SUPPLEMENTAL MATERIAL

Arterial Stiffness and Chronic Kidney Disease Progression in Children

Karolis Azukaitis[1], Marietta Kirchner[2], Anke Doyon[3], Mieczysław Litwin[4], Aysun Bayazit[5], Ali Duzova[6], Nur Canpolat[7], Augustina Jankauskiene[1], Rukshana Shroff[8], Anette Melk[9], Uwe Querfeld[10], Franz Schaefer[3] and 4C Study Investigators

[1]Clinic of Pediatrics, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[2]Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany
[3]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg University Hospital, Heidelberg, Germany
[4]Department of Nephrology and Arterial Hypertension, the Childrens Memorial Health Institute, Warsaw, Poland
[5]Department of Pediatric Nephrology, Cukurova University, Adana, Turkey
[6]Division of Pediatric Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey
[7]Department of Pediatric Nephrology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey
[8]UCL Great Ormond Street Institute of Child Health, London, UK
[9]Department of Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany
[10]Department of Pediatric Gastroenterology, Nephrology and Metabolic Diseases, Charite´–Universitätsmedizin Berlin, Berlin, Germany

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Supplemental Methods

PWV measurement procedure

The patients were investigated in a quiet room, avoiding any outside disturbances. A period of 15 minutes of rest was required before the measurements were performed. Measurements were performed in a supine position with head and shoulders tilted by approximately 30°. Neck cuff was placed on the neck with the neck pad over the right carotid artery and tightened collar-tight. Thigh cuff was placed on patient's upper right thigh and tightened. Removing pants or trousers was not required, unless proper tightening of the cuff was impossible. No talking or moving was allowed during the measurements. Three measurements each capturing at least 10 beats with good quality waves in the screen were performed. The mean value of these three measurements was used for further analysis.

PWV values were standardized using reference data that was specifically derived by the 4C Study Consortium using same device, same pathway measurement and similar measurement procedure. (1)

Statistical analysis

All data was checked for outliers by investigating extreme values with consideration of patient-specific longitudinal trends and assessing clinical plausibility.

Univariable linear regression was performed to assess the association of variables at baseline with absolute PWV. Next, variables with $p<0.2$ were selected as candidate variables for a multivariable mixed effects model with a random center effect to determine associations with PWV at baseline. A full model including all candidate variables and a model after variable selection (stepwise forward-backward, entry level of $p<0.2$, stay level $p<0.1$) were considered. In case of known inter-correlation (systolic and diastolic BP, MAP, serum lipids), variables resulting in a better model fit were chosen in the full model. Vitamin D levels (25-OH-vitamin D3) were only measured at baseline and in a subgroup so the basic full model was built without this variable. A supplementary analysis was performed repeating the full model with vitamin D included restricted to the subgroup. Similar models were built with PWVz restricting the analysis to patients who were <17 years at baseline (see explanation below) and using standardized instead of absolute values of BP and height.

Twenty datasets were imputed using the R package mice and miceadds with method 2l.pmm to impute continuous data and seed=0920 for reproducibility. Rubin's rule was used to pool results. Imputation diagnostic included visual inspection of the distribution of imputed and original data by build-in functions of the mice package e.g. bwplot.

The Cox proportional hazard model with time-varying PWVz was built by specifying starting and stopping time for each record. Multiple intervals per person were defined to account for the change in covariate values. (2) In each interval (start, stop) the covariates are constant and a new interval begins when a new value was observed (next visit). Additionally, time-varying BMI z-score, systolic BP z-score and log-UACR were included. As eGFR is part of the event definition, only the baseline value was included as covariate and not the time-varying variable.

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2. Thomas L, Reyes EM. Tutorial: Survival Estimation for Cox Regression Models with Time-Varying Coefficients Using SAS and R. Journal of Statistical Software, Code Snippets 61(1): 1–23, 2014

Principal investigators of the 4C Study Group

The principal investigators of the 4C Study included the following:

Pediatric Nephrology, University Children's Hospital Vienna, Vienna, Austria: Klaus Arbeiter, MD; Department of Pediatrics I, Medical University, Innsbruck, Austria: Alejandra Rosales, MD; University Hospital Motol, Prague, Czech Republic: Jiri Dusek, MD; Pole Medico-Chirugical de Pediatrie, Hôpital de Hautepierre, Strasbourg, France: Ariane Zaloszyc, MD; Pediatric Nephrology, Charité Campus Virchow-Klinikum, Berlin, Germany: Uwe Querfeld, MD, and Jutta Gellermann, MD; Pediatric Nephrology Immunology and Hypertensiology, University Children's Hospital, Cologne, Germany: Max Liebau, MD, and Lutz Weber, MD; Pediatric Nephrology, University Children's Hospital, Erlangen, Germany: Evelin Muschiol, MD; Pediatric Nephrology, University Children's Hospital, Essen, Germany: Rainer Büscher, MD; Pediatric Nephrology, UKE University Children's Hospital, Hamburg, Germany: Jun Oh, MD; Pediatric Nephrology, Hannover Medical School, Hannover, Germany: Anette Melk, MD, Daniela Thurn-Valassina, MD, and Dieter Haffner, MD; Division of Pediatric Nephrology, Center for Children and Adolescents, Heidelberg, Germany: Franz Schaefer, MD; Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Freiburg, Germany: Charlotte Gimpel, MD; Division of Pediatric and Nephrology, Center for Pediatrics and Adolescent, Jena, Germany: Ulrike John, MD; Children's Dialysis Center, Town Hospital St Georg, Leipzig, Germany: Simone Wygoda MD; KfH Kidney Center for Children, Marburg, Germany: Nikola Jeck, MD; Pediatric Nephrology, University Children's Hospital, Rostock, Germany: Marianne Wigger, MD; Pediatric Nephrology and Dialysis, Ospedale Maggiore, Policlinico, Milano, Italy: Sara Testa, MD; Dialysis and Transplantation, Department of Pediatrics, Dipartimento di Pediatria Salus Pueri, Padova, Italy: Luisa Murer, MD; Division di Nefrologia e Dialisi, Ospedale Pediatrico Bambino Gesú, Roma, Italy: Chiara Matteucci, MD; Center for Pediatrics, University Children's Hospital, Vilnius, Lithuania: Augustina Jankauskiene, MD, and Karolis Azukaitis, MD; Dialysis Unit, PA Children's Hospital, Cracow, Poland: Dorota Drozdz, MD; Pediatric Nephrology, Instituto Giannina Gaslini, Genova, Italy: Francesca Lugani, MD; Department of Pediatric and Adolescent Nephrology, University Medical School, Gdańsk, Poland: Aleksandra Zurowska, MD; Pomeranian Academy of Medicine, Clinic of Pediatrics, Szczecin, Poland: Marcin Zaniew, MD; Nephrology, Kidney, Transplantation and Hypertension, Children's Memorial Health Institute, Warsaw, Poland: Mieczyslaw Litwin, MD, and Anna Nimierska, MD; Serviçio de Pediatria, Hospital de São João, Porto, Portugal: Ana Teixeira, MD; University Children's Hospital, Belgrade, Serbia: Amira Peco-Antic, MD, and Dusan Paripovic, MD; Nephrology, University Children's Hospital, Zürich, Switzerland: Guido Laube, MD; Cocuk Nefrolojisi Bilim Dali, Cukurova Universitesi Tip Fakültesi, Adana, Turkey: Ali Anarat, MD, and Aysun Bayazit, MD; Pediatric Nephrology, Hacettepe University, Ankara, Turkey: Ali Duzova, MD, and Yelda Bilginer, MD; Pediatric Nephrology, Cerrahpasa Medical Faculty, Istanbul, Turkey: Salim Caliskan, MD, Nur Canpolat, MD, and Mahmut Civilibal, MD; Pediatric Nephrology, Ege University, Izmir, Turkey: Sevgi Mir, MD, and Betül Sözeri, MD; Pediatric Nephrology, University Children's Hospital, Münster, Germany: Brigitta Kranz, MD; Department of Pediatrics, Sant'Orsola-Malphighi Hospital, Bologna, Italy: Francesca Mencarelli, MD; Inselspital Children's Hospital, Bern, Switzerland: Brigitte Dorn, MD; Pediatric Nephrology, University Tip Faculty of Medicine Cebeci Kampusu Cocuk, Ankara, Turkey: Fatos Yalcinkaya, MD; Faculty of Medicine, Baskent University, Ankara, Turkey: Esra Baskin, MD; Diskapi Children's Hospital, Ankara, Turkey: Nilgun Cakar, MD; Pediatric Nephrology, Gazi University Hospital, Ankara, Turkey: Oguz Soylemezoglu, MD; Department of Pediatric Nephrology, Istanbul Medical Faculty, Çapa-Istanbul, Turkey: Sevinc Emre, MD; Pediatric Nephrology, Goztepe Educational and Research Hospital, Istanbul, Turkey: Cengiz Candan, MD; Pediatric Nephrology, Bakirkoy Children's Hospital, Istanbul, Turkey: Aysel Kiyak, MD; Pediatric Nephrology, Sisli Educational and Research Hospital, Istanbul, Turkey: Gul Ozcelik, MD; Pediatric Nephrology, Marmara University Medical Faculty, Istanbul, Turkey: Harika Alpay, MD; Nephrology, Great Ormond Street Hospital, London, United Kingdom: Rukshana Shroff, MD; Service de Néphrologie Pédiatrique, Universite Hôpital Femme Mère Enfant, Lyon, France: Bruno Rachin, MD; Service de Pédiatrie, Centre de Reference Maladies Renales Rares du Sud-Quest, Bordeaux, France: Jerome Harambat, MD; Pediatric Nephrology, Zabrze, Poland: Maria

