ONLINE SUPPLEMENT

Cardiovascular Phenotypes in Children with Chronic Kidney Disease: Findings from the 4C Study

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Observer training and standardization of measurements:

All measurements in the 55 centers were performed by 7 observers who were jointly trained in several sessions prior to the start of the study and used the same model of a portable ultrasound device. All examinations were performed in a standardized manner according to the study protocol and dedicated observer training, including measurement of resting BP and instructions about the choice of cuff size and preferred side of measurement as recommended by international guidelines (*4th report,Pediatrics 2004; ESH European Pediatric hypertension guidelines, J Hypertens 2009*).

All imaging modalities of CVD surrogate markers are observer-dependent. The intraclass coefficients and CVs describe the agreement of IMT and PWV between observers. The CCA and CV values were derived from 55 paired measurements obtained by observer pairs on volunteering healthy children during the training period. No systematic differences between the observers were noted (mean differences close to 0) both for the cIMT and the PWV measurements. While the oscillometric PWV measurements also showed extremely high precision (ICC 0.8-1.0, CV 5.6-5.8%), inter-observer variability of the cIMT measurements was slightly higher with a CV of 7.3% and an ICC of 0.42. This corresponds to an observer related SD of 0.03 mm. The SD of the cIMT measurements in the 4C cohort was around 0.06 mm. Hence, the observer-related imprecision of the measured cIMT approximates half a standard deviation of the observed cIMT distribution in the 4C cohort. This compares to an average 1.7 SD increase over the healthy controls.

Office blood pressure

Office BP was taken by physicians (the study coordinators) during their visit to each center as part of the medical exam immediately prior to the cIMT and LVMI measurements. In all centers, oscillometric devices validated for use in children were employed. The devices undergo periodic maintenance service and recalibration according to EU legal requirements for medical devices.

The BP-SDS were calculated on the basis of the normative data published by the National High Blood Pressure Education program (Pediatrics 2004); these reference values are based on classic auscultatory BP measurements.

Blood pressure readings obtained with oscillometric devices differ variably from

sphygmomanometric measurements; while most comparative studies found higher measurements with oscillometric readings, others observed even lower mean values (*Ingelfinger JR, NEJM 2014; 370:2316-2325*). The level of agreement probably depends to a large degree on the protocols of measurement applied.

Until recently, oscillometric BP data have been compared with auscultatory BP reference data due to the absence of normative data obtained with oscillometric devices. In 2011, the KIGGS Study published normative oscillometric BP values based on more than 14.000 healthy German children and adolescents (*Neuhauser et al. Pediatrics 201; 127(4):e978-88*). The comparison of the KIGGS and the 4th Report reference percentiles revealed only minor differences - and if anything slightly lower values with oscillometric measurements. The European oscillometric reference data was not available at the time the 4C Study protocol was designed.

No statistically significant correlation between CKD stage (3a, 3b, 4, 5) and office systolic or diastolic BP SDS was found. Similarly, there was no correlation of BP measurements with the eGFR.

Assessment of GFR

Serum creatinine was measured enzymatically, and serum cystatin C using the turbidimetric assay of Roche. This assay has been shown to be in excellent agreement with the DAKO assay used in the original study in which the Cystatin C/creatinine based GFR estimation equation was established (intercept -0.025, slope 1.012, R^2 0.998; *Grubb et al, Clinical Chemistry 2014, 60: 974-986*).

Ambulatory hypertension

The 4C Study protocol was written in early 2008, shortly before the first AHA statement was published, and based the definition of ambulatory hypertension on measured MAP rather than systolic BP, diastolic BP and/or BP load. This decision was based on the fact that oscillometric devices directly measure mean arterial pressure (MAP) and back-calculate systolic and diastolic BP by use of manufacturer-specific software algorithms, resulting in significant variability compared with systolic and diastolic BP values obtained by auscultation. Also, 24h MAP was highly predictive of renal survival in the ESCAPE trial.

We performed an additional analysis of ambulatory hypertension prevalences according to the 2014 update of the AHA recommendations. Since BP load was not reported in the online eCRF, this parameter was only available in 313 profiles that were also uploaded for central ABPM analysis. The results are shown in Table **S-2**.

