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ORIGINAL RESEARCH

# Progression of Carotid Intima-Media Thickness in Children of the Cardiovascular Comorbidity in Children With Chronic Kidney Disease Study: Risk Factors and Impact of Blood Pressure Dynamics

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**BACKGROUND:** Carotid intima-media thickness (cIMT) may identify early alterations in the vascular phenotype in children with chronic kidney disease (CKD).

**METHODS AND RESULTS:** Investigation of longitudinal changes in cIMT SD scores (SDS) in 670 patients from the 4C Study (Cardiovascular Comorbidity in Children With CKD Study), aged 6 to 17 years, with CKD stage 3 to 5 at baseline.

The longitudinal trajectory of cIMT SDS over up to 8 years was examined using a longitudinal mixed-effects model. The yearly progression rate in cIMT SDS (β=0.20 [95% CI, 0.13–0.28]) remained positive during the initial 4.5-year follow-up period but slowed down quadratically with increasing observation time (β=−0.02 [95% CI, −0.03 to −0.01]). Risk factors for increased cIMT SDS included time since baseline, younger age, higher height SDS, female sex, elevated diastolic blood pressure, and lower serum albumin, but not estimated glomerular filtration rate. In patients with progressive CKD, higher albuminuria was additionally associated with an increase in cIMT SDS. In patients with stable CKD, serum phosphate and time were the only risk factors identified for elevated cIMT SDS. Annual rates of change in blood pressure were positively correlated with the rate of change in cIMT SDS within the first 4.5 years (for systolic: β=0.42 [95% CI, 0.22–0.62]; for diastolic: β=1.56 [95% CI, 1.01–2.11]).

**CONCLUSIONS:** The results show a significant longitudinal increase in cIMT SDS in children with CKD. Changes in blood pressure are associated with the progression of cIMT SDS, suggesting a relevant impact of blood pressure modulation on cIMT SDS.

**Key Words:** cardiovascular disease ■ carotid intima-media thickness ■ chronic kidney disease ■ hypertension ■ pediatric

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## CLINICAL PERSPECTIVE

### What Is New?

- The carotid intima-media SD score trajectory over up to 8 years in children with chronic kidney disease of the 4C (Cardiovascular Comorbidity in Children With CKD) Study demonstrates a markedly elevated increase compared with what would be anticipated based on age-related changes.
- Diastolic blood pressure is identified as a predominant risk factor for increased carotid intima-media thickness SD score; furthermore, the rate of change of carotid intima-media thickness SD score is correlated with blood pressure modulation over time.

### What Are the Clinical Implications?

- It may be hypothesized that optimal blood pressure control may contribute to the slowing of carotid intima-media thickness SD score increase in children with chronic kidney disease.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **4C Study** | Cardiovascular Comorbidity in Children With CKD study |
| **cIMT** | carotid intima-media thickness |
| **KRT** | kidney replacement therapy |
| **LMM** | linear mixed-effects model |
| **P-CKD** | progressive chronic kidney disease |
| **PWV** | pulse wave velocity |
| **S-CKD** | stable chronic kidney disease |
| **SDS** | SD score |

Cardiovascular disease is a major complication of chronic kidney disease (CKD) and the leading risk factor for long-term survival. Although cardiovascular events are rare in children with CKD, subclinical cardiovascular changes occur at all stages of the disease,[1,2] though their progression and the impact of modifiable risk factors remain unclear.

Carotid intima-media thickness (cIMT) is a robust marker of vascular phenotype, correlating with lifetime cardiovascular risk, and has been studied extensively in conditions with elevated cardiovascular risk, including the pediatric population and CKD.[3–6] Its noninvasive, radiation-free nature with the ability to detect early cardiovascular changes makes it particularly valuable for use in the pediatric population.[7,8] In addition, our group established age- and sex-specific cIMT reference values for healthy children, enabling comparisons in disease settings.[9]

We used cIMT measurements to describe the vascular phenotype of the 4C (Cardiovascular Comorbidity in Children With CKD) Study, a longitudinal observational study that started in 2010 and spanned up to 8 years. It included the observation of children and adolescents with an estimated glomerular filtration rate (eGFR) between 10 and 60 mL/min per 1.73 $m^2$ and before renal replacement therapy at the time of study entry.[10] Further cardiovascular measures in the study included pulse wave velocity and morphologic and functional echocardiographic measures.

Baseline findings of the 4C Study revealed significant cardiovascular alterations in CKD, including increased cIMT, pulse wave velocity, left ventricular mass index, and high rates of uncontrolled hypertension.[11] Subsequent analyses identified blood pressure (BP) as a key driver of vascular changes.[12]

Building on these findings, we conducted a longitudinal analysis of 4C Study data to model cIMT progression, identify covariates influencing cIMT, and assess whether changes in BP predict cIMT trajectory over time in children with CKD.

## METHODS

### Design and Implementation of the 4C Study

The 4C Study, initiated in 2009, prospectively followed 704 patients aged 6 to 17 years with a baseline GFR of 10 to 60 mL/min per 1.73 $m^2$ in 55 pediatric nephrology units across 12 European countries. Upon inclusion, only patients before kidney replacement therapy (KRT) were eligible to participate in the study.[10] However, after start of KRT, patients were prospectively followed in separate substudies.[13,14]

Exclusion criteria were active systemic vasculitis, primary cardiovascular anomalies, renal vascular anomalies, and anomalies of the limbs preventing diagnostic procedures.

The morphology and function of the heart and the large arteries were evaluated on an annual basis using noninvasive methods including measurement of the cIMT, pulse wave velocity, and echocardiography. A variety of clinical, anthropometric, biochemical, and pharmacological risk factors were monitored prospectively and can be related to the cardiovascular status of the patients.

In the 4C Study, regional investigators underwent training and traveled annually to individually assigned sites for the performance of cardiovascular measurements (pulse wave velocity, cIMT recording, echocardiography, BP measurements) in participants. At annual visits and at additional 6-month visits, patient history

and anthropometry were recorded, and a laboratory workup was performed at both local and central levels.

The 4C Study was approved by the Ethics Committee of Heidelberg University (S-032/2009) and the institutional review boards at each participating institution.[10] Written informed consent was obtained from all parents and participants as appropriate. The study was registered at ClinicalTrials.gov on August 7, 2009, with the identifier (NCT01046448). The data and methods used in the analysis will be made accessible to any researcher for the purpose of reproducing the results or replicating the procedures, in accordance with the AHA Journals' Implementation of the Transparency and Openness Promotion Guidelines.

## Measurement of Carotid Intima Media Thickness and of Covariates

cIMT was assessed in patients enrolled in the 4C Study in accordance with the Mannheim IMT consensus.[15] Patients were positioned supine with their necks slightly extended and the head turned slightly in the direction opposite to that in which the measurement was being taken. Image acquisition was conducted with a 12L5 linear array probe of a mobile cardiovascular ultrasound device (Acuson P50, Siemens Medical Solutions USA, Inc.) at an angle of the probe of 45°. The common carotid artery was visualized and recorded in longitudinal view at end-diastole, thus enabling the analysis of the area 1 to 2 cm below the bifurcation. Image analysis was conducted at the far wall of the common carotid artery using Syngo US Workplace (Siemens Medical Solutions USA, Inc.). The measured cIMT values were standardized for sex and age by calculation of SD scores (SDS; normal range +2 to −2) as described previously using normal values derived from an independent healthy cohort of >1000 children.[9] For the normative healthy reference cohort with equivalent measurement devices and methological set-up, the analysis of measurement variation revealed an intraclass correlation coefficient of 0.42 and an interobserver coefficient of variation of 7.3%.[9]

With the exception of hemoglobin, intact parathyroid hormone, serum bicarbonate, and ferritin, biochemical analyses were conducted at a centralized facility. The standard laboratory techniques were used to measure the serum and urinary concentrations of albumin and creatinine and the serum concentrations of phosphorus, calcium, albumin, intact parathyroid hormone, bicarbonate, low-density lipoprotein and high-density lipoprotein cholesterol, CRP (C-reactive protein), and uric acid. The eGFR was calculated according to the updated Schwartz equation.[16] BP was measured locally with oscillometric devices that have been validated for use in pediatric patients and with appropriate cuff sizes. BP values were normalized to SDS according to age, sex, and height.[17] Height and body mass index SDS were calculated based on World Health Organization reference data.

## Data Preprocessing, Inclusion of Patients and Visits, and Analysis Objectives

The analysis included all patients with at least 1 valid cIMT measurement before dropout or before the initiation of KRT and with eGFR <60 mL/min per 1.73m$^2$. cIMT measurements were conducted at the annual clinical visits or within a 3-month window centered on this date. All visits before the initiation of KRT and until 8 years after the baseline visit were included in the analysis. This resulted in the inclusion of 670 patients with at least 1 valid cIMT measurement and a total of 2221 visits with valid cIMT values. The initial visit that satisfied the inclusion criteria for each patient was designated as the baseline visit (Figure 1).