Szczepanska, MD; Dortcelik Children’s Hospital, Bursa, Turkey: Hakan Erdogan, MD; Uludag University, Bursa, Turkey: Osman Donmez, MD; Department of Pediatric Nephrology, University of Gaziantep, Gaziantep, Turkey: Ayse Balat, MD; Tepecik Training and Research Hospital, Izmir, Turkey: Nejat Aksu, MD; Department of Pediatric Nephrology, Inonu Universtiy Medical School, Malatya, Turkey : Yilmaz Tabel, MD; Pediatric Nephrology Department, Celal Bayar University, Manisa, Turkey: Pelin Ertan, MD; and Pediatric Nephrology, Sanliurfa Children’s Hospital, Sanliurfa, Turkey: Ebru Yilmaz, MD.

Supplemental Table 1. Classification of primary kidney diseases

Diagnosis group	Diagnoses
CAKUT	Vesico-ureteral reflux; Bladder anomalies; Urethral anomalies; Reflux nephropathy. Renal hypo/dysplasia; Renal dystopia; Renal aplasia; Renal hypoplasia; Renal dysplasia; Multicystic dysplasia; Segmental dysplasia; Oligomeganephronia; Renal duplication; Ureter of upper renal pelvis inserting caudally; Pyelo-ureteral junction stenosis; Ureter fissus or duplex; Megaureter; Ectopic ureter; Ureterocele; Other; Syndromal malformation; Autosomal dominant polycystic kidney disease; Autosomal recessive polycystic kidney disease.
Glomerulopathies	IgA nephropathy; Wegener's glomerulonephritis; Henoch-Schoenlein purpura associated glomerulonephritis; Lupus nephritis; Congenital nephrotic syndrome; Infantile nephrotic syndrome; Syndromal nephrotic syndrome; Minimal change glomerulopathy; Focal segmental glomerulosclerosis; Membranous glomerulopathy; Mesangioproliferative nephropathy; Membranoproliferative glomerulonephritis; Rapidly progressing glomerulonephritis; Postinfectious glomerulonephritis; Alport syndrome.
CKD post-AKI	Post-ischemic CKD; Hemolytic uremic syndrome.
Tubulointerstitial	Tubulopathy; Interstitial nephropathy; Cystinosis; Oxalosis; Nephrocalcinosis; Nephronophtisis; Metabolic nephropathies.
Other	Diabetic glomerulopathy; Renovascular disease; Other; Unknown

Supplemental Table 2. Univariable (pairwise deletion of missing values) and multivariable regression (mixed model with random center effect, restricted to the subgroup of patients with available 25(OH)-vitamin D3, full model including all candidate variables with p<.20) with absolute PWV at baseline as the dependent variable

		Univariable regression		Multivariable regression (n=480)		
	Estimate	**95% CI**	**p value**	**Estimate**	**95% CI**	**p value**
Age, year	0.101	0.083; 0.118	<0.001	0.033	-0.006; 0.071	0.09
Sex (ref: girls)	0.048	-0.086; 0.181	0.70	-	-	-
Diagnosis other (ref: non-CAKUT)	-0.095	-0.233; 0.042	0.18	-0.072	-0.208; 0.062	0.29
SGA (ref: yes)	0.054	-0.125; 0.234	0.55	-	-	-
BMI, per 1 z-score	-0.006	-0.055; 0.044	0.83	-	-	-
Height, per cm	0.016	0.013; 0.019	<0.001	0.006	-0.001; 0.012	0.09
Systolic BP, per mmHg	0.023	0.019; 0.027	<0.001	-	-	-
Diastolic BP, per mmHg	0.027	0.022; 0.031	<0.001	-	-	-
MAP, per mmHg	0.029	0.025; 0.034	<0.001	0.024	0.019; 0.029	<0.001
HR, per bpm	-0.002	-0.007; 0.003	0.47	-	-	-
eGFR, per ml/min/1.73 m^2	0.0004	-0.005; 0.005	0.89	-	-	-
Hemoglobin, per g/dL	0.065	0.027; 0.105	0.001	0.004	-0.035; 0.043	0.85
Bicarbonate, per mEq/L	0.004	-0.014; 0.022	0.65	-	-	-
Cholesterol, per mg/dL	0.001	-0.001; 0.002	0.41	-	-	-
LDL cholesterol, per mg/dL	0.001	-0.001; 0.002	0.51	-	-	-
HDL cholesterol, per mg/dL	-0.005	-0.010; -0.001	0.02	-0.005	-0.010; -0.001	0.01
Uric acid, per mg/dL	0.012	-0.024; 0.047	0.52	-	-	-
Serum calcium, per mg/dL	-0.076	-0.163; 0.011	0.09	0.095	-0.002; 0.191	0.06
Corrected serum calcium, per mg/dL	-0.046	-0.137; 0.045	0.32	-	-	-
Serum phosphate, per mmol/L	0.005	-0.050; 0.059	0.87	-	-	-
Serum albumin, per g/L	-0.006	-0.017; 0.006	0.33	-	-	-
Log-UACR	0.083	0.048; 0.118	<0.001	0.024	-0.011; 0.059	0.18
Log-ferritin	-0.093	-0.154; -0.032	0.003	-0.079	-0.139; -0.019	0.01
Log-CRP	0.039	-0.0002; 0.079	0.05	-0.0003	-0.039; 0.039	0.99
Log-PTH	0.048	-0.014; 0.110	0.13	0.002	-0.064; 0.068	0.95
Log-25(OH)-vitamin D3	-0.151	-0.230; -0.072	<0.001	-0.094	-0.164; -0.024	0.009

