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Associations of Estradiol With Mortality and Health Outcomes in Patients Undergoing Hemodialysis: A Prospective Cohort Study

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Abstract

Background: Both lower and higher estradiol (E2) levels have been associated with increased mortality among women with kidney failure. However, robust data are still lacking.
Objective: We investigated the interaction of diabetes and age on linear and nonlinear associations between E2 levels, adverse outcomes, and health-related quality of life (HRQOL) in Canadian women undergoing hemodialysis (HD).
Design: Population-based cohort study; data from Canadian Kidney Disease Cohort Study (CKDCS).
Setting & patients: A total of 427 women undergoing HD enrolled in the CKDCS.
Measurements: Baseline E2 (in pmol/L) and E2 tertiles (<38 pmol/L, 38-95 pmol/L, >95 pmol/L).
Methods: Cox-proportional hazards used for all-cause and cardiovascular disease (CVD) mortality. Fine-Gray models used for incident CVD. Mixed models used for Health Utilities Index Mark 3 (HUI3), Kidney Disease Quality of Life Physical Component Scores (KDQOL12-PCS), and Mental Component Scores (KDQOL12-MCS).
Results: Over a median follow-up of 3.6 (interquartile range [IQR]: 1.6-7.5) years, 250 (58.6%) participants died; 74 deaths (29.6%) were CV-related. Among 234 participants without prior CV events, 80 (34.2%) had an incident CVD event. There were no significant linear associations between E2 and all-cause mortality, CVD mortality, and incident CVD. However, E2 showed a significant concave association with all-cause mortality, but not with CVD mortality and incident CVD. Among patients aged ≥63 years, higher E2 levels were associated with lower HUI3 scores, mean difference (MD) = –0.062 per 1 – SD pmol/L, 95% confidence interval (CI) = –0.112 to –0.012, but the opposite was observed in younger patients (<63 years) in whom higher E2 levels were associated with higher HUI3 scores (MD = 0.032 per 1 – SD pmol/L, 95% CI = 0.008-0.055), $P_{interaction}$ = .045. No associations were observed among E2, KDQOL12-PCS (MD = –0.15 per 1 – SD pmol/L, 95% CI = –1.15 to 0.86), and KDQOL12-MCS (MD = –0.63 per 1 – SD pmol/L, 95% CI = –1.82 to 0.57).
Limitations: Unmeasured confounding and small sample size.
Conclusions: The association between E2 and all-cause mortality may be nonlinear, while no association was observed for CVD mortality, incident CVD, KDQOL12-PCS, and KDQOL12-MCS. Furthermore, the association between serum E2 and HUI3 was modified by age: Higher levels were associated with higher utility among women aged <63 years and the converse observed among older women.

Abrégé

Contexte: Les taux faibles comme les taux élevés d'estradiol (E2) ont été associés à une mortalité accrue chez les femmes souffrant d'insuffisance rénale. Les données fiables à ce sujet font cependant encore défaut.
Objectif: Nous avons étudié l'incidence du diabète et de l'âge sur les associations linéaires et non linéaires entre les niveaux d'E2, les issues défavorables et la qualité de vie liée à la santé (QVLS) chez les Canadiennes suivant des traitements d'hémodialyse (HD).
Conception: Étude de cohorte en population réalisée à partir des données de la Canadian Kidney Disease Cohort Study (CKDCS).
Sujets et cadre de l'étude: 427 femmes sous HD inscrites à la CKDCS.
Mesures: Le taux d'E2 initial (pmol/L) et les taux d'E2 tertiles (<38 pmol/L; 38-95 pmol/L; >95 pmol/L).

