovascular events and event rates by altitude stratum. The incidences of the non-fatal cardiovascular events studied, namely myocardial infarction and stroke, were generally very similar within each altitude group. Cardiovascular death occurred four to five times more frequently than each of the two non-fatal cardiovascular events.

Unadjusted analyses showed that altitude was associated with each of the cardiovascular outcomes of the study, with the rates of myocardial infarction, stroke and cardiovascular death being 31% (95% CI: 21–40%), 32% (95% CI: 21–41%) and 23% (95% CI: 18–27%) lower among patients living >6000 ft compared with patients residing at or near sea level. These findings were only marginally attenuated in multivariable models that adjusted for an abundance of observed patient characteristics. Additionally adjusting for several laboratory measurements and BMI in the 65% subsample attenuated the associations slightly and widened confidence limits, but the overall results were consistent with multivariable models in the full population. The risk of experiencing any one of the cardiovascular outcomes was 3% (95% CI: 2–4%), 4% (95% CI: 1–6%), 20% (95% CI: 17–24%) and 19% (95% CI: 12–26%) lower in patients residing between 250 and 1999, 2000 and 3999, 4000 and 5999 and ≥6000 ft, respectively, compared with otherwise similar patients who resided at or near sea level.

Overall, we observed 574 063 deaths during follow-up: 257 955 (44.93%) were reported as cardiovascular, 238 852 (41.61%) were non-cardiovascular and in 77 256 patients...
Table 1. Baseline characteristics of study subjects, by elevation group

<table>
<thead>
<tr>
<th>N (%) or mean (± SD)</th>
<th>&lt;250 ft</th>
<th>250–1999 ft</th>
<th>2000–3999 ft</th>
<th>4000–5999 ft</th>
<th>≥6000 ft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects (row %)</td>
<td>3 96 770 (40.3)</td>
<td>5 36 863 (54.5)</td>
<td>27 642 (2.8)</td>
<td>18 634 (1.9)</td>
<td>4 356 (0.4)</td>
</tr>
<tr>
<td>Age, years</td>
<td>62.0 (±15.4)</td>
<td>62.2 (±15.3)</td>
<td>61.6 (±14.8)</td>
<td>60.7 (±15.3)</td>
<td>60.3 (±15.1)</td>
</tr>
<tr>
<td>Male gender</td>
<td>2 13 656 (53.9)</td>
<td>2 88 852 (53.8)</td>
<td>15 145 (54.8)</td>
<td>10 467 (56.2)</td>
<td>2 385 (54.8)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2 27 482 (57.3)</td>
<td>3 67 730 (68.5)</td>
<td>23 622 (85.5)</td>
<td>14 932 (80.1)</td>
<td>3 105 (71.3)</td>
</tr>
<tr>
<td>Black</td>
<td>1 48 739 (37.5)</td>
<td>1 50 368 (28.0)</td>
<td>2085 (7.5)</td>
<td>1206 (6.5)</td>
<td>192 (4.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>18 973 (4.8)</td>
<td>12 612 (2.4)</td>
<td>323 (1.2)</td>
<td>511 (2.7)</td>
<td>69 (1.6)</td>
</tr>
<tr>
<td>Native American</td>
<td>1 576 (0.4)</td>
<td>6153 (1.2)</td>
<td>1612 (5.8)</td>
<td>1985 (10.7)</td>
<td>990 (22.7)</td>
</tr>
<tr>
<td>Medicaid coverage</td>
<td>1 02 637 (25.9)</td>
<td>1 21 727 (22.7)</td>
<td>6632 (24.0)</td>
<td>3729 (20.0)</td>
<td>1006 (23.1)</td>
</tr>
<tr>
<td>Hemodialysis (versus PD)</td>
<td>3 67 650 (92.7)</td>
<td>4 85 720 (90.5)</td>
<td>24 087 (87.1)</td>
<td>16 884 (90.6)</td>
<td>3797 (87.2)</td>
</tr>
</tbody>
</table>