Supplemental Table 3. Multivariable mixed regression model with random center effect including variables after stepwise variable selection (with log-25(OH)-vitamin D3 levels included among candidate variables) with absolute PWV at baseline as the dependent variable (n=483)

Parameter	Estimate	95% CI	p value
Age, per 1 year older	0.065	0.046; 0.083	<0.001
MAP, per 1 mmHg higher	0.025	0.020; 0.030	<0.001
Serum calcium, per 1 mg/dL higher	0.083	-0.005; 0.171	0.06
HDL cholesterol, per 1 mg/dL higher	-0.005	-0.009; -0.0008	0.02
Log-25(OH)-vitamin D3, per 1 log higher	-0.106	-0.174; -0.037	0.003
Log-ferritin, per 1 log higher	-0.080	-0.137; -0.023	0.006

Supplemental Table 4. Univariable (pairwise deletion of missing values) and multivariable regression (mixed model with random center effect, restricted to the subgroup of patients with available 25(OH)-vitamin D3, full model including all candidate variables) with PWVz at baseline as the dependent variable restricted to patients with age ≤ 17 years at baseline

	Univariable regression			Multivariable regression (N=451)		
	Estimate	**95% CI**	**p value**	**Estimate**	**95% CI**	**p value**
Age, per 1 year older	-0.069	-0.110; -0.027	0.001	-0.071	-0.118; -0.025	0.03
Sex (ref: girls)	-0.235	-0.509; 0.040	0.09	0.016	-0.267; 0.299	0.91
Diagnosis other (ref: non-CAKUT)	-0.017	-0.303; 0.268	0.91	-	-	-
SGA (ref: yes)	-0.081	-0.447; 0.285	0.66	-	-	-
BMI, per 1 z-score higher	-0.012	-0.120; -0.096	0.83	-	-	-
Height, per 1 z-score higher	-0.362	-0.461; -0.263	<0.001	-0.305	-0.409; -0.200	<0.001
Systolic BP, per 1 z-score higher	0.404	0.301; 0.507	<0.001	-	-	-
Diastolic BP, per 1 z-score higher	0.554	0.426; 0.683	<0.001	0.508	0.378; 0.638	<0.001
HR, per 1 bpm higher	0.014	0.003; 0.025	0.01	0.001	-0.011; 0.012	0.92
eGFR, per 1 ml/min/1.73 m^2 higher	-0.005	-0.017; 0.007	0.42	-	-	-
Hemoglobin, per 1 g/dL higher	-0.042	-0.130; 0.046	0.35	-	-	-
Bicarbonate, per 1 mEq/L higher	-0.031	-0.070; 0.009	0.12	0.007	-0.037; 0.050	0.76
Cholesterol, per 1 mg/dL higher	0.002	-0.0004; 0.005	0.10	-	-	-
LDL cholesterol, per 1 mg/dL higher	0.003	-0.0008; 0.007	0.13	0.001	-0.003; 0.005	0.51
HDL cholesterol, per 1 mg/dL higher	-0.002	-0.012; 0.008	0.68	-	-	-
Uric acid, per 1 mg/dL higher	-0.077	-0.152; -0.001	0.05	0.029	-0.050; 0.108	0.47
Serum calcium, per 1 mg/dL higher	-0.136	-0.328; 0.057	0.17	0.121	-0.112; 0.353	0.31
Corrected serum calcium, per 1 mg/dL higher	-0.033	-0.234; 0.167	0.75	-	-	-
Serum phosphate, per 1 mg/dL higher	0.135	0.017; 0.252	0.03	0.022	-0.114; 0.159	0.75
Serum albumin, per 1 g/dL higher	-0.184	-0.440; 0.072	0.16	0.029	-0.273; 0.331	0.85
Log-UACR, per 1 log higher	0.152	0.077; 0.227	<0.001	0.025	-0.061; 0.111	0.56
Log-ferritin, per 1 log higher	-0.173	-0.314; -0.032	0.02	-0.142	-0.276; -0.007	0.04
Log-CRP, per 1 log higher	0.063	-0.025; 0.150	0.16	-0.009	-0.099; 0.082	0.85
Log-PTH, per 1 log higher	0.163	0.029; 0.298	0.02	0.016	-0.136; 0.168	0.84
Log-25(OH)-vitamin D3, per 1 log higher	-0.302	-0.476; -0.127	<0.001	-0.193	-0.361; -0.025	0.02