Given the large variability in eGFR among patients in the analyzed cohort, which may be associated with varying risk profiles for cardiovascular disease, the analysis was conducted using data from the entire cohort as well as from patients with either stable or progressive renal failure. Patients who initiated KRT, exhibited a decline in kidney function of at least 50%, or reached an eGFR <10 mL/min per 1.73 m$^2$ during the follow-up period were classified as having progressive CKD (P-CKD). In contrast, patients who did not fulfill these criteria were classified as having stable CKD (S-CKD).

## Statistical Analysis

Descriptive statistics were calculated for cIMT SDS, anthropometric measures, CKD stage, biochemical measures, and antihypertensive therapy status for all patients and all annual visits. Descriptive statistics were calculated as frequencies (and corresponding percentages) for categorical variables, means±SDs for continuous variables with a normal distribution and medians (and interquartile ranges) for those with a skewed distribution (Tables 1 and 2).

## Linear Mixed-Effects Model Formulation

Multivariable linear mixed-effects models (LMM) were formulated in an analogous manner per patient group (all patients, patients with P-CKD, patients with S-CKD) to estimate the fixed effects (fitted average relationships) between explanatory covariates and cIMT SDS based on the longitudinal data and to generalize these effects to the corresponding underlying populations. To ensure unbiased and precise inference of these average population-level effects we specified an appropriate covariance structure for each LMM to account for unsystematic variability not explained by each model's estimated mean profiles. As suggested by Diggle,[18]

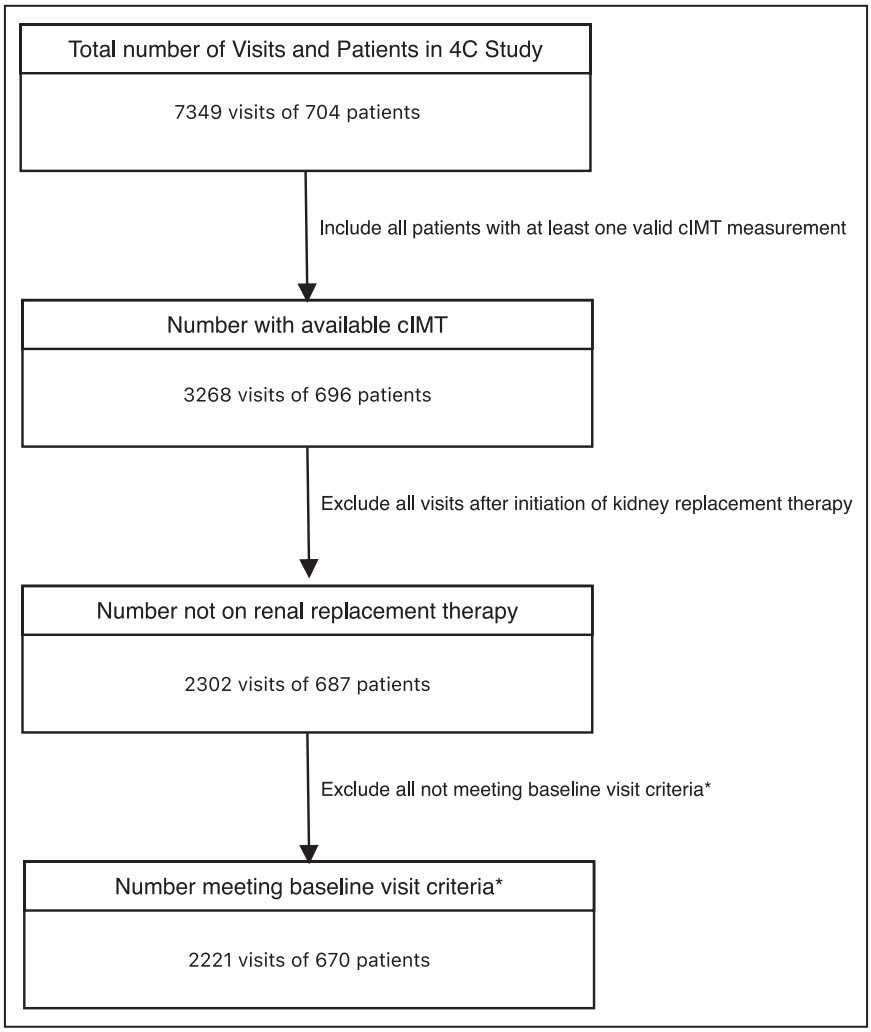


**Figure 1. Patient and visit selection (*baseline visit criteria: eGFR<60 mL/min per 1.73 m², age 6–17 years).**
cIMT indicates carotid intima-media thickness; eGFR, estimated glomerular filtration rate; and 4C, Cardiovascular Comorbidity in Children With CKD study.

Molenberghs and Verbeke,[19] and Cheng et al.,[20] we determined the models' covariance structures based on preliminary LMM with the most elaborate mean structure that accounted for clinically plausible main effects and interactions of explanatory covariates, thereby removing potential systematic variability from the data. Our preliminary LMM with complex mean structure included the average effects on cIMT SDS of continuous time, of time,[2] of all remaining candidate explanatory covariates (listed in the following paragraph), and of those covariates' 2-way interactions with time. The Akaike information criterion[21] and likelihood ratio tests were used to select random effects and residual covariance structures with the best model fit (see Tables S1 through S3). Final LMM per patient group modeled unsystematic cIMT SDS variability characterized by dependence of measurements (cluster level 1) nested within patients (cluster level 2) and by dependence between measurements of patients treated at the same centers (cluster level 3) by a 3-level hierarchical random effects covariance structure with center-level random intercepts, patient-level random intercepts, patient-level linear random slopes, and patient-level quadratic random slopes. Modeling decreasing residual variability within patients for increasing observation time $t$ (reflecting decreasing measurement error potentially evoked by training effects of local investigators) with a time-dependent reduction factor $e^{\hat{\delta}t}$ for residual variance $\widehat{\sigma^2}$ further improved the model fit of all 3 LMM (see Tables S1 through S3).

The second model building step aimed at simplifying the complex mean structure used in the first model building step to avoid overfitting. As the primary interest of the LMM analysis was to estimate the average effects of kidney function and BP (estimated GFR, eGFR, log[albuminuria]), and prospective follow-up time on

