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Abstract

Seasons and climate influence the regulation of blood pressure (BP) in the general population and in hemodialysis patients. It is unknown if this phenomenon varies across the world. Our objective was to estimate BP seasonality in hemodialysis patients from different geographical locations. Patients from 7 European countries (Spain, Italy, France, Belgium, Germany, United Kingdom, Sweden) participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) on years 2007-2011 were studied. Factors influencing pre- and post-dialysis systolic (SBP) and diastolic BP (DBP) levels were analyzed by mixed models. There were 9655 patients (median age 68; 59% male) from 263 facilities, seen every four months during a median duration of 1.3 year. Pre- and post-dialysis SBP increased by a mean estimate and 95% confidence interval of 5.1 [3.7 ; 6.4] and 4.4 [2.9 ; 5.9] mmHg for each 10°-increase in latitude (1111km to the North). In the longitudinal analysis, pre-dialysis SBP was lower in summer and higher in winter (difference: 1.7 [1.3 ; 2.2] mmHg), with greater differences in southern locations ($P_{interaction}$=0.04). Pre-dialysis SBP was inversely associated with outdoor temperature (-0.8 [-1.0 ; -0.5] mmHg/7.2°C), with steeper slopes in southern locations ($P_{interaction}$=0.005). Results were similar for pre-dialysis DBP. In conclusion, there is a geographical and seasonal gradient of blood pressure in European hemodialysis patients. There is a need to consider these effects when evaluating and treating blood pressure in this population and potentially in others.

keywords: renal dialysis, blood pressure, seasons, weather, geography, longitudinal studies

INTRODUCTION

Cardiovascular diseases are the main cause of mortality worldwide and their impact is increasing.[1] While age-specific cardiovascular mortality rates decreased in the past decades, the number of cases is increasing as a consequence of population growth and aging.[1] Hypertension is a major cause of cardiovascular diseases and its treatment remains a challenge for modern medicine.[2] Blood pressure (BP) level is conditioned by genetic as well as environmental factors and follows cyclic patterns of various periods corresponding to days (circadian rhythm) and years (seasonal cycle).[3] These patterns are clinically important as they may interfere with the diagnosis of hypertension and may have utility as indicators of a patient's cardiovascular status. In addition, cyclic patterns are likely to affect the actual cardiovascular risk that patients are exposed to.

Hypertension is very common in hemodialysis (HD) patients, in whom the prevalence often exceeds 90% at the moment of dialysis initiation.[4] In this population, BP level is closely monitored and adjusted mainly through correction of volume overload and use of BP-lowering medications. Still, analyzing change in BP over a 4-year period, we observed a clear seasonal pattern with higher BP in winter and lower BP in summer.[5] This phenomenon was later confirmed in other studies across the world, but not all.[6–11] The seasonal change in BP is correlated with several climatic parameters namely external temperature, humidity, rainfall and daylight span, suggesting that BP level and seasonality would vary across locations with different climates.[5,7,12] There are supportive results from the general population, in whom geographical gradients in BP and hypertension were observed (higher BP in populations closer to the poles).[13,14] Across independent samples from the general population across the world, BP seasonality was reported to follow a geographic trend.[15] However, it is not known if such a geographic trend can be observed for within-patient BP seasonal change in HD patients. The presence of seasonal variations in this closely monitored population would confirm a strong influence of external factors on BP levels.

The objectives of our study were to assess seasonality (effect of season or climate exposure) and the influence of location (country or latitude) on pre- and post-dialysis BP level in HD patients, as well as their interaction. We analyzed data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to answer these questions. The DOPPS is a longitudinal observational study designed to describe dialysis practice and patient characteristics and outcome across the world, using nationally representative samples of HD facilities and patients.[16,17] The study of the European subset is the focus of a collaboration entitled EURODOPPS, between the DOPPS and the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA). EURODOPPS consists in longitudinal data from a large population of HD patients living in a wide geographical area with different climates.

METHODS

Study population

The DOPPS is an international prospective study of adult HD patients. This study considered prevalent HD patients (dialysis vintage ≥ 6 months) from 7 European countries (Spain, Italy, France, Belgium, Germany, United Kingdom, Sweden) participating in DOPPS phases 3 and 4 (2005-2011). Study approval was obtained by a central institutional review board and local ethics committees. Informed patient consent was obtained in accordance with local requirements.

An average of 30 patients were randomly enrolled from dialysis facilities treating 20 patients or more, randomly selected by strata of region and facility type (dialysis organization size, rural/urban, free-standing/hospital-based) according to the frequency of facilities within each stratum. An algorithm was developed to randomly select 20 to 40 prevalent patients by facility, depending on facility size. Replenishment strategies were used during follow-up: patients who died or departed the facility were replaced on the facility's anniversary of study start (DOPPS 3) or every four months (DOPPS 4) via random selection among new patients. Case-mix details and comorbidities were collected at study entry. Every four months, laboratory values, BP, weight, dialysis prescription and BP-lowering medications were extracted from patient records. Pre- and post-dialysis systolic BP (SBP) and diastolic BP (DBP) were measured immediately before and after the dialysis session preferably in sitting position by trained professionals (nurses or nephrologists). BP measurement was performed according to local clinical practice. Intradialytic weight loss was calculated as the difference between pre- and post-dialysis weights, expressed in percent of post-dialysis weight. Although re-sampling of patients across phases could occur, populations or facilities from different phases were considered independent. We defined baseline as the first observation of initially sampled patients and replenishment patients from each facility and phase.