Méthodologie: Des modèles à risques proportionnels de Cox ont été utilisés pour mesurer la mortalité toutes causes confondues et la mortalité liée aux maladies cardiovasculaires (MCV). Des modèles Fine-Gray ont été utilisés pour mesurer les MCV incidentes; et des modèles mixtes ont été utilisés pour calculer l'indice Health Utilities Index Mark 3 (HUI3) et les scores des composantes physique (KDQOL12-PCS [Physical Component Score]) et mentale (KDQOL12-MCS [Mental Component Score])) du questionnaire sur la qualité de vie (KDQOL).
Résultats: Au cours d'un suivi médian de 3,6 ans (intervalle interquartile [IIQ]: 1,6 à 7,5 ans), 250 participantes (58,6 %) sont décédées; 74 décès (29,6 %) étaient liés à un événement CV. Parmi les 234 participantes sans événements cardiovasculaires antérieurs, 80 (34,2 %) ont vécu un événement incident de MCV. Aucune association linéaire significative n'a été observée entre le taux d'E2 et la mortalité toutes causes confondues, la mortalité par MCV ou les MCV incidentes. Le taux d'E2 a cependant montré une association concave significative avec la mortalité toutes causes confondues, mais pas avec la mortalité par MCV ni avec les MCV incidentes. Chez les patientes âgées de 63 ans et plus, des taux élevés d'E2 ont été associés à des scores HUI3 plus faibles (différence moyenne [DM] = -0,062 par 1-SD pmol/L; intervalle de confiance à 95 % [IC95]: -0,112 à 0,012); alors qu'on a observé le contraire chez les patientes plus jeunes (< 63 ans), où des taux élevés d'E2 étaient plutôt associés à des scores plus élevés d'HUI3 (DM = 0,032 par 1-SD pmol/L; IC95: 0,008 à 0,055; *p*=0,045). Aucune association n'a été observée entre le taux d'E2, le KDQOL12-PCS (DM = -0,15 par 1-SD pmol/L; IC 95: -1,15 à 0,86) et le KDQOL12-MCS (DM = -0,63 par 1-SD pmol/L; IC95: -1,82 à 0,57).
Limites: Facteurs de confusion non mesurés; échantillon de petite taille.
Conclusion: Il pourrait exister une association non linéaire entre le taux d'E2 et la mortalité toutes causes confondues. Aucune association n'a toutefois été observée entre le taux d'E2 et la mortalité par MCV, les MCV incidentes, le KDQOL12-PCS et le KDQOL12-MCS. En outre, l'association entre le taux sérique d'E2 et l'HUI3 a été modifiée par l'âge: des taux plus élevés d'E2 ont été associés à un indice de santé plus élevé (HUI) chez les femmes âgées de moins de 63 ans, alors que l'inverse a été observé chez les femmes plus âgées.

Keywords
estradiol, hemodialysis, diabetes, all-cause mortality, cardiovascular mortality, health-related quality of life

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Introduction

Women with kidney failure are more likely to die prematurely compared with men with kidney failure—losing on average 3.6 years more life than men.[1] In patients with kidney failure, hypothalamic-pituitary-gonadal (HPG) axis disruption is common.[2] Elevated prolactin and disrupted gonadotropin-releasing hormone production results in lower estradiol (E2) production among women with kidney failure.[3] Due to the loss of cardioprotective and anti-inflammatory properties of E2, premature menopause, osteoporosis, and accelerated progression of cardiovascular disease (CVD) and mortality can occur as a result.[4]

Although most women with kidney failure are postmenopausal (older), their premenopausal counterparts exhibit E2 levels at postmenopausal levels.[5] Consequently, premature menopause and sexual dysfunction occur—2 conditions linked with increased mortality and CVD risks, as well as lower health-related quality of life (HRQOL) among women with kidney failure.[6-10] Chronic reduction in endogenous estrogen exposure (EEE) has been thought to contribute to increased mortality.[11,12]

Diabetes is common among patients with kidney failure.[9,13] Dialysis complicates glycemic control[14] and in turn increases CV risks and complications.[15] Patients with diabetes have higher mortality rates and worse health outcomes compared with those without diabetes.[16,17] Furthermore, mortality rates are higher in women with diabetes compared with their male counterparts.[7,17,18] However, uncertainty remains in regard to whether diabetes could alter associations among E2, mortality, and HRQOL in patients undergoing hemodialysis (HD).

Observational data have linked both low and high endogenous E2 levels with all-cause and CVD mortality[9] in women undergoing HD. We previously reported partially concordant results, where higher E2 levels were associated with increased all-cause mortality, but not with CVD mortality.[13]

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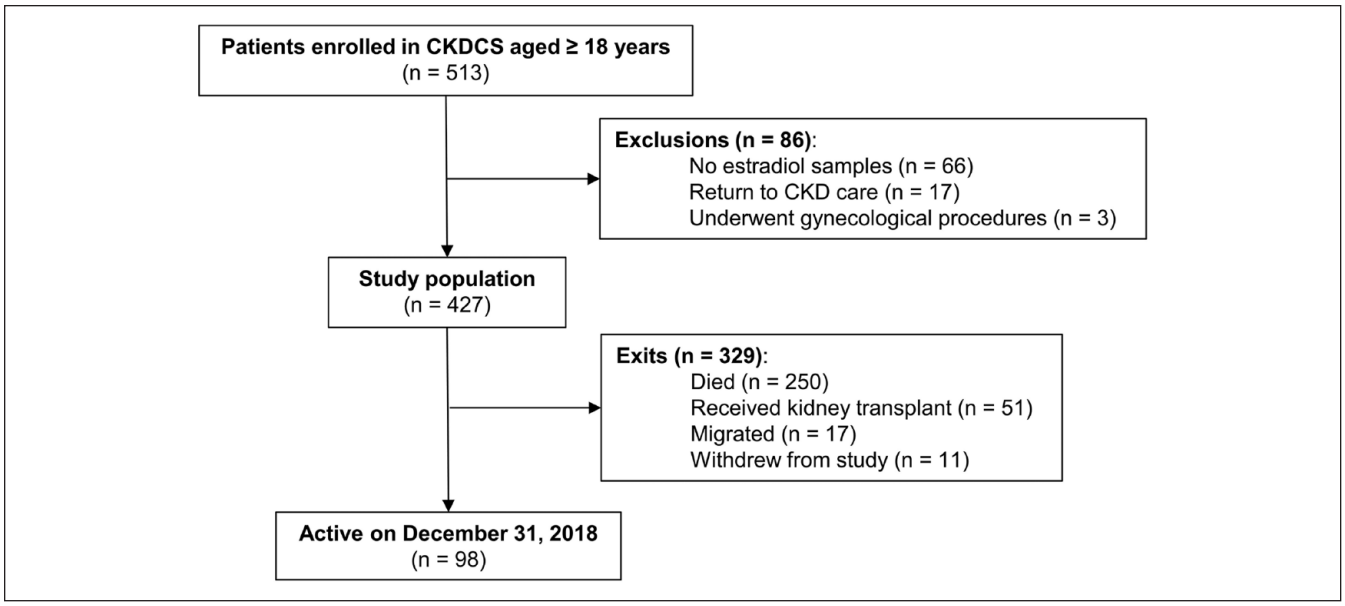