**Table 1. Patient Characteristics, According to Visit**

| | Baseline visit | 2-year visit | 4-year visit | 6-year visit |
|---|---|---|---|---|
| No. (% patients remaining) | 670 (100) | 390 (65.0) | 190 (31.7) | 57 (10.0) |
| Male sex, n (% at visit) | 442 (66.0) | 259 (66.4) | 128 (67.4) | 39 (68.4) |
| Follow-up time in years (Q1–Q3) | 0 (0–0) | 2.2 (1.9–2.2) | 4.36 (4.0–4.9) | 6.39 (6.0–6.9) |
| Age, y ±SD | 12.2±3.3 | 14.0±3.3 | 15.4±3.22 | 17.3±2.91 |
| Cause of CKD | | | | |
| Congenital anomaly of the kidney and urinary tract, n (% at visit) | 465 (69.4) | 298 (76.4) | 146 (76.8) | 48 (84.2) |
| Glomerulopathy, n (% at visit) | 59 (8.8) | 14 (3.6) | 7 (3.7) | 2 (3.5) |
| Tubulointerstitial diseases, n (% at visit) | 83 (12.4) | 49 (12.6) | 19 (10.0) | 3 (5.3) |
| Postacute kidney injury CKD, n (% at visit) | 35 (5.2) | 19 (4.9) | 13 (6.8) | 3 (5.3) |
| Others, n (%) | 28 (4.2) | 10 (2.6) | 5 (2.6) | 1 (1.8) |
| Antihypertensive therapy | | | | |
| Total n (% at visit) | 372 (55.5) | 258 (66.2) | 124 (65.3) | 34 (59.6) |
| Renin-angiotensin system antagonists, n (% at visit) | 284 (42.4) | 189 (48.5) | 89 (46.8) | 24 (42.1) |
| Calcium channel blockers, n (% at visit) | 109 (16.3) | 100 (25.6) | 52 (27.4) | 14 (24.6) |
| Diuretics, n (% at visit) | 57 (8.5) | 30 (7.7) | 17 (8.9) | 5 (8.8) |
| Others, n (% at visit) | 86 (12.8) | 58 (14.9) | 34 (17.9) | 15 (26.3) |
| Anthropometric data | | | | |
| Body mass index SDS ±SD | 0.11±1.27 | 0.19±1.23 | 0.03±1.24 | −0.15±1.86 |
| Height SDS ±SD | −1.32±1.33 | −1.29±1.35 | −1.27±1.44 | −1.53±1.60 |
| Systolic BP SDS ±SD | 0.80±1.33 | 0.68±1.31 | 0.54±1.34 | 0.79±1.34 |
| Diastolic BP SDS ±SD | 0.68±1.07 | 0.51±1.03 | 0.43±0.98 | 0.51±0.95 |
| cIMT (mm) ±SD | 0.45±0.06 | 0.46±0.05 | 0.48±0.05 | 0.47±0.04 |
| cIMT SDS ±SD | 1.57±1.41 | 1.70±1.17 | 1.90±1.05 | 1.45±0.91 |
| Laboratory analysis | | | | |
| Estimated glomerular filtration rate, mL/min per 1.73 $m^2$ ±SD | 27.0±11.5 | 24.2±11.7 | 24.2±11.9 | 23.6±12.2 |
| Serum calcium, mmol/L ±SD | 2.26±0.19 | 2.45±0.21 | 2.41±0.20 | 2.44±0.17 |
| Serum albumin, g/L ±SD | 38.8±5.9 | 41.2±4.6 | 41.8±4.2) | 42.6±4.5 |
| Serum intact parathyroid hormone, pmol/L (Q1–Q3) | 12.8 (7.4–23.6) | 12.9 (6.6–24.6) | 12.6 (7.8–25.8) | 14.5 (6.6–28.1) |
| Serum bicarbonate, mmol/L ±SD | 21.3±3.6 | 21.4±3.2 | 21.8±3.1 | 21.6±3.6 |
| Serum phosphate, mmol/L ±SD | 1.55±0.37 | 1.55±0.33 | 1.53±0.39 | 1.52±0.46 |
| Low-density lipoprotein cholesterol, mg/dL (Q1–Q3) | 92 (72–118) | 96 (73–121) | 96.00 (74–117) | 83 (70–116) |
| High-density lipoprotein cholesterol, mg/dL (Q1–Q3) | 46 (37–56) | 51 (42–51) | 50.00 (40–60) | 44.00 (38–49) |
| C-reactive protein, mg/dL (Q1–Q3) | 0.55 (0.22–2.06) | 0.59 (0.23–2.08) | 0.64 (0.24, 1.90) | 1.50 (0.82–6.08) |
| Serum uric acid, mg/dL ±SD | 6.49±1.78 | 6.97±1.79 | 6.79±1.62 | 7.21±1.86 |
| Albuminuria, mg/g creatinine (Q1–Q3) | 356 (91–1245) | 365 (97–1280) | 557 (132–1286) | 507 (151–873) |

Data given as n (%), mean±SD, or median (25th and 75th percentile) as appropriate. BP indicates blood pressure; cIMT, carotid intima-media thickness; CKD, chronic kidney disease; and SDS, SD score.



cIMT SDS, the explanatory covariates eGFR, albuminuria, BP, and continuous time were always retained across model iterations during covariate backward elimination (covariate inclusion threshold; $P \leq 0.05$). The potential confounder covariates age at study entry, sex, and renal diagnosis were always retained across model iterations during covariate backward elimination, and the following remaining candidate covariates were specified as eligible for elimination: serum albumin, high-density lipoprotein, low-density lipoprotein, phosphate, albumin-corrected calcium, serum bicarbonate, uric acid, log[ferritin], log[CRP], log[intact parathyroid hormone], hemoglobin, body mass index SDS, and height SDS. All explanatory covariates were time varying (repeatedly measured) with the exception of the time-invariant covariates age at study entry, sex, and renal diagnosis. As covariates' individual effects on cIMT SDS may systematically change with increasing observation time, 2-way interaction terms of each explanatory covariate with continuous observation time had been added to the complex starting configurations of all LMM but specified as removable terms during covariate elimination. The quadratic effect of time on cIMT SDS was also specified as a removable effect during

covariate elimination. Restricted maximum likelihood estimation was used to fit the 3 LMM during all model building stages.

LMM were fitted to 20 imputed data sets and the estimated LMM parameters were pooled in accordance with Rubin's Rule.[22] Pooled parameters were assessed to make decisions during model building and are reported in this article for the final LMM of each patient population (all patients, patients with P-CKD, patients with S-CKD). The pooled $\beta$estimates of the fixed effects (and 95% CI) along with $P$ values obtained from the Wald tests on these coefficients are reported in Tables 3 through 5. The $R^2_\beta$ metric[23] was used to quantify the proportion of the cIMT SDS variability explained conjointly by all average effects of explanatory covariate (terms) included in a final LMM. Using the pooled estimates of the covariance components of each final LMM, variability in cIMT SDS left unexplained by the average effects was derivable as intercenter variability, interpatient variability, and within-patient residual variability. A decomposition of the cIMT SDS variability according to the hierarchical cluster levels modeled by the final LMM of all patients is presented in the results section. The pooled random effect and residual covariance parameter estimates are reported in Tables S4 through S6. Derived intrapatient correlations of cIMT SDS between specific time intervals of follow-up relative to baseline are also presented in the results section for the final LMM of the overall patient population. The lme function from the nlme package[24] was used in R Studio version 4.2.2[25,26] for LMM. The detailed development of the models and related model diagnostics, equations for deriving the $R^2_\beta$ and intrapatient correlations metrics, and the model-derived variability decompositions are presented in Data S1.

### Postfit Correlations of Absolute Linear Patient-Level Change per Year in cIMT SDS With Absolute Linear Patient-Level Change per Year in Blood Pressure SDS

Patients' individual yearly rates of change in cIMT SDS (Δ cIMT SDS) were calculated based on predicted values from the final LMM of all patients for the first 4.5 years of follow-up. Yearly rates of change in systolic and diastolic BP SDS (Δ diastolic BP SDS and Δ systolic BP SDS) during the first 4.5 years of follow-up were derived from 2 separate LMM that predicted individual patient trajectories over time. Simple linear least-squares regression was used to assess whether patients' yearly change rates in cIMT SDS were associated with their corresponding yearly change rates in BP, and Pearson correlation coefficients quantified the strength of these associations. Further details on the implementation of this analysis are provided in Data S1 (including Figures S1 through S3 and Tables S1 through S6).

## RESULTS

Figure 1 illustrates the patient and visit selection process in accordance with the established inclusion criteria. The majority of patients (69%) was diagnosed with congenital anomalies of the kidney and urinary tract as the underlying kidney disease. Additionally, 12.4% of patients had a tubulointerstitial kidney disorder, 8.8% had a glomerulopathy, and 5.2% had CKD following acute kidney injury for various reasons, including hemolytic uremic syndrome, sepsis, and postnatal asphyxia. The proportion of patients with antihypertensive therapy increased at the 2-year and 4-year follow-up visits in comparison to the baseline assessment. Both systolic and diastolic BP exhibited a decline over the course of the study (Table 1).

Table 1 presents the patient characteristics at baseline and at the 2-, 4-, and 6-year follow-up visits. Table 2 displays the baseline characteristics according to whether patients showed P-CKD or S-CKD. The mean cIMT at baseline was 0.45±0.06 mm, and the mean cIMT SDS was 1.57±1.41. At the time of study entry, the cIMT SDS was increased by >2 SDS in 32.4% of patients. Of the 670 patients, 393 (58.7%) were diagnosed with P-CKD. Of the 393 patients in this group, 161 (41.0%) patients experienced a decline in eGFR of greater than 50%, 76 (19.3%) reached an eGFR of <10 mL/min per 1.73 $m^2$ and 156 of 393 (39.7%) initiated KRT. The remaining patients (n=277 of 670, 41.3%) were classified as having S-CKD. The 2 groups differed significantly for their eGFR at baseline (31.5±12 versus 20.9±9.6 mL/min per 1.73 $m^2$, $P$<0.001), systolic and diastolic BP ($P$=0.026/0.023), serum calcium ($P$=0.004), albumin ($P$<0.001), serum phosphate ($P$=0.002), intact parathyroid hormone ($P$=0.007), bicarbonate ($P$<0.001) and albuminuria ($P$<0.001). (Table 2). At the baseline measurement, the distribution of cIMT and cIMT SDS was found to be virtually identical in patients with S-CKD and those with P-CKD (Table 2).

A median of 3 (2–5) cIMT measurements per patient were available in the overall analysis cohort corresponding to a median follow-up duration of 2.08 (0.44–4.14) years per patient. Patients with stable renale function contributed longer total observation durations compared with patients with progressive renal failure (S-CKD: 2.62 (0.99–4.44) years; P-CKD: 1.97 (0.0–4.06) years).

