

Changes in the cardiovascular risk profile in children approaching kidney replacement therapy



Priyanka Khandelwal,^a Jonas Hofstetter,^b Karolis Azukaitis,^c Aysun Bayazit,^d Anke Doyon,^b Ali Duzova,^e Nur Canpolat,^f Ipek Kaplan Bulut,^g Lukasz Obyrck,^h Bruno Ranchin,ⁱ Dusan Paripovic,^j Sevcan Bakkaloglu,^k Harika Alpay,^l Klaus Arbeiter,^m Mieczyslaw Litwin,^h Ariane Zalozyc,ⁿ Fabio Paglialonga,^o Dagmara Borzych-Duzalka,^p Claus Peter Schmitt,^b Anette Melk,^q Uwe Querfeld,^r Franz Schaefer,^b and Rukshana Shroff,^{a,*} on behalf of the 4C and 3H study investigators

^aDivision of Pediatric Nephrology, UCL Great Ormond Street Hospital and Institute of Child Health, London, UK

^bCenter for Pediatrics and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany

^cClinic of Pediatrics, Institute of Clinical Medicine, Vilnius University, Vilnius, Lithuania

^dDepartment of Pediatric Nephrology, School of Medicine, Cukurova University, Adana, Türkiye

^eDivision of Pediatric Nephrology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Türkiye

^fDivision of Pediatric Nephrology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Türkiye

^gDepartment of Pediatric Nephrology, Ege University Faculty of Medicine, Izmir, Türkiye

^hDepartment of Nephrology, Kidney Transplantation and Arterial Hypertension, The Children's Memorial Health Institute, Warsaw, Poland

ⁱPediatric Nephrology Unit, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Université de Lyon, Lyon, France

^jDepartment of Pediatric Nephrology, University Children's Hospital, Belgrade, Serbia

^kPediatric Nephrology Unit, Gazi University Hospital, Ankara, Türkiye

^lDepartment of Pediatric Nephrology, Marmara University Medical School, Istanbul, Türkiye

^mDivision of Pediatric Nephrology and Gastroenterology, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

ⁿPediatric Nephrology Unit, Hôpital de la Haute-pierre, Strasbourg, France

^oPediatric Nephrology, Dialysis and Transplant Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

^pPediatric Nephrology Unit, Medical University of Gdansk, Gdansk, Poland

^qDepartment of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany

^rDepartment of Pediatric Gastroenterology, Nephrology and Metabolic Diseases, Charité Universitätsmedizin, Berlin, Germany

Summary

Background Despite significant cardiovascular (CV) morbidity in children on dialysis and after kidney transplantation, data on the evolution of CV damage in children with chronic kidney disease (CKD) approaching kidney replacement therapy (KRT) is unknown.

Methods The burden, progression, and predictors of CV damage before KRT onset were explored in two prospective multicenter cohorts from Europe and Canada: Cardiovascular Comorbidity in Children with CKD (4C) and Haemodiafiltration, Heart and Height (3H) studies, conducted from 2009–19 and 2013–16, respectively. CV damage and risk factors were evaluated (i) cross sectionally at KRT-start (n = 248), and (ii) longitudinally over the 2-years preceding KRT start (n = 157; 331 patient-visits). Longitudinal analyses with mixed-effects models estimated associations of modifiable CV risk factors with change in carotid intima-media thickness (cIMT) standard deviation score (SDS), pulse wave velocity (PWV-SDS), left ventricular (LV) mass and systolic dysfunction.

Findings 248 patients, age 14.3 (12.2, 16.2) years were evaluated at median 35 (28–114) days before KRT start. Elevated cIMT-SDS and PWV-SDS were present in 43% and 25%, and LV hypertrophy and systolic dysfunction in 49% and 33%. Aortic stiffness and LV hypertrophy significantly increased, especially in the year before KRT start (adjusted odds ratio, OR 0.33, P = 0.002 and OR 0.54, P = 0.01, respectively). 79% of children had >3 modifiable CV risk factors at KRT onset. Diastolic BP and BMI were strongly associated with a linear increase in all CV measures. After controlling for CV risk factors, the time to KRT onset no longer predicted the burden of CV damage.

Interpretation This comprehensive CV evaluation shows the progressive accrual of modifiable risk factors and a high burden of CV damage in the years preceding KRT onset. CV damage in the pre-KRT period is preventable.

Funding Supported by EU4Health Programme (101085068) and Kidney Research UK (RP39/2013).

eClinicalMedicine
2024;74: 102708

Published Online 3 July

2024

<https://doi.org/10.1016/j.eclinm.2024.102708>

*Corresponding author. University College London Great Ormond Street Hospital for Children and Institute of Child Health, London, WC1N 3JH, UK.
E-mail address: Rukshana.Shroff@gosh.nhs.uk (R. Shroff).

Copyright © 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Kidney replacement therapy (KRT); Carotid intima-media thickness (cIMT); Pulse wave velocity (PWV); Left ventricular mass index (LVMI); Mid-wall fractional shortening

Research in context

Evidence before this study

A systematic literature search was conducted to find longitudinal data on changes in CV measures before KRT onset in children and adolescents with advanced chronic kidney disease (CKD). PubMed was searched up to February 24, 2024, using the terms: "intima-media thickness" OR "pulse wave velocity" OR "systolic dysfunction" OR "fractional shortening" OR "left ventricular mass" OR "left ventricular hypertrophy" OR "aortic stiffness" OR "arteriopathy" OR "carotid thickness" OR "cardiac geometry"; AND "chronic kidney disease"; AND "prospectiv*" OR "longitudinal*" OR "observational OR follow-up"; AND "adolescent OR adolescen*" OR "child*" OR "pediatr*" OR "paediatr*". Nine studies examining predictors of time-varying left ventricular hypertrophy, cardiac structure and function, and pulse wave velocity were identified, however, patients with mild-moderate CKD were included, the vast majority of whom did not require KRT. The relationship between modifiable CV risk factors with evolution of CV damage in the years preceding KRT was not evaluated.

Added value of this study

This prospective study enrolled 248 children and adolescents with advanced CKD (stages 4–5) from two independent multicenter prospective cohorts and examined 331 patient-visits within 2-years before KRT start. Multiple abnormal CV measures and CV risk factors were present in 80–90% of patients approaching KRT. CV damage progressively accumulated over time, particularly one year before KRT onset. Modifiable risk factors, especially diastolic BP and body mass index were strongly associated with a linear increase in CV damage over time. After controlling for CV risk factors, the time to KRT onset no longer predicted CV damage.

Implications of all the available evidence

In the years preceding KRT onset children have accrued a high burden of CV damage, largely associated with traditional and uremic risk factors. Risk factors for CV damage are modifiable and their early diagnosis and management before KRT onset is crucial to mitigate CV damage.

Introduction

Cardiovascular (CV) disease is the leading cause of death in children receiving kidney replacement therapy (KRT).¹ According to the American Heart Association, children with end-stage kidney disease are at the highest risk for developing CV disease.² Converging evidence from epidemiological, clinical, and basic science research indicates that dialysis initiation is associated with exposure to CV risk factors leading to well-recognized complications of maladaptive cardiomyopathy, accelerated athero- and arteriosclerosis, and vascular calcification, with increased risk of adverse CV outcomes.³ While intensified dialysis and pre-emptive transplantation may mitigate the progression of sub-clinical CV damage,^{4,5} CV mortality remains unacceptably high, accounting for ~30% of all deaths on dialysis and after transplantation.¹ This suggests that the burden of CV damage accrued before KRT onset cannot be ameliorated by KRT and may continue to influence long-term outcomes.

Validated measures to evaluate subclinical CV disease include carotid artery intima-media thickness (cIMT) and pulse wave velocity (PWV), which indicate arteriosclerosis and arterial stiffness respectively, and abnormalities in left ventricular (LV) mass and systolic function. These CV measures have been associated with future CV events in

adults.^{6–8} Although changes in CV measures are well documented in children on dialysis or after kidney transplantation, little is known about the evolution of CV damage and its association with CV risk factors in the pre-KRT chronic kidney disease (CKD) population,^{9–12} with no longitudinal studies that examine the evolution of morphological and functional CV changes in advanced pre-KRT CKD. We hypothesized that children with pre-KRT CKD have a high burden of modifiable CV risk factors that lead to structural and functional CV damage. Therefore, we comprehensively examined the burden, progression and predictors of CV damage in the years preceding KRT onset in patients from two international prospective pediatric CKD cohorts.