Figure 1. Participant flowchart.
Note. CKDCS = Canadian Kidney Disease Cohort Study; CKD = chronic kidney disease.

However, these observations were not as expected: In the general population, chronic E2 deprivation (eg, premature menopause) is associated with increased mortality and lower HRQOL.[2,4,19] In addition, despite the potential benefits of hormone replacement therapy (HRT) on HRQOL,[20] associations between endogenous E2 and HRQOL have not been extensively evaluated among women on HD. As Tanrisev et al[9] previously suggested possible nonlinear associations among E2, all-cause mortality, and CVD mortality, we aim to re-analyze the data using splines, also adding information on HRQOL.

E2 could be of prognostic and therapeutic relevance as high mortality and lower HRQOL associated with both HD and diabetes necessitate the identification of novel treatments to minimize those risks in kidney failure.[12,13] Using data from a prospective, multicenter study of women undergoing HD in Canada,[6] we investigated the linear and nonlinear associations among endogenous E2 levels, all-cause and CVD mortality, incident CVD, and HRQOL. We further investigated whether these associations are modified by diabetes or age, both of which could influence E2 levels and/or the risk of adverse outcomes.

Design and Methods

Study Design

We performed a secondary analysis of a prospective cohort study involving HD patients. Data were collected via participant interviews, chart reviews, and clinical databases at baseline (start of HD), month 6, and years 1, 2, 5, and 10. Demographics, medical and social history, weight, comorbidities, and HRQOL were ascertained at baseline and updated at each visit when participants received HD treatment. Modality transitions (ie, changes in dialysis types) were tracked throughout follow-up.[21]

Participants

Eligible participants were recruited between February 2005 and November 2012 from Alberta Kidney Care–North and South programs.[21] Written informed consent was obtained and relevant research ethics boards approved the study (Pro00002385, REB15-1048). This study is reported according to the STROBE guidelines.[22] Women (≥18 years old) initiating thrice weekly in-center HD across 4 Canadian dialysis centers (Calgary, Edmonton, Ottawa, and Vancouver) were eligible for inclusion. Participants who were unwilling or unable to provide informed consent, were without E2 measurements (n = 66), underwent gynecological procedures (n = 3), or returned to chronic kidney disease (CKD) care (n = 17) were excluded (Figure 1). In the current analysis, participants were followed until death (n = 250), kidney transplantation (n = 51), migration outside the study region (n = 17), withdrawal of consent (n = 11), or the end of the study period (December 31, 2018; n = 98), whichever came sooner. Details of the Canadian Kidney Disease Cohort Study are presented elsewhere.[21]

Covariates

Participants did a structured interview to collect information on demographic variables (age, sex, and ethnicity). Further parameters (ie, body mass index [BMI], predialysis systolic

blood pressure [SBP], albumin, diabetes, primary cause of kidney failure, smoking status, and comorbidities) were assessed by chart review. Smoking status was classified as nonsmokers (never smoked) or smokers (former and current smokers). Comorbidities included coronary artery disease, heart failure, hypertension, peripheral vascular disease, stroke, diabetes mellitus, chronic respiratory disease, cancers, chronic liver diseases, psychiatric illness, and substance misuse. None of the women included in the current study were taking exogenous sex hormones.

Estradiol

Sera from blood samples were collected at baseline within 3 months of HD session initiation. Sera were processed and frozen in 0.5 mL cryovials at –85°C within 72 hours of sample collection. Frozen sera samples were analyzed for baseline serum E2 at a central laboratory using certified routine methods (mass-spectrometry). Due to the high prevalence of amenorrhea among women with kidney failure,[23] menstrual status was not considered during sample collection. Ramesh et al[13] did not find significant associations between storage duration and HD center with E2 levels.