This comparison shows that inclusion of BP load criteria in the assessment of ambulatory hypertension is problematic. A large proportion of patients in our cohort had normal mean 24-hour BP but elevated BP load and was therefore unclassifiable.

In an additional analysis, hypertension was classified according to the AHA criteria *(Flynn et al. Hypertension 2014;63,1116-1135)*, but using 24h MAP and MAP load instead of 24-h systolic BP, systolic load, or 24-h diastolic BP and diastolic load (**Table S-3)**.

Additional analyses (**Table S-4)** were performed using the approach of the CKiD investigators (*Samuels et al, Hypertension 2012, 60:43-50)* who consider children with normal mean BP but high load to be hypertensive*;* children with unclassified AHA BP parameters are considered masked hypertensive.

Figure S-3 summarizes the differences in ambulatory hypertension prevalence related to the choice of criteria. These differences are mainly caused by the variable consideration of BP load.

The classification scheme proposed by an AHA work group (Flynn et al. 2014) introduces additional categories (pre-hypertension, severe ambulatory hypertension) but still leaves almost 1 in 5 patients unclassifiable since patients with isolated BP load elevation cannot be categorized.

When ambulatory hypertension was defined by the 24-hour mean arterial pressure only as done in the ESCAPE Trial, the observed prevalence of overt hypertension was nearly 50% lower and the prevalence of normotension 40% higher than when patients with elevated BP load but normal 24-hour BP were considered hypertensive, as applied by the CKiD investigators. The apparent prevalence of masked hypertension tripled when patients with isolated elevation of BP load were categorized as masked hypertensive.

The analysis also demonstrates that when applying the same criteria, the prevalence of the individual ambulatory BP categories was very similar in the European 4C and the North American CKiD cohorts.

Table S-1. Patient characteristics by country of residence.

	Turkey	Germany	France	Italy	Poland	UK	Austria	Serbia	Other*
N	328	103	61	50	41	35	17	17	36
Age (y)	12.3 (3.3)	12.3 (3.3)	11.8 (3.5)	11.8 (3.4)	12.4 (2.8)	11.4 (3.1)	13.3 (3.6)	11.6 (3.4)	12.0 (3.7)
Time since CKD diagnosis (y)	3.9 (3.4)	7.4 (4.3)	8.3 (5.0)	7.4 (4.8)	11.0 (4.2)	7.5 (4.8)	6.5 (6.2)	7.4 (4.2)	8.2 (3.7)
% male	59.1	76.7%	72.1%	70.0%	70.7%	65.7%	76.5%	64.7%	58.3%
% parental consanguinity	33.5	4.4	8.9	4.2	0	20.0	5.9	0	0
% CAKUT/glom.pathy/ other	70/7/23	60/17/23	61/2/37	72/8/20	83/0/17	69/17/14	76/12/12	88/0/12	64/8/28
Birth history									
Gestational age (weeks)	38.8 (2.0)	37.9 (3.5)	38.7 (2.1)	38.9 (1.8)	38.0 (2.0)	38.6 (2.4)	38.3 (4.1)	39.3 (2.1)	38.0 (2.4)
Birth weight (kg)	3.2 (0.6)	3.1 (0.8)	3.2 (0.5)	3.2 (0.5)	3.1 (0.7)	3.3 (0.6)	2.9 (0.7)	3.2 (0.7)	3.1 (0.5)
Birth length (cm)	49.3 (2.4)	49.5 (5.9)	48.5 (3.7)	50.0 (1.8)	53.9 (4.8)	52.6 (2.4)	49.0 (4.9)	51.9 (2.7)	49.9 (2.8)
% small for gestational age	18.6	14.8%	13.6%	15.6%	18.2%	17.4%	27.3%	37.5%	15.2%
eGFR (ml/min/1.73m^2)	28 (10)	27 (10)	33 (11)	27 (11)	31 (10)	24 (9)	27 (10)	32 (13)	28 (9)
Height SDS	-1.87 (1.40)	-0.48 (1.27)	-1.03 (0.95)	-1.17 (1.09)	-0.97 (1.43)	-1.27 (1.16)	-0.76 (0.88)	-1.50 (1.35)	-0.86 (1.38)
% height < 3rd perc.	47.3	5.8	19.7	22.0	17.1	31.4	11.8	23.5	19.4
BMI SDS	0.13 (1.31)	0.20 (2.10)	-0.08 (1.24)	-0.10 (1.43)	0.56 (2.22)	0.64 (1.28)	0.07 (1.05)	-0.19 (1.89)	0.07 (1.34)
% malnourished	7.9	6.8	11.5	10.0	2.4	2.9	5.9	17.6	11.1
% overweight/obese	23.2	20.4	16.4	20.0	29.3	42.9	11.8	29.4	22.2
Physical activity (% none/1-2h/ 3-4h/>4h per wk)	27/13/ 52/0	23/31/ 24/22	20/22/ 33/25	20/49/ 18/13	0/6/ 14/80	34/23/ 14/29	17/18/ 12/53	18/12/ 6/65	25/42/ 14/19