Methods

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study design and participants

Patients were included from two prospective multicenter cohort studies: the Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) study and the Haemodiafiltration, Heart and Height (3H) study,

both with published study designs and primary outcomes.^{4,13,14} The 4C study is a prospective cohort of CKD patients aged 6–17 years with an estimated glomerular filtration rate (eGFR) between 10 and 60 ml/min/1.73 m² enrolled from 55 centers in 12 European countries. The 3H study is a multicenter, non-randomized, parallel-arm interventional study comparing CV outcomes on different dialysis modalities in children between 5 and 20 years of age from 28 paediatric dialysis centers in 10 countries across Europe and Canada. Details of study design and investigations are in [Supplementary Methods S1](#) (p.2).

We identified patients already enrolled in these cohorts who had CKD stages 4–5 approaching KRT, and those with a study visit up to 200 days before or 20 days after KRT start (time point T₀) were included. Data from visits up to 750 days before time point T₀ were included for longitudinal assessment. These visits occurred approximately one (n = 110) and two years (n = 64) before KRT start (time points T₋₁ and T₋₂; [Fig. 1](#)).

CV measures

Vascular and echocardiographic measures including carotid intima-media thickness (cIMT), pulse wave velocity (PWV), left ventricular (LV) mass index and mid-wall fractional shortening were measured in the 4C and 3H studies following identical protocols as previously described.^{13–15}

I Carotid intima-media thickness: Briefly, high-resolution ultrasound of the common carotid

artery was used to obtain cIMT measurements using a portable 8-MHz annular array ultrasound device (Acuson P50; Siemens Medical Solutions USA, Inc.) with integrated digital image evaluation software (Syngo US Workplace; Siemens Medical Solutions USA, Inc), according to the Mannheim consensus.¹⁶ Five segments of the left and right common carotid artery in the anterior-posterior projection were examined and averaged. All examinations were performed by eight trained investigators as described previously.^{14,16} cIMT values were normalized to derive age and sex-specific standard deviation scores (SDS) from published reference ranges.¹⁶

II Pulse wave velocity: Aortic PWV was measured with a validated oscillometric Vicorder device using the distance from the suprasternal notch to the femoral recording point via the umbilicus as path length, according to a standardized procedure.¹⁷ Briefly, patients were investigated in a quiet room after 15 min of rest. Measurements were performed in a supine position with head and shoulders tilted to approximately 30°. The neck cuff was placed with the neck pad over the right carotid artery. The thigh cuff was placed on the patient's upper right thigh and tightened. No talking or moving was allowed during the measurements. Three measurements each capturing at least 10 beats with good quality waves were performed, and the mean value used for further analysis. PWV was standardized to derive sex and height-specific SDS from published

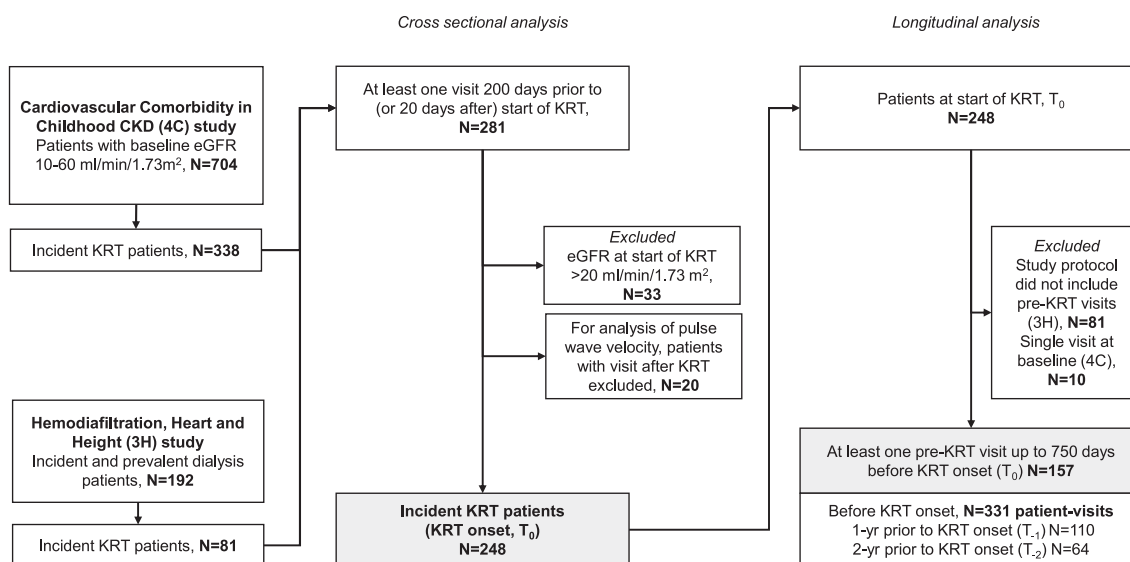


Fig. 1: Flow of study participants included from the prospective 4C and 3H study cohorts. Parameters at initiation of kidney replacement therapy (KRT) were analysed cross-sectionally in 248 patients (T₀). Of these, 157 patients with at least one visit before KRT initiation were included for longitudinal analyses. Data at visits 1-year (T₋₁) and 2-year (T₋₂) prior to KRT start were available in 110 and 66 patients respectively. CKD chronic kidney disease, eGFR estimated glomerular filtration rate.

reference ranges.¹⁷ PWV standardized to height has been used in the present analysis, based on previous data showing underestimation of PWV when standardized to age in a growth-restricted population¹⁸; data on PWV standardized to age is shown as [Supplementary Analysis](#).

- III *Left ventricular mass index*: Two-dimensional transthoracic echocardiography was performed in accordance with the guidelines of the American Society of Echocardiography.¹⁹ LV mass was analysed from LV wall thickness and chamber dimensions, that were viewed on the parasternal long axis or M-mode short axis at the midventricular level, on three consecutive beats.¹⁹ LV mass index was defined as the ratio of LV mass to $(\text{height}^{2.16} + 0.09)$ for age-independent normalization of LV mass. LV mass index $\geq 45.0 \text{ g/m}^{2.16}$, representing the 95th percentile, was defined as LV hypertrophy²⁰; this partition value showed no false-positivity for identification of LV hypertrophy in previous validation cohorts.²⁰ Relative wall thickness was normalized to age, and a cutoff value of 0.38, was used to define concentric geometry.²¹ Mid-wall fractional shortening was calculated as suggested by Lang et al.¹⁹ and, systolic dysfunction was defined as mid-wall fractional shortening $< 15.7\%$.¹¹

Modifiable risk factors

We examined modifiable (*i*) traditional CV risk factors: body mass index (BMI) SDS, level of physical activity (< 1 , $1-2$, ≥ 3 h/week), and blood pressure (BP SDS, both clinic and ambulatory (classification detailed in [Supplementary Methods S1](#)), (*ii*) uremic risk factors: calcium, phosphate, intact parathyroid hormone (iPTH), hemoglobin, bicarbonate, albumin, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride, and (*iii*) urine albumin-creatinine ratio.

Statistical analysis

Data were summarized as median (interquartile range) and number (percentage), as appropriate, and analysed using R version 4.3.2. (R Core Team 2021). Right-skewed continuous variables used in regression analyses were log-transformed, as required. The 'nlme' package was used for longitudinal linear mixed-effect modelling. Tests for significance between groups included the Wilcoxon rank-sum and Chi-squared test. Two-tailed $P < 0.05$ was considered significant.

The evolution of CV risk factors and CV measures (cIMT-SDS, PWV-SDS, LV mass index and mid-wall fractional shortening) was studied in 157 patients with pre-KRT measurements available at T_0 as well as at T_{-1} , T_{-2} , or both. The average rate of change (linear slope) of each parameter was estimated by longitudinal linear mixed-effect models with random patient-level

intercepts while statistically controlling for patients' visit age, sex, and country. A supplementary analysis was performed to restrict these analyses to patients with non-glomerular disease. Changes in the prevalence of elevated cIMT and PWV (defined as > 2 SDS for both), LV hypertrophy and systolic dysfunction (mid-wall fractional shortening $< 15.7\%$) were analysed by longitudinal logistic mixed-effect regression with random patient-level intercepts, statistically controlling for patients' visit age, sex, and country.

These association between *CV risk factors with CV measures* were tested separately for the entire patient sample ($n = 248$) at KRT onset using multivariable linear regression, and longitudinally within patients ($n = 157$) across the 2-year observation period by multivariable linear mixed-effect models with random patient-level intercepts. The final set of covariates per modelled cardiovascular measure was determined using Akaike information criterion (AIC)-based variable backward elimination. The starting set of explanatory covariates comprised those that were always retained in the final model such as visit age, sex, country, time-varying estimated GFR, (and time to KRT onset in the case of linear mixed-effect models), and all CV risk factors including BMI SDS, etiology (glomerular/non-glomerular), systolic BP SDS, diastolic BP SDS, 24-hr mean ambulatory blood pressure (MAP) SDS, calcium, phosphate, intact parathyroid hormone (iPTH), hemoglobin, bicarbonate, albumin, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride, high-sensitivity C-reactive protein (hs-CRP), and urine albumin-creatinine ratio. To ensure estimation precision for the effects of risk factor covariates multicollinearity was reduced by including systolic BP SDS, diastolic BP SDS, and 24-hr MAP SDS in separate models. Variance inflation factors were calculated for all candidate explanatory covariates in linear and logistic mixed-effects models before variable backward elimination and never exceeded a value of 4. As urine albumin levels were only measured in a subgroup at KRT onset, it was considered in a separate model.