Geographical and seasonal exposures

Meteorological records over the years 2005-2011 were obtained from the national weather institutes of Belgium, France, and United Kingdom, the Global Historical Climatology Network Monthly and Daily Databases and the European Climate Assessment & Dataset of Monthly Indices.[18–25] Monthly mean of daily minimum, maximum and mean outdoor temperature, monthly cumulative sunshine duration and monthly cumulative rainfall (normalized by square-root transformation) were available for all seven countries. Monthly mean of daily mean humidity was available in Belgium, Germany and Spain. Monthly mean of daily maximum wind speed (normalized by logarithm transformation) was available in France, Germany and Spain. Monthly mean of daily mean atmospheric pressure was available in Belgium, Germany, Spain and Sweden. Dialysis units were matched to the closest meteorological station based on geographical coordinates, and climate records were matched to clinical observations based on the month of the year.

Geographical exposure of patients was defined as the country of the dialysis unit or the latitude of the matched meteorological station. Latitudes are set to 0° at the equator and 90° at the poles. We considered an increase in latitude of 10° (i.e. 1111km to the North in the Northern Hemisphere) as the unit of change. Exposure to seasons was based on the month of observation as: Winter (December, January and February), Spring (March, April and May), Summer (June, July and August), and Autumn (September, October, November).

Statistical analysis

Our objective was to test the association of seasonality and location (and their interaction) with pre- and post-dialysis BP level. The dataset consisted of repeated measures of BP nested within patients and dialysis facilities. We modeled BP level using mixed models with seasonality (season or climate), location (country or latitude) and their interaction seasonality×location as fixed effects. The hierarchical structure was accounted for by allowing random intercepts at the patient and facility levels. The DOPPS phase, time from the start of the phase, and the interactions time×phase, time×country, time×country×phase were included to control for differences in baseline BP level and longitudinal trends in BP ("unadjusted model"). The adjusted model additionally included baseline patient characteristics (age, gender, dialysis vintage, body mass index (BMI), smoking, comorbidities) and baseline dialysis prescription (vascular access, blood flow, weekly hours of dialysis, dialysate sodium) as fixed effects. Models of BP were not adjusted for diagnosis of hypertension and use of antihypertensive therapies at baseline. Indeed, we were interested in BP estimates irrespective of the prevalence of hypertension. Concerning antihypertensive therapies, although it would have been interesting to control for the BP-lowering effect, we observed that the number of medication types was in fact associated with higher blood pressure (*data not shown*), highlighting selection bias rather than treatment effect.

Stratified analyses were performed to test the robustness of pre-dialysis SBP results from the adjusted model in relevant subgroups (gender, age, baseline diagnosis of hypertension, number of BP-lowering therapies, dialysis duration and dialysate sodium concentration, mean SBP during follow-up, and tertiles of intradialytic weight loss and post-dialysis BMI).

Results are expressed as mean ± standard deviation (SD), median and interquartile range (IQR) and estimates and 95% confidence intervals [CI]. An alpha level of 0.05 was used for all statistical tests and all P-values are two-sided. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

The study included 9655 patients and over 50 000 observations (Figure S1). The median follow-up was 1.3 (0.7 ; 2.3) years and there was an average of 5.4 ± 2.5 observations per patient. Patients were dialyzed in 263 facilities corresponding to 121 meteorological stations across 7 European countries (figure 1A). Patients from different countries displayed differences in baseline characteristics, including pre-dialysis and post-dialysis BP (table 1). In mixed models, BP level was significantly associated with countries or latitude, in the way that patients from northern locations had higher pre- and post-dialysis BP (figure 1B). For each 10°-increase in latitude, pre-dialysis SBP and DBP increased by 5.1 [3.7 ; 6.4] and 1.7 [0.8 ; 2.6] mmHg. Adjusting on patients and dialysis characteristics did not affect results. In Germany, SBP was lower than expected based on its northern location (observed, 133 [131 ; 135] mmHg; estimated at a latitude of 51°, 139 [138 ; 140] mmHg).

Pre-dialysis BP was significantly associated with seasons, while post-dialysis BP was not (figure 2A and 2B). On average, pre-dialysis SBP was 1.7 [1.3 ; 2.2] mmHg lower in summer compared to winter and for pre-dialysis DBP, the difference was of 0.8 [0.5 ; 1.0] mmHg. The seasonal difference in pre-dialysis SBP differed among countries (figure 2C, $P<0.001$). The effect was the highest in Italy and lowest in Belgium, where it was null. The seasonal effect was attenuated in northern locations, as indicated by the significant interaction of season with latitude (table 2, figure 2C). Results were similar after adjusting for patient and dialysis characteristics (table S1).

All climate parameters varied with seasons and countries (table S2). Pre-dialysis SBP was closely and inversely related to outdoor temperature with a lower effect in the north (figure 3, table 2). Accounting for patient and dialysis characteristics, the average difference per 10°C was the greatest in United Kingdom (-2.1 mmHg), but taking into account the temperature range, the greatest difference was observed in Italy (-3.9 mmHg for a change from the 10^{th} to the 90^{th} percentile), figure 3. Results were similar with minimum and maximum outdoor temperatures (*data not shown*). Sunshine duration was similarly associated with lower pre-dialysis SBP, although to a lower extent (table 2). In contrast, we did not observe any association between post-dialysis SBP and seasons, outdoor temperature or sunshine duration (*data not shown*), suggesting that the dialysis-induced modifications overcome any other influential factors of BP tested in the present study. Pre-dialysis SBP was associated with wind speed and rainfall in a latitude-dependent manner (table 2). Greater rainfall was associated with lower pre-dialysis SBP in northern locations and higher SBP in southern places. While wind speed was not significantly associated with SBP at an average European latitude (50°), greater wind speed was significantly associated with higher pre-dialysis SBP in the south. Pre-dialysis SBP was higher in humid periods; it was not associated with atmospheric pressure (table 2). Results were globally similar with DBP (table S1).