* ‚Other': Switzerland (n=12), Lithuania (n=9), Portugal (n=9), Czech Republic (n=6).

Table S-2: Ambulatory HTN according to AHA 2014 definition*

	Stage 3a	**Stage 3b**	**Stage 4**	**Stage 5**	**All**
N	17	111	160	25	313
Confirmed normotension	2 (11.8%)	38 (34.2%)	62 (38.8%)	4 (16.0%)	106 (33.9%)
White coat hypertension	1 (5.9%)	7 (6.3%)	9 (5.6%)	3 (12.0%)	20 (6.4%)
Pre-hypertension	1 (5.9%)	20 (18.0%)	18 (11.3%)	3 (12.0%)	42 (13.4%)
Masked hypertension	3 (17.6%)	12 (10.8%)	22 (13.8%)	3 (12.0%)	40 (12.8%)
Ambulatory hypertension	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Severe ambulatory hypertension	4 (23.5%)	11 (9.9%)	21 (13.1%)	9 (36.0%)	45 (14.4%)
Unclassified	*6 (35.3%)*	*21 (18.9%)*	*28 (17.5%)*	*3 (12.0%)*	*58 (18.5%)*

* **Normal BP**: Office BP < 90th and 24h BP < 95th and load < 25%. **White coat hypertension**: Office SBP or DBP ≥ 95th and 24h BP < 95th and load < 25%. **Pre hypertension**: Office SBP or DBP ≥ 90th or > 120/80mm Hg and 24h BP < 95th and load SBP or DBP ≥ 25%. **Masked hypertension**: Office BP < 95th and 24h SBP or DBP > 95th pct and load SBP or DBP ≥ 25%. **Ambulatory hypertension**: Office SBP or DBP > 95th perc and 24h SBP or DBP > 95th pct and 25% ≤ (load SBP or DBP) ≤ 50%. **Severe Ambulatory hypertension**: Office SBP or DBP > 95th perc and 24h SBP or DBP > 95th pct and load SBP or DBP >50 %.

Table S-3: Prevalence of hypertension according to AHA 2014 definition using ABPM MAP instead of systolic/diastolic BP values.**

	Stage 3a	Stage 3b	Stage 4	Stage 5	All
N	17	111	160	25	313
Confirmed normotension	4 (23.5%)	45 (40.5%)	73 (45.6%)	5 (20.0%)	127 (40.6%)
White coat hypertension	1 (5.9%)	4 (3.6%)	5 (3.1%)	3 (12.0%)	13 (4.2%)
Pre-hypertension	5 (29.4%)	18 (16.2%)	13 (8.1%)	3 (12.0%)	39 (12.5%)
Masked hypertension	1 (5.9%)	10 (9.0%)	23 (14.4%)	5 (20.0%)	39 (12.5%)
Ambulatory hypertension	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Severe ambulatory hypertension	1 (5.9%)	11 (9.9%)	17 (10.6%)	7 (28.0%)	36 (11.5%)
Unclassified	*5 (29.4%)*	*22 (19.8%)*	*29 (18.1%)*	*2 (8.0%)*	*58 (18.5%)*