To determine the association of structural and functional CV measures, the association over time of (*i*) cIMT-SDS with PWV-SDS, and (*ii*) LV mass index with mid-wall fractional shortening were analysed. To find the association of cIMT-SDS with PWV-SDS over time, multivariable linear mixed-effect models with patient-level random intercepts were employed, statistically controlled for patients' age, sex, and country, (and additionally for systolic BP and diastolic BP in different models) in 3 subgroups: patients with (*i*) elevated cIMT at all time points T_0 , T_{-1} and T_{-2} (*ii*) elevated cIMT at any time-point T_0 , T_{-1} or T_{-2} , (*iii*), and normal cIMT (≤ 2 SDS) at all time points. The association between LV mass index and mid-wall fractional shortening was examined in a multivariable linear mixed-effect model with patient-level random intercepts, statistically

controlled for patients' age, sex, and country (and additionally for systolic BP and diastolic BP in different models).

Ethics statement

Ethical aspects and details of the data acquisition are described elsewhere.^{13,14} Both the 4C and 3H studies were designed and performed according to the Declaration of Helsinki. The protocols were approved by each local institutional review boards. Written informed consent was obtained from the parents and adolescents, and assent from younger children.

Role of the funding source

The study sponsors had no role in the study design; access to the dataset; collection, analysis or interpretation of data; writing of the report; or the decision to submit the paper for publication. Prof. Shroff and Prof. Schaefer had full access to the dataset and were responsible for the decision to submit for publication.

Results

Characteristics of patients

A total of 248 patients of median age 14.3 (12.2, 16.2) years, were evaluated at a median of 35 (28, 114) days before KRT start (T_0), with a median eGFR of 12.2 (8.1, 14.6) ml/min/1.73 m². The study flow is shown in Fig. 1 and Table 1 shows their characteristics at T_0 . Parameters of 157 of 248 patients included for longitudinal analysis were similar to the overall cohort (Supplementary Table S1).

Modifiable CV risk factors

Patients had a high prevalence of modifiable CV risk factors including anemia (52%), metabolic acidosis (60%), hyperphosphatemia (58.1%), hyperparathyroidism (72.5%), and dyslipidemia (35.7% had ≥ 2 abnormal lipid levels) at KRT start (Table 2). Hypertension was present in 127 (51.2%) patients. Among 170 patients with ABPM records, ambulatory hypertension was present in 80 (47.1%) and masked hypertension in 25 (14.6%). Of 84 (38.4%) patients receiving antihypertensive agents, >2 agents were prescribed in 43 (19.6%). Uncontrolled hypertension was present in 40 of 66 (60.6%) patients prescribed antihypertensive agents, while a further 48 (50%) with ambulatory hypertension were untreated. 15 (6%) were obese, 55 (22.2%) overweight and 81 (34%) performed little or no physical activity. Multiple CV risk factors occurred concurrently with 91.9% and 78.6% of the cohort having >2 and >3 CV risk factors, respectively.

CV risk factors worsened with CKD progression from T_{-2} to T_0 (adjusted eGFR slope, -4.72 ± 0.35 ml/min/1.73 m² per year; Table 2). Median 24-hr MAP SDS was elevated at 1.6 (0.4, 2.4) SDS at KRT onset ($N = 106$) and remained constantly elevated over time (Table 2). Levels

of phosphate, iPTH, and triglyceride showed linear increases with time until KRT start ($P < 0.001$ for all, Table 2). Analysis in a subgroup of patients with non-glomerular etiology ($N = 147$) showed similar slope coefficients (Supplementary Table S2).

The CV risk profile of patients starting dialysis ($n = 166$) or pre-emptive transplant recipients ($n = 82$) is shown in Table 1. Median eGFR at KRT onset was significantly lower in the dialysis group (10.6 vs. 13.8 ml/min/1.73 m²; $P < 0.001$). On adjusting for eGFR at KRT onset, diastolic BP SDS was higher in the dialysis group (Table 1). Also, hemoglobin and albumin concentrations were lower, and iPTH and hs-CRP higher in patients starting dialysis (Table 1).

CV measures

CV measures at KRT onset

In total, 175 (75.8%) patients had at least one abnormal CV measure at KRT start, defined by an elevated cIMT, PWV, LV hypertrophy or systolic dysfunction. Elevated cIMT and PWV (defined as values > 2 SDS) were present in 98 (42.6%) and 58 (24.8%) patients at KRT start, respectively. LV hypertrophy and systolic dysfunction were present in 111 (49.3%) and 47 (32.9%) patients, respectively. Patients with concentric LV hypertrophy, present in 70 (31.1%), had higher prevalence of systolic dysfunction compared to those with eccentric LV hypertrophy (54% versus 8%, respectively; $P < 0.001$).

PWV-SDS at KRT onset was higher in patients starting dialysis than in those receiving a pre-emptive kidney transplant, but was comparable between the groups when adjusted for eGFR at KRT onset (Table 1) cIMT-SDS, LV mass index and mid-wall fractional shortening were comparable (Table 1).

Changes in CV measures in the years preceding KRT onset

The trajectory of CV measures over the 2-year observation period is shown in Fig. 2. A longitudinal linear mixed-effect model analysis controlling for visit age, sex and country showed a significant increase in PWV-SDS and LV mass index over the 2-years preceding KRT onset ($\beta = 0.18 \pm 0.08$ SDS per year; $P = 0.02$, and $\beta = 2.04 \pm 0.73$ g/m^{2.16} per year; $P = 0.006$, respectively; Table 2). The population-level average of cIMT-SDS and mid-wall fractional shortening remained unchanged in the 2-year observation period until KRT onset (Fig. 2) which was corroborated by a non-significant slope in a longitudinal linear mixed-effect model (Table 2). Fig. 3 shows the prevalence of elevated cIMT, elevated PWV, LV hypertrophy and systolic dysfunction during follow-up. The prevalence of elevated PWV-SDS significantly increased with time in the year prior to KRT-onset from T_{-1} to T_0 (adjusted odds ratio, OR 0.33, 95% CI 0.17–0.66, $P = 0.002$; Fig. 3, Supplementary Table S3). Similarly, proportion of patients with LV hypertrophy, chiefly concentric in geometry, significantly increased over 2-years follow-up from T_{-2} to T_0 (adjusted OR 0.54,