Supplemental Table 5. Multivariable mixed regression model with random center effect including variables after stepwise variable selection (with log-25(OH)-vitamin D3 levels included among candidate variables) (n=462) with PWVz at baseline as the dependent variable restricted to subjects with age ≤ 17 years at baseline

Parameter	Estimate	95% CI	p value
Age, per 1 year older	-0.073	-0.115; -0.031	<0.001
Height, per 1 z-score higher	-0.296	-0.395; -0.198	<0.001
Diastolic BP, per 1 z-score higher*	0.526	0.404; 0.647	<0.001
Log-25(OH)-vitamin D3, per 1 log higher	-0.206	-0.357; -0.056	0.007
Log-ferritin, per 1 log higher	-0.143	-0.270; -0.016	0.03

*Model with diastolic BP z-score showed best model fit by AIC compared to systolic BP z-score (1664 and 1680, respectively).

Supplemental Table 6. Associations of time-dependent explanatory variables with absolute PWV over time (n=2295 observations from 667 individuals).

	Time-fixed effects		Time-varying effects		
	Estimate	**95% CI**	**Estimate**	**Estimate*Time interaction**	**95% CI time interaction**
Observation time, per 1 year	0.036	-0.005; 0.076	0.130	-	-
Observation time, per years^2	0.011	0.005; 0.017	0.009	-	-
Age at baseline, per 1 year older	0.064	0.043; 0.085	0.065	-0.002	-0.009; 0.006
Female sex	-0.039	-0.131; 0.052	-0.024	-0.007	-0.045; 0.031
Diagnosis (ref: CAKUT)	0.092	-0.005; 0.189	0.075	0.015	-0.023; 0.052
BMI, per 1 z-score higher	-0.027	-0.056; 0.003	-0.038	0.007	-0.004; 0.018
Height, per 1 cm higher	0.003	-0.001; 0.006	0.002	0.000	-0.001; 0.002
Mean arterial pressure, per 1 mmHg higher*	0.010	0.008; 0.011	0.011	-0.001	-0.001; 0.000
eGFR, per 1 ml/min/1.73 m^2 higher	-0.001	-0.005; 0.003	-0.001	0.000	-0.002; 0.001
Hemoglobin, per 1 g/dL higher	0.019	-0.004; 0.041	0.012	0.003	-0.008; 0.014
Serum bicarbonate, per 1 mmol/L higher	0.002	-0.008; 0.011	0.007	-0.003	-0.008; 0.002
HDL cholesterol, per 1 mg/dL higher	-0.002	-0.004; 0.001	-0.003	0.001	-0.001; 0.002
LDL cholesterol, per 1 mg/dL higher	0.001	0.000; 0.002	0.001	0.000	0.000; 0.001
Corrected serum calcium, per 1 mg/dL higher	0.028	-0.016; 0.071	0.050	-0.012	-0.034; 0.010
Serum albumin, per 1 g/dL higher	0.053	-0.018; 0.125	0.050	0.001	-0.034; 0.036
Log-UACR, per 1 log higher	0.054	0.030; 0.079	0.043	0.006	-0.005; 0.017
Log-ferritin, per 1 log higher	-0.047	-0.088; -0.006	-0.068	0.010	-0.005; 0.025
Log-CRP, per 1 log higher	-0.002	-0.023; 0.019	0.001	-0.001	-0.010; 0.009
Log-PTH, per 1 log higher	0.002	-0.031; 0.034	0.020	-0.012	-0.028; 0.005

*Model with MAP showed best model fit by AIC compared to systolic and diastolic BP (4530, 4540 and 4581, respectively).

*Explanation: the effects on the left (time-fixed effects) are assumed constant over time and can be interpreted as the effect of the covariate if the other variables are held fix (mean effect over time). The effects on the right are for the covariates time=0 (Estimate) and e.g. effect of age for time=1 is 0.064 – 0.001 which means that the effect gets smaller over time. The effect of age for time=2 is 0.064 – 2*0.001 and so on.*

AIC, Akaike Information Criterion; BMI, body mass index; CAKUT, congenital anomalies of kidney and urinary tract; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; heart rate; LDL, low-density lipoprotein; PTH, parathormone; UACR, urinary albumin-to-creatinine ratio.