LMMs estimated a statistically significant positive linear effect (β=0.20 [95% CI, 0.13–0.28], degrees of freedom [DF]=1542, $P$<0.0001) and a negative quadratic effect of time on cIMT SDS (β=-0.02 [95% CI, −0.03 to −0.01], DF=1542, $P$<0.0001), Table 3. The quadratic time effect on cIMT SDS corresponds to a slowed and eventually attenuated increase in cIMT SDS toward the end of the observation period. This pattern of association was also identified within the analyzed subgroups with S-CKD (Table 4) and P-CKD (Table 5).

**Table 2. Characteristics of Patients With Stable Chronic Kidney Disease and of Patients With Progressive Chronic Kidney Disease at Baseline**

| | All | Stable CKD | Progressive CKD | *P* value |
|---|---|---|---|---|
| No. (% of all patients) | 670 (100) | 277 (41.3) | 393 (48.7) | |
| Male sex, n (%) | 442 (66.0) | 183 (66.1) | 259 (65.9) | 0.965 |
| Follow-up time, y (Q1–Q3) | 2.32 (0.85–4.51)* | 2.99 (1.15–5.35)* | 1.86 (0.71–3.89)* | <0.001 |
| Age, y ±SD | 12.2±3.30 | 12.4±3.57 | 12.1±3.17 | 0.200 |
| Cause of CKD | | | | |
| Congenital anomaly of the kidney and urinary tract, n (%) | 465 (69.4) | 213 (76.9) | 252 (64.1) | 0.009 |
| Glomerulopathy, n (%) | 59 (8.8) | 19 (6.9) | 40 (10.2) | |
| Tubulointerstitial, n (%) | 83 (12.4) | 23 (8.3) | 60 (15.3) | |
| Postacute kidney injury CKD. n (%) | 35 (5.2) | 13 (4.7) | 22 (5.6) | |
| Others, n (%) | 28 (4.2) | 9 (3.2) | 19 (4.8) | |
| Antihypertensive therapy | | | | |
| Total n (%) | 372 (56.0)* | 139 (50.2)* | 233 (59.3)* | 0.019* |
| Renin-angiotensin system antagonists, n (%) | 284 (42.4) | 115 (41.5) | 169 (43.0) | 0.701 |
| Calcium channel blockers, n (%) | 109 (16.3)* | 26 (9.4)* | 83 (21.1)* | <0.001* |
| Diuretics, n (%) | 57 (8.5) | 24 (8.7) | 33 (8.4) | 0.93 |
| Others, n (%) | 86 (12.8) | 11 (4.0) | 17 (4.3) | 0.821 |
| Anthropometric data | | | | |
| Body mass index SDS ±SD) | 0.11±1.27 | 0.07±1.31 | 0.14±1.25 | 0.536 |
| Height SDS ±SD | −1.32±1.33 | −1.22±1.23 | −1.39±1.39 | 0.096 |
| Systolic BP SDS ±SD | 0.80±1.33* | 0.67±1.29* | 0.90±1.35* | 0.026* |
| Diastolic BP SDS ±SD | 0.68±1.07* | 0.57±1.05* | 0.76±1.08* | 0.023* |
| cIMT, mm ±SD | 0.45±0.06 | 0.45±0.06 | 0.45±0.06 | 0.961 |
| cIMT SDS ±SD | 1.57±1.41 | 1.55±1.37 | 1.59±1.43 | 0.755 |
| Laboratory analysis | | | | |
| Estimated glomerular filtration rate, mL/min per 1.73 $m^2$ ±SD | 27.00.49±11.50* | 32.1±11.50* | 23.5±10.10* | <0.001* |
| Serum calcium, mmol/L ±SD | 2.26±0.19* | 2.28±0.16* | 2.24±0.20* | 0.004* |
| Serum albumin, g/L ±SD | 38.80.±5.91* | 40.3±4.56)* | 37.8±6.51* | <0.001* |
| Serum intact parathyroid hormone, pmol/L (Q1–Q3) | 12.8 (7.35–23.6)* | 10.4 (6.68–18.28)* | 15.1 (8.16–28.8)* | 0.007* |
| Serum bicarbonate, mmol/L ±SD | 21.3±3.6* | 21.9± 3.4* | 20.9±3.7* | <0.001* |
| Serum phosphate, mmol/L ±SD | 1.55±0.373* | 1.50±0.396* | 1.59±0.352* | 0.002* |
| Low-density lipoprotein cholesterol, mg/dL (Q1–Q3) | 92.9 (72.1–118.0)* | 90.6 (70.3–114.0)* | 93.8 (74.0–121.0)* | 0.002* |
| High-density lipoprotein cholesterol, mg/dL (Q1–Q3) | 46.1 (37.3–56.3) | 47.0 (39.3–56.4) | 45.2 (35.9–56.2) | 0.379 |
| C-reactive protein, mg/dL (Q1–Q3) | 0.55 (0.22–2.06) | 0.54 (0.23–2.01) | 0.55 (0.21–2.16) | 0.835 |
| Serum uric acid, mg/dL ±SD | 6.49±1.78 | 6.44±1.79 | 6.52±1.78 | 0.586 |
| Albuminuria, mg/g creatinine (Q1–Q3) | 356.0 (91.2–1241.0)* | 144 (42.3–459.0)* | 696 (178.0–1885.0)* | <0.001* |

Data given as n (%), mean±SD, or median (25th and 75th percentile) as appropriate. Reported *P* values correspond to probabilities under the null hypothesis that there is no true difference for a listed measure between patients with stable chronic kidney disease and patients with progressive chronic kidney disease. Chi-square tests were used for categorical measures, and paired *t* tests, or Kruskal–Wallis tests for continuous measures as appropriate for the measure's frequency distribution. BP indicates blood pressure; cIMT, carotid intima-media rhickness; CKD, chronic kidney disease; and SDS, SD score.

*Statistical significance was set at $P < 0.05$.

In the total cohort, girls, younger patients, and taller patients were at risk for higher cIMT SDS (β=0.20 [95% CI, 0.06–0.34], DF=610, *P*=0.0063; β=−0.05 [95% CI, −0.07 to −0.03], DF=610, *P*<0.0001; and β=0.10 [95% CI, 0.05–0.15], DF=610, *P*=0.0002). Diastolic BP was found to be a significant predictor of cIMT SDS (β=0.13 [95% CI, 0.05–0.21], DF=1542, *P*=0.001), whereas systolic BP showed no association of statistical significance with

**Table 3. Pooled Average Population-Level Effect Estimates (Fixed Effects) of Explanatory Covariates on Carotid Intima-Media Thickness SD Scores in a Linear Mixed-Effects Model of All Patients**

| Fixed effect | β | SE | 95% CI | DF | *P* value |
|---|---|---|---|---|---|
| Intercept | 2.7857 | 0.3154 | 2.1675 to 3.4039 | 1542 | <0.0001 |
| Estimated glomerular filtration rate, mL/min per 1.73 m$^2$ | −0.0015 | 0.0027 | −0.0068 to 0.0039 | 1542 | 0.5786 |
| Log(albuminuria), mg/g creatinine | 0.0038 | 0.0192 | −0.0338 to 0.0414 | 1542 | 0.8431 |
| Systolic blood pressure, SDS | 0.0359 | 0.0244 | −0.0119 to 0.0838 | 1542 | 0.1414 |
| Diastolic blood pressure, SDS | 0.1310* | 0.0398* | 0.0529 to 0.2092* | 1542* | 0.0010* |
| Serum albumin | −0.0152* | 0.0055* | −0.0259 to −0.0045* | 1542* | 0.0058* |
| Height, SDS | 0.0983* | 0.0264* | 0.0465 to 0.1502* | 1542* | 0.0002* |
| Time, y from baseline | 0.2048* | 0.036* | 0.1343 to 0.2753* | 1542* | <0.0001* |
| Time*Time | −0.0238* | 0.0055* | −0.0346 to −0.013* | 1542* | <0.0001* |
| Diastolic blood pressure (SDS)*time | −0.0426* | 0.0115* | −0.0651 to −0.0202* | 1542* | 0.0002* |
| Sex, female | 0.1981* | 0.0722* | 0.0566 to 0.3396* | 610* | 0.0063* |
| Age at study entry, y | −0.0468* | 0.0103* | −0.0671 to −0.0265* | 610* | <0.0001* |
| Diagnosis (glomerulopathies) | −0.132 | 0.1449 | −0.4161 to 0.1520 | 610 | 0.3627 |
| Diagnosis (postacute kidney injury) | −0.1825 | 0.1593 | −0.4949 to 0.1300 | 610 | 0.2524 |
| Diagnosis (tubulointerstitial) | −0.1622 | 0.1041 | −0.3664 to 0.0421 | 610 | 0.1197 |
| Diagnosis (other) | 0.0011 | 0.1848 | −0.3613 to 0.3634 | 610 | 0.9952 |

Time*time: quadratic effect of time in the model. Diastolic blood pressure (SDS)*time: interaction term between diastolic blood pressure SDS and time. DF indicates degrees of freedom; and SDS, SD score.