__Normal BP__: Office SBP < 90th and 24h MAP < 95th and load MAP < 25%. **White coat hypertension: Office SBP ≥ 95th and 24h MAP < 95th and load MAP < 25%. **Pre hypertension**: Office SBP ≥ 90th or > 120 mm Hg and 24h MAP < 95th and load MAP ≥ 25%. **Masked hypertension**: Office SBP < 95th and 24h MAP > 95th pct and load MAP ≥ 25%. **Ambulatory hypertension**: Office SBP > 95th perc and 24h MAP > 95th pct and 25% ≤ load MAP ≤ 50%. **Severe Ambulatory hypertension**: Office SBP > 95th perc and 24h MAP > 95th pct and load MAP >50 %.

Table S-4: Classification of ambulatory hypertension according to CKID definition***

	Stage 3a	Stage 3b	Stage 4	Stage 5	All
N	17	111	160	25	313
Confirmed Normotension	5 (29.4%)	44 (39.6%)	68 (42.5%)	4 (16.0%)	121 (38.7%)
White coat hypertension	0 (0.0%)	2 (1.8%)	5 (3.1%)	2 (8.0%)	9 (2.9%)
Masked hypertension	7 (41.2%)	39 (35.1%)	64 (40.0%)	8 (32.0%)	118 (37.7%)
Ambulatory hypertension	5 (29.4%)	26 (23.4%)	23 (14.4%)	11 (44.0%)	65 (20.8%)

*** **Confirmed normotension**: Office SBP < 95th AND wake AND sleep 24h MAP < 95th AND wake AND sleep MAP load < 25%. **White coat hypertension**: Office SBP ≥ 95th AND wake AND sleep 24h MAP < 95th AND wake AND sleep MAP load < 25%. **Masked hypertension**: Office SBP < 95th AND either wake OR sleep 24h MAP ≥ 95th pct OR either wake OR sleep MAP load ≥ 25%. **Ambulatory hypertension**: Office SBP ≥ 95th perc AND either wake OR sleep 24h MAP ≥ 95th pct OR either wake OR sleep MAP load ≥ 25%

Table S-5. Linear regression models of surrogate markers at study entry (full model).

	LVMI (n=493)		**cIMT SDS (n=510)**		**PWV SDS (n=513)**	
	ß	p	ß	P	ß	p
Intercept	70.59 ± 8.49	<.001	1.46 ± 1.07	0.175	-0.885 ± 1.21	0.464
Age (years)	-0.862 ± 0.237	0.0003	-0.010 ± 0.030	0.740	-0.098 ± 0.033	0.004
Female sex	-2.751 ± 1.10	0.013	0.326 ± 0.139	0.019	0.250 ± 0.154	0.105
CAKUT diagnosis	-0.131 ± 1.15	0.910	0.166 ± 0.146	0.258	-0.042 ± 0.162	0.797
Physical activity >2h/wk	-3.969 ± 1.05	0.0002	0.270 ± 0.132	0.041	0.058 ± 0.146	0.691
Pubertal (B/G stage >2)	1.51 ± 1.56	0.332	0.050 ± 0.198	0.799	0.290 ± 0.219	0.186
BMI SDS	1.40 ± 0.385	0.0003	0.079 ± 0.048	0.102	-0.049 ± 0.053	0.362
Systolic BP (SDS)	1.14 ± 0.381	0.003	0.211 ± 0.047	<.001	0.374 ± 0.056	<.001
HDL cholesterol (mg/dl)	-0.089 ± 0.036	0.015	0.00008 ± 0.005	0.987	-0.009 ± 0.005	0.093
LDL cholesterol (mg/dl)	-0.027 ± 0.014	0.052	-0.002 ± 0.002	0.197	0.001 ± 0.002	0.506
Serum 25OHD (ng/ml)	0.014 ± 0.04	0.724	-0.013 ± 0.005	0.010	-0.009 ± 0.006	0.112
eGFR (ml/min/1.73m^2)	-0.263 ± 0.102	0.010	-0.0002 ± 0.013	0.987	0.022 ± 0.014	0.119
Serum albumin (g/L)	-0.198 ± 0.092	0.031	-0.015 ± 0.012	0.213	0.005 ± 0.013	0.703
log urine albumin/creat	-0.026 ± 0.335	0.938	0.02 ± 0.042	0.634	0.123 ± 0.047	0.009
Serum phosphorus (mM)	-0.478 ± 1.38	0.729	0.679 ± 0.178	0.0002	0.342 ± 0.195	0.080
iPTH (ng/ml)	-0.001 ± 0.02	0.973	-0.0003 ± 0.002	0.888	0.007 ± 0.003	0.008
Serum cystatin C	-0.406 ± 1.11	0.715	0.069 ± 0.14	0.620	0.115 ± 0.155	0.461
Serum uric acid (mmol/L)	-0.171 ± 0.28	0.543	-0.021 ± 0.036	0.561	0.002 ± 0.040	0.950