Outcomes

Primary outcomes were all-cause mortality, CVD mortality, and incident CVD (stroke, transient ischemic attack, coronary artery disease, heart failure, or peripheral vascular disease). Death was ascertained by chart review, and other outcomes were determined based on administrative data from the provincial health ministry (ie, Alberta Health). Our algorithm for defining CVD mortality with *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes has been published previously.[24] Incident CVD was captured for those without prevalent CVD at baseline. Secondary outcomes were HRQOL, assessed using the Health Utilities Index Mark 3 (HUI3) instruments[25] and the physical (PCS) and mental (MCS) component scores of the Kidney Disease Quality of Life (KDQOL12) instrument.[26] HUI3 scores range from –0.36 to 1.00; scores below 0 reflects a health state that was considered to be worse than death, whereas 1.00 indicates perfect health. The suggested minimal clinically important difference (MCID) for HUI3 scores is 0.03.[25,27,28] KDQOL12-PCS and KDQOL12-MCS values range from 0 to 100, where 0 indicates death and 100 indicates perfect health.

Statistical Analyses

Descriptive statistics of the study participants are presented stratified by tertiles of E2, and shown as frequency (percentages) for categorical variables or medians (interquartile range [IQR]) for continuous variables. E2 was analyzed as a continuous variable to increase statistical power. The association among E2, all-cause mortality, and CVD mortality was estimated by calculating hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox-proportional hazards models. The association among E2 and incident CVD, HRs, and their corresponding 95% CIs were calculated using Fine-Gray models (subdistribution hazard) with death as a competing risk.[29] For the prospective associations of E2 with HRQOL measures (ie, HUI3, KDQOL12-PCS, and KDQOL12-MCS scores), difference in means (MDs) and their corresponding 95% CIs were calculated using linear mixed models. Participants were modeled as random effects and visit timepoints (ie, baseline, month 6, years 1, 2, 5, and 10) as fixed effects.

As Tanrisev et al[9] previously suggested possible nonlinear associations among E2, all-cause mortality, and CV mortality, we parametrized E2 with restricted cubic splines with 3 knots (placed at the fifth, 50th, and 95th percentiles). As the splines indicated a concave shape, we replaced the restricted cubic splines with quadratic and linear terms for E2. Nonlinearity was tested with this latter model.

All models were adjusted for baseline age, BMI, ethnicity, predialysis SBP, glomerulonephritis, diabetes, CVD, mental health (smoking status, substance misuse, and psychiatric disorder), other serious illnesses (cancer, chronic respiratory disease, chronic liver disease, and dementia), and albumin. Linear and quadratic terms were used for BMI, given its U-shaped association with mortality. Missing data were present for the following covariates: BMI (1.6%), predialysis SBP (1.2%), and serum albumin (11.0%). Thus, missing data were estimated via multiple imputations using multivariable normal regression; the number of iterations (16) was greater than the maximum fraction (11%) of missingness.[30] In subgroup analyses, we assessed whether diabetes status (yes vs no) and age (above or below the median age of 63 years) modified the associations between E2 and assessed outcomes using interaction terms.

We analyzed E2 as tertiles during sensitivity analysis due to skewness of E2 measurements and the limited interpretability of log-transforming the exposure variable. A 2-sided p value of <0.05 was used as a threshold for statistical significance. All analyses were done in Stata/MP 17.0 (www.stata.com).

Results

Baseline characteristics of 427 women undergoing HD stratified by tertiles are shown in Table 1. Median follow-up was 3.6 years (IQR: 1.6–7.5 years; range: 4 days–13.7 years). The median age of participants was 63 years (50–73 years) and the majority were white (76.1%). Most women had diabetes (53.6%). Of 229 patients with diabetes, 21 (9.2%) had type 1 diabetes. Women with the highest E2 levels were younger, had lower BMI, lower systolic blood pressure, and were more likely to smoke. While women in the middle tertile had the lowest HUI3 and KDQOL12-PCS scores, women

Table 1. Baseline Characteristics of the Study Population.