In subgroup analyses, we observed that the rise in pre-dialysis SBP from Summer to Winter was greater in female patients (figure 4). It was also greater in patients without hypertension, with lower mean follow-up SBP or at times where fewer BP-lowering drugs were prescribed (figure 4). The seasonal change was greater when larger intradialytic weight loss (≥ 2.5%) was reported. In contrast, longer dialysis sessions (> 12 h/week) were associated with smaller BP seasonality. The seasonal change was not apparently affected by age, BMI or dialysate sodium concentration.

DISCUSSION

In a large population of European HD patients, we observed international differences in pre- and post-dialysis BP, even when controlling for differences in patients and dialysis characteristics. Interestingly, we identified for the first time a North-South gradient of BP in HD patients with higher levels near the pole. Mean pre-dialysis SBP was more than 10 mmHg higher in UK compared to Spain. The reasons for this are certainly multi-factorial and probably include differences in environmental, genetic and cultural background, physical activity and medical handling. Similar BP gradients are present in the general population,[14,26] but it is surprising that it remained in HD patients whose BP is both closely monitored and strongly influenced by dialysis procedures. A clinical impact of geographical disparities of BP on public health is expected. In observational studies of HD patients, the risk of cardiovascular mortality is associated with both lower and higher BP level.[27–29] Low BP is a sign of cardiac dysfunction associated with short-term mortality.[4] In contrast, elevated BP is directly related to mortality and pharmacological BP reductions improve the cardiovascular risk.[30,31] In the past years, in Germany, BP decreased while the use of antihypertensive therapies and polymedication increased.[32] This likely explains the relatively low BP observed in German HD patients in our study, despite a high prevalence of hypertension. The North-South gradients of BP and mortality could be blunted by public health initiatives.[33,34]

In accordance with results from single-center studies and an international registry of HD patients, we confirmed at the individual level that pre-dialysis BP was significantly lower in summer compared to winter.[5,7,10,35] That these results were observed in patients whose BP is frequently monitored for a tight control suggests a considerable effect of seasonality, whether it is direct or mediated by other factors. For the first time, we reported that the magnitude of the seasonal effect varied between countries and with latitude in HD patients. Seasonality was less pronounced at the pole, in agreement with observations from the general population.[15]

The magnitude of seasonal changes was around 2 mmHg for pre-dialysis SBP and 1 mmHg for DBP. This is in line with methodologically comparable literature,[9,35] while other studies reported peak-to-peak amplitudes up to 12 mmHg.[5,7] The size of the effect that we reported was probably blunted by the limited time frequency of data collection. In 59 HD patients, we observed that SBP varied by 6 to 9 mmHg between extreme months (i.e., May and November) while the estimate of seasonal change (from summer to winter) was 3 mmHg (*unpublished data*). Likewise, we can expect in the present study that mean change in SBP between extreme months could be two- or three-fold higher than the reported seasonal change. Nonetheless, there were geographical disparities in seasonality, with average seasonal change in SBP ranging from 3 mmHg in Italy to null in Belgium. This is not the first time that a lack of seasonality is reported.[11] This could be explained by a seasonal adjustment of BP medical handling or other factors.

Climate is expected to be responsible for seasonal patterns. With regards to BP, the influence of climate may occur through temperature-induced vasoconstriction and dilation, UV-related vitamin D synthesis, climate- or exercise-related perspiration and changes in dietary and water intake.[14] We observed that increasing outdoor temperatures were consistently associated with lower pre-dialysis BP. Both outdoor and indoor temperatures have been shown to influence the level of BP.[15] Low temperatures have a direct effect on vasoconstriction, while high temperatures trigger sweating to evacuate body heat. BP displays an acute response to ambient temperature (within minutes to hours), in addition to a persistent effect maintained over weeks.[36] For the first time, we report in HD patients a greater effect of outdoor temperature on BP in southern locations. Longer sunshine duration was also associated with lower pre-dialysis BP although it is mainly the result of its tight link with outdoor temperature. In a warm and humid climate, a limitation of sweating occurs despite elevated body temperature, due to skin saturation in water.[37] Compared to dry conditions, a reduced sweating rate results in higher BP, more importantly in HD patients with limited urinary water output. This is consistent with the direct association between humidity and BP level that we observed in the present study and in a previous work.[12] Wind may also influence BP by promoting sweating in hot and humid environments. This is in contrast with the observed association between windy episodes and higher BP in southern locations. Maximum wind speed recorded over the month may well not be a relevant measure of wind exposure. Interestingly, we found that patients with greater intra-dialytic weight loss were more sensitive to seasons, supporting the view that over-hydration allows a greater leeway to change. Nonetheless, hydration-independent mechanisms should not be undermined as suggested by the simultaneous increase in extracellular water content and decrease in BP in summer recently reported.[35]

The understanding and correction of BP seasonality is of utmost clinical value. On the one hand, seasonality may interfere with the assessment of mid-term longitudinal trends in BP, hence improperly reflecting the efficacy of BP-lowering strategies. On the other hand, HD patients suffer from excess mortality in winter, potentially related to the higher BP in winter.[9,10,30] In older individuals, a 3 mmHg-decrease in SBP is associated with a 12% reduction in cardiovascular mortality.[38] Finally, BP variability itself is associated with cardiovascular morbi-mortality.[3] Given the high cardiovascular risk of dialyzed patients, a moderate effect on blood pressure can represent a consequent gain in life-years overall. Seasonal variations in BP could be avoided by adapting dialysis prescription and antihypertensive therapies, preferably in winter in order to minimize BP, provided that it is acceptable for patients.

