Seasonal and Secular Trends of Cardiovascular, Nutritional, and Inflammatory Markers in Patients on Hemodialysis

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Abstract

Background All life on earth has adapted to the effects of changing seasons. The general and ESKD populations exhibit seasonal rhythms in physiology and outcomes. The ESKD population also shows secular trends over calendar time that can convolute the influences of seasonal variations. We conducted an analysis that simultaneously considered both seasonality and calendar time to isolate these trends for cardiovascular, nutrition, and inflammation markers.

Methods We used data from adult patients on hemodialysis (HD) in the United States from 2010 through 2014. An additive model accounted for variations over both calendar time and time on dialysis. Calendar time trends were decomposed into seasonal and secular trends. Bootstrap procedures and likelihood ratio methods tested if seasonal and secular variations exist.

Results We analyzed data from 354,176 patients on HD at 2436 clinics. Patients were 59±6 years old, 57% were men, and 61% had diabetes. Isolated average secular trends showed decreases in pre-HD systolic BP (pre-SBP) of 2.6 mm Hg (95% CI, 2.4 to 2.8) and interdialytic weight gain (IDWG) of 0.35 kg (95% CI, 0.33 to 0.36) yet increases in post-HD weight of 2.76 kg (95% CI, 2.58 to 2.97). We found independent seasonal variations of 3.3 mm Hg (95% CI, 3.1 to 3.5) for pre-SBP, 0.19 kg (95% CI, 0.17 to 0.20) for IDWG, and 0.62 kg (95% CI, 0.46 to 0.79) for post-HD weight as well as 0.12 L (95% CI, 0.11 to 0.14) for ultrafiltration volume, 0.41 ml/kg per hour (95% CI, 0.37 to 0.45) for ultrafiltration rates, and 3.30 (95% CI, 2.90 to 3.77) hospital days per patient year, which were higher in winter versus summer.

Conclusions Patients on HD show marked seasonal variability of key indicators. Secular trends indicate decreasing BP and IDWG and increasing post-HD weight. These methods will be of importance for independently determining seasonal and secular trends in future assessments of population health.

Introduction

The earth’s tilt and spherical shape give rise to seasons. All life on earth has adapted to the effects of changing seasons. Rhythms in normal physiology have been observed to vary by seasons and associate with dietary trends, cardiovascular health, immune function, and mortality rates in the general and ESKD populations (1–6). However, secular trends could potentially confound and convolute seasonal variations previously observed.

The ESKD population has been suggested to exhibit seasonal rhythms in several clinical parameters and morbidity/mortality rates (4,5,7,8). Cardiovascular event rates are higher in patients on hemodialysis (HD) in winter versus summer months and associate with fluctuations in BPs (5,9–11). Interdialytic weight gain (IDWG) is higher in winter as well, suggesting a potential relationship with fluid status and BP (5). The inflammatory status also increases in winter versus summer months as observed through changes in influenza-like illnesses rates, C-reactive protein, and neutrophil-to-lymphocyte ratio (NLR) levels (5,7,12). Moreover, nutritional status of patients with ESKD has seasonal rhythms, with higher albumin levels during winter (5).

Although seasonal rhythms seem to be related to distinct variations in several clinical parameters, trends over time depend on multiple factors, and there is a potential for confounding with dialysis time/vintage and/or secular changes in practice patterns and technology. For instance, all-cause, cardiovascular, and infection-related hospitalization rates have decreased in patients with ESKD over the last decade (13). Concurrently, hospitalizations for fluid overload have
increased as well as incidence of influenza and sepsis (13–15). Hemoglobin (Hgb) levels also had a sharp decrease starting in 2007, secondary to safety signals with use of erythropoietin-stimulating agents to achieve higher Hgb targets (14).

Prior studies of seasonality have not accounted for longitudinal trends over calendar time (secular trends) and dialysis vintage that could confound observations and incorrectly estimate or mask seasonal trends. In this study, we evaluated whether seasonal variations exist in an array of clinical variables accounting for calendar time and dialysis vintage. To reduce potential bias in estimation, we modeled trends over both calendar time and dialysis vintage jointly using an additive model. We hypothesized that seasonal variations would be found in clinical markers of cardiovascular function, nutritional health, and inflammation. We also characterized the profiles of secular trends over time accounting for seasonal variations and dialysis vintage.