Reported comorbidities

- Hypertension: 3 00 736 (75.8) | 4 18 049 (77.9) | 21 625 (78.2) | 14 564 (78.2) | 3451 (79.2) |
- Heart failure: 1 23 078 (31.0) | 1 73 345 (32.3) | 8090 (29.3) | 4791 (25.7) | 1220 (28.0) |
- ASHD: 95 927 (24.2) | 1 41 995 (26.5) | 6308 (22.8) | 3929 (21.1) | 866 (19.9) |
- Cerebrovascular disease: 34 356 (8.7) | 50 919 (9.5) | 2109 (7.6) | 1306 (7.0) | 326 (7.5) |
- PVD: 54 043 (13.6) | 77 603 (14.5) | 3528 (12.8) | 2215 (11.9) | 609 (14.0) |
- Diabetes mellitus: 1 86 197 (46.9) | 2 67 440 (49.8) | 15 334 (55.5) | 10 245 (55.0) | 2488 (57.1) |
- COPD: 25 010 (6.3) | 44 795 (8.3) | 1975 (7.1) | 1127 (6.5) | 1220 (28.0) |
- Cancer: 20 569 (5.2) | 32 235 (6.0) | 1386 (5.0) | 880 (4.7) | 230 (5.3) |
- Inability to transfer: 6440 (1.6) | 8546 (1.6) | 342 (1.2) | 180 (0.9) | 38 (0.9) |
- Inability to ambulate: 16 913 (4.3) | 23 188 (4.3) | 962 (3.5) | 609 (3.3) | 124 (2.9) |
- Baseline ESA use: 1 16 792 (29.4) | 1 52 788 (28.5) | 6512 (23.6) | 4469 (24.0) | 1033 (23.7) |
- BMI (kg/m²): 27.0 (±7.2) | 27.5 (±7.3) | 27.1 (±6.9) | 26.9 (±6.6) | 26.4 (±6.1) |
- Serum hemoglobin (g/dL): 9.8 (±1.8) | 9.9 (±1.8) | 10.0 (±1.8) | 10.3 (±1.8) | 10.3 (±1.9) |
- eGFR (mL/min/1.73m²): 9.2 (±5.0) | 9.6 (±5.2) | 9.6 (±5.0) | 8.9 (±4.3) | 8.5 (±4.1) |
- Serum albumin (g/dL): 3.2 (±0.7) | 3.2 (±0.7) | 3.1 (±0.7) | 3.2 (±0.7) | 3.1 (±0.7) |

*COPD, chronic obstructive pulmonary disease; ASHD, arteriosclerotic heart disease; PVD, peripheral artery vascular disease; PD, peritoneal dialysis; ESA, erythropoiesis stimulating agent.

With lower incidences of myocardial infarction, stroke, cardiovascular mortality and their composite cardiovascular outcome. Adjusting for demographic characteristics, comorbidities, dialysis modality and biometric measurements did not appreciably alter the crude rate ratios, suggesting a robust association between altitude and these cardiovascular outcomes. The most pronounced relative reduction across altitude strata was observed for myocardial infarction, in which patients living >6000 ft showed a 26% decrease in incidence compared to patients living near sea level.

Our results show an 18% reduced cardiovascular mortality for patients in the highest elevation group compared with those patients living near sea level. This reduction is slightly more accentuated but generally similar to the previously observed 15% rate reduction between the highest and lowest levels of altitude for mortality from any cause in these patients [1]. This finding is not surprising since cardiovascular causes are considered to be responsible for 44% of deaths among dialysis patients and are thus the main driver of overall mortality in dialysis populations [9].

In light of the observation by de Jager et al. [10] that—compared with the general population—dialysis patients experience similar (8- to 9-fold) excess mortality from both cardiovascular and non-cardiovascular causes, we also investigated the association between altitude and non-cardiovascular mortality. In contrast to cardiovascular death, there was no meaningful association between altitude and death from non-cardiovascular causes. The fact that altitude is shown to selectively attenuate the risk of cardiovascular mortality in dialysis patients suggests that there are underlying biological mechanisms that are
activated at higher altitudes to protect these patients from cardiovascular risk. These findings need to be considered with caution, however, and residual confounding remains a possibility [11–13].

Prior studies have highlighted differences by race in the risk of cardiovascular disease in both the US general and dialysis populations [6, 14, 15], although the evidence is mixed in regards to the cardiovascular risk in the Native American population, with studies showing both increased and decreased mortality rates relative to Caucasians depending on the era and region of the study [16, 17]. The observed modification of the associations between altitude and cardiovascular risk for Native Americans relative to Caucasians may suggest presence of genetic dispositions that selectively favor Native Americans living at higher altitude. Further study is warranted to explore the mechanisms behind these observations. From an epidemiological perspective, it is important to discuss the certain scenarios that would render our observations spurious. Firstly, patient selection could have played a role if patients with advanced chronic kidney disease who were at increased cardiovascular risk had opted to move to a lower location prior to start of dialysis or if they had refrained from commencing dialysis when it was deemed necessary. We do not consider this option very plausible. Alternatively, it would be concerning if patients who commenced dialysis at higher altitude were systematically different, especially regarding their cardiovascular risk, compared with patients initiating dialysis at lower altitude. For characteristics that we observed in our cohort study, some comorbid conditions were more prevalent at higher altitude (e.g. diabetes), whereas others were less prevalent (e.g. arteriosclerotic heart disease), with most differences not very pronounced or obvious across altitude strata. In addition, findings from sociodemographics-adjusted models and more comprehensive models that included additional information indicated quite minimal confounding by these disease characteristics. Unobserved confounders may still exist, such as vitamin D concentrations, differences in wasting or certain environmental factors (e.g. ultraviolet light exposure).