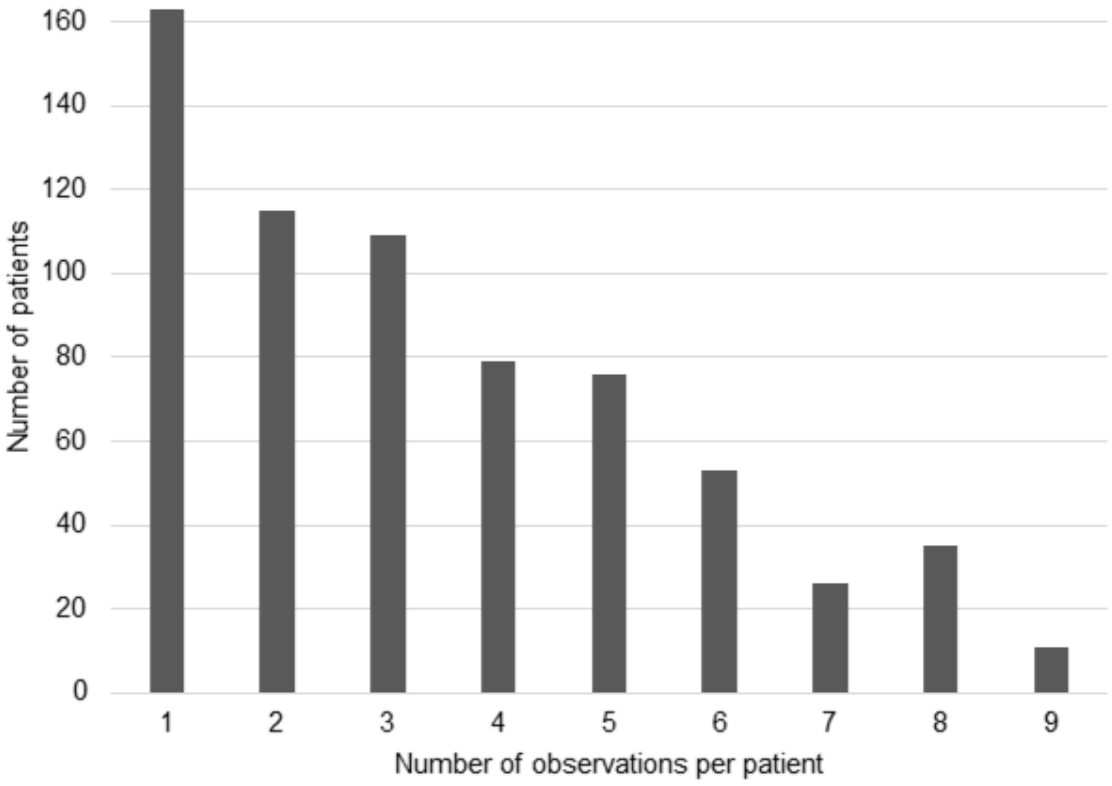
Supplemental Table 7. Associations of time-dependent explanatory variables with PWVz over time (n=1813 observations from 628 individuals)

	Time-fixed effects		Time-varying effects		
	Estimate	**95% CI**	**Estimate**	**Estimate*Time interaction**	**95% CI time interaction**
Observation time, per 1 year higher	-0.121	-0.206; -0.036	0.452	-	-
Observation time, per years^2	0.019	0.005; 0.033	0.022	-	-
Age at baseline, per 1 year older	-0.051	-0.083; -0.018	-0.053	0.005	-0.011; 0.022
Female sex	0.257	0.054; 0.459	0.146	0.097	0.016; 0.178
Diagnosis (ref: CAKUT)	0.174	-0.045; 0.392	0.193	-0.022	-0.107; 0.062
BMI, per 1 z-score higher	-0.048	-0.112; 0.017	-0.072	0.014	-0.013; 0.041
Height, per 1 z-score higher	-0.299	-0.370; -0.227	-0.327	0.025	-0.002; 0.052
Diastolic BP, per 1 z-score higher	0.299	0.235; 0.363	0.338	-0.023	-0.055; 0.008
eGFR, per 1 ml/min/1.73 m^2 higher	0.001	-0.007; 0.009	0.002	-0.001	-0.004; 0.003
Hemoglobin, per 1 g/dL higher	0.050	-0.001; 0.101	0.030	0.009	-0.017; 0.036
Serum bicarbonate, per 1 mEq/L higher	0.003	-0.017; 0.023	0.016	-0.007	-0.018; 0.004
HDL cholesterol, per 1 mg/dL higher	-0.004	-0.009; 0.002	-0.005	0.000	-0.002; 0.003
LDL cholesterol, per 1 mg/dL higher	0.003	0.001; 0.005	0.003	0.000	-0.001; 0.001
Corrected serum calcium, per 1 mg/dL higher	0.059	-0.039; 0.157	0.132	-0.042	-0.096; 0.012
Serum albumin, per 1 g/dL higher	0.157	-0.003; 0.317	0.209	-0.027	-0.111; 0.058
Log-uACR, per 1 log higher	0.110	0.058; 0.162	0.106	0.003	-0.020; 0.026
Log-ferritin, per 1 log higher	-0.111	-0.194; -0.029	-0.134	0.017	-0.019; 0.052
Log-CRP, per 1 log higher	0.008	-0.039; 0.054	0.005	0.004	-0.018; 0.025
Log-PTH, per 1 log higher	0.019	-0.051; 0.089	0.063	-0.032	-0.072; 0.008