Materials and Methods

Study Design

We studied the effects of seasonality and era on clinical and laboratory parameters over 5 years in patients on HD. We simultaneously analyzed seasonal effects and secular changes using nonparametric smoothing spline models to fit data and calculate the magnitude of both secular changes and concurrent seasonal variations. The protocol was reviewed by the New England Independent Review Board (NEIRB), which determined that this analysis of anonymized data was exempt and did not require consent (NEIRB #5723; Needham Heights, MA). Analysis was performed in adherence with the Declaration of Helsinki.

Setting and Participants

We used existing data previously captured during HD performed at Fresenius Kidney Care outpatient clinics in the United States. The data were collected in an anonymized manner from the Fresenius Medical Care North America Knowledge Center Data Warehouse, which is a private electronic health record database.

We included data from all adult patients (age ≥18 years old) treated with HD anytime during the study period of January 1, 2010 to December 31, 2014. This included data from patients being actively treated by HD before and after January 1, 2010 as well as patients who initiated HD anytime during the study period. We only excluded data from pediatric patients (age <18 years old) and patients with no HD treatment data available in any month.

Patients who temporarily discontinued outpatient HD (e.g., switch to peritoneal dialysis, switch to home HD, or hospitalization with inpatient HD) or permanently discontinued dialysis (e.g., recovery of renal function, transplant, withdrawal from dialysis, or death) had data included for every month that there was one or more treatment records available. The follow-up period started on January 1, 2010 for patients who were actively treated by HD at the beginning of the study period or at the first date of HD for patients who initiated HD during the study period.

Variables

We assessed variables related to cardiovascular function, nutrition, and inflammation. Cardiovascular parameters included pre-HD systolic BP (SBP) and pre-HD diastolic BP (DBP). Nutritional parameters included albumin levels, creatinine levels, body mass index (BMI), Hgb, pre-HD and post-HD weights, IDWG, and IDWG as a percentage of the post-HD weight (IDWG percentage). Parameters related to inflammation included white blood cell (WBC) counts, NLR, and pre-HD and post-HD body temperatures. We also assessed exploratory variables for ultrafiltration volume (UFV), ultrafiltration rate (UFR), and hospital admission/day rates. Variables with more than one value available per month were averaged monthly.

The effects of era were defined as secular changes in population average monthly values from January 2010 through the 5-year follow-up period. Seasonal variations in average monthly values were defined as winter (December through February), spring (March through May), summer (June through August), and autumn (September through November).

Analyses of Descriptive Data

We tabulated the baseline descriptive statistics on patient characteristics for categorical variables and mean values over the 5-year observational period for continuous variables.

### Table 1. Patient characteristics

| Parameter           | Mean (SD), Percentage, or Median (IQR)* |
|---------------------|----------------------------------------|
| Age, yr             | 58.59 (15.34)                          |
| Men, %              | 56.7                                   |
| White race, %       | 63.2                                   |
| Hispanic ethnicity, %| 13.9                                   |
| HD vintage, yr      | 2.75 (4.17)*                           |
| Body mass index, kg/m²| 29.37 (11.66)                         |
| Diabetes, %         | 61.2                                   |
| Pre-HD SBP, mm Hg   | 148.62 (21.30)                         |
| Pre-HD DBP, mm Hg   | 77.20 (12.81)                          |
| Pre-HD weight, kg   | 83.92 (23.48)                          |
| Post-HD weight, kg  | 81.58 (23.08)                          |
| Pre-HD temperature, °C| 36.34 (0.30)                          |
| Post-HD temperature, °C| 36.42 (0.28)                          |
| IDWG, kg            | 2.55 (1.15)                            |
| IDWG as percentage of post-HD weight | 3.18 (1.28) |
| Albumin, g/dl       | 3.86 (0.42)                            |
| Creatinine, mg/dl   | 8.30 (3.08)                            |
| Hemoglobin, g/dl    | 11.00 (1.17)                           |
| White blood cell count, per 10⁹/L | 6.93 (2.70) |
| Neutrophil-to-lymphocyte ratio | 4.13 (3.34) |

*Median (IQR): interquartile range; HD, hemodialysis; SBP, systolic BP; DBP, diastolic BP; IDWG, interdialytic weight gain.

*Descriptive statistics represent the baseline characteristics for categorical variables and mean values over the 5-year observational period for continuous variables.
variables are reported as mean and SD. Categorical variables are reported as counts and proportions.