Characteristic	Low E2 tertile (<38 pmol/L) (n = 140)	Middle E2 tertile (38-95 pmol/L) (n = 144)	High E2 tertile (>95 pmol/L) (n = 143)	*P* value
Age (years)	64 (57, 75)	67 (57, 74)	56 (41, 66)	<.001
BMI (kg/m^2)	27 (23, 31)	27 (22, 33)	26 (21, 34)	.939
Systolic BP (mmHg)	141 (125, 154)	138 (124, 158)	135 (115, 151)	.021
Ethnicity (%)				
White	106 (75.7)	114 (79.2)	105 (73.4)	.169
Indigenous	10 (7.1)	16 (11.1)	20 (14.0)	
Other	24 (17.1)	14 (9.7)	18 (12.6)	
Smoker (%)	14 (10.0)	23 (16.0)	29 (20.4)	.053
Diabetes (%)	73 (52.1)	80 (55.6)	76 (53.1)	.838
GN/autoimmune (%)	17 (12.1)	25 (17.4)	29 (20.3)	.177
Comorbidities[a] (%)				
CVD	63 (45.0)	72 (50.0)	58 (40.6)	.275
Mental health	42 (30.0)	46 (31.9)	55 (38.5)	.286
Other serious illnesses	47 (33.6)	43 (29.9)	33 (23.1)	.141
HRQOL measures				
HUI3	0.72 (0.46, 0.85)	0.64 (0.42, 0.83)	0.69 (0.48, 0.87)	.536
KDQOL12-PCS	31 (26, 38)	30 (24, 39)	31 (25, 37)	.900
KDQOL12-MCS	48 (38, 58)	43 (37, 54)	43 (35, 50)	.081
Albumin (g/L)	34 (31, 37)	34 (31,37)	32 (28, 36)	.053
Estradiol (pmol/L)	19 (19, 29)	63 (48, 77)	169 (118, 294)	<.001

Note. Measure of central tendencies is reported as medians with corresponding 25th and 75th percentiles. *P* values calculated for differences only between estradiol tertiles. E2 = estradiol; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; GN = glomerulonephritis; HRQOL = health-related quality of life; HUI3 = Health Utilities Index mark 3 scores; KDQOL12-PCS = Kidney Disease Quality of Life Physical Component Score; KDQOL12-MCS = Kidney Disease Quality of Life Mental Component Score.

[a]Comorbidities include CVD (cerebrovascular disease, coronary artery disease, heart failure, and peripheral vascular disease), mental health (smoking status, substance misuse, and psychiatric disorder), and other serious illnesses (cancer, chronic respiratory disease, chronic liver disease, and dementia).

in the lower tertile had higher KDQOL12-MCS scores. Moreover, median E2 levels did not differ based on diabetes status (63 vs 65 pmol/L; $P = .750$).

Over the study period, 250 (58.6%) participants died, and 74 (29.6%) of those deaths were ascribed to CV-related causes. No significant associations were observed among E2, all-cause mortality (HR = 1.05; 95% CI = 0.89-1.23 per 1 – SD E2 increase), and CV mortality (HR = 0.99; 95% CI = 0.69-1.41 per 1 – SD E2 increase) after adjustment. Among 234 participants without prior CV events, 80 (34.2%) had an incident CVD event. No significant linear associations were observed between E2 and incident CVD, even after considering competing events (HR = 1.01; 95% CI = 0.83-1.22 per 1 – SD E2 increase). Age and diabetes did not significantly modify these associations (interaction *P* all ≥ .208).

We saw that models with a quadratic term for E2 might produce a better fit compared with the linear models. The Bayesian information criterion values for the quadratic models were consistently lower than those from the linear models for all-cause mortality, CVD mortality, and incident CVD. E2 showed a concave association with all-cause mortality (nonlinear $P = .022$): E2 levels below 200 pmol/L are positively associated with all-cause mortality risk, while no association or potentially a very weak inverse association was suggested for E2 levels above 200 pmol/L (Figure 2A). Although quadratic models were a better fit for our data, no significant nonlinear associations were observed between E2 and CVD mortality (nonlinear $P = .163$), or incident CVD (nonlinear $P = .385$) (Figure 2B and C).

E2 was not significantly associated with HUI3 scores (MD = 0.008; 95% CI = –0.015 to 0.031 per 1 – SD E2 increase) (Table 2). However, age modified this association ($P = .045$). Among patients aged ≥63 years, higher E2 levels were associated with lower HUI3 scores, MD = –0.062 per 1 – SD E2 increase, 95% CI = –0.112 to –0.012, but the opposite was observed in younger patients (<63 years) in whom higher E2 levels were associated with higher HUI3 scores (MD = 0.032 per 1 – SD E2 increase, 95% CI = 0.008-0.055) (Table 3).

No significant associations were observed between E2 and KDQOL12-PCS (MD = –0.15; 95% CI = –1.15 to 0.86 per 1 – SD E2 increase) or KDQOL12-MCS scores (MD = –0.63; 95% CI = –1.82 to 0.57 per 1 – SD E2 increase) (Table 2). No other significant effect modification by age or diabetes was found (all interactions $P \geq .176$).

