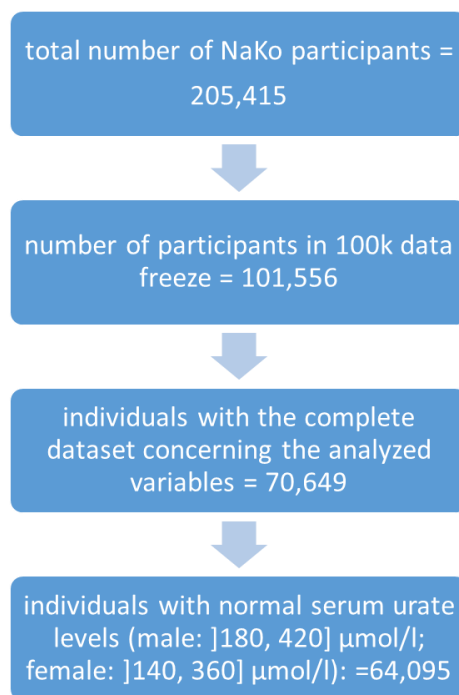


Physiological serum uric acid concentrations correlate with arterial stiffness in a sex-dependent manner.

O. Thews, T. Schmid, A. Kluttig, A. Wienke, M. Zinkhan, W. Ahrens, T. Bärnighausen, H. Brenner, S. Castell, B. Lange, W. Lieb, K.H. Greiser, M. Dörr, L. Krist, S.N. Willich, V. Harth, N. Obi, M. Leitzmann, A. Peters, B. Schmidt, M. B. Schulze, H. Völzke, M. Nauck, S. Zylla, A. Hannemann, T. Pischon, I.M. Velásquez, M. Girndt, C. Grossmann, M. Gekle

Additional file 1

Fig. S01: Flow chart numbers of included participants



Tab. S03a: Linear regression analyses relating serum urate concentrations (exposure variable) to pulse wave velocity (outcome variable), adjusting for relevant confounders for individuals **with age <31 years** (n=6063; complete model: $r^2=0.254$. SD = standard deviation, IQR = interquartile range).

Variable	Mean \pm SD	Median (IQR)	Regression coefficient (confidence interval)	p-value
Arterial pulse wave velocity (m/s)	8.64 \pm 0.97	8.6 (8.0 - 9.3)		
Serum urate ($\mu\text{mol/l}$)	266 \pm 74	258 (212 - 314)	0.0008 (0.0004; 0.0012)	<0.001
Sex (male, female)	male: 43.6% female: 56.4%		-0.146 (-0.214; -0.078)	<0.001
Age (years)	26.2 \pm 2.7	26 (24 - 28)	0.060 (0.052; 0.068)	<0.001
BMI (kg/m^2)	24.1 \pm 4.3	23.4 (21.2 - 26.1)	-0.021 (-0.027; -0.016)	<0.001
Smoking (never, past, present)	never: 57.9% past: 16.3% present: 25.8%		past: 0.004 (-0.056; 0.065) present: 0.04 (-0.012; 0.093)	0.885 0.131
Alcohol intake (g/day)	8.2 \pm 13.1	4.44 (1.50 - 9.70)	-0.0005 (-0.0022; 0.0012)	0.575
HbA1c (mmol/mol)	32.7 \pm 3.8	33 (30 - 35)	0.003 (-0.002; 0.009)	0.263
HDL cholesterol (mmol/l)	1.57 \pm 0.41	1.53 (1.28 - 1.82)	0.038 (-0.023; 0.098)	0.224
LDL cholesterol (mmol/l)	2.67 \pm 0.73	2.59 (2.15 - 3.12)	0.093 (0.063; 0.124)	<0.001
Serum creatinine ($\mu\text{mol/l}$)	70.6 \pm 15.5	69 (61 - 79)	-0.002 (-0.004; 0.000)	0.011
Physical activity (MET-min/week)	7165 \pm 9156	3720 (1680 - 8840)	$-6.94 \cdot 10^{-7}$ ($-3.04 \cdot 10^{-6}$; $1.65 \cdot 10^{-6}$)	0.562
Systolic blood pressure (mmHg)	120.4 \pm 12.4	120 (112 - 128)	0.032 (0.030; 0.034)	<0.001
Anti-hypertensive drugs (yes/no)	yes: 1.9% no: 98.1%		0.222 (0.065; 0.380)	0.006
Lipid-lowering drugs (yes/no)	yes: 0.5% no: 99.5%		-0.084 (-0.388; 0.220)	0.589
Urate-lowering drugs (yes/no)	yes: 0.1% no: 99.9%		0.807 (0.065; 1.548)	0.033