Characteristic	Total N = 248	Initiating dialysis, N = 166	Pre-emptive transplant, N = 82
Age, years	14.3 (12.2, 16.2)	14.4 (12.2, 16.4)	14.0 (12.2, 16.1)
Boys	155 (62.5)	98 (59.0)	57 (69.5)
eGFR, ml/min/1.73m ²	12.2 (8.1, 14.6)	10.6 (6.8, 14.2)	13.8 (12.1, 15.7)
Height SDS	-1.6 (-2.6, -0.5)	-1.8 (-2.8, -0.6)	-1.0 (-2.0, 0.2)
Years with eGFR <60 ml/min/1.73 m ²	7.3 (4.0, 12.3)	6.2 (4.0, 11.5)	8.9 (4.0, 13.0)
Etiology			
Non-glomerular	224 (90.3)	144 (86.8)	80 (97.6)
Glomerular	24 (9.7)	22 (13.3)	2 (2.4)
Systolic blood pressure, SDS	1.3 (0.3, 2.2)	1.4 (0.4, 2.4)	1.0 (0.1, 1.9)
Diastolic blood pressure, SDS	0.9 (0.1, 1.6)	0.9 (0.2, 1.8)	0.6 (0.1, 1.3)
24-h MAP, SDS ^a	1.9 (0.7, 2.7)	2.0 (0.7, 3.0)	1.6 (0.3, 2.1)
Body mass index SDS	0.0 (-0.8, 0.8)	-0.1 (-0.9, 0.9)	0.2 (-0.6, 0.9)
Physical activity			
<1 h/week	81 (34.0)	53 (33.3%)	28 (35.4%)
1-2 h/week	102 (42.9)	72 (45.3%)	30 (38.0%)
≥3 h/week	55 (23.1)	34 (21.4%)	21 (26.6%)
Cardiovascular measures			
Carotid intima-media thickness SDS	1.65 (1.04, 2.52)	1.7 (1.1, 2.5)	1.8 (1.2, 2.4)
Pulse wave velocity SDS	0.89 (-0.28, 2.03)	1.3 (-0.1, 2.2)	0.5 (-0.4, 1.3)
Left ventricular mass index, g/m ^{2.16}	44.4 (36.4, 57.2)	44 (35, 57)	44 (37, 54)
Left ventricular hypertrophy	111 (49.3)	77 (50)	34 (47.9)
Concentric	70 (31.1)	46 (29.9)	24 (33.8)
Eccentric	41 (18.2)	31 (20.1)	10 (14.1)
Concentric left ventricular modelling	42 (36.8)	28 (18.2)	14 (19.7)
Mid-wall fractional shortening, % ^a	17.0 (15.1, 19.2)	16.8 (15.0, 18.6)	17.4 (15.2, 19.4)
Systolic dysfunction ^a	47 (32.9)	22 (31.9)	25 (33.8)
Biochemistry			
Hemoglobin, g/dL	10.9 (9.9, 11.9)	10.7 (9.7, 11.7)	11.4 (10.2, 12.2)
Albumin, g/dL	4.1 (3.7, 4.4)	4.0 (3.6, 4.3)	4.1 (3.8, 4.5)
Calcium, mg/L	9.5 (8.8, 10.1)	9.3 (8.7, 9.9)	9.7 (9.0, 10.4)
Phosphorus, mg/L	5.4 (4.8, 6.5)	5.5 (4.8, 6.6)	5.2 (4.7, 6.3)
25-hydroxy Vitamin D, ng/mL ^a	20.6 (9.4, 34)	22.4 (10, 34.2)	13.6 (6.3, 27.2)
Intact PTH, pg/mL	476 (179, 165)	988 (291, 2828)	165 (59, 475)
Bicarbonate, mEq/L	21 (18.3, 23.5)	21 (18.1, 23)	21.6 (19, 24)
LDL cholesterol, mg/dL	89 (68, 111)	86 (64, 105)	98 (73, 124)
HDL cholesterol, mg/dL	44 (36, 52)	43 (35, 50)	47 (37, 57)
Triglyceride, mg/dL	144 (114, 197)	143 (114, 191)	144.3 (114, 212)
C-reactive protein, mg/dL	0.12 (0.03, 0.34)	0.13 (0.05, 0.45)	0.05 (0.02, 0.19)
Urine-albumin-creatinine ratio, g/g ^a	1.5 (0.4, 3.2)	2.0 (0.5, 3.4)	0.9 (0.2, 2.2)
Therapy^a			
Antihypertensive agents			
RAASi	31 (14.2)	27 (17.8)	4 (6.0)
Calcium channel blockers	58 (23.4)	44 (29.0)	14 (20.9)
Beta blockers	21 (8.5)	17 (11.2)	4 (5.9)
Diuretics	8 (3.2)	7 (4.7)	1 (1.5)
Nil	135 (61.6)	89 (58.6)	46 (68.7)
Phosphate binders			
Calcium based	75 (34.3)	60 (36.1)	15 (18.3)
Non-calcium based	62 (28.3)	54 (32.5)	8 (9.8)
Erythropoiesis stimulating agent	125 (57.1)	100 (20.2)	25 (30.5)

Values are median (interquartile range) or N (%). eGFR estimated glomerular filtration rate, HDL high density lipoprotein; LDL low density lipoprotein cholesterol, MAP mean ambulatory blood pressure, PTH parathyroid hormone, SDS standard deviation score, RAASi renin angiotensin aldosterone synthase inhibitor. SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; albumin to grams per liter, multiply by 10.0; calcium to millimoles per liter, multiply by 0.25; phosphorus to millimoles per liter, multiply by 0.323; 25-hydroxy Vitamin D, to nanomoles per liter, multiply by 2.496; Intact PTH to nanograms per liter, multiply by 1.0; bicarbonate to millimoles per liter, multiply by 1.0; LDL cholesterol to millimoles per liter, multiply by 0.0259; HDL cholesterol to millimoles per liter, multiply by 0.0259; triglyceride to millimoles per liter, multiply by 0.0113; C-reactive protein, to milligrams per liter, multiply by 10.0. ^a24-h mean arterial pressure, mid-wall shortening/systolic dysfunction, 25-hydroxy vitamin D, urine albumin and information on therapy available 170, 143, 114, 163 and 219 patients in the whole cohort, respectively.

Table 1: Clinical and biochemical characteristics at onset of kidney replacement therapy.

Parameters	Cut-off	Prevalence, % (95% CI) N = 248	Slope ± SE ^a (unit per year) N = 157	P
eGFR, ml/min/1.73m ²	-	-	-4.72 ± 0.35	<0.001
Cardiovascular measures				
Carotid intima-media thickness SDS	>2	42.6 (36.3, 49.1)	0.02 ± 0.08	0.83
Pulse wave velocity SDS	>2	24.8 (19.6, 30.8)	0.18 ± 0.08	0.02
Left ventricular mass index, g/m ^{2.16}	>45	49.3 (42.8, 55.9)	2.04 ± 0.73	0.006
Mid-wall fractional shortening, % ^b	<15.7	32.9 (25.2, 40.6)	-0.24 ± 0.26	0.35
Risk factors				
Body mass index SDS	>1.04	22.2 (17.4, 27.8)	0.04 ± 0.05	0.43
Systolic blood pressure SDS	≥2	29.8 (24.4, 35.9)	0.29 ± 0.10	0.003
Diastolic blood pressure SDS	≥2	16.5 (12.4, 21.7)	0.16 ± 0.07	0.03
24-hr mean ambulatory pressure SDS ^c	≥2	47.1 (39.6, 54.6)	0.19 ± 0.13	0.14
Hemoglobin, g/dL	<11.0	52.0 (45.7, 58.3)	-0.18 ± 0.09	0.05
Bicarbonate, mEq/L	<22.0	60.0 (53.6, 66.1)	-0.10 ± 0.21	0.62
Calcium, mg/L	<8.8	20.3 (15.6, 25.9)	0.02 ± 0.02	0.20
Phosphate, mg/L	5-16 yr > 5.8 >16 yr > 4.8	58.1 (51.8, 64.1)	0.16 ± 0.02	<0.001
Intact PTH, pg/mL	>200	72.5 (66.5, 77.8)	7.62 ± 2.21	<0.001
LDL cholesterol, mg/dL	≥130	13.6 (9.7, 18.5)	0.82 ± 2.14	0.70
HDL cholesterol, mg/dL	<40	65.5 (59.2, 71.4)	-1.44 ± 0.83	0.09
Triglyceride, mg/dL	<10-yr: ≥100 ≥10-yr: ≥130	64.4 (58.2, 70.3)	19.9 ± 4.53	<0.001
Albumin, g/dL	<4.0	42.5 (36.4, 48.9)	0.25 ± 0.36	0.49

CI confidence intervals, eGFR estimated glomerular filtration rate, HDL high density lipoprotein; LDL low density lipoprotein, PTH parathyroid hormone, SDS standard deviation score. SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; albumin to grams per liter, multiply by 10.0; calcium to millimoles per liter, multiply by 0.25; phosphorus to millimoles per liter, multiply by 0.323; Intact PTH to nanograms per liter, multiply by 1.0; bicarbonate to millimoles per liter, multiply by 1.0; LDL cholesterol to millimoles per liter, multiply by 0.0259; HDL cholesterol to millimoles per liter, multiply by 0.0259; triglyceride to millimoles per liter, multiply by 0.0113. ^aSlope estimates and standard errors (SE) are obtained from a linear-mixed-effect model which adjusted for patients' visit age, sex, and country; linear mixed-effect models were specified with patient-level random intercepts and were applied to N = 157 patients with visits at KRT onset (T₀) and at least one pre-KRT visit (at T₋₂, T₋₁, or both). Positive linear slope estimates indicated increasing parameters towards KRT onset, and vice versa. ^bN = 143 available for calculation of prevalence and slope. ^cN = 170 and N = 106 available for calculation of prevalence and slope.

Table 2: Prevalence of abnormal cardiovascular measures and risk factors at onset of kidney replacement therapy (KRT) and the change in the two years preceding KRT onset.

95% CI 0.34–0.87; $P = 0.01$, [Fig. 3](#); and adjusted OR 0.55, 95% CI 0.34–0.88; $P = 0.01$; [Supplementary Table S4](#)). Although the prevalence of systolic dysfunction increased from 20.7% at T₋₂ to 32.9% at KRT start, it was not statistically significant ($P = 0.13$; [Fig. 3](#)).