Table S-6: Multiple ordinal regression of cumulative intermediate cardiovascular endpoint score at study entry (full model).

	Odds Ratio	95% confidence limit	p
Age (years)	0.979	0.899-1.065	0.617
Female sex	1.088	0.74-1.60	0.668
CAKUT diagnosis	1.48	0.983-2.213	0.061
Time since CKD diagnosis (years)	0.947	0.904-0.992	0.0227
Birth weight (g)	0.798	0.56-1.138	0.213
Pubertal	0.854	0.50-1.46	0.563
Gestational age	1.049	0.956-1.152	0.313
BMI SDS	1.314	1.14-1.52	0.0002
Physical activity >2h/week vs. ≤2h/week	1.122	0.78-1.613	0.434
Systolic blood pressure SDS	1.332	1.160-1.529	<.001
eGFR (ml/min/1.73 m2)	1.002	0.967-1.038	0.93
Serum cystatin C	1.064	0.720-1.574	0.755
log Urine albumin/creat	1.077	0.961-1.207	0.205
log CRP (log mg/l)	0.988	0.882-1.107	0.834
Serum uric acid (mmol/L)	0.967	0.873-1.072	0.526
LDL cholesterol (mg/gl)	1.001	0.996-1.006	0.684
HDL cholesterol (mg/gl)	0.992	0.979-1.006	0.283
Serum calcium (mmol/L)	0.737	0.293-1.850	0.516
Serum phosphorus (mmol/L)	1.682	1.033-2.737	0.036
iPTH (ng/ml)	1.002	0.995-1.009	0.576
Serum bicarbonate (mmol/L)	0.967	0.918-1.018	0.20
Serum albumin (g/L)	1.031	0.993-1.070	0.109
Hemoglobin (g/dl)	0.867	0.766-0.980	0.023

Figure S-1: Distribution of underlying renal diagnoses. Numbers represent percentages.

Abbreviations: CAKUT: congenital anomalies of the kidney and urinary tract
PKD: polycystic kidney disease
HUS: hemolytic uremic syndrome