*Statistical significance was set at $P < 0.05$.

cIMT SDS (β=0.04 [95% CI, −0.01 to 0.08], DF=1542, *P*=0.141). Additionally, lower serum albumin levels were found to be associated with higher cIMT SDS (β=-0.02 [95% CI, −0.03 to −0.01], DF=1542, *P*<0.0058). The effects of baseline age, height, sex, and albumin on cIMT SDS remained consistent throughout the study period. The negative interaction between diastolic BP and time (β=-0.04 [95% CI, −0.07 to −0.02], DF=1542, *P*=0.0002) indicated a systematic decrease in the positive linear relationship between diastolic BP and cIMT SDS toward the end of the observation period (Table 3). Serum low-density lipoprotein and high-density lipoprotein levels and other candidate covariates not listed with fixed effect estimates in Table 3 were excluded from the LMM during *P* value based variable backward elimination.

In the group of patients with P-CKD, albuminuria (β=0.05 [95% CI, −0.002 to 0.102], DF=850, *P*=0.06) and higher diastolic BP (β =0.11 [95% CI, 0.01–0.212], DF=850, *P*=0.04) were identified as contributing factors to higher cIMT SDS, in addition to young age (β=-0.05 [95% CI, −0.08 to −0.03], DF=339, *P*=0.0002), height SDS (β=0.11 [95% CI, 0.04–0.17], DF=850, *P*=0.0013), and female sex (β=0.30 [95% CI, 0.11–.48], DF=339, *P*=0.0016) (Table 5). The impact of diastolic BP on cIMT SDS exhibited a notable decline over time (β=-0.06 [95% CI, −0.09 to −0.03], DF=850, *P*=0.0002). In the subgroup of patients with S-CKD serum phosphate (β=0.24 [95% CI, 0.02–0.49], DF=686, *P*=0.03) was the sole significant risk factor for higher cIMT SDS in addition to time (Table 4).

Figures 2 through 4 illustrate sensitivity analyses of longitudinal average population-level cIMT SDS profiles as fitted by the LMM based on median baseline value settings of all individual explanatory covariates and a modification of a single explanatory covariate's baseline median value by ±2*SD. The sensitivity plots presented in Figures 2 through 4 are provided separately for boys and girls as well as for the entire population and for the S- and P-CKD subpopulations, respectively.

In the LMM for the overall cohort, the average population-level effects of the identified cardiovascular risk factors with statistical significance on average for all patients jointly explained 10.9% ($R^2_\beta = 0.109$) of the total cIMT SDS variance in the overall cohort. The remaining unexplained variance was decomposed by the LMM into 47.0% of interpatient variability ($\hat{\sigma}^2_{inter-patient} = 0.792$), 11.2% of intercenter variability ($\hat{\sigma}^2_{inter-center} = 0.189$), and into 41.8% of cIMT measurement error ($\hat{\sigma}^2_{residual} = 0.703$). The LMM estimated that the measurement error $\hat{\sigma}^2_{residual}$ in the total cIMT SDS variance systematically declined by a factor of $e^{-0.1t}$ with increasing yearly follow-up duration *t*, pointing toward improved cIMT measurement accuracy and precision by the regional investigators over time (see Data S1, Equation I).

The intrapatient correlations indicated that the baseline cIMT SDS measurements were moderately correlated with the cIMT SDS measurements at 1 year of follow-up duration ($\widehat{IPC}(Y_{mi0}, Y_{mi(1)}) = 0.36$). The estimated intrapatient correlation between cIMT SDS at baseline and subsequent cIMT SDS measurements exhibited a gradual decline with increasing time intervals to an $\widehat{IPC}(Y_{mi0}, Y_{mi(2.4)}) = 0.01$ at 2.4 years of prospective follow-up relative to baseline.

**Table 4. Pooled Average Population-Level Effect Estimates (Fixed Effects) of Explanatory Covariates on Carotid Intima-Media Thickness SD Scores in a Linear Mixed-Effects Model of Patients With Stable Kidney Function**

| Fixed effect | β | SE | 95% CI | DF | *P* value |
|---|---|---|---|---|---|
| Intercept | 1.3102 | 0.3600 | 0.6046 to 2.0158 | 686 | 0.0003 |
| Estimated glomerular filtration rate, mL/min per 1.73 $m^2$ | 0.0078 | 0.0043 | −0.0007 to 0.0163 | 686 | 0.0701 |
| Log(albuminuria), mg/g creatinine | −0.0232 | 0.0267 | −0.0756 to 0.0292 | 686 | 0.3852 |
| Systolic blood pressure, SDS | 0.0202 | 0.038 | −0.0544 to 0.0947 | 686 | 0.5952 |
| Diastolic blood pressure, SDS | 0.0682 | 0.0449 | −0.0200 to 0.1564 | 686 | 0.1292 |
| Phosphate, mmol/L | 0.2408 | 0.1110 | 0.0228 to 0.4587 | 686 | 0.0304 |
| Time, y from baseline | 0.2473 | 0.0525 | 0.1443 to 0.3503 | 686 | <0.0001 |
| Time*Time | −0.0331 | 0.0080 | −0.0488 to 0.0174 | 686 | <0.0001 |
| Sex, female | 0.1019 | 0.1154 | −0.1246 to 0.3284 | 218 | 0.3782 |
| Age at study entry, y | −0.0241 | 0.0160 | −0.0555 to 0.0073 | 218 | 0.1335 |
| Diagnosis (glomerulopathies) | −0.1701 | 0.2528 | −0.6662 to 0.3260 | 218 | 0.5017 |
| Diagnosis (postacute kidney injury) | −0.1780 | 0.2718 | −0.7115 to 0.3554 | 218 | 0.5132 |
| Diagnosis (tubulointerstitial) | −0.1534 | 0.1928 | −0.5317 to 0.2250 | 218 | 0.4271 |
| Diagnosis (other) | 0.2563 | 0.3451 | −0.4209 to 0.9336 | 218 | 0.4585 |

Time*time: quadratic effect of time in the model. DF indicates degrees of freedom; and SDS, SD score.

Based on the fitted patient-level cIMT SDS values by the final LMM for the overall cohort, patients' yearly cIMT SDS change rates (Δ cIMT SDS) within the first 4.5 years of follow-up were derived. Patients' yearly change rates in BP SDS (Δ diastolic BP SDS and Δ systolic BP SDS) were derived as patient-level slope estimates (linear time effect+patient-level random slope) from 2 additionally fitted LMM (see Data S1, Equation V). The median yearly Δ cIMT SDS of 0.1 (0.0–0.2) corresponded to a median percentual change in cIMT SDS per year within patients of 8.3 (–0.1 to 20.6) % (see also Figure S4). The median yearly percentual changes per year within patients for systolic and diastolic BP SDS were –5.2 (–11.4 to 1.0) % and –6.0 (–11.3 to –3.3) %, respectively (see also Figures S5 and S6). To evaluate whether systematic BP changes in CKD patients within the first 4.5 years of follow-up predicted patients' linear rate of change in cIMT SDS 2 simple linear models regressed Δ cIMT SDS either on Δ systolic BP SDS (linear model I) or on Δ diastolic BP SDS (linear model II). The linear models estimated that Δ cIMT SDS was predicted by both Δ systolic BP SDS (β=0.42 [95% CI, 0.22–0.62], DF=501, *P*<0.001, Pearson r=0.17) and Δ diastolic BP SDS (β=1.56 [95% CI, 1.01–2.11], DF=501, *P*<0.001, Pearson r=0.24), indicating a dynamic positive association between BP changes and cIMT SDS changes within the first 4.5 years of prospective observation (Figure 5).

## DISCUSSION

This is the first prospective study to examine the evolution of cIMT in a large cohort of children with CKD over an 8-year period. The findings of our study indicate that the mean cIMT values at the outset of the study were higher than those observed in a large group of healthy controls. Furthermore, there was a significant increase in cIMT SDS over the course of the study. The increase in cIMT SDS was observed to be less pronounced over the extended observation period. The initial 4.5-year follow-up period revealed a positive correlation between the rate of change in cIMT SDS and the rate of change in BP SDS. The present study identified associations between several established general and CKD-associated cardiovascular risk factors and cIMT SDS. These included diastolic BP, serum phosphate, serum albumin, and albuminuria.