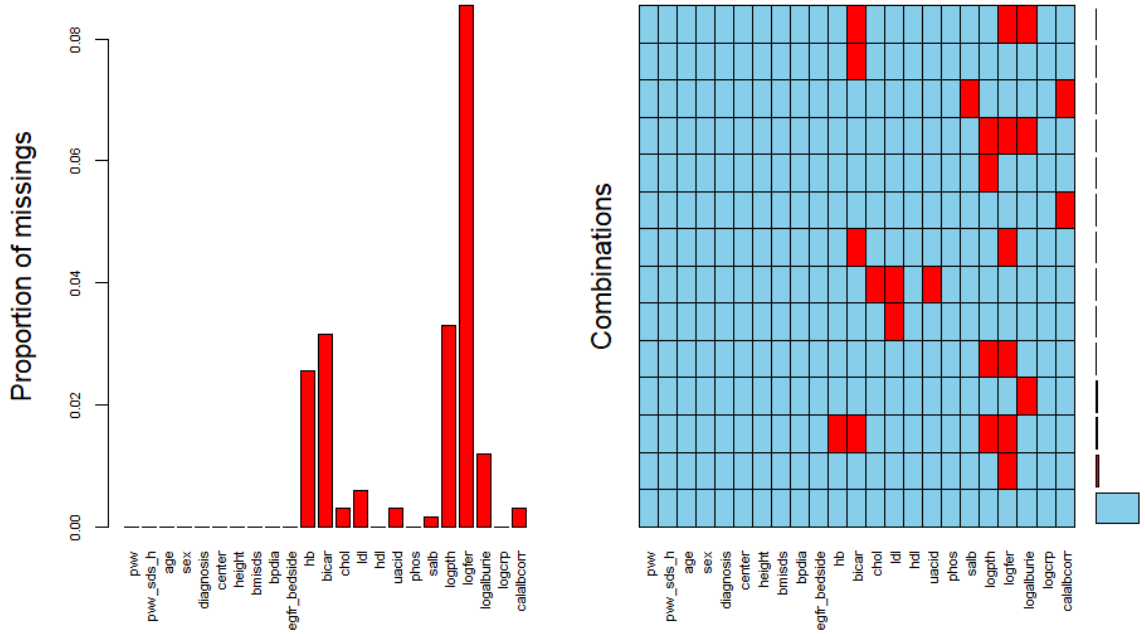
*Model with diastolic BP z-score showed best model fit by AIC compared to systolic BP z-score (6075 and 6106, respectively).

*Explanation: the effects on the left (time-fixed effects) are assumed constant over time and can be interpreted as the effect of the covariate if the other variables are held fix (mean effect over time). The effects on the right are for the covariates are for time=0 (Estimate) and e.g. effect of age for time=1 is 0.064 – 0.001 which means that the effect gets smaller over time. The effect of age for time=2 is 0.064 – 2*0.001 and so on.*

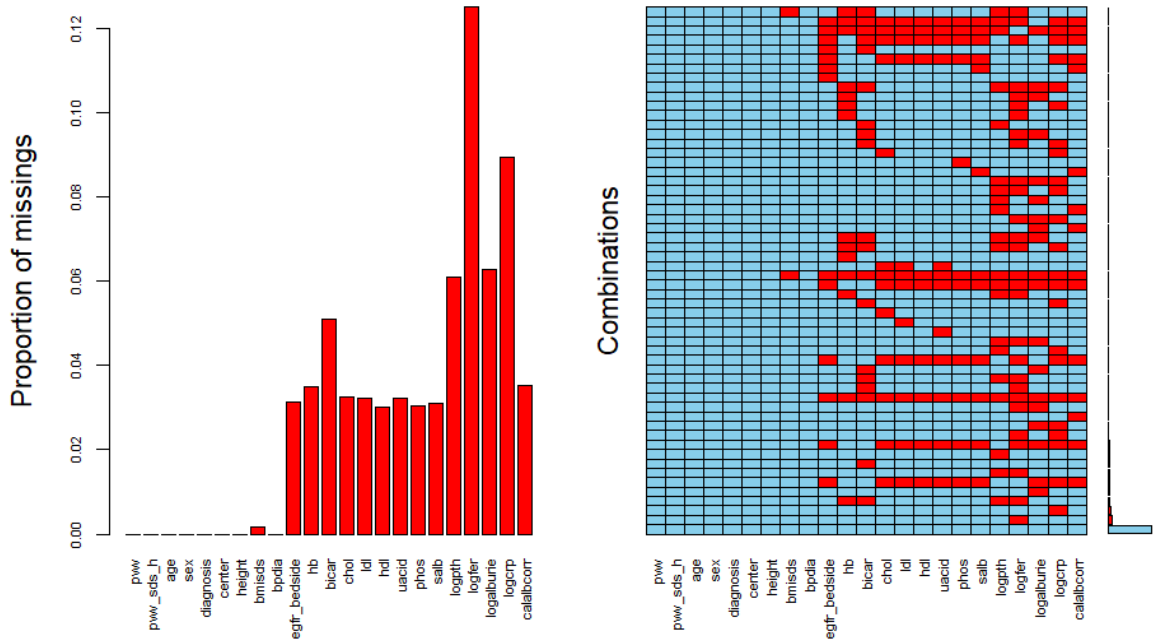
Supplemental Figure 1. Distribution of the number of observations per patient of the overall sample (n=667)