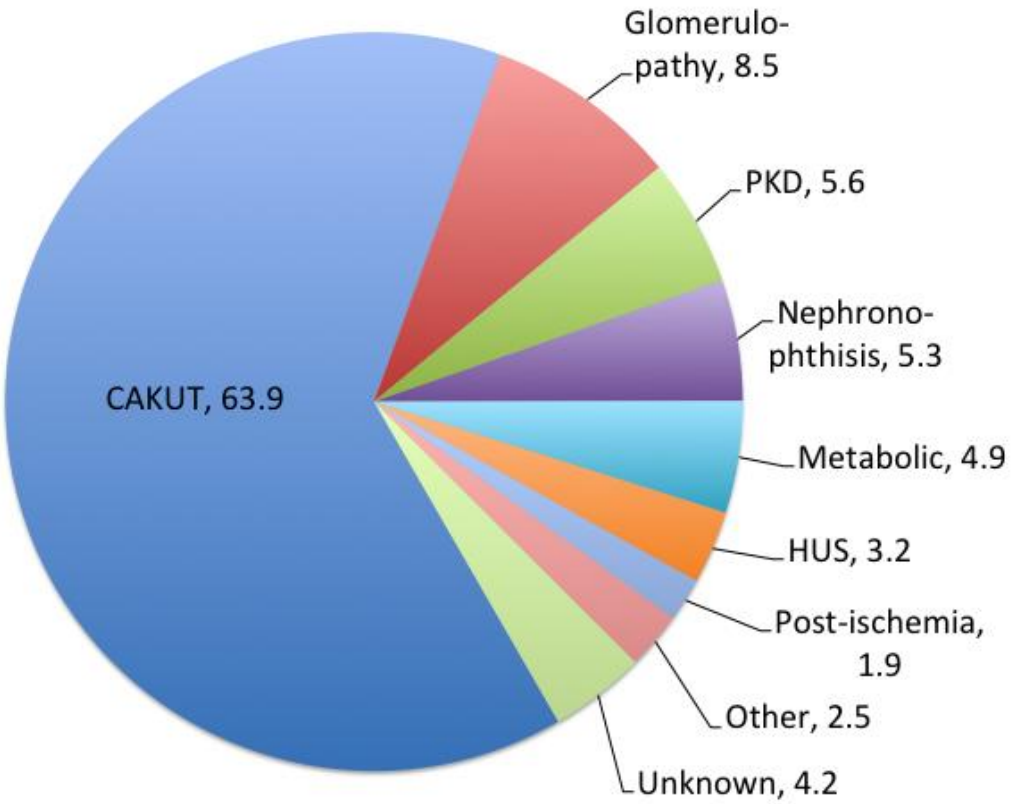
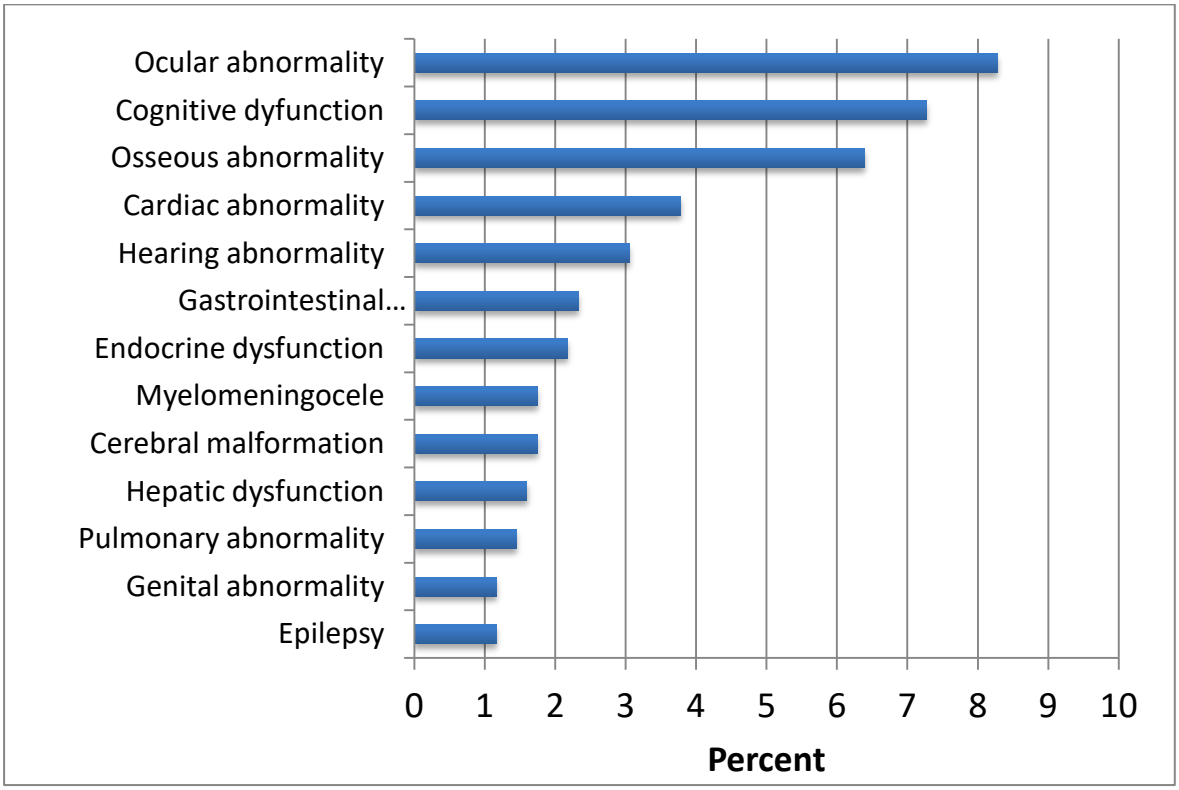
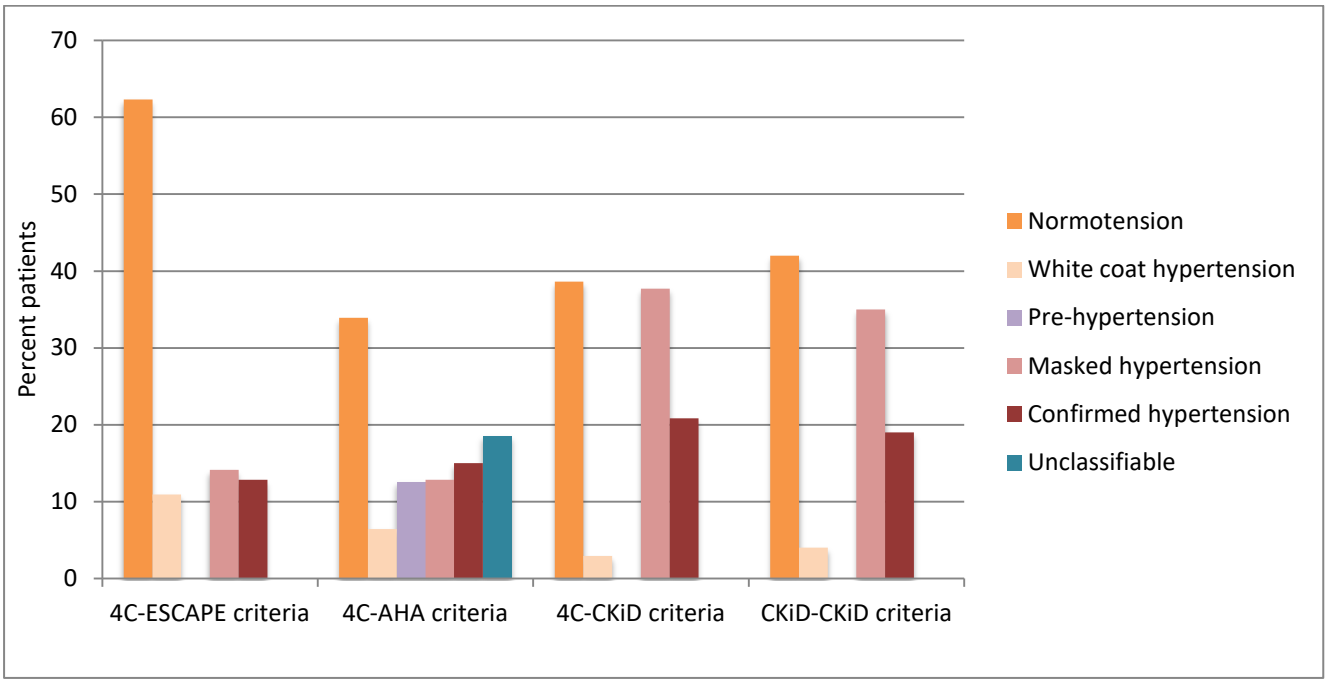


Figure S-2: Associated comorbid conditions.



Statistical testing was performed for differences between children with or without additional co-morbid conditions in the 4C cohort. The major conditions (ocular abnormality, cognitive dysfunction) did not associate with the surrogate CV outcome parameters. Also, a sensitivity analysis omitting all patients with reported comorbidities revealed no differences with respect to the predictor variables identified in the multivariate models.

Figure S-3. Ambulatory hypertension prevalence according to the choice of criteria



APPENDIX

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