Association between structural and functional CV measures

The proportion of patients with structural CV damage (elevated cIMT-SDS, LV hypertrophy) significantly exceeded those with functional abnormalities (elevated PWV-SDS, systolic dysfunction) at all time points (Chi-squared $P < 0.01$; [Fig. 3](#)). Positive linear increase in PWV-SDS was associated with higher cIMT in a longitudinal linear mixed-effect model adjusted for visit age, sex, country and time-varying eGFR ($\beta = 0.13$, 95% CI 0.06, 1.91; $P = 0.06$), with this association reaching statistical significance when limited to patients with elevated cIMT-SDS ($\beta = 0.61$, 95% CI 0.12–1.10; $P = 0.03$), even after controlling for systolic and diastolic BP ($\beta = 0.71$, $P = 0.01$ and $\beta = 0.66$, $P = 0.02$, respectively; [Supplementary Table S5](#)). A linear decrease in mid-wall fractional shortening was associated with higher LV mass index in a

longitudinal linear mixed-effect model adjusted for visit age, sex, country and time-varying eGFR ($\beta = -0.06$, 95% CI -0.03 , -0.09 ; $P < 0.001$); the association remained significant on adjusting for systolic and diastolic BP ([Supplementary Table S6](#)).

Predictors of changes in CV measures

The predictors of CV measures in multivariable regression models at KRT onset are shown in [Supplementary Tables S7 and S8](#). On multivariable longitudinal linear mixed-effect model analysis, diastolic BP ($\beta = 0.15$, $P = 0.02$), BMI SDS ($\beta = 0.14$, $P = 0.02$), and iPTH ($\beta = 0.005$, $P = 0.01$) were significant predictors of cIMT-SDS over time till KRT start ([Table 3](#); model with best fit highlighted). PWV-SDS showed significant positive linear relationships with diastolic BP ($\beta = 0.15$, $P = 0.03$), 24-hr MAP ($\beta = 0.31$, $P < 0.001$), BMI SDS ($\beta = 0.19$, $P = 0.01$), physical activity of less than 1–2 h/week ($\beta = -0.41$, $P = 0.04$), high levels of LDL-C ($\beta = 0.01$, $P < 0.001$), and hypoalbuminemia ($\beta = -0.04$, $P = 0.04$) ([Table 3](#)). LV mass index showed positive linear association with systolic and diastolic BP

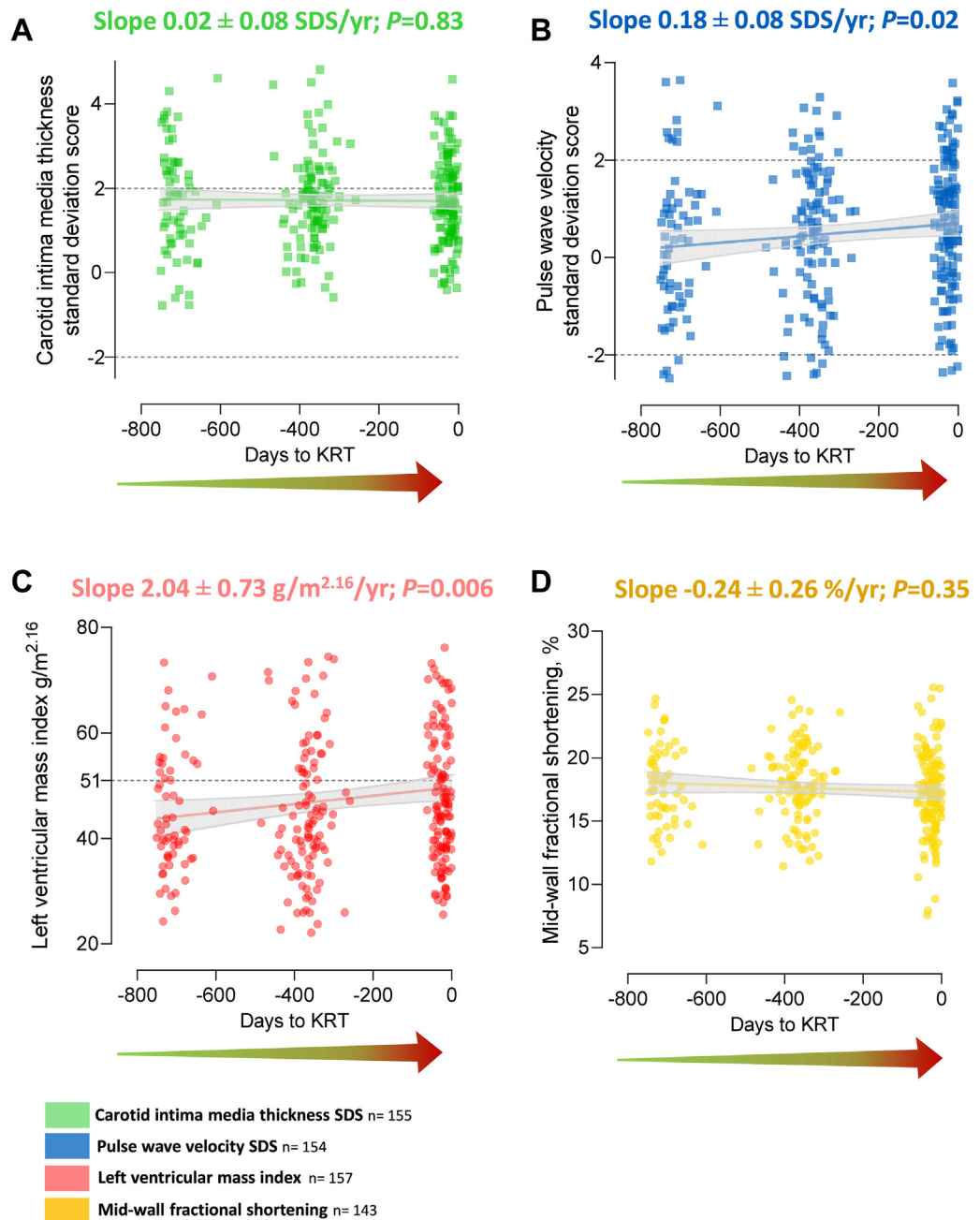


Fig. 2: Scatter plots showing (A) carotid intima-media thickness standard deviation score (SDS), (B) pulse wave velocity SDS, (C) left ventricular mass index, and (D) mid-wall fractional shortening in the 2-years prior to kidney replacement therapy (KRT) onset. Lines show predicted mean trajectory, grey areas are 95% confidence intervals. Slopes (\pm standard errors) represent one unit (SDS, g/m^{2.16} or %) change per year and are regression coefficients obtained in a linear mixed-effect model with patient-level random intercepts, controlling for patients' visit age, gender and country.

in separate models ($\beta = 1.32$, $P = 0.005$; $\beta = 1.44$, $P = 0.02$), and with BMI SDS ($\beta = 1.85$, $P = 0.006$), physical activity of less than 3 h/week ($\beta = -5.4$, $P = 0.008$), metabolic acidosis ($\beta = -0.66$, $P = 0.005$), hypoalbuminemia ($\beta = -0.35$, $P = 0.01$), and eGFR

($\beta = -0.46$, $P = 0.003$) (Table 3). Low serum albumin predicted significant increase of mid-wall fractional shortening over time in all models ($\beta = 0.08$, $P = 0.04$). Models with PWV standardized to age are shown in Supplementary Table S9.

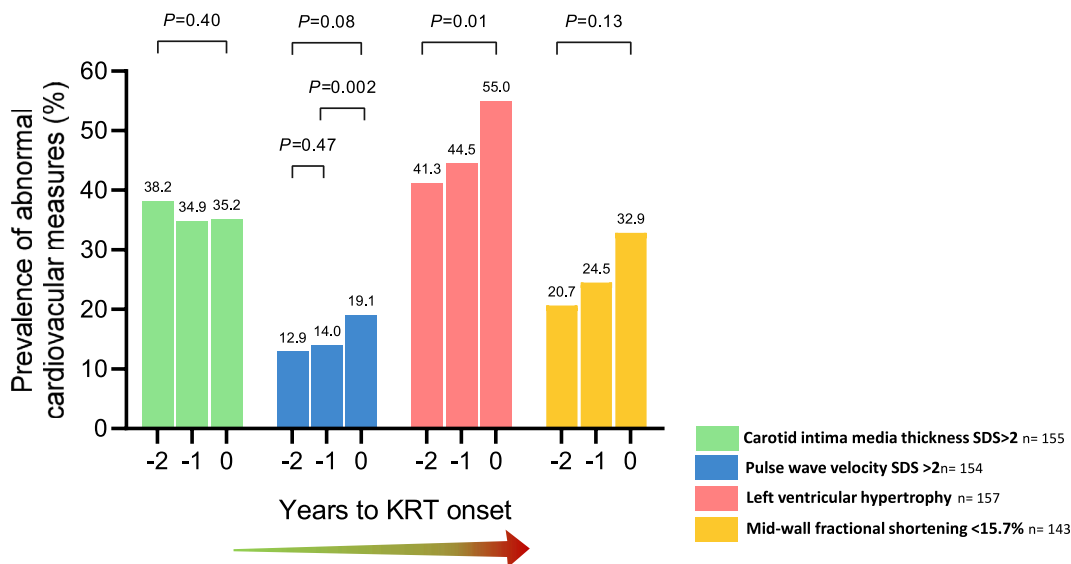


Fig. 3: Prevalence of cardiovascular damage in the form of elevated carotid intima-media thickness (>2 standard deviation score (SDS)), elevated pulse wave velocity (>2 SDS), left ventricular hypertrophy (left ventricular mass index >45 g/m^{2.16}) and systolic dysfunction (mid-wall fractional shortening <15.7%) at onset, 1-yr and 2-yr before onset of kidney replacement therapy (KRT). P values represent change in prevalence per year, obtained from a logistic mixed-effect model with patient-level random intercepts, controlling for patients' visit age, gender, and country. Prevalence of elevated elevated carotid intima-media thickness SDS was higher than elevated pulse wave velocity SDS (Chi squared $P < 0.001$, at all time points), prevalence of left ventricular hypertrophy was higher than systolic dysfunction (Chi squared $P < 0.001$, $P = 0.002$ and $P = 0.01$, at onset, 1-yr and 2-yr before KRT start, respectively).