The study design, which entailed the distribution of patients across more than 50 centers over the course of 8 years, necessitated comprehensive planning to ensure the timely conduct of synchronized visits and cardiovascular measurements. Of particular importance was the performance of annual cardiovascular assessments by jointly trained regional investigators from the ESCAPE network (European Sudden Cardiac Arrest Network Towards Prevention, Education and New Effective Treatments), who had undergone joint training and were responsible for conducting assessments at their individually assigned study sites. These assessments were conducted using identical portable devices, which helped to minimize observer-related variation in measurements. Consequently, the 4C Study cohort represents a unique data set in terms of its aligned methodology, cohort size, and implementation.

Prior research has documented elevated cIMT values in both adult and pediatric patients with CKD. For instance, the CKiD (Chronic Kidney Disease in Children) study observed increased cIMT in early CKD[27] and several studies conducted by the ESCAPE consortium have also demonstrated elevated cIMT in

**Table 5. Pooled Average Population-Level Effect Estimates (Fixed Effects) of Explanatory Covariates on cIMT SDS in a Linear Mixed-Effects Model of Patients With Progressive Kidney Failure**

| Fixed effect | β | SE | 95% CI | DF | *P* value |
|---|---|---|---|---|---|
| Intercept | 2.0694 | 0.2782 | 1.5243 to 2.6147 | 850 | <0.0001 |
| Estimated glomerular filration rate, mg/min/1.73m$^2$ | −0.0026 | 0.0042 | −0.0108 to 0.0056 | 850 | 0.5361 |
| Log(albuminuria), mg/g creatinine | 0.0498 | 0.0264 | −0.0020 to 0.1015 | 850 | 0.0596 |
| Systolic blood pressure, SDS | 0.0453 | 0.0318 | −0.0172 to 0.1077 | 850 | 0.1547 |
| Diastolic blood pressure, SDS | 0.1101 | 0.0521 | 0.0078 to 0.2124 | 850 | 0.0349 |
| Height, SDS | 0.1047 | 0.0325 | 0.0409 to 0.1685 | 850 | 0.0013 |
| Time, y from baseline | 0.1495 | 0.0495 | 0.0524 to 0.2465 | 850 | 0.0026 |
| Time*Time | −0.0154 | 0.0076 | −0.0304 to 0.0004 | 850 | 0.0430 |
| Diastolic blood pressure (SDS)*Time | −0.0575 | 0.0155 | −0.0878 to 0.0272 | 850 | 0.0002 |
| Sex, female | 0.2983 | 0.0935 | 0.1148 to 0.4818 | 339 | 0.0016 |
| Age at study entry, y | −0.0543 | 0.0143 | −0.0824 to 0.0262 | 339 | 0.0002 |
| Diagnosis (glomerulopathies) | −0.0995 | 0.1747 | −0.4423 to 0.2432 | 339 | 0.5694 |
| Diagnosis (postacute kidney injury) | −0.1383 | 0.1934 | −0.5177 to 0.2412 | 339 | 0.4750 |
| Diagnosis (tubulointerstitial) | −0.2146 | 0.1246 | −0.4591 to 0.0299 | 339 | 0.0859 |
| Diagnosis (other) | −0.0817 | 0.2162 | −0.5058 to 0.3424 | 339 | 0.7057 |

Time*time: quadratic effect of time in the model.

Diastolic blood pressure (SDS)*time: interactive term between diastolic blood pressure SD score (SDS) and time. DF indicates degrees of freedom; and SDS, SD score.

all CKD stages.[4,28] However, the trajectory of cIMT in childhood CKD over extended time periods remains unknown due to the absence of long-term longitudinal studies. The present study encompasses a period of up to 8 years, which coincides with a crucial phase of growth. The use of cIMT SDS permitted the discernment of changes over time, independent of the natural course of cIMT due to age and sex. At the outset of the study, the cIMT values observed in the 4C cohort patients were already elevated in comparison to the normal values obtained from healthy children.[11] This discrepancy continued to grow over the course of the study, as evidenced by the positive effect observed in the LMM equation. These findings indicate a notable thickening of the cIMT in children with CKD over time, independent of age and sex.

The reasons for the deceleration of cIMT increase toward the end of the observation period remain hypothetical. Even though the increase of cIMT SDS was independent of age in the multivariate model, a certain role of age cannot be excluded. By default, the cohort is significantly younger during the early phase of the study and cIMT SDS in general shows an inverse relationship with age in the study. It thus appears reasonable to suggest that younger ages may be more susceptible to factors that influence cIMT changes, such as BP. Another hypothesis is that informative dropout due to the initiation of KRT may have influenced the slope of cIMT SDS at the extended observation period. For this reason, patients with and without P-CKD were analyzed as separate subgroups to ascertain whether there were any differences between patients who discontinued the study earlier and those who remained in the study. However, both groups demonstrated a more pronounced initial increase and a subsequent flattening of the curve. Earlier stages of CKD did not appear to be associated with a heightened risk of cIMT progression, as there was no correlation between eGFR and cIMT progression in any of the models. However, the decade-long duration of the study may have positively influenced the awareness of secondary complications of CKD in participating centers, ultimately resulting in intensified treatment. The demonstrably observed effect of a decrease in diastolic BP in the cohort, together with a higher proportion of patients on antihypertensive therapy, may be the consequence of these factors, which may have contributed to a slowing of the progression of cIMT SDS rather than a continuous increase of cIMT SDS.

The literature on the relationship between high BP and cIMT in healthy children is inconclusive.[29] Our previous study, which established normative values for cIMT in over 1000 healthy children, revealed a significant correlation between systolic BP and cIMT, consistent with the findings of other studies.[9,29] In cross-sectional studies of CKD, correlations between systolic BP and cIMT have been identified in patients undergoing dialysis and transplantation, as well as in those with CKD.[11,28,30] In the cross-sectional analysis of the baseline cardiovascular measurements in the 4C study cohort,[11] systolic BP was identified as a risk factor for higher cIMT SDS. It is noteworthy that a significant