Our study has some limitations. Data collection was not specifically designed for the purpose, preventing to precisely estimate the magnitude of seasonal change. Still, the study was based on large nationally-representative populations of European HD patients which warrants the validity of regional BP estimates and the robustness of geographical trends. Of note, these trends may not be maintained beyond temperate areas.[10] Secondly, the measurement of BP was not standardized but taken according to usual practice. Although this could affect observed international differences, it is unlikely to influence within-patient and within-center change in BP. Finally, the relevance of our results should not be minimized by the reported effect size, which does not reflect existing inter-individual variability. Some patients may be insensitive to seasons, while others probably face important seasonal changes. For instance, BP seasonality was smaller in patients with elevated BP or receiving many BP-lowering therapies. Finally, although this study was performed in HD patients, there is strong evidence that results in the general population would be comparable.[14,15]

PERSPECTIVES

For the first time, analyzing data from over 9500 patients, we showed that BP level was lower in HD patients living in southern European countries. This effect may be surprising given the fact that dialyzed patients are frequently hypertensive and that their BP is strongly influenced by medical procedures (dialysis, antihypertensive therapies). This particularly relevant in the context of international comparisons of health status and outcome. The reasons for this remain to be confirmed, but differences in climate, diet, lifestyle and medical strategies could be involved.

In addition, we confirmed the presence of BP seasonality in a large cohort of nationally representative samples and found that BP displayed greater seasonal changes in southern places. Seasonality was explained by climate, and most importantly by outdoor temperature. For the same change in outdoor temperature, the change in SBP was greater in southern locations. Preventing the winter rise of BP could limit the excess winter mortality. BP seasonality should be taken into account by clinicians when defining BP goals and antihypertensive strategies.

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References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-2128. doi:10.1016/S0140-6736(12)61728-0.

2. Kotchen TA, Cowley AW, Liang M. Ushering Hypertension Into a New Era of Precision Medicine. *JAMA*. 2016;315(4):343. doi:10.1001/jama.2015.18359.

3. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol*. 2013;10(3):143-155. doi:10.1038/nrcardio.2013.1.

4. Ok E, Asci G, Chazot C, Ozkahya M, Mees EJD. Controversies and problems of volume control and hypertension in haemodialysis. *The Lancet*. 2016;388(10041):285-293. doi:10.1016/S0140-6736(16)30389-0.

5. Argilés A, Mourad G, Mion C. Seasonal changes in blood pressure in patients with end-stage renal disease treated with hemodialysis. *N Engl J Med*. 1998;339(19):1364-1370. doi:10.1056/NEJM199811053391904.

6. Tozawa M, Iseki K, Iseki C, Morita O, Yoshi S, Fukiyama K. Seasonal blood pressure and body weight variation in patients on chronic hemodialysis. *Am J Nephrol*. 1999;19(6):660-667. doi:13538.

7. Spósito M, Nieto FJ, Ventura JE. Seasonal variations of blood pressure and overhydration in patients on chronic hemodialysis. *Am J Kidney Dis*. 2000;35(5):812-818. doi:10.1016/S0272-6386(00)70249-6.

8. Cheung AK, Yan G, Greene T, et al. Seasonal variations in clinical and laboratory variables among chronic hemodialysis patients. *J Am Soc Nephrol JASN*. 2002;13(9):2345-2352.

9. Usvyat LA, Carter M, Thijssen S, et al. Seasonal variations in mortality, clinical, and laboratory parameters in hemodialysis patients: a 5-year cohort study. *Clin J Am Soc Nephrol CJASN*. 2012;7(1):108-115. doi:10.2215/CJN.03880411.

10. Guinsburg AM, Usvyat LA, Etter M, et al. Seasonal variations in mortality and clinical indicators in international hemodialysis populations from the MONDO registry. *BMC Nephrol*. 2015;16:139. doi:10.1186/s12882-015-0129-y.

11. Fine A. Lack of seasonal variation in blood pressure in patients on hemodialysis in a North American center. *Am J Kidney Dis Off J Natl Kidney Found*. 2000;36(3):562-565. doi:10.1053/ajkd.2000.16194.

12. Argilés A, Lorho R, Servel M-F, Chong G, Kerr PG, Mourad G. Seasonal modifications in blood pressure are mainly related to interdialytic body weight gain in dialysis patients. *Kidney Int*. 2004;65(5):1795-1801. doi:10.1111/j.1523-1755.2004.00569.x.

13. Elford J, Phillips A, Thomson AG, Shaper AG. Migration and geographic variations in blood pressure in Britain. *BMJ*. 1990;300(6720):291-295.

14. Rostand SG. Ultraviolet Light May Contribute to Geographic and Racial Blood Pressure Differences. *Hypertension*. 1997;30(2):150-156. doi:10.1161/01.HYP.30.2.150.

15. Barnett AG, Sans S, Salomaa V, Kuulasmaa K, Dobson AJ, WHO MONICA Project. The effect of temperature on systolic blood pressure. *Blood Press Monit*. 2007;12(3):195-203. doi:10.1097/MBP.0b013e3280b083f4.

16. Young EW, Goodkin DA, Mapes DL, et al. The Dialysis Outcomes and Practice Patterns Study (DOPPS): An international hemodialysis study. *Kidney Int*. 2000;57:S74-S81. doi:10.1046/j.1523-1755.2000.07413.x.

17. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA. The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. *Am J Kidney Dis Off J Natl Kidney Found*. 2004;44(5 Suppl 2):7-15.

18. Météo Belgique. Météo en Belgique : Archive des stations. http://www.meteobelgique.be/premium/observation/archive-des-stations.html. Published 2015. Accessed September 29, 2015.