Analyses of Secular and Seasonal Trends

To account for variations over both calendar time and dialysis vintage, we consider an additive smoothing spline model with two components: a function for era/secular trends over calendar time and a function for trend over time on HD. Specifically, we consider the model

\[ y(s,t) = f(s) + g(t) + \varepsilon(s,t), \]

where \( y(s,t) \) is the observation of a variable at calendar time \( s \) and time on HD \( t \), \( f(s) \) corresponds to the trend over calendar time, \( g(t) \) corresponds to the trend over time on HD, and \( \varepsilon(s,t) \) values are random errors that are assumed to be independent and identically distributed. For identifiability, we assume that the integration of \( g(t) \) over its domain equals zero. For flexibility, we model both functions \( f \) and \( g \) using splines. Specifically, we model the function \( f \) using a linear-periodic spline, which decomposes the trend over calendar time into two components: seasonal rhythm and secular trend (16). We model the function over time on HD \( g \) using a cubic spline (16). Even though the trend over time on HD is interesting, we present the estimates and Bayesian confidence intervals (16) for seasonal variations and secular trends (i.e., two components in the function \( f \)) to narrow the scope of this investigation.

Analyses were conducted with R version 3.4.4 (17) using package assist (18). We tested the significance of seasonal variations using both \( F \) and likelihood ratio test statistics, with \( P \) values calculated on the basis of 500 bootstrap samples. The \( P \) values for the hypothesis of nonzero seasonal trend

![Figure 1. Decreasing secular trends in Pre-HD SBP with seasonal variations highest in winter and lowest in summer over calendar time. The blue line in the top graph represents the combined secular (long-term) and seasonal trend fitted to the real data. The red line in the middle graph shows the long-term component with 95% Bayesian confidence intervals in gray. The red line in the bottom graph displays the seasonal component with 95% Bayesian confidence intervals in gray.](image-url)
for all variables are $P<0.001$. Therefore, all variables have statistically significant trends. We computed the magnitudes of secular and seasonal trends as the difference between maximum and minimum values of spline estimates and 95% confidence intervals (95% CIs) on the basis of 500 bootstrap samples.

**Results**

**Setting**

We assessed data from 354,176 adult patients on HD treated at 2436 outpatient clinics in the United States from 2010 through 2014.

**Patient Characteristics**

Patients were mean age of 59±15 years old, 57% were men, 63% were white race, 14% were Hispanic, 61% had diabetes, and mean dialysis vintage was 3.87 years (Table 1).

**Secular Trends and Seasonal Variations in Cardiovascular Parameters**

Raw secular trends showed a gradual decrease in pre-HD SBP/DBP over the 5 years, with remarkable variations between seasons (Figure 1, Supplemental Figure 1). Isolation of distinct secular trends apart from seasonal trends identified pre-HD SBP/DBP has decreased in a relatively linear manner from 2010 through 2014. Segregation of distinct seasonal trends revealed consistent patterns of seasonal variations with higher pre-HD SBP/DBP levels in winter versus summer. The overall influence of isolated trends reveals a mean secular decrease in pre-HD SBP of $-2.6$ mm Hg (95% CI, $-2.4$ to $-2.8$) over the 5 years, with mean seasonal variations in pre-HD SBP of $3.3$ mm Hg (95% CI, 3.1 to 3.5) (Table 2). Consistent findings were observed for pre-HD DBP.

**Secular Trends and Seasonal Variations in Inflammatory Measures**

Raw trends over time in NLR showed fluctuating increases over the 5 years (Figure 2), and WBC counts showed a decrease starting in 2012 that increased by the end of 2014 (Supplemental Figure 2). The segregation of trends found similar secular patterns in NLR and WBC counts. Both NLR and WBC counts varied seasonally, with peak levels in winter and nadir in summer. The overall effect of isolated trends is detailed in Table 2.

Trends in raw data showed that pre-HD/post-HD body temperatures had no clear secular changes yet small seasonal variations (Figure 3, Supplemental Figure 3). Separation of trends found that pre-HD/post-HD body temperatures decreased slightly from 2010 through 2014. Pre-HD body temperature increased over summer and decreased over winter, with post-HD body temperature displaying inverse seasonal variations. The overall effect of separated trends is shown in Table 2.