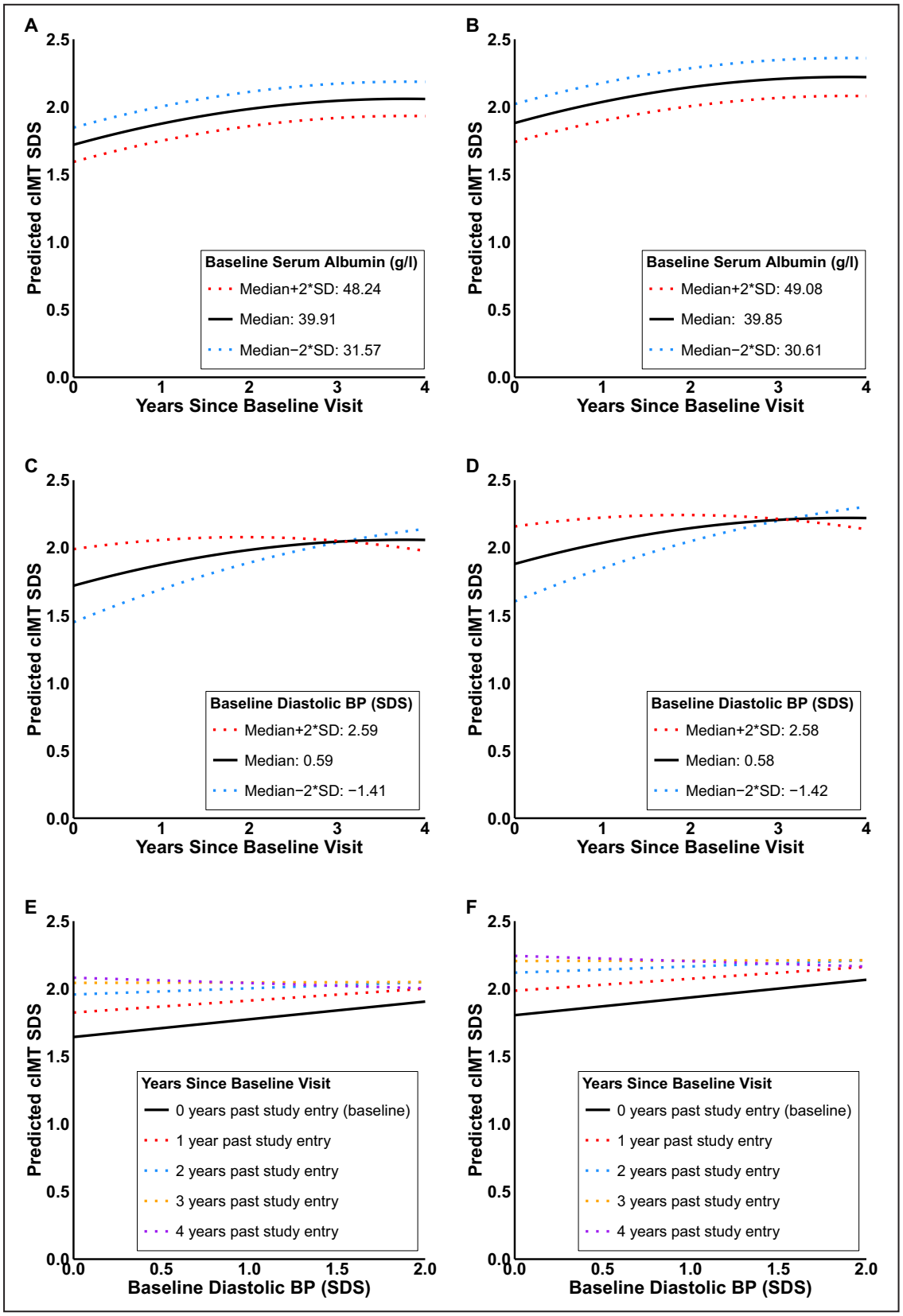


**Figure 2. Average population-level cIMT SDS prediction for male (A, C, E) and female (B, D, F) patients (baseline age: 11 years), with congenital anomalies of the kidney and urinary tract diagnosis based on median baseline covariate values.**

BP indicates blood pressure; cIMT, carotid intima-media thickness; and SDS, SD score.

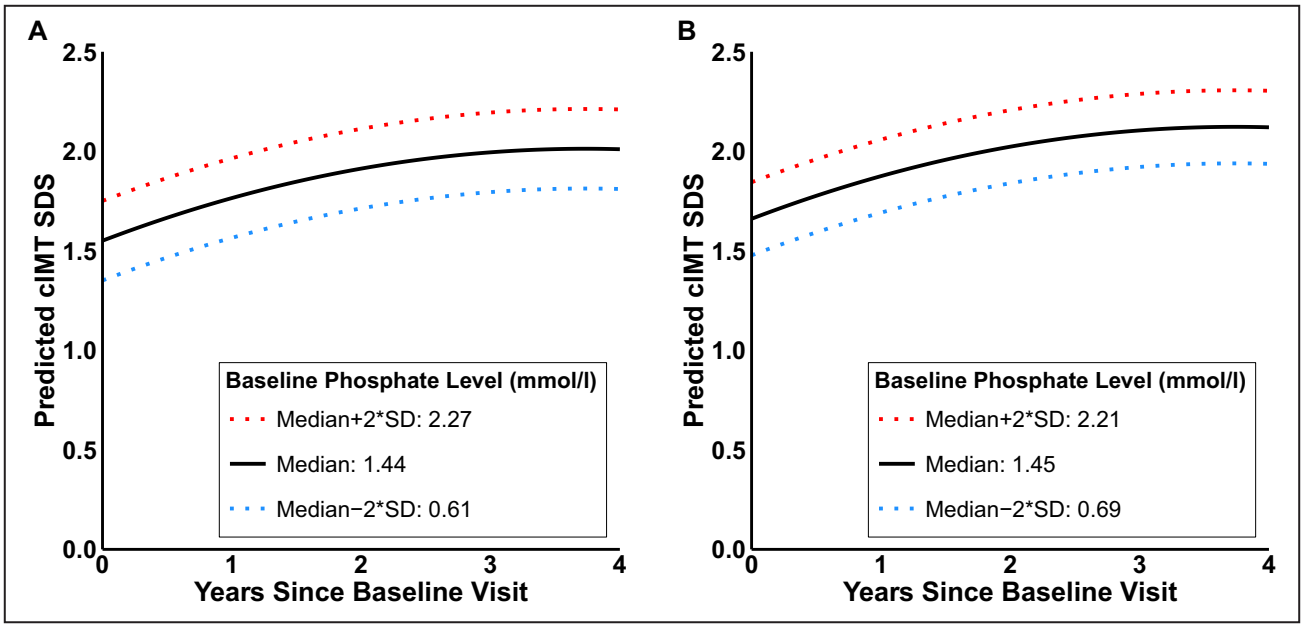


**Figure 3. Average population-level cIMT SDS prediction for male (A) and female (B) patients (baseline age: 11 years), with congenital anomalies of the kidney and urinary tract diagnosis and stable chronic kidney disease based on median baseline covariate values.**
cIMT indicates carotid intima-media thickness; and SDS, SD score.

association between diastolic BP and cIMT SDS was observed in the overall cohort and in the subgroup of patients with progressive kidney failure, but not in those with stable kidney function. This is consistent with the findings of Shroff et al., who identified diastolic BP as a significant risk factor for increased cIMT in children approaching KRT.[31] It can be postulated, therefore, that patients with more advanced CKD who experience progressive fluid overload and increased diastolic BP are at a higher risk of developing increased cIMT compared with those in earlier and more S-CKD stages. This is consistent with the longitudinal analysis of pulse wave velocity in patients from the 4C Study, which also identified diastolic but not systolic BP as a relevant risk factor for increased vascular stiffness.[12] It is also noteworthy that the correlation between diastolic BP and cIMT, as measured at each visit over the course of the present study, weakened over time. This may be attributed to the smaller patient population at the study's conclusion and more effectively managed BP levels at later observations.

The observed association between the dynamics of cIMT SDS and BP over time is a notable finding that suggests a potential influence of changes in BP on the progression of cIMT. In pediatric patients with CKD, a small study in children with hypertension demonstrated that lowering BP through antihypertensive treatment resulted in a reduction of cIMT after 1 year of follow-up.[32] A comprehensive meta-analysis of over 119 controlled trials in adults by Willeit et al. demonstrated that therapeutic intervention could effectively reduce cIMT progression, ultimately leading to a reduction in cardiovascular disease.[33]

The analysis identified female sex and young age as predictive factors for increased cIMT. Although this is an intriguing finding, the higher risk for increased cIMT at a younger age may reflect varying time spans of disease burden in younger patients, who are predominantly affected by congenital anomalies of the kidney and urinary tract and longer histories of CKD. The impact of sex in our study was most prominent in the subgroup of patients with progressive kidney failure. This finding corroborates parallel analyses of large-artery function in the 4C cohort, where elevated carotid-femoral pulse-wave velocity was consistently found to be higher and to progress more rapidly in girls compared with boys, both before KRT and after initiation of dialysis or transplantation.[12,14] Additionally, the ARIC (Atherosclerosis Risk in Communities) study in adults also found an increased risk for cardiovascular disease in female patients.[34] This contributes to the growing body of knowledge regarding sex-based differences in medicine,[35] particularly regarding cardiovascular disease risk profiles and progression.[36,37]

Although kidney function was not a significant predictor of cIMT in the total study cohort, we identified distinct risk profiles for cardiovascular disease within our population, contingent on the progression of CKD. This suggests that concomitant factors associated with