During sensitivity analysis, women in the highest E2 tertile had higher all-cause mortality risk (HR =1.61, 95% CI =

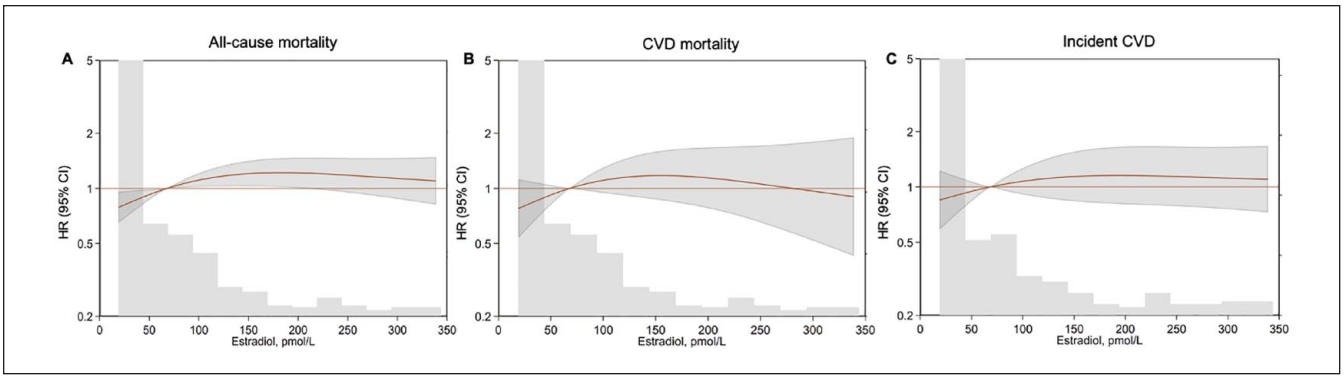

Figure 2. Nonlinear associations between E2, all-cause mortality, CVD mortality, and incident CVD.
Note. Nonlinear associations between (A) E2 and all-cause mortality (nonlinearity $P = .022$), (B) E2 and CVD mortality (nonlinearity $P = .163$), and (C) E2 and incident CVD (nonlinearity $P = .385$). In (C), the plateau in spline function at low E2 levels is likely due to the exclusion of older participants with a prior CV event. When older participants with a prior CV event were included, the spline function in Figure 2C bore closer resemblance to those of (A) and (B) (not shown). Nonlinearity was investigated by introducing a linear and quadratic term to the models with all-cause and CV mortality, as well as incident CVD outcomes. Solid line represents the estimated HRs of the spline function for all-cause mortality, CV mortality, and incident CVD. Shaded gray area represents the 95% CI of the spline HR estimation, respectively. The histograms illustrate the population density of the E2 concentrations. E2 = estradiol; CVD = cardiovascular disease; CV = cardiovascular; HR = hazard ratio; CI = confidence interval.

Table 2. Adjusted Mean Differences for HRQOL Measures per 1 – SD Higher Level of E2.

Instrument	No of measures (participants)	MD (95% CI)
HUI3	1251 (378)	0.008 (−0.015 to 0.031)[a]
KDQOL12–PCS	716 (300)	−0.145 (−1.149 to 0.859)
KDQOL12–MCS	716 (300)	−0.627 (−1.821 to 0.567)

Note. MD (95% CI) calculated per 1 – SD increment of E2 and adjusted for age, BMI, systolic blood pressure, ethnicity (white/Indigenous/other), glomerulonephritis, diabetes, CVD (stroke, transient ischemic attack, coronary artery disease, heart failure, and peripheral vascular disease), mental health (smoking status, substance misuse, and psychiatric disorder), other serious illnesses (cancer, chronic respiratory disease, chronic liver disease, and dementia), and albumin. Participants were modeled as random effects and visit timepoints (ie, baseline, month 6, years 1, 2, 5, and 10) as fixed effects. HRQOL = health-related quality of life; E2 = estradiol; MD = mean difference; CI = confidence interval; HUI3 = Health Utilities Index Mark 3 scores; KDQOL12-PCS = Kidney Disease Quality of Life Physical Component Score; KDQOL12-MCS = Kidney Disease Quality of Life Mental Component Score; BMI = body mass index; CVD = cardiovascular disease.
[a]*P* value for interaction with age = .045. Age was dichotomized into < 63 and ≥63 years.

Table 3. Adjusted Mean Differences for HUI3 Scores by Age per 1 – SD Higher Level of E2.

Age	No of measures (participants)	MD (95% CI)
<63 years	601 (187)	0.032 (0.008 to 0.055)
≥63 years	650 (191)	–0.062 (–0.112 to –0.012)

Note. MDs (95% CI) calculated per 1 – SD E2 increase and adjusted for age, BMI, systolic blood pressure, ethnicity (white/Indigenous/other), glomerulonephritis, diabetes, CVD (stroke, transient ischemic attack, coronary artery disease, heart failure, and peripheral vascular disease), mental health (smoking status, substance misuse, and psychiatric disorder), other serious illnesses (cancer, chronic respiratory disease, chronic liver disease, and dementia) and albumin. HUI3 = Health Utilities Index Mark 3 scores; E2 = estradiol; MD = mean difference; CI = confidence interval; BMI = body mass index; CVD = cardiovascular disease.