19. Météo France. Données Publiques de Météo-France - Données mensuelles. https://donneespubliques.meteofrance.fr/?fond=produit&id_produit=114&id_rubrique=37. Published 2015. Accessed September 29, 2015.

20. Met Office. Climate Historic - Met Office. http://www.metoffice.gov.uk/public/weather/climate-historic/#?tab=climateHistoric. Published 2015. Accessed September 29, 2015.

21. Menne MJ, Durre I, Vose RS, Gleason BE, Houston TG. An Overview of the Global Historical Climatology Network-Daily Database. *J Atmospheric Ocean Technol*. 2012;29(7):897-910. doi:10.1175/JTECH-D-11-00103.1.

22. Menne, Matthew J., Durre, Imke, Korzeniewski, Bryant, et al. Global Historical Climatology Network - Daily (GHCN-Daily), Version 3. http://dx.doi.org/10.7289/V5D21VHZ. Published 2012. Accessed September 29, 2015.

23. Global Historical Climatology Network. Global Historical Climatology Network monthly mean temperature data set, version 3. http://www.ncdc.noaa.gov/ghcnm. Published 2015. Accessed September 29, 2015.

24. European Climate Assessment & Dataset. Indices data. http://www.ecad.eu/download/millennium/millennium.php. Published 2015. Accessed September 29, 2015.

25. Lawrimore JH, Menne MJ, Gleason BE, et al. An overview of the Global Historical Climatology Network monthly mean temperature data set, version 3. *J Geophys Res*. 2011;116(D19). doi:10.1029/2011JD016187.

26. Cabrera SE, Mindell JS, Toledo M, Alvo M, Ferro CJ. Associations of Blood Pressure With Geographical Latitude, Solar Radiation, and Ambient Temperature: Results From the Chilean Health Survey, 2009–2010. *Am J Epidemiol*. 2016;183(11):1071-1073. doi:10.1093/aje/kww037.

27. Zager PG, Nikolic J, Brown RH, et al. “U” curve association of blood pressure and mortality in hemodialysis patients. *Kidney Int*. 1998;54(2):561-569. doi:10.1046/j.1523-1755.1998.00005.x.

28. Robinson BM, Tong L, Zhang J, et al. Blood pressure levels and mortality risk among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2012;82(5):570-580. doi:10.1038/ki.2012.136.

29. Duranton F, Duny Y, Szwarc I, et al. Early changes in body weight and blood pressure are associated with mortality in incident dialysis patients. *Clin Kidney J*. 2016;9(2):287-294. doi:10.1093/ckj/sfv153.

30. Heerspink HJL, Ninomiya T, Zoungas S, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *The Lancet*. 2009;373(9668):1009-1015. doi:10.1016/S0140-6736(09)60212-9.

31. Charra B, Calemard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. *Kidney Int*. 1992;41(5):1286-1291. doi:10.1038/ki.1992.191.

32. Sarganas G, Knopf H, Grams D, Neuhauser HK. Trends in Antihypertensive Medication Use and Blood Pressure Control Among Adults With Hypertension in Germany. *Am J Hypertens*. 2016;29(1):104-113. doi:10.1093/ajh/hpv067.

33. van Dijk PCW, Zwinderman AH, Dekker FW, et al. Effect of general population mortality on the north-south mortality gradient in patients on replacement therapy in Europe. *Kidney Int*. 2007;71(1):53-59. doi:10.1038/sj.ki.5002008.

34. Vartiainen E, Laatikainen T, Peltonen M, et al. Thirty-five-year trends in cardiovascular risk factors in Finland. *Int J Epidemiol*. 2010;39(2):504-518. doi:10.1093/ije/dyp330.

35. Broers NJH, Usvyat LA, Marcelli D, et al. Season affects body composition and estimation of fluid overload in haemodialysis patients: variations in body composition; a survey from the European MONDO database. *Nephrol Dial Transplant*. 2014;30(4):676-681. doi:10.1093/ndt/gfu367.

36. Modesti PA. Season, temperature and blood pressure: a complex interaction. *Eur J Intern Med*. 2013;24(7):604-607. doi:10.1016/j.ejim.2013.08.002.

37. Gisolfi CV, Wilson NC, Claxton B. Work-heat tolerance of distance runners. *Ann N Y Acad Sci*. 1977;301:139-150.

38. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet Lond Engl*. 2002;360(9349):1903-1913.

Novelty and Significance:

What Is New

- In European HD patients, there is a geographical gradient of BP: higher level in northern locations.
- In these patients, BP varies seasonally: it increases in Winter and in colder periods.
- BP seasonality varies with latitude: it is larger in patients from southern locations.

What Is Relevant?

- Transient increases in BP and high BP variability increase the risk of cardiovascular disease.
- BP seasonality could be prevented.

Summary

In southern places, BP is lower and displays greater seasonal changes. This may affect the diagnosis of hypertension and the risk of adverse outcome.

Figure legends

Figure 1: Geographical distribution of facilities (A) and facility average in pre-dialysis systolic blood pressure (SBP) by latitude (B). Locations are represented by meteorological stations, one point may represent several facilities. Pre-dialysis SBP was 5.1 [3.7 ; 6.4] mmHg higher per 10°-increase in latitude, P < 0.001 (unadjusted mixed model).

Figure 2: Mean SBP (solid line) and DBP (dashed line) by season (A and B) and magnitude of seasonal differences in pre-dialysis SBP by country (C). Pre-dialysis SBP and DBP increased from Summer to Winter by 1.7 [1.3 ; 2.2] and 0.8 [0.5 ; 1.0] mmHg. There was no difference in post-dialysis BP (SBP: 0.0 [-0.4 ; 0.5]; DBP: 0.1 [-0.2 ; 0.3] mmHg). The seasonal change in SBP decreased by 0.8 [0.1 ; 1.5] mmHg for a 10°-increase in latitude (P = 0.04). Estimates and 95% CI from unadjusted mixed models. Win: winter, Sp: spring, Sum: summer, Aut: Autumn.