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**Table 2. Magnitude of secular and seasonal trends and confidence intervals**

| Changes/Variations | Mean Patients per Month | Minimum Patients among All Months | Secular Trend | Seasonal Trend |
|--------------------|------------------------|----------------------------------|---------------|---------------|
| **Cardiovascular parameters** | | | | |
| Pre-HD DBP, mm Hg | 103,129 | 81,324 | -1.0 (-0.9 to -1.2) | 1.6 (1.4 to 1.7) |
| Pre-HD SBP, mm Hg | 103,137 | 81,328 | -2.6 (-2.4 to -2.8) | 3.3 (3.1 to 3.5) |
| **Inflammatory parameters** | | | | |
| Post-HD temperature, °C | 103,965 | 81,926 | -0.052 (-0.050 to -0.056) | 0.073 (0.070 to 0.076) |
| Pre-HD temperature, °C | 103,136 | 81,324 | 0.046 (0.042 to 0.050) | 0.068 (0.064 to 0.072) |
| White blood cell count, per 10⁶/L | 90,242 | 72,329 | 0.51 (0.48 to 0.54) | 0.25 (0.23 to 0.29) |
| Neutrophil-to-lymphocyte ratio | 52,944 | 30,657 | 0.465 (0.430 to 0.506) | 0.334 (0.299 to 0.374) |
| **Nutritional parameters** | | | | |
| IDWG as percentage of post-HD weight | 102,299 | 80,130 | -0.51 (-0.50 to -0.53) | 0.22 (0.21 to 0.24) |
| IDWG, kg | 102,400 | 80,208 | -0.35 (-0.33 to -0.36) | 0.19 (0.17 to 0.20) |
| Pre-HD weight, kg | 103,137 | 81,327 | 2.57 (2.39 to 2.79) | 0.70 (0.55 to 0.87) |
| Post-HD weight, kg | 103,967 | 81,928 | 2.76 (2.58 to 2.97) | 0.62 (0.46 to 0.79) |
| Albumin, g/dl | 92,516 | 74,475 | -0.135 (-0.130 to -0.142) | 0.087 (0.082 to 0.092) |
| Body mass index, kg/m² | 101,980 | 80,190 | 0.69 (0.63 to 0.76) | 0.22 (0.17 to 0.29) |
| Creatinine, mg/dl | 91,543 | 73,617 | 2.57 (2.39 to 2.79) | 0.70 (0.55 to 0.87) |
| Hemoglobin, g/dl | 98,832 | 78,354 | -0.86 (-0.84 to -0.87) | 0.17 (0.15 to 0.18) |
| **Ultrafiltration parameters** | | | | |
| ULFV, L | 103,076 | 81,281 | -0.32 (-0.30 to -0.33) | 0.12 (0.11 to 0.14) |
| UFR, ml/kg per h | 102,862 | 81,128 | -1.50 (-1.45 to -1.55) | 0.41 (0.37 to 0.45) |
| **Hospitalization counts** | | | | |
| Hospital admissions, PPY | 104,658 | 82,530 | -0.62 (-0.56 to -0.68) | 0.42 (0.37 to 0.47) |
| Hospital days, PPY | 12,977 | 11,472 | -4.02 (-3.61 to -4.48) | 3.30 (2.90 to 3.77) |

HD, hemodialysis; DBP, diastolic BP; SBP, systolic BP; IDWG, interdialytic weight gain; ULF, ultrafiltration volume; UFR, ultrafiltration rate; PPY, per patient year.
Secular Trends and Seasonal Variations in Nutrition Measures

Trends in raw data for IDWG and IDWG as a percentage of the post-HD weight showed small gradual decreases from 2010 through 2014, with variations between seasons (Figure 4, Supplemental Figure 4). Isolation of trends found small linear secular decreases in IDWG along with seasonal variations. The overall influence of separated secular trends was a mean decrease in IDWG of $-0.35 \text{ kg (95\% CI, } -0.33 \text{ to } -0.36)$ along with mean seasonal variations of 0.19 kg (95\% CI, 0.17 to 0.20). Consistent findings were seen for IDWG as a percentage of the post-HD weight (Table 2).

Trends over time for pre-HD/post-HD weight and BMI included relatively linear increases over the study period (Figure 5, Supplemental Figures 5 and 6). Segregation of trends revealed pronounced linear secular increases in weight and BMI from 2010 to 2013, which then became relatively stable through 2014; there were small yet remarkable seasonal variations for decreased weight and BMI in summer versus winter. The overall effects of separated trends found a mean secular increase in post-HD weight of 2.76 kg (95\% CI, 2.58 to 2.97), with mean seasonal variations of 0.62 kg (95\% CI, 0.46 to 0.79). Findings for pre-HD weight and BMI exhibited consistent trends (Table 2).