1.16-2.23) compared with women in the lowest E2 tertile. No significant associations were observed between E2 tertiles, CVD mortality, and incident CVD.

Discussion

The current study attempted to delineate associations among E2, mortality, and HRQOL using data from a prospective cohort of 427 women receiving maintenance HD in Canada. Over a median follow-up of 3.6 years (IQR = 1.6-7.5 years), significant concave associations were observed between E2 levels and all-cause mortality, but not with CVD mortality and incident CVD. Furthermore, E2 levels were not associated with HUI3, KDQOL12-PCS, or KDQOL12-MCS scores. However, the association between E2 and HUI3 scores was significantly modified by age. For every 1 – SD increase in serum E2, HUI3 scores were higher for younger women (<63 years), but were lower among older women (≥63 years). No other associations reported herein were modified by age or diabetes.

Ramesh et al[13] used the same database to analyze the relation between E2 and mortality, and found that over a shorter mean follow-up period of 2.9 years, women in the 2 highest E2 quintiles had higher all-cause mortality risk compared with those in the lowest quintile. Another study by Tanrisev et al[9] reported a U-shaped association among E2, all-cause mortality, and CVD mortality over a 3-year follow-up period among 283 women receiving maintenance HD. Both studies reported associations between higher E2 levels and increased

all-cause mortality risk,[9,13] consistent to our observations. However, the concave association between E2 and all-cause mortality contradicts with abovementioned observations of Tanrisev et al.[9] This discrepancy could be potentially attributed to the inclusion of younger participants in our study (≥18 years old), compared with Tanrisev et al[9] where only women >45 years old were included. Furthermore, Tanrisev et al measured serum E2 levels in participants who were on dialysis for >6 months, whereas E2 levels in our study were measured within 3 months of starting HD.

The mechanism for the putative association between E2 and mortality (in the general population and/or HD patients) is not well understood, although could be related to effects on the CV system or inflammation.[31] E2 deficiency could promote vascular calcification[32,33] and inflammation.[34-36] While proinflammatory cytokines can inhibit gonadal E2 production, it can stimulate aromatase activity to induce peripheral conversion of androgens to estrogens.[37] In critically ill patients with high inflammatory burden,[9,38] higher serum E2 levels have been linked with increased mortality[9,13,37,39-41]—potentially explaining a portion of the nonlinear association characterized by a positive association between E2 and all-cause mortality. The other portion toward the right-hand side, characterized by wide CIs suggesting either no association or potentially a very weak inverse association between E2 and all-cause mortality (Figure 2A), could be due to the low proportion of women with higher E2 levels. Nevertheless, causality or pathophysiological significance cannot be demonstrated due to the observational nature of these studies (including ours). Higher E2 levels among women who died do not necessarily indicate a harmful excess. Conversely, elevated E2 may not have pathophysiological significance. Higher E2 levels may simply reflect a state of poor health, and its associations with mortality in the kidney population remains unclear. Nevertheless, the null associations between E2 levels with CVD mortality and incident CVD in the current study might be due to the relatively short follow-up time (median = 3.6 years) and low number of participants reaching these endpoints.

In a 12-month study involving women aged between 18 and 45 years with kidney failure on HD with E2 levels <30 pg/mL (<110 pmol/L) and secondary amenorrhea, women given transdermal 17β-estradiol and cyclic addition of norethisterone had significantly increased mean E2 levels (from 20.5 to 46.8 pg/mL or 75 to 172 pmol/L), resumed regular menstruation, showed lower prolactin levels, and reported significantly better libido and HRQOL compared with controls.[20] These findings are consistent with our observations that for younger women on HD, higher HUI3 scores were significantly associated with higher E2 levels. In contrast, among older women on HD, lower HUI3 scores were significantly associated with higher E2 levels. This may be due to the higher prevalence of comorbidities such as CVD and diabetes among the older population, known to negatively impact HRQOL in HD patients.[6] Building on this, older women on HD in our study may have experienced a longer period of reduced EEE prior to HD initiation compared with younger women. Endogenous estrogen exposure and early menopause have been associated with increased CVD mortality,[11] lower physical health, and lower psychological well-being,[12] leading to lower HRQOL. Although the association between E2 levels and HUI3 scores among younger and older women suggest clinically important changes,[27] contextualizing minimal clinically important scores remains challenging in patients with kidney disease. Therefore, more research is needed in this area.

In a placebo-controlled randomized trial in 3721 postmenopausal women, treatment with 0.625 mg conjugated equine estrogen plus 2.5/5.0 mg medroxyprogesterone conferred small but significant improvements in HRQOL.[42] Another trial in 2763 postmenopausal women given the same treatment reported mixed effects on HRQOL, depending on whether menopausal symptoms were present: Women with flushing had improved emotional measures, whereas women without flushing had worse physical measures.[43] However, these studies were conducted among women without kidney disease. Reports on HRT usage among women with kidney failure only included surrogate outcomes.[44] Therefore, studies are still needed to assess the effects of HRT on women with kidney disease as data are still lacking.