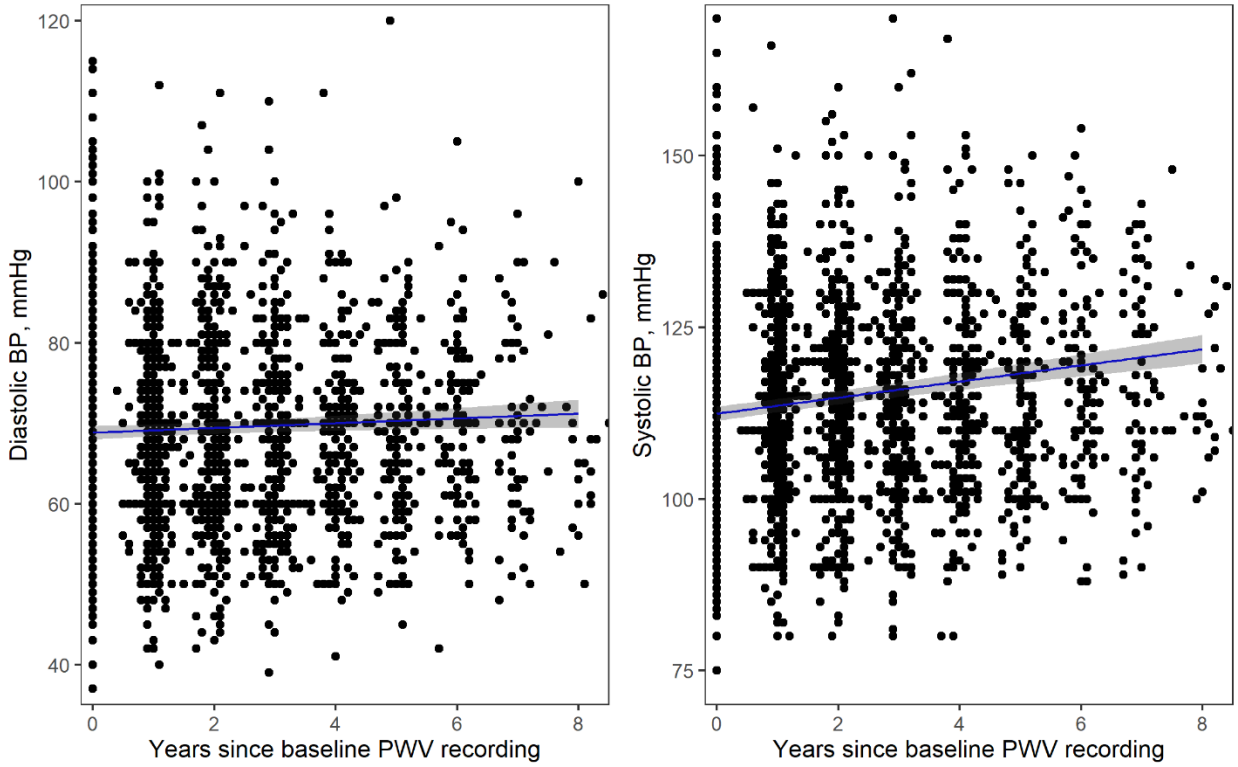
Supplemental Figure 2. The proportions and patterns of missing data at baseline.
Left panel: Proportion of missing values for each variable (667 total observations); Right panel: missing data pattern (blue cell = variable not missing, red cell = variable missing) with proportion of each pattern on the right y-axis presented as a bar. 89% of observations are complete (last row).



Supplemental Figure 3. The proportions and patterns of missing data during follow-up.
Left panel: Proportion of missing values for each variable (2295 total observations) Right panel: missing data pattern (blue cell = variable not missing, red cell = variable missing) with proportion of each pattern on the right y-axis presented as a bar. 76% of observations are complete (last row).



Supplemental Figure 4. Change of absolute diastolic BP and systolic BP over time during the observation period.
Blue area represents 95% CI. Black dots show the observed data and the line shows the predicted mean BP trajectory. The prediction was based on a generalized additive mixed effects model with a penalized spline fixed effect for time to account for possible non-linear effect of time and patient-individual random intercept and slopes.



Supplemental Figure 5. Change of diastolic BP and systolic BP Z scores over time during the observation period.
Blue area represents 95% CI. Black dots show the observed data and the line shows the predicted mean BP trajectory. The prediction was based on a generalized additive mixed effects model with a penalized spline fixed effect for time to account for possible non-linear effect of time and patient-individual random intercept and slopes.