Trends in raw data for albumin levels showed an inverse U-shaped secular trend from 2010 through 2014 (Supplemental Figure 7), whereas creatinine levels had slight decreases from 2010 to 2011 that increased and became stable in 2012 through 2014 (Supplemental Figure 8). Separation of trends identified consistent secular trends for albumin coinciding with
small seasonal variations that were lower in summer versus winter. Isolation of trends for creatinine values showed similar secular changes to raw trends, with seasonal variations for higher levels in summer compared with winter. The overall effect of separated trends is presented in Table 2.

Raw trends in Hgb levels showed predominant decreases in late 2011 with no apparent seasonal differences (Supplemental Figure 9). Segregation of trends showed consistent secular trends in Hgb levels and revealed small, consistent seasonal variations, with lowest levels in late spring and highest levels in late fall. The overall effect of segregated trends is shown in Table 2.

**Secular Trends and Seasonal Variations in Ultrafiltration**

Trends in raw data for UFV and UFR showed steady decreases over time, with fluctuations across seasons (Figures 6 and 7). Separation of trends showed linear secular decreases from 2010 through 2014, with seasonal variations with decreases in summer versus winter months. The overall influence of separated secular trends was a mean decrease in UFR of $-1.50$ ml/kg per hour (95% CI, $-1.45$ to $-1.55$), with mean seasonal variations of $0.41$ ml/kg per hour (95% CI, $0.37$ to $0.45$); consistent trends were found for UFV (Table 2).

**Secular Trends and Seasonal Variations in Hospitalizations**

Raw trends for hospital admissions and days per patient year (PPY) showed secular decreases with seasonal variations (Figure 8, Supplemental Figure 10). Isolation of secular trends found that hospitalization rates slowly decreased from 2010 to 2011, more rapidly decreased from 2012 to

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**Figure 3.** Decreasing secular trends in Post-HD Temperature with seasonal variations highest in winter and lowest in summer over calendar time. The blue line in the top graph represents the combined secular (long-term) and seasonal trend fitted to the real data. The red line in the middle graph shows the long-term component with 95% Bayesian confidence intervals in gray. The red line in the bottom graph displays the seasonal component with 95% Bayesian confidence intervals in gray.
2013, and slightly increased in 2014. Remarkable seasonal variations were observed in hospitalization rates, being highest in winter compared with summer. The overall effect of segregated secular trends found mean decreases in hospital days of -2.40 days PPY (95% CI, -2.36 to -2.44), with seasonal variations of 3.30 days PPY (95% CI, 2.90 to 3.77); consistent patterns were observed for hospital admissions (Table 2).

**Discussion**

Our findings have established patterns of physiologic rhythms across seasons in patients on HD independent of secular changes over calendar time and changes with dialysis time/vintage. Patients on HD seemed to, on average, exhibit a diminished cardiovascular health, with more inflammation in winter months compared with summer months. Although most nutritional markers followed consistent seasonal patterns, albumin, creatinine, and Hgb levels increased in winter months. Hospitalization rates had strong seasonal variations, accounting for about 3 more days hospitalized PPY in the winter versus summer months. Many observed seasonal changes seem meaningful. Seasonality may not be accounted for in current care models, but it should possibly be considered by physicians, providers, and payors. We have also established secular trends in health markers over calendar time, which are independent of seasonal and dialysis time changes. Patients on HD have experienced improvements in cardiovascular health markers and hospitalization rates over calendar time yet worsened
nutrition and inflammation. Practice patterns may be driving some of these findings and are important to recognize.

SBP, DBP, NLR, WBC, albumin, creatinine, Hgb, IDWG, pre-HD/post-HD weight, body composition, UFR, and hospitalization rates have been suggested to have seasonal rhythms in the HD population, many irrespective of climate zone (5,7–9,11,19–21). However, some select reports have not shown significant seasonal variations in BP, albumin, and Hgb levels (8,22). By isolating the seasonal variations in a population in the Northern Hemisphere, we found results consistent with the majority of the literature yet more clearly marked and persistent in magnitude. To the best of our knowledge, the application of the flexible nonparametric method to separate seasonal and secular changes is new in nephrology.