Diabetes has been associated with altered sex hormone levels, worse cardiometabolic profile, and increased mortality risk.[7,45] Reports conflict concerning E2 levels in women with diabetes in comparison with those without diabetes,[45-47] and may not extend to those with kidney disease. Furthermore, in advanced stages of diabetes with kidney failure, the relationships of serum E2 and study outcomes might be blurred by morbidity burden and severity of kidney failure. This could explain why we did not observe effect modification by diabetes status on the relationships between serum E2 concentrations and study outcomes.

As amenorrhea is common among women on HD, ascertaining menopausal status among this patient population remains challenging.[23,48] Although menopause is defined as the secondary absence of menses for at least 12 months,[49] amenorrhea among women with kidney disease does not necessitate a postmenopausal classification as amenorrhea can be reversed with continued HD or kidney transplantation.[50,51] Due to menstrual cycle variation, E2 levels of healthy premenopausal women can range between 73.4 and 2753.5 pmol/L.[52] However, E2 levels of premenopausal women on dialysis do not vary as expected,[3,23] and can also be seen in the current study as the 75th percentile of the highest E2 tertile is 294 pmol/L (Table 3). As such, our findings are solely based on E2 levels and age.

Our study has several strengths, including data from a well-characterized HD population and a prospective, multicenter design. We were able to ascertain which participants underwent gynecological procedures and adjust for multiple confounders such as malignancies and chronic respiratory

disorders. Also, our data were collected over a relatively long follow-up period (≈14 years). Furthermore, we were able to include data for HRQOL.

Our study also has some limitations. E2 is primarily bound to sex hormone–binding globulin (SHBG), and only free fractions can bind receptors and elicit physiological responses. The unavailability of SHBG measurements precluded estimation of free E2 levels in our study. Furthermore, hormonal diagnostic cut-offs typically used to determine menopausal status are not reliable for women with kidney failure,[13] as the hormonal-hypothalamic pituitary axis is disturbed by progressive kidney disease and eventual failure.[53] Thus, the impact of menopausal status on the associations between E2 and assessed outcomes could not be evaluated in the present study. Another limitation is that we did not collect information on sex or intersex categorizations in the current study. In addition, patients dropped out over time, so we had insufficient power to address effect modification by diabetes status and outcomes of interest. Moreover, because a single E2 measurement at baseline was used, we could not monitor changes in E2 levels over time and evaluate its effects with our outcomes of interest. Nevertheless, it has been previously shown that single sex hormone measurements can adequately represent long-term sex hormone levels.[54] We also excluded participants with missing data. As those excluded were not significantly different from included participants (Supplemental Table S1), the exclusions are unlikely to have affected our study findings. Finally, despite our efforts to adjust for known risk factors, we were unable to adjust for C-reactive protein (an inflammation marker)[55] and frailty.[56] In addition, residual confounding is possible due to the nature of observational studies.

Conclusions

Data from a well-characterized prospective cohort of 427 women on HD in Canada suggest that the association between E2 and all-cause mortality may be nonlinear. Furthermore, E2 was not significantly associated with CVD mortality, incident CVD, KDQOL12-PCS, and KDQOL12-MCS. However, data for the relationship between E2 levels and HUI3 were mixed, with higher E2 levels associated with higher HUI3 scores among younger women (<63 years), and with lower HUI3 scores among older women (≥63 years). Diabetes status did not modify the relationships. Therefore, further work is warranted on the associations of E2 and adverse health outcomes among women with kidney failure on HD.

Ethics Approval and Consent to Participate

Written informed consent was obtained and relevant research ethics boards approved the study (Pro00002385, REB15-1048).

Consent for Publication

All listed authors herein consented to the publication of this paper.

Availability of Data and Materials

The data are not publicly available due to national data protection laws and restrictions imposed by relevant research ethics boards to ensure data privacy of the study participants. However, the data that support the findings of this study are available upon reasonable request from the Research Manager for the Kidney Health Research Group, Natasha Wiebe.

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Author Contributions

L.L. and A.K.B. developed the research idea and study design. L.L. and N.W. developed the statistical analysis plan. L.L. wrote the manuscript with support from N.W. and A.K.B. N.W., S.R., S.A., S.K., J.-J.C., P.Stenvinkel, M.T., and A.K.B. acquired the data. N.W. analyzed the data and its interpretation was supported by L.L., N.W., S.R., S.A., S.K., J.-J.C., P.Stenvinkel, P.Senior, M.T., A.B., and B.T. A.K.B. is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors provided critical feedback, helped shape the manuscript, and approved the final version of the manuscript.

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Supplemental Material

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