The inclusion of identified risk factor effects in the above longitudinal linear mixed-effect models resulted in non-significant linear slopes, indicating that time to KRT onset ceases to be a predictive covariate for patients' burden of CV damage when the known modifiable risk factors are adjusted for (Table 3).

Discussion

This study comprehensively evaluates the longitudinal progression and predictors of CV damage in children with pre-KRT CKD. The study found that three-quarters of patients showed evidence of subclinical CV damage, and nearly 80% had >3 modifiable traditional or uremic risk factors at KRT start. CV damage measures progressively accumulated over time, particularly one year before KRT onset. Modifiable CV risk factors, especially BP and BMI, strongly associated with and influenced the linear increase in CV damage with time. Notably, our statistical models confirm that the linear slopes of CV measures become non-significant once the associated CV risk factors are controlled for, indicating that the progression of CV damage is not inevitable. Children have a lifetime of KRT ahead of them, so early intervention before KRT start is essential to mitigate CV damage, as shown by a randomized controlled trial in adults²² and a post-hoc analysis of the ESCAPE trial,¹¹ demonstrating lower post-dialysis CV mortality,²²

regression of LV mass index,¹¹ and systolic dysfunction¹¹ with strict pre-KRT BP control.

Although we do not have hard outcome measures in pediatric studies, measures of subclinical CV damage are validated predictors of future CV mortality. cIMT, a well-established surrogate measure of coronary artery disease, has been correlated with hard endpoints including strokes and myocardial infarction in adults without CKD²³ and CV events in CKD.⁶ Similarly, increased PWV has been associated with higher mortality rates even in young adults on dialysis⁶ and improved the prediction of CV mortality-risk in pre-KRT CKD beyond classical risk factors.⁷ Systolic dysfunction, a well-recognized consequence of CKD progression in adults, predicts cardiac failure and mortality in KRT.⁸ Therefore, subclinical CV damage well before KRT start in our cohort, has important clinical relevance. Previous studies have examined the trajectory of PWV-SDS,²⁴ cIMT-SDS,²⁵ LV mass index,^{9,11,12} and mid-wall fractional shortening,^{11,26} but also included patients with mild-moderate CKD who did not progress to require KRT.

We found a significant linear increase in arterial stiffness and LV mass in the years preceding KRT, similar to findings in adults with advanced CKD.^{27,28} The progressive accumulation of CV damage measures, especially one year before KRT start, emphasizes the need to consider CV health when determining the

Parameters	Model 1: Inclusion of systolic BP SDS, N = 157			Model 2: Inclusion of diastolic BP SDS, N = 157			Model 3: Inclusion of 24-hr mean ambulatory pressure (MAP) SDS, N = 106				
	β	95% CI	P	Parameters	β	95% CI	P	Parameters	β	SE	P
Predictors of carotid intima-media thickness SDS											
(Intercept)	2.25	1.40, 3.10	<0.001	(Intercept)	2.20	1.37, 3.04	<0.001	(Intercept)	2.34	1.12, 3.56	<0.001
Years to KRT onset	0.16	-0.08, 0.40	0.21	Years to KRT onset	0.17	-0.07, 0.41	0.17	Years to KRT onset	0.22	-0.12, 0.57	0.21
Systolic BP SDS	0.05	-0.04, 0.14	0.27	Diastolic BP SDS	0.15	0.03, 0.26	0.02	24-hr MAP SDS	0.09	-0.02, 0.19	0.13
BMI SDS	0.13	0.02, 0.24	0.02	BMI SDS	0.14	0.03, 0.24	0.02	-	-	-	-
iPTH	0.005	0.00, 0.01	0.02	iPTH	0.005	0.001, 0.01	0.01	iPTH	0.01	0.00, 0.01	0.02
Predictors of pulse wave velocity SDS											
(Intercept)	-2.37	-4.52, -0.21	0.04	(Intercept)	-1.34	-4.52, 0.42	0.14	(Intercept)	-3.36	-5.31, -1.4	0.001
Years to KRT onset	-0.14	-0.38, 0.09	0.25	Years to KRT onset	-0.14	-0.33, 0.09	0.25	Years to KRT onset	0.01	-0.25, 0.28	0.91
Glomerular disease	1.12	0.20, 2.04	0.02	Glomerular disease	0.99	0.13, 1.89	0.03	Diastolic BP SDS	0.15	0.01, 0.29	0.03
BMI SDS	0.21	0.06, 0.35	0.007	BMI SDS	0.19	0.05, 0.33	0.01	BMI SDS	0.19	0.05, 0.33	0.01
Activity 1-2 h/wk	-0.42	-0.81, -0.02	0.04	Activity 1-2 h/wk	-0.41	-0.81, -0.02	0.04	Activity 1-2 h/wk	-3.90	-8.61, 0.79	0.11
Activity ≥ 3 h/wk	-0.31	-0.74, 0.13	0.18	Activity ≥ 3 h/wk	-0.32	-0.76, 0.11	0.15	Activity ≥ 3 h/wk	-5.86	-10.6, -1.09	0.02
LDL cholesterol	0.01	0.00, 0.01	0.001	LDL cholesterol	0.01	0.00, 0.01	<0.001	LDL cholesterol	0.01	0.00, 0.01	0.001
Albumin	-0.04	0.01, 0.08	0.01	Albumin	-0.04	0.01, 0.07	0.04	Albumin	-0.03	0.00, 0.07	0.07
Predictors of left ventricular mass index											
(Intercept)	66.7	49.1, 84.3	<0.001	(Intercept)	68.6	51.0, 86.2	<0.001	(Intercept)	55.1	36.4, 73.9	<0.001
Years to KRT onset	0.63	-1.53, 2.80	0.57	Years to KRT onset	0.44	-1.70, 2.58	0.69	Years to KRT onset	-0.22	-3.07, 2.64	0.88
eGFR	-0.46	-0.76, -0.17	0.003	eGFR	-0.50	-0.76, -0.18	0.003	eGFR	-0.33	-0.70, 0.05	0.10
Systolic BP SDS	1.32	0.43, 2.21	0.005	Diastolic BP SDS	1.44	0.22, 2.66	0.02	Diastolic BP SDS	1.44	0.22, 2.66	0.02
BMI SDS	1.85	0.57, 3.12	0.006	BMI SDS	2.05	0.78, 3.31	0.002	BMI SDS	3.12	1.54, 4.71	0.003
Activity 1-2 h/wk	-2.70	-6.36, 0.97	0.15	Activity 1-2 h/wk	-3.17	-6.83, 0.49	0.10	Activity 1-2 h/wk	-3.90	-8.61, 0.79	0.11
Activity ≥ 3 h/wk	-5.41	-9.29, -1.53	0.008	Activity ≥ 3 h/wk	-6.38	-10.3, -2.49	0.002	Activity ≥ 3 h/wk	-5.86	-10.6, -1.09	0.02
Bicarbonate	-0.66	-1.10, -0.22	0.005	Bicarbonate	-0.59	-1.14, -0.26	0.003	Bicarbonate	-0.90	-1.45, -0.34	0.003
Albumin	-0.35	-0.61, -0.09	0.01	Albumin	-0.41	-0.60, -0.07	0.02	Albumin	0.08	0.004, 0.15	0.04
Predictors of mid-wall fractional shortening											
(Intercept)	14.0	9.4, 18.6	<0.001	(Intercept)	14.0	9.4, 18.6	<0.001	(Intercept)	15.1	11.2, 19.0	<0.001
Years to KRT onset	0.16	-0.56, 0.88	0.67	Years to KRT onset	0.16	-0.56, 0.88	0.67	Years to KRT onset	0.01	-0.71, 0.72	0.98
eGFR	0.08	-0.02, -0.18	0.12	eGFR	0.08	-0.02, -0.18	0.12	eGFR	0.05	-0.05, 0.15	0.31
HDL cholesterol	-0.03	-0.06, 0.00	0.06	HDL cholesterol	-0.03	-0.06, 0.00	0.06	HDL cholesterol	-0.03	-0.06, 0.00	0.06
Phosphate	1.12	-0.19, 2.42	0.10	Phosphate	1.12	-0.19, 2.42	0.10	Phosphate	1.12	-0.19, 2.42	0.10
Albumin	0.08	0.004, 0.15	0.04	Albumin	0.08	0.004, 0.15	0.04	Albumin	0.08	0.004, 0.15	0.04
								iPTH	-0.0	-0.02, 0.01	0.52