We observed independent seasonal fluctuations of about 3 mm Hg for SBP, 1.5 mm Hg for DBP, 0.3 for NLR, 0.25 per 10^9/L for WBC counts, 0.1°C for post-HD body temperature, 0.1 g/dl for albumin, 0.25 mg/dl for creatinine, 0.2 g/dl for Hgb, 0.7 kg for pre-HD weight, 0.6 kg for post-HD weight, 0.2 kg for IDWG, 0.2 kg/m^2 for BMI, 0.1 L for UFV, 0.4 ml/kg per hour for UFR, 0.4 PPY for hospital admissions, and 3.3 PPY for hospital days, which were all highest in winter and lowest in summer. This adds validity to previous findings, and it suggests that seasonality might be considered in the management of patients on HD, in particular for BP and weight/fluid control, which seem to exhibit clinically meaningful fluctuations across the seasons. Given that we found that all-cause hospital admission and day rates were substantially higher in winter months and given that others have found similar trends in all-cause hospital and cardiovascular event rates in the HD population (5,8,9), further research may be warranted to assess if there is a potential relationship between seasonal
changes in BP, vascular tone, fluid retention, and heart failure (7,23,24). Influenza/respiratory infection rates in patients with ESKD also exhibit seasonal variations that peak in the winter months and may be related to changes in the cardiovascular and inflammation markers that we observed (12). In the general population, associations between cardiovascular events and respiratory infections are postulated to occur through coagulation/immune system activation and/or endothelium dysfunction (25–28). Despite this, systemic and catheter-related infections seem to exhibit opposite seasonal fluctuations, being highest in the summer months (29).

Taken together, the majority of signals suggest there might be a more compromised health state in patients in the winter versus summer, with exception of increases in albumin, creatinine, and Hgb levels in the winter months. These observations may be driven by higher food intake in temperate climates during the winter months that include iron-rich meats. The findings related to markers of fluid regulation seem to suggest that it is important to more frequently assess dry weight in the winter months to avoid inadvertent fluid overload. Trends for UFV and UFR being increased in the winter months, coinciding with increased weights and IDWG, might be representative of clinical responses to patients gaining body fluid, although further studies are required to test these relationships. Supporting this hypothesis, another study previously showed higher UFR in the winter months with consistent magnitude and found that a higher proportion of patients used UFR rates >13 ml/kg per hour in the winter (21). Patients on HD also tend to experience decreases in lean body mass and increases in fat mass in the winter months (20), which might make fluid...

Figure 6. | Decreasing secular trends in ultrafiltration volume (UFV) with seasonal variations highest in winter and lowest in summer over calendar time. The blue line in the top graph represents the combined secular (long-term) and seasonal trend fitted to the real data. The red line in the middle graph shows the long-term component with 95% Bayesian confidence intervals in gray. The red line in the bottom graph displays the seasonal component with 95% Bayesian confidence intervals in gray.
management more challenging. Use of bioimpedance might be optimal for the establishment of dry weight targets in differing seasons, but further research is needed.

The joint assessment of secular trends most remarkably shows that BPs, IDWG, UFV, UFR, and hospitalization rates have been decreasing, whereas inflammation and post-HD weight have been increasing over calendar time. It is possible that secular changes in UFV, UFR, IDWG, and post-HD weight are associated with unfavorable practice patterns in the determination of dry weight and/or targets for fluid removal. Trends in UFV and UFR are possibly related to higher UFRs being identified to be associated with higher rates of morbidities and mortality (30–32) and regulatory discussions to have UFR added to the pay for performance Quality Incentive Program during this timeframe (33). Secular trends indicate that practice patterns for BP management steadily improved as seen by decreases in mean levels by >2.5 mm Hg over the 5-year period. Despite the expectation that increases in IDWG would associate negatively with BP control, this was not observed in the isolated trends. Also, we found that hospitalization rates have been generally decreasing over time, consistent with trends in US Renal Data System (USRDS) data (14), and these observations could possibly be related to decreasing BPs and UFR. However, further studies would be needed to determine associations.

Although this longitudinal study over 5 years in a nationally representative sample has many strengths, it has some limitations. The mean age of our population, including incident and prevalent patients on HD, is slightly younger than estimates by the USRDS report of point prevalent assessments in 2010 for incident (mean age of 63 years old) and prevalent (mean age of 61 years old) patients.