Figure 3: Mean pre-dialysis SBP level by outdoor temperature by country. Temperature is displayed from the 10th to the 90th percentile of each country. The effect of temperature was significant (P < 0.001) and associated with the country ($P_{interaction}$ = 0.004). Estimates from mixed models adjusting for baseline patient and dialysis characteristics.

Figure 4: Subgroup analysis of seasonal change in SBP. Estimates and 95% CI for the change in SBP from Summer to Winter at a latitude of 50° obtained from mixed models adjusting for baseline patient and dialysis characteristics with the exception of the grouping variable. BPL drug: blood pressure lowering drug.

Table 1. Patients characteristics at baseline by country

Chacteristics	Spain	Italy	France	Germany	Belgium	United Kingdom	Sweden
Number of patients	1571	1384	1401	1556	1246	1144	1353
Age (year)	64.0 ± 15.6	66.1 ± 13.7	65.4 ± 15.2	64.8 ± 14.3	68.5 ± 13.6	61.5 ± 15.6	64.8 ± 14.2
Gender (% Male)	59%	59%	58%	59%	57%	58%	65%
Years on dialysis	2.0 (0.8 ; 5.4)	2.7 (0.8 ; 6.7)	2.3 (0.8 ; 5.9)	2.0 (0.8 ; 5.1)	1.7 (0.8 ; 4.2)	2.3 (0.8 ; 5.7)	1.8 (0.8 ; 4.9)
BMI (kg/m²)	25.2 ± 4.5	24.8 ± 5.1	25.3 ± 5.6	26.5 ± 5.2	25.7 ± 5.1	26.3 ± 5.4	25.9 ± 6.0
Laboratory values							
Serum albumin (g/L)	38 ± 5	38 ± 6	37 ± 5	40 ± 6	38 ± 5	38 ± 5	35 ± 5
Serum sodium (mEq/L)	138 ± 4	138 ± 4	137 ± 3	139 ± 3	138 ± 4	137 ± 3	139 ± 3
Serum potassium (mEq/L)	5.3 ± 0.8	5.3 ± 0.9	4.9 ± 0.8	5.2 ± 0.8	4.9 ± 0.7	5.0 ± 0.8	4.8 ± 0.7
Blood pressure (mmHg)							
Pre-dialysis SBP	133 ± 23	134 ± 23	139 ± 25	133 ± 21	139 ± 24	143 ± 25	140 ± 27
Pre-dialysis DBP	71 ± 13	72 ± 13	72 ± 15	72 ± 12	71 ± 14	74 ± 15	74 ± 14
Post-dialysis SBP	126 ± 23	129 ± 24	132 ± 25	127 ± 21	132 ± 23	132 ± 25	135 ± 27
Post-dialysis DBP	69 ± 13	71 ± 13	70 ± 15	70 ± 12	69 ± 13	69 ± 14	72 ± 14
Number of BPL drug types (%)							
0	40%	40%	24%	10%	28%	34%	17%
1-3	56%	55%	70%	68%	69%	59%	68%
≥ 4	4%	5%	6%	22%	3%	7%	15%
Dialysis parameters							
Blood flow (mL/min)	353 ± 50	302 ± 47	326 ± 47	293 ± 48	330 ± 75	332 ± 61	330 ± 52
Dialysis duration (hr/week)	12.0 ± 2.3	11.5 ± 1.8	12.0 ± 1.9	13.3 ± 2.3	12.0 ± 2.0	11.3 ± 1.7	13.0 ± 2.4
Dialysis duration (min/session)	233 ± 33	227 ± 24	241 ± 33	265 ± 44	241 ± 37	228 ± 31	254 ± 37
Intradialytic weight loss (% of post-dialysis weight)	3.1 ± 1.4	3.7 ± 1.5	3.4 ± 1.5	2.6 ± 1.6	2.7 ± 1.5	2.4 ± 1.3	2.7 ± 1.5
Dialysate Sodium concentration (mEq/L)	140 ± 1	141 ± 2	141 ± 2	138 ± 2	140 ± 2	138 ± 1	139 ± 2
Vascular access (%)							
Arteriovenous fistula	67%	78%	75%	79%	56%	70%	55%
Synthetic graft	8%	4%	8%	8%	3%	5%	10%
Catheter	26%	19%	17%	13%	41%	25%	34%

Table 1. Patients characteristics at baseline by country *(continued).*

Chacteristics	Spain	Italy	France	Germany	Belgium	United Kingdom	Sweden
Cardiovascular comorbidities (% yes)							
Hypertension	86%	74%	87%	92%	82%	70%	84%
Congestive heart failure	36%	18%	34%	34%	36%	16%	30%
Coronary heart disease	33%	34%	39%	57%	49%	39%	46%
Peripheral vascular disease	31%	30%	40%	34%	35%	19%	28%
Cerebrovascular disease	16%	16%	15%	20%	22%	14%	18%
Other CVD	41%	30%	38%	40%	47%	22%	39%
Non cardiovascular comorbidities (% yes)							
Diabetes	31%	28%	35%	40%	38%	28%	41%
Psychiatric disorders	20%	14%	12%	13%	17%	12%	14%
Lung disease	18%	14%	13%	13%	19%	7%	9%
Cancer	15%	15%	16%	16%	19%	14%	17%
Neurologic disease	12%	11%	11%	17%	15%	8%	10%
Recurrent cellulitis	8%	8%	8%	12%	12%	6%	12%
Smoking status (%)							
Active	11%	12%	13%	17%	15%	16%	13%
Former	33%	28%	31%	20%	29%	20%	33%
Non Smoker	49%	45%	48%	51%	43%	42%	42%
Unknown	7%	15%	8%	12%	13%	22%	12%

Footnote: Countries are ordered from South to North. Values are mean ± SD, median (IQR) or percentages. All P-values for differences between countries are < 0.05.