BP blood pressure, BMI body mass index, HDL high density lipoprotein, LDL low density lipoprotein, iPTH intact parathyroid hormone, KRT kidney replacement therapy, MAP mean ambulatory blood pressure, SDS standard deviation score. Three separate longitudinal, linear mixed-effects models were obtained per modelled cardiovascular measure after Akaike information criteria (AIC) based variable backwards elimination of three different candidate covariate pools. Model 1: Included systolic BP SDS in the candidate covariate pool but neither diastolic BP SDS, nor 24-hr MAP. Model 2: Included diastolic BP SDS in the candidate covariate pool but neither systolic BP SDS, nor 24-hr MAP. Model 3: Included 24-hr MAP in the candidate covariate pool but neither systolic BP SDS, nor diastolic BP SDS. The model with the best model fit by AIC is highlighted. Model 2 showed best fit compared to model 1 for regression of carotid intima-media thickness SDS (AIC 798 vs. 802) and pulse wave velocity SDS (AIC 877 vs. 879); model 1 showed the best fit compared to model 2 for regression of left ventricular mass index (AIC 1981 vs. 1984). Models adjusted for age, sex, country and estimated glomerular filtration rate.

Table 3: Time-varying associations of cardiovascular measures over 2-year follow-up prior to the onset of kidney replacement therapy.

timing of KRT initiation. Subclinical CV measures have not been examined as outcomes in registry studies that showed no significant difference in mortality, access to transplantation, or growth with early versus late KRT initiation.²⁹ Prospective studies in children have shown an improvement in BP and attenuated progression of cIMT with hemodiafiltration,⁴ improved LV mass index 6-months after initiating hemodialysis,³⁰ and stable or even improving vascular measures with pre-emptive transplantation.^{5,31} Despite antihypertensive medications, 60% of our cohort had uncontrolled hypertension.

Further studies are required to explore the role of an earlier KRT start to limit preventable CV damage in cases where rigorous control of CV risk factors is not possible with medical management.

We observed a strikingly high prevalence of multiple modifiable traditional and uremic CV risk factors that were strongly associated with CV damage. More than one-half of the cohort had ambulatory hypertension, anemia, acidosis, hyperparathyroidism, hyperphosphatemia, or hypoalbuminemia. Patients with mild-moderate CKD enrolled in the CKiD cohort were

similarly found to have multiple traditional CV risk factors in one-quarter of the cohort.³² The present study confirms previously reported associations of CV risk factors with cIMT, PWV and LV hypertrophy in children with pre-KRT CKD, including exposure to mineral dysregulation (high levels of PTH, low calcium and acidosis that contributes to a pro-calcific milieu),^{10,25} anemia,^{12,15} dyslipidemia,^{24,33} and low serum albumin.³⁴ Previous publications from the CKiD cohort showed persistence of hypertension and dyslipidemia in 20–50% patients over median follow up of 4 and 6.5 years, respectively, with worsening dyslipidemia in patients with faster declining GFR, worsening proteinuria, and increasing BMI.^{35,36} Results from our study emphasize the extent to which these risk factors are inadequately treated in leading centers and the need to reinforce therapeutic targets to improve CV health in pre-KRT CKD.

Importantly, we show that traditional risk factors such as BP and BMI have a substantial independent impact on CV damage. Even in the non-CKD population of otherwise healthy children, it has been shown that these CV risk factors in childhood predict subclinical CV damage as well as CV events in mid-adulthood. A 35-year follow-up study of ~38,000 healthy children showed that traditional CV risk factors (BMI, systolic BP, total cholesterol, triglyceride, and smoking) were independently associated with CV events in mid-adulthood.³⁷ We found a strong association of diastolic BP on almost all measures of CV remodelling. This is consistent with the well-established association of clinic and ambulatory hypertension with LV hypertrophy,^{12,38} PWV,³⁹ and cIMT³³ in pre-KRT CKD, with recent reports of long-term association on cIMT even in children without CKD.⁴⁰

While CKD was traditionally thought to be a state of malnutrition, in keeping with the global pandemic of childhood obesity, we found that approximately 20% of the cohort was overweight or obese. Notably, BMI and physical inactivity independently predicted LV mass and PWV. Adiposity has been associated with LV mass⁴¹ and PWV³⁴ in children with mild-moderate and advanced CKD, respectively. BMI is also the strongest independent predictor of LV mass and predicts accelerated deterioration of vascular structure and function, even in children without CKD.^{42,43} Obesity prevention and treatment in children with CKD is essential, stressing the importance of behavioural modifications such as increasing physical activity, weight loss, and reducing screen time to improve CV health.

Our study suggests that early structural CV damage precedes functional abnormalities. We believe that maladaptive arterial wall remodelling triggers compensatory adaptive mechanisms like carotid lumen dilatation to mitigate the effect of increasing cIMT on shear stress.^{10,25,44,45} Circumferential sclerosis or calcium

deposition would ultimately stiffen the artery once these adaptive mechanisms are exhausted. Our findings that patients with high cIMT >2 SDS exhibit a linear increase in PWV, and accelerated increase of aortic stiffness nearer to KRT onset, support the above hypotheses. While an observation period of 2-years is adequate allow changes in cIMT-SDS,^{5,25} the differential effect of carotid dilatation causing a relative increase in carotid lumen to wall cross-sectional area may explain a relatively stable but high cIMT over time.^{10,44,45} We propose that as CKD progresses, the increased LV mass becomes maladaptive, compromising cardiac function, as shown by the strong negative association we observed between systolic function and LV mass.

However, there are limitations to this study including its observational nature which precludes causal inference. Due to the explorative nature of the study, no formal sample size estimation was performed. The overrepresentation of patients with CAKUT limits generalizability of results to patients with glomerular diseases, who are at an even greater CV risk. The data did not allow for examination of center-specific treatment regimens. Some potential risk factors, such as 25-hydroxy vitamin D levels and urine output, were not measured in all patients and could not be included. The reliability of albuminuria as a CV risk factor at low eGFR is uncertain. Levels of physical activity assessed in the study are extremely low, and assessment of a wider range of activity will be useful in future studies. Although many exploratory statistical models were used as sensitivity analyses, they might have increased the probability of false positive results. The strengths of our study are its novel findings, prospective multicenter design, and being the largest study exploring longitudinal changes in burden of CV damage in pre-KRT CKD.

In conclusion, in the years preceding KRT onset children have accrued a high burden of CV damage, largely from modifiable risk factors. Controlling for these risk factors mitigated the linear progression of CV damage in our statistical models. The changing profile of modifiable CV risk factors highlights the need for early diagnosis, careful monitoring, and aggressive management from the earliest stages of CKD to optimize CV health.

Contributors

Professor Shroff and Professor Schaefer had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualisation: RS.

Acquisition and interpretation of data: PK, JH, RS.

Writing—original draft: PK, JH, RS, FS, UQ, CPS.

Writing—critical review for important intellectual content: KAZ, AB, ADo, ADu, NC, IKB, LO, BR, DP, SB, HA, KAr, ML, AZ, FP, DBD, CPS, AM, UQ, FS, RS.

Formal analysis: JH, PK.

Funding acquisition: RS, FS.

Administrative, technical, or material support: Nil.

Supervision: RS.

Data sharing statement

Data access may be permitted on a case-by-case basis upon request to the corresponding author only. Investigators can submit an expression of interest to the corresponding author.

Declaration of interests

Professor Franz Schaefer had received a research grant from Fresenius Medical Care that is paid to his academic institution.

Acknowledgements

The authors are indebted to all 4C and 3H collaborators, who are listed in the Appendix (Supplementary materials p.13).

Support for the 4C Study was received from the ERA-EDTA Research Programme, the KfH Foundation for Preventive Medicine and the German Federal Ministry of Education and Research (01EO0802) and Roche Organ Transplant Research Foundation (365520785). The study was also supported by the European Reference Network for Rare Kidney Diseases (ERKNet), which is funded by the European Union within the framework of the EU4Health Programme (101085068).