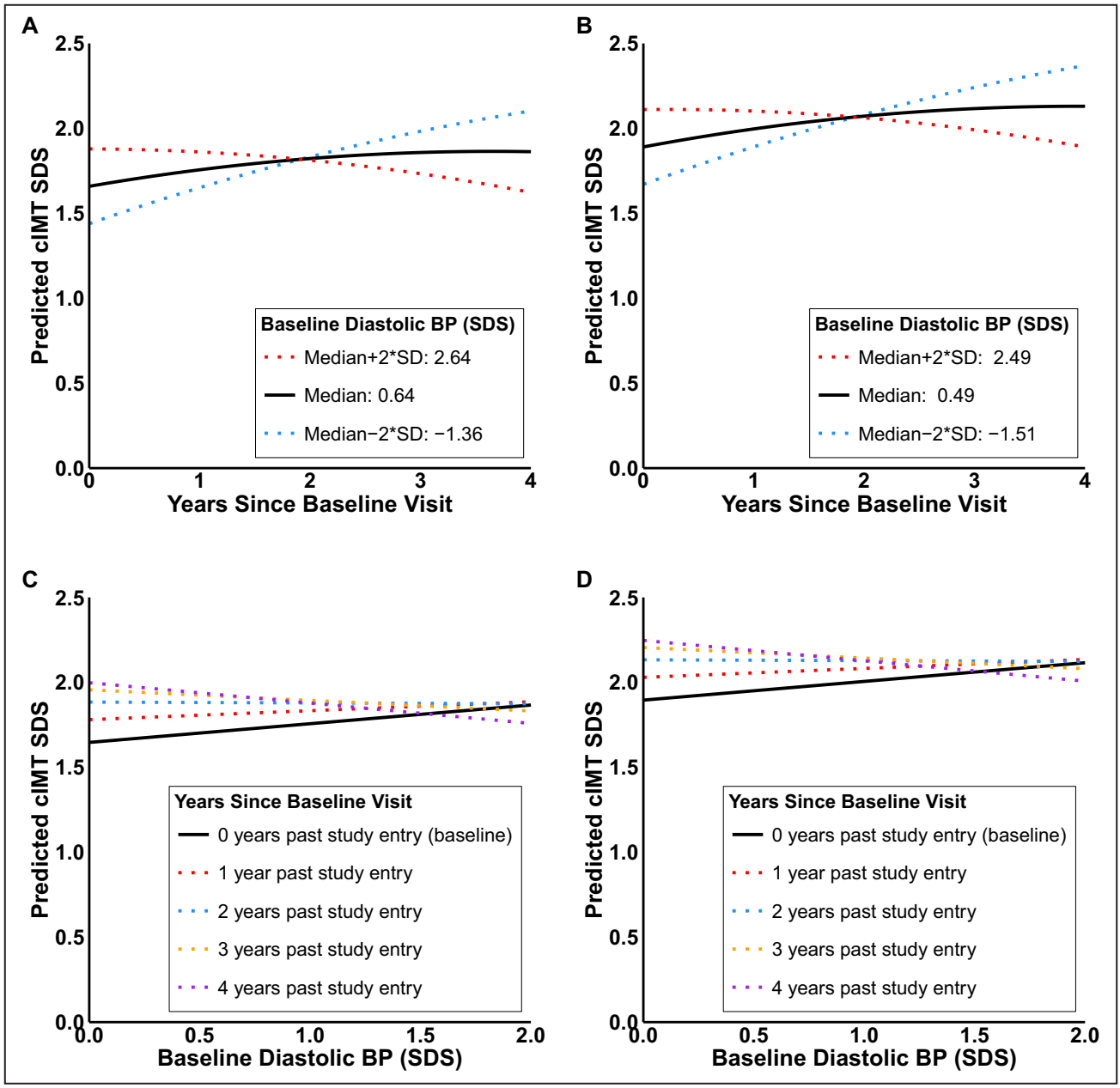


**Figure 4. Average population-level cIMT SDS prediction for male (A, C) and female (B, D) patients (baseline age: 11 years), with congenital anomalies of the kidney and urinary tract diagnosis and progressive chronic kidney disease based on median baseline covariate values.**

BP indicates blood pressure; cIMT, carotid intima-media thickness; and SDS, SD score.

P-CKD may exert a greater influence on the development of cardiovascular disease than eGFR decline.

A reduction in serum albumin in the overall cohort, and albuminuria in the group with P-CKD, were found to be significantly and time-independently associated with cIMT SDS. Low serum albumin levels have been linked to vascular calcifications, an increased incidence of cardiovascular events, and cardiovascular mortality in patients with CKD and patients receiving dialysis.[38–42] Moreover, a significant association to increased cIMT has been observed in a study of children undergoing peritoneal dialysis.[43] Additionally, low serum albumin is associated with an increased propensity for calcification, which is a strong predictor of overall mortality in adults with predialysis CKD.[44] Furthermore, albumin is recognized as a marker of inflammation and protein-energy wasting in CKD. It may therefore also have an active role in vascular remodeling.[45]

In addition to the existing literature on the detrimental impact of elevated serum phosphate levels on

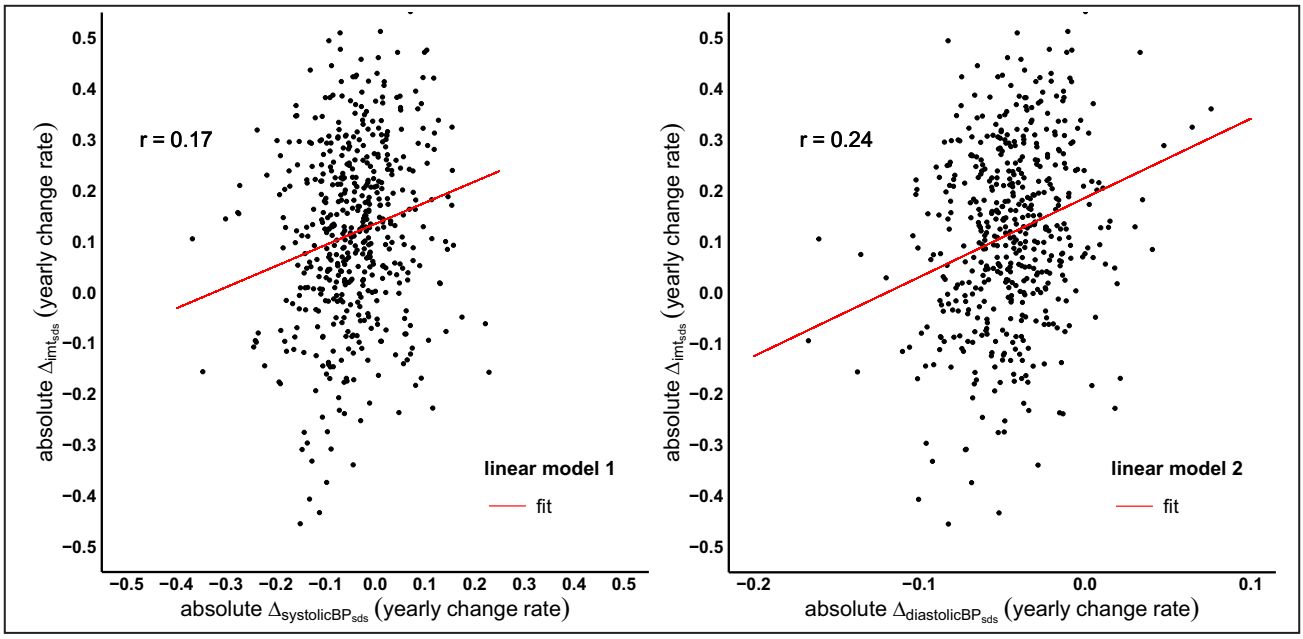


**Figure 5. Progression of cIMT SDS depending on BP SDS dynamics over time.**
Test for linear relationships between absolute change per year in cIMT SDS (Δ cIMT SDS) with absolute change per year in systolic blood pressure BP SDS (Δ systolic BP SDS) and diastolic blood pressure BP SDS (Δ diastolic BP SDS) within first 4.5 years of follow-up. BP indicates blood pressure; cIMT, carotid intima-media thickness; and SDS, SD score.

vessel morphology in CKD,[4,28,46] a recent analysis from the CRIC (Chronic Renal Insufficiency Cohort) study has confirmed a positive correlation between serum phosphate levels and coronary artery calcification in a large cohort of adult patients with CKD.[47] Interestingly, the effect of serum phosphate was observed only in the group with S-CKD. In the group with P-CKD, the influence of other factors, such as BP, may have been more significant than that of phosphate.

## Limitations

This is the largest longitudinal study of cIMT and its progression in children with CKD to date. However, it is observational only and all assumptions and conclusions are based on correlational associations. A paucity of data exists regarding the extent of measurement error in comparable studies. Our analysis indicated a large proportion of measurement error that was more prominent at baseline and decreased thereafter. It would be beneficial to determine, whether this is an inherent limitation of the method or if further investment in measurement performance and alignment of methods, beyond those already performed, would be advantageous.

The additional, unexplained variability in the regression model may originate from risk factors of clinical significance at the individual patient level, although not at the population level. Such interpatient variation may, for example, be attributable to differential genetic susceptibility. This underscores the necessity for further research to explain the individual course of the cardiovascular phenotype.

## CONCLUSIONS

In conclusion, this prospective long-term observational study of a large pediatric cohort with CKD reveals an already increased cIMT SDS at study entry compared with a group of healthy controls that significantly progressed during the study follow-up, with an attenuation of the progression toward the end of the study. Several traditional cardiovascular risk factors could be identified as predictors for increased cIMT SDS, such low serum albumin, increased diastolic BP, and serum phosphate. Younger patients were significantly more at risk for increased cIMT SDS and there was a significant sex difference especially for patients with P-CKD with increased cIMT SDS in female patients. Importantly, there was a relationship between the yearly BP change rate as a modifiable risk factor and cIMT SDS progression. Further research should try to reduce the amount of measurement error in cIMT measurements and also address yet unidentified average population-level and patient-specific risk factors and the interaction of treatment of modifiable risk factors such as BP on individual progression of cIMT. Our findings highlight that all pediatric patients with CKD, independent of CKD stage, should be screened for modifiable cardiovascular risk factors and treated accordingly, because this population is,

and will be later in life, particularly prone to cardiovascular complications.

## APPENDIX

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## Disclosures

None.

## Supplemental Material

Data S1
Tables S1–S6
Figures S1–S6

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