Table 2. Association of seasonality and monthly climate with pre-dialysis SBP, accounting for latitude.

	Effect of Climate (mmHg)		**Effect of Climate × Latitude** (mmHg)	
Model (Unit of change)	**Estimate and 95% CI**	**P-value**	**Estimate and 95% CI**	**P-value**
Seasons ($\Delta_{\text{Win-Sum}}$)	1.8 [1.3 ; 2.3]	< 0.001	-0.8 [-1.7 ; -0.01]	0.04
Mean outdoor Temperature (7.2°C)	-0.8 [-1.0 ; -0.5]	< 0.001	0.4 [0.1 ; 0.8]	0.005
Cumulative sunshine duration (89 h)	-0.6 [-0.8 ; -0.3]	< 0.001	-	-
Maximal wind speed (4.6 km/h)	0.0 [-0.5 ; 0.4]	0.09	-0.9 [-1.5 ; -0.2]	0.008
Cumulative rainfall (47 mm)	-0.1 [-0.3 ; 0.2]	0.5	-0.4 [-0.7 ; -0.04]	0.03
Mean humidity (10.7%)	0.4 [0.0 ; 0.7]	0.03	-	-
Mean atmospheric pressure (4.8 hPa)	0.1 [-0.2 ; 0.4]	0.3	-	-

Footnote: Each line reports the results for the effect of Climate and Climate × Latitude on pre-dialysis SBP level estimated from different models. Results were obtained from mixed models adjusting on latitude, baseline age, gender, dialysis vintage, BMI, smoking, comorbidities, vascular access, blood flow, weekly hours of dialysis and dialysate sodium. Climate estimates are given for a 1-SD increase at a latitude of 50°, Climate×Latitude estimates are given for both a 1-SD increase in climate effect and a 10°-increase in latitude (1111km North).

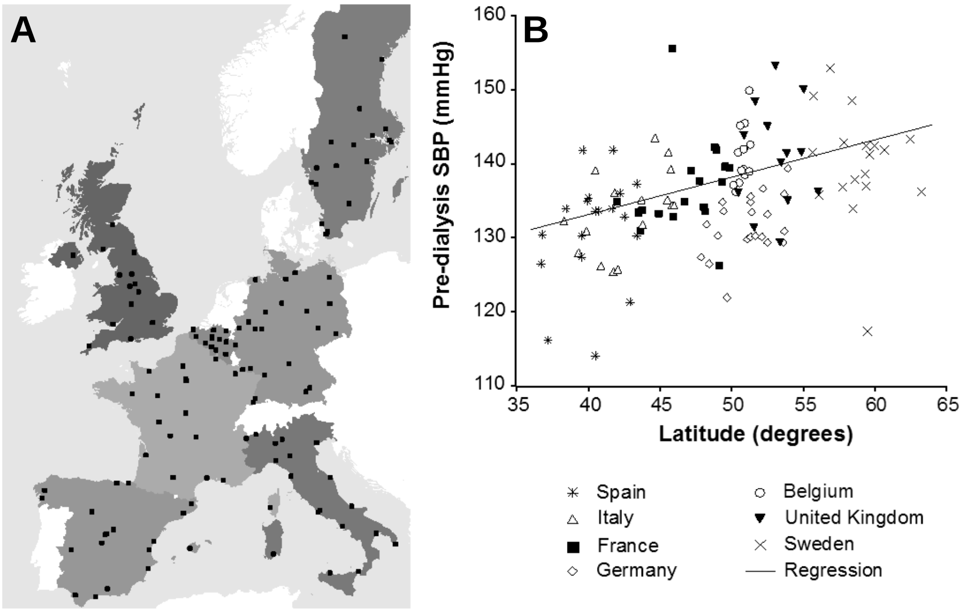

A
B
160
150
140
130
120
110
Pre-dialysis SBP (mmHg)
35
40
45
50
55
60
65
Latitude (degrees)
Spain
Italy
France
Germany
Belgium
United Kingdom
Sweden
Regression