The 3H study was sponsored by Kidney Research UK (RP39/2013). A part of the work took place in the Biomedical Research Centre at UCL Great Ormond Street Hospital for Children, London.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2024.102708>.

References

- United States Renal Data System. 2022 USRDS annual data report: Epidemiology of kidney disease in the United States. <https://adr.usrds.org/2022>. Accessed November 2, 2023.
- de Ferranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e603–e634.
- Shroff R, Long DA, Shanahan C. Mechanistic insights into vascular calcification in CKD. *J Am Soc Nephrol*. 2013;24:179–189.
- Shroff R, Smith C, Ranchin B, et al. Effects of hemodiafiltration versus conventional hemodialysis in children with ESKD: the HDF, heart and height study. *J Am Soc Nephrol*. 2019;30:678–691.
- Schmidt BMW, Sugianto RI, Thurn D, et al. Early effects of renal replacement therapy on cardiovascular comorbidity in children with end-stage kidney disease: findings from the 4C-T study. *Transplantation*. 2018;102:484–492.
- Kouis P, Kousios A, Kanari A, Kleopa D, Papatheodorou SI, Panayiotou AG. Association of non-invasive measures of subclinical atherosclerosis and arterial stiffness with mortality and major cardiovascular events in chronic kidney disease: systematic review and meta-analysis of cohort studies. *Clin Kidney J*. 2020;13:842–854.
- Karras A, Haymann JP, Bozec E, et al. Large artery stiffening and remodeling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease. *Hypertension*. 2012;60:1451–1457.
- Patel N, Yaqoob MM, Aksentijevic D. Cardiac metabolic remodeling in chronic kidney disease. *Nat Rev Nephrol*. 2022;18:524–537.
- Tranaeus Lindblad Y, Vavilis G, Axelsson J, Herthelius M, Barany P. Assessing longitudinal trends in cardiac function among pediatric patients with chronic kidney disease. *Pediatr Nephrol*. 2016;31:1485–1497.
- Litwin M, Wuhl E, Jourdan C, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol*. 2005;16:1494–1500.
- Matteucci MC, Chinali M, Rinelli G, et al. Change in cardiac geometry and function in CKD children during strict BP control: a randomized study. *Clin J Am Soc Nephrol*. 2013;8:203–210.
- Kupferman JC, Aronson Friedman L, Cox C, et al. BP control and left ventricular hypertrophy regression in children with CKD. *J Am Soc Nephrol*. 2014;25:167–174.
- Shroff R, Bayazit A, Stefanidis CJ, et al. Effect of haemodiafiltration vs conventional haemodialysis on growth and cardiovascular outcomes in children - the HDF, heart and height (3H) study. *BMC Nephrol*. 2018;19:199.
- Querfeld U, Anarat A, Bayazit AK, et al. The cardiovascular comorbidity in children with chronic kidney disease (4C) study: objectives, design, and methodology. *Clin J Am Soc Nephrol*. 2010;5:1642–1648.
- Schaefer F, Doyon A, Azukaitis K, et al. Cardiovascular phenotypes in children with CKD: the 4C study. *Clin J Am Soc Nephrol*. 2017;12:19–28.
- Doyon A, Kracht D, Bayazit AK, et al. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. *Hypertension*. 2013;62:550–556.
- Thurn D, Doyon A, Sozeri B, et al. Aortic pulse wave velocity in healthy children and adolescents: reference values for the vicorder device and modifying factors. *Am J Hypertens*. 2015;28:1480–1488.
- Kis E, Csepke O, Horvath Z, et al. Pulse wave velocity in end-stage renal disease: influence of age and body dimensions. *Pediatr Res*. 2008;63:95–98.
- Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
- Chinali M, Emma F, Esposito C, et al. Left ventricular mass indexing in infants, children, and adolescents: a simplified approach for the identification of left ventricular hypertrophy in clinical practice. *J Pediatr*. 2016;170:193–198.
- de Simone G, Daniels SR, Kimball TR, et al. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertension*. 2005;45:64–68.
- Ku E, Glidden DV, Johansen KL, et al. Association between strict blood pressure control during chronic kidney disease and lower mortality after onset of end-stage renal disease. *Kidney Int*. 2015;87:1055–1060.
- Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467.
- Azukaitis K, Kirchner M, Doyon A, et al. Arterial stiffness and chronic kidney disease progression in children. *Clin J Am Soc Nephrol*. 2022;17:1467–1476.
- Litwin M, Wuhl E, Jourdan C, et al. Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. *Nephrol Dial Transplant*. 2008;23:2552–2557.
- Brady TM, Townsend K, Schneider MF, et al. Cystatin C and cardiac measures in children and adolescents with CKD. *Am J Kidney Dis*. 2017;69:247–256.
- Tholen S, Klofat K, Pan CR, et al. Progression of aortic pulse wave velocity in patients with chronic kidney disease. *J Clin Hypertens*. 2013;15:833–838.
- Agarwal R. Longitudinal study of left ventricular mass growth: comparative study of clinic and ambulatory systolic blood pressure in chronic kidney disease. *Hypertension*. 2016;67:710–716.
- Preka E, Bonthuis M, Harambat J, et al. Association between timing of dialysis initiation and clinical outcomes in the paediatric population: an ESPN/ERA-EDTA registry study. *Nephrol Dial Transplant*. 2019;34:1932–1940.
- Melhem N, Savis A, Wheatley A, et al. Improved blood pressure and left ventricular remodelling in children on chronic intermittent haemodialysis: a longitudinal study. *Pediatr Nephrol*. 2019;34:1811–1820.
- Grabitz C, Sugianto RI, Doyon A, et al. Long-term effects of kidney transplantation compared with dialysis on intima-media thickness in children—results from the 4C-T study. *Transplantation*. 2024;108:1212–1219.
- Wilson AC, Schneider MF, Cox C, et al. Prevalence and correlates of multiple cardiovascular risk factors in children with chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:2759–2765.
- Brady TM, Schneider MF, Flynn JT, et al. Carotid intima-media thickness in children with CKD: results from the CKiD study. *Clin J Am Soc Nephrol*. 2012;7:1930–1937.
- Karava V, Printza N, Dotis J, et al. Body composition and arterial stiffness in pediatric patients with chronic kidney disease. *Pediatr Nephrol*. 2019;34:1253–1260.
- Reynolds BC, Roem JL, Ng DKS, et al. Association of time-varying blood pressure with chronic kidney disease progression in children. *JAMA Netw Open*. 2020;3:e1921213.

- 36 Saland JM, Kupferman JC, Pierce CB, et al. Change in dyslipidemia with declining glomerular filtration rate and increasing proteinuria in children with CKD. *Clin J Am Soc Nephrol*. 2019;14:1711–1718.
- 37 Jacobs DR Jr, Woo JG, Sinaiko AR, et al. Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med*. 2022;386:1877–1888.
- 38 Sinha MD, Gu H, Douiri A, et al. Intensive compared with less intensive blood pressure control to prevent adverse cardiac remodelling in children with chronic kidney disease (HOT-KID): a parallel-group, open-label, multicentre, randomised, controlled trial. *Lancet Child Adolesc Health*. 2023;7:26–36.
- 39 Sinha MD, Keehn L, Milne L, Sofocleous P, Chowienczyk PJ. Decreased arterial elasticity in children with nondialysis chronic kidney disease is related to blood pressure and not to glomerular filtration rate. *Hypertension*. 2015;66:809–815.
- 40 Meng Y, Sharman JE, Koskinen JS, et al. Blood pressure at different life stages over the early life course and intima-media thickness. *JAMA Pediatr*. 2024;178:133–141.
- 41 Brady TM, Roem J, Cox C, et al. Adiposity, sex, and cardiovascular disease risk in children with CKD: a longitudinal study of youth enrolled in the chronic kidney disease in children (CKiD) study. *Am J Kidney Dis*. 2020;76:166–173.
- 42 Fabi M, Meli M, Leardini D, et al. Body mass index (BMI) is the strongest predictor of systemic hypertension and cardiac mass in a cohort of children. *Nutrients*. 2023;15.
- 43 Buschges J, Schaffrath Rosario A, Schienkiewitz A, et al. Vascular aging in the young: new carotid stiffness centiles and association with general and abdominal obesity - the KIGGS cohort. *Atherosclerosis*. 2022;355:60–67.
- 44 Lalayiannis AD, Ferro CJ, Wheeler DC, et al. The burden of subclinical cardiovascular disease in children and young adults with chronic kidney disease and on dialysis. *Clin Kidney J*. 2022;15:287–294.
- 45 Briet M, Collin C, Karras A, et al. Arterial remodeling associates with CKD progression. *J Am Soc Nephrol*. 2011;22:967–974.