Figure 7. Decreasing secular trends in ultrafiltration rate (UFR) with seasonal variations highest in winter and lowest in summer over calendar time. The blue line in the top graph represents the combined secular (long-term) and seasonal trend fitted to the real data. The red line in the middle graph shows the long-term component with 95% Bayesian confidence intervals in gray. The red line in the bottom graph displays the seasonal component with 95% Bayesian confidence intervals in gray.
However, given that the mean age of transplant recipients was 52 years old per the USRDS report (34), the age in our cohort of patients may be more reflective of the overall ESKD population, including those who transitioned from HD and received a transplant during the 5 years of the study. Seasonal and secular trends were identified, but we did not conduct any multivariate analyses to provide evidence of clinical parameters being associated with outcomes. The study is generalizable specifically to the HD population in North America. Geographical differences within North America were not evaluated. Also, we did not consider changes in medication use across the seasons, which may have had the potential to influence changes in BP’s and Hgb levels. We did not have data available on dietary protein intake, which could potentially mask the changes in albumin levels in the winter months. This study used data from outpatient medical records and did not include data during hospitalizations. Therefore, these seasonal trends may not represent the full spectrum of fluctuations given that physiologic disturbances might be the greatest during hospitalization events. Furthermore, we did not consider changes in methods for laboratory collection and assays, and secular trends of laboratory variables may be in part representative of laboratory methods. Lastly, we did not have objective measures of fluid status (e.g., bioimpedance) available in the United States, rendering our reasoning regarding secular and seasonal dynamics of fluid status speculative (35). Repeating the analysis in HD populations that undergo routine bioimpedance measurements (36) would shed light on secular and seasonal trends of fluid status.
In conclusion, we found that the changing of the seasons brings about clinically meaningful changes in the physiology of patients on HD that are independent of dialysis vintage and secular changes due to practice patterns and technologies. The winter months are associated with diminished cardiovascular and nutritional health states, a higher level of inflammation, and higher hospitalization rates. Although further research is needed to provide evidence of associations in individual clinical parameters on outcomes, seasonal trends may be important to consider in assessments of population health.

**Author contributions**

Z. Terner, L.A. Usvyat, P. Kotanko, and Y. Wang conceptualized the study; Z. Terner, L.A. Usvyat, and Y. Wang were responsible for data collection and formal analysis; Z. Terner, A. Long, L.A. Usvyat, and Y. Wang were responsible for validation and visualization; Z. Terner, A. Long, M. Reviriego-Mendoza, J.W. Larkin, L.A. Usvyat, P. Kotanko, F.W. Maddux, and Y. Wang were responsible for investigation and methodology, and reviewed and edited the manuscript; and Z. Terner, A. Long, M. Reviriego-Mendoza, and J.W. Larkin were responsible for project administration and writing the original manuscript.

**Disclosures**

Fresenius Medical Care provided the deidentified data used for this study and infrastructural support for the management of the study data, analysis design, and composition of this manuscript. A. Long, M. Reviriego-Mendoza, J. Larkin, L. Usvyat, and F. Maddux are employees of Fresenius Medical Care in the Medical Office. L. Usvyat, P. Kotanko, and F. Maddux have shares in ownership in Fresenius Medical Care. P. Kotanko is an employee of Renal Research Institute, a wholly owned subsidiary of Fresenius Medical Care. P. Kotanko receives honoraria from Up-To-Date and is on the Editorial Boards of *Blood Purification* and *Kidney and Blood Pressure Research*. F. Maddux has directorships in the American National Bank & Trust and is chairman of Pacific Care Renal Foundation 501(c)(3) nonprofit. Z. Terner and Y. Wang declare no relevant conflicts of interest.

**Supplemental Material**

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000352019/-/DCSupplemental.

Supplemental Figure 1. Trends of prehemodialysis diastolic BP over calendar time.

Supplemental Figure 2. Trends of white blood cell count over calendar time.

Supplemental Figure 3. Trends of prehemodialysis temperature over calendar time.

Supplemental Figure 4. Trends of interdialytic weight gain as percentage of posthemodialysis weight over calendar time.

Supplemental Figure 5. Trends of prehemodialysis weight over calendar time.

Supplemental Figure 6. Trends of body mass index over calendar time.

Supplemental Figure 7. Trends of albumin over calendar time.

Supplemental Figure 8. Trends of creatinine over calendar time.

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