Figure 1

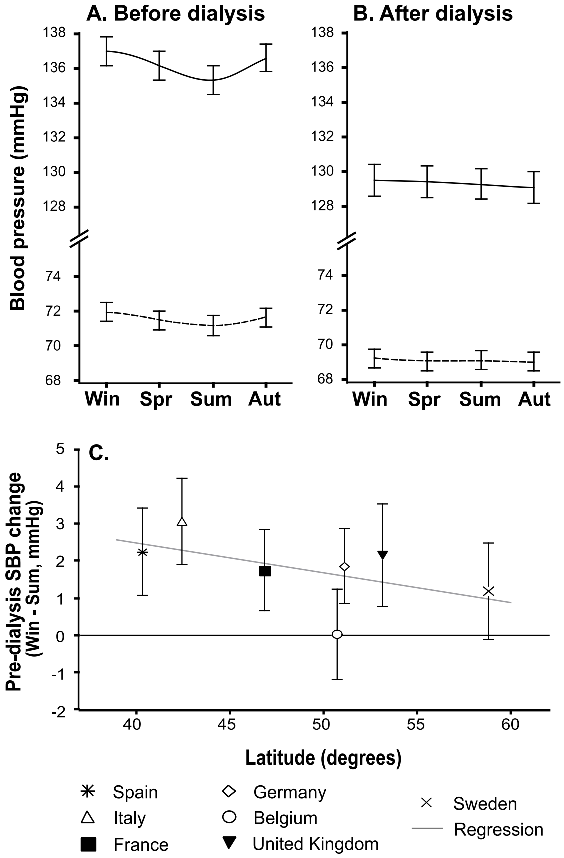

A. Before dialysis
B. After dialysis
Blood pressure (mmHg)
138
136
134
132
130
128
74
72
70
68
Win
Spr
Sum
Aut
C.
Pre-dialysis SBP change (Win - Sum, mmHg)
5
4
3
2
1
0
-1
-2
40
45
50
55
60
Latitude (degrees)
Spain
Italy
France
Germany
Belgium
United Kingdom
Sweden
Regression

Figure 2

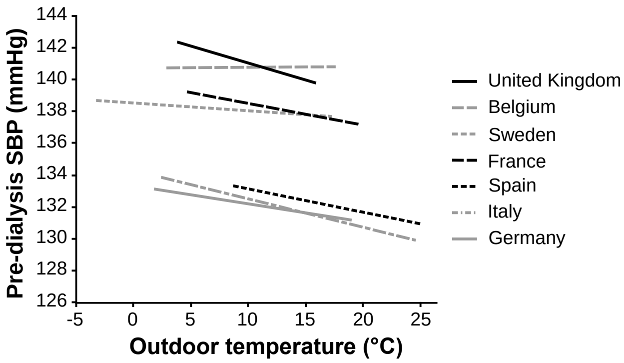
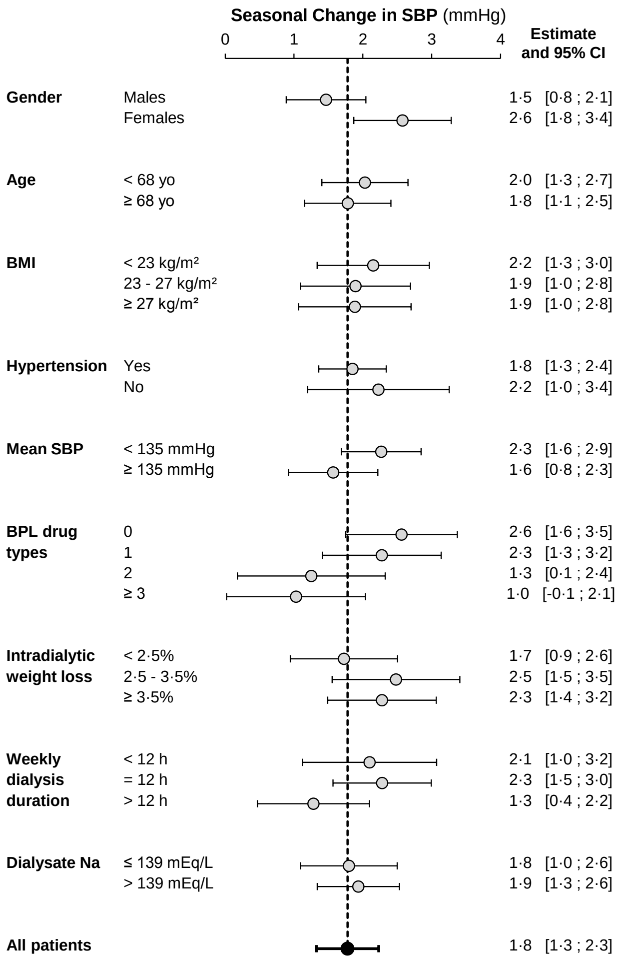

144
142
140
138
136
134
132
130
128
126
Pre-dialysis SBP (mmHg)
-5
0
5
10
15
20
25
Outdoor temperature (°C)
United Kingdom
Belgium
Sweden
France
Spain
Italy
Germany

Figure 3



Seasonal Change in SBP (mmHg)
0 1 2 3 4
Estimate and 95% CI
Gender
Males
Females
1·5 [0·8 ; 2·1]
2·6 [1·8 ; 3·4]
Age
< 68 yo
≥ 68 yo
2·0 [1·3 ; 2·7]
1·8 [1·1 ; 2·5]
BMI
< 23 kg/m²
23 - 27 kg/m²
≥ 27 kg/m²
2·2 [1·3 ; 3·0]
1·9 [1·0 ; 2·8]
1·9 [1·0 ; 2·8]
Hypertension
Yes
No
1·8 [1·3 ; 2·4]
2·2 [1·0 ; 3·4]
Mean SBP
< 135 mmHg
≥ 135 mmHg
2·3 [1·6 ; 2·9]
1·6 [0·8 ; 2·3]
BPL drug types
0
1
2
≥ 3
2·6 [1·6 ; 3·5]
2·3 [1·3 ; 3·2]
1·3 [0·1 ; 2·4]
1·0 [-0·1 ; 2·1]
Intradialytic weight loss
< 2·5%
2·5 - 3·5%
≥ 3·5%
1·7 [0·9 ; 2·6]
2·5 [1·5 ; 3·5]
2·3 [1·4 ; 3·2]
Weekly dialysis duration
< 12 h
= 12 h
> 12 h
2·1 [1·0 ; 3·2]
2·3 [1·5 ; 3·0]
1·3 [0·4 ; 2·2]
Dialysate Na
≤ 139 mEq/L
> 139 mEq/L
1·8 [1·0 ; 2·6]
1·9 [1·3 ; 2·6]
All patients
1·8 [1·3 ; 2·3]

Figure 4