From a biological perspective, HIF pathways could be hypothesized to be responsible for the observed selective reduction in cardiovascular mortality compared to non-cardiovascular mortality. HIF-1 is a key mediator of the biological processes involved with adaptation to chronic hypoxia and defense against acute hypoxia and is activated in response to ischemic conditions such as those experienced by persons at high altitudes. HIF-1’s regulation of growth factors, heme oxygenase-1, inducible nitric oxide synthase, and others has been well characterized [18, 19]. It has been suspected that HIF-1α, the oxygen-sensitive subunit of HIF-1, has an indirect effect on the incidence and severity of cardiovascular events in hemodialysis patients possibly through its effect on vascular endothelial growth factor (VEGF), heme oxygenase-1, inducible nitric oxide synthase, and decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians decreased mortality rates relative to Caucasians.
In conclusion, we found a graded reduction in incidence and mortality rates specific to cardiovascular events in dialysis patients residing at higher altitude compared to patients residing near sea level. This observation was only slightly attenuated even after adjusting for a large number of patient characteristics and is consistent with previous studies that have demonstrated the protective effect of altitude on cardiovascular endpoints.

To date, no previous study has examined cardiovascular endpoints in dialysis patients as a function of altitude. Examining, these outcomes are particularly critical for this patient population since cardiovascular mortality in dialysis patients represents 44% of total mortality [9]. Several studies have previously observed that mortality rates for coronary heart disease and cerebrovascular disease, especially for males, decreased with increasing altitude in the general population [34–36]. More recently, a general population study of Swiss adults has shown a similar inverse trend between cardiovascular outcome and altitude. The authors specifically investigated the differences in mortality due to coronary heart disease and stroke for a range of altitudes and ultimately observed a 12% decrease in mortality due to stroke per 1000 m in elevation, which roughly correlates with our results [37]. Also similar to our results of non-fatal myocardial infarction, mortality from CAD was even more reduced at higher altitude, by 22% per 1000 m elevation. As one of the discussants of that article remarked, HIF-1 activation at higher altitude lowers the amount of stored iron as measured by ferritin, which leads to down-regulation of hepcidin and induces ferroportin. Of note, evidence is accumulating that hepcidin is a risk factor for atherosclerosis [38].

Our study is limited by the fact that we cannot directly establish the cause(s) of the observed associations. We did not have access to biological specimens that would have allowed us to quantify specific markers of HIF activation or its downstream effects. There is certainly the possibility that our results could be due to residual confounding by unobserved patient characteristics that are traditional risk factors for cardiovascular events, such as alcohol intake and smoking or environmental factors correlated with altitude. However, we note that our adjusted hazard ratios differed little from our unadjusted estimates. Further research with more detailed clinical data on patients, notably vitamin D levels, serum cholesterol levels, hepcidin levels and iron status parameters, would help refine our understanding of the observed protective effect of altitude on cardiovascular endpoints in dialysis patients [39]. Another limitation is that our findings are primarily driven by Caucasian individuals given the predominance of whites at all altitude strata, and so the generalizability of our results are somewhat compromised. In addition, we were unable to compare our findings with the risk of cardiovascular events in the general population. Data sources providing cause of death for the general public use different methods of ascertainment than the USRDS, a possible source of bias. Finally, information on any differences in case mix beyond demographics is not available. Although the reporting of comorbid conditions using the Medical Evidence Form is of limited quality, any limitations in validity would have to arise from differential biases across altitude, which is unlikely.

In conclusion, we found a graded reduction in incidence and mortality rates specific to cardiovascular events in dialysis patients residing at higher altitude compared to patients residing near sea level. This observation was only slightly attenuated even after adjusting for a large number of patient characteristics and is consistent with previous studies that have demonstrated the protective effect of
HIF-1 activation on the cardiovascular system. We propose that HIF-1 plays an important role in conferring a protective effect on cardiovascular outcomes in dialysis patients.

Supplementary data

Supplementary tables 1 and 2 are available online at http://ndt.oxfordjournals.org

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Access to data statement. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement. Dr W.W. reports having served on advisory boards of Affymax/Takeda, Amgen, Astellas/Fibrogen, Fresenius/Vifor, GlaxoSmithKline and Sandoz/Hexal. He has received unrestricted research support from Fibrogen. Dr M.A.B. has received research support from Amgen, Rockwell Medical and Pfizer. He has sat on advisory boards for Amgen and Pfizer but has not accepted honoraria for these activities. Mr M.H. and Dr J.L. have no competing interests to disclose.

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