Tab. S03b: Linear regression analyses relating serum urate concentrations (exposure variable) to pulse wave velocity (outcome variable), adjusting for relevant confounders for individuals **with age 31-50 years** (n=24523; complete model: $r^2=0.323$. SD = standard deviation, IQR = interquartile range).

Variable	Mean \pm SD	Median (IQR)	Regression coefficient (confidence interval)	p-value
Arterial pulse wave velocity (m/s)	9.79 \pm 1.43	9.7 (8.9 - 10.6)		
Serum urate ($\mu\text{mol/l}$)	271 \pm 78	262 (213 - 321)	0.0009 (0.0006; 0.0012)	<0.001
Sex (male, female)	male: 45.6% female: 54.4%		-0.137 (-0.182; -0.093)	<0.001
Age (years)	43.1 \pm 5.6	44 (39 - 48)	0.052 (0.050; 0.055)	<0.001
BMI (kg/m^2)	25.9 \pm 4.8	25.1 (22.6 - 28.3)	-0.019 (-0.022; -0.015)	<0.001
Smoking (never, past, present)	never: 46.8% past: 29.2% present: 23.9%		past: -0.028 (-0.064; 0.007) present: 0.014 (-0.025; 0.052)	0.112 0.479
Alcohol intake (g/day)	9.1 \pm 14.7	4.06 (1.18 - 11.09)	0.0008 (-0.0003; 0.0019)	0.136
HbA1c (mmol/mol)	34.9 \pm 5.2	35 (32 - 37)	0.017 (0.014; 0.02)	<0.001
HDL cholesterol (mmol/l)	1.54 \pm 0.42	1.5 (1.23 - 1.79)	-0.068 (-0.111; -0.024)	0.002
LDL cholesterol (mmol/l)	3.22 \pm 0.86	3.14 (2.61 - 3.75)	0.068(0.05; 0.087)	<0.001
Serum creatinine ($\mu\text{mol/l}$)	71.6 \pm 14.4	70 (62 - 80)	-0.002 (-0.003; -0.001)	0.001
Physical activity (MET-min/week)	7124 \pm 9613	3320 (1240 - 9120)	$7.09 \cdot 10^{-7}$ ($-8.40 \cdot 10^{-7}$; $2.26 \cdot 10^{-6}$)	0.370
Systolic blood pressure (mmHg)	124.0 \pm 14.4	123 (114 - 133)	0.044 (0.043; 0.045)	<0.001
Anti-hypertensive drugs (yes/no)	yes: 10.5% no: 89.5%		0.181 (0.130; 0.233)	<0.001
Lipid-lowering drugs (yes/no)	yes: 2.5% no: 97.5%		0.186 (0.089; 0.284)	<0.001
Urate-lowering drugs (yes/no)	yes: 0.6% no: 99.4%		0.204 (0.006; 0.402)	0.044

Tab. S03c: Linear regression analyses relating serum urate concentrations (exposure variable) to pulse wave velocity (outcome variable), adjusting for relevant confounders for individuals **with age >50 years** (n=40063; complete model: $r^2=0.350$. SD = standard deviation, IQR = interquartile range).

Variable	Mean \pm SD	Median (IQR)	Regression coefficient (confidence interval)	p-value
Arterial pulse wave velocity (m/s)	11.61 \pm 1.87	11.4 (10.3 - 12.7)		
Serum urate ($\mu\text{mol/l}$)	298 \pm 80	292 (240 - 349)	0.0011 (0.0009; 0.0014)	<0.001
Sex (male, female)	male: 48.5% female: 51.5%		-0.165 (-0.205; -0.125)	<0.001
Age (years)	60.3 \pm 5.8	60 (55 - 65)	0.093 (0.090; 0.095)	<0.001
BMI (kg/m^2)	27.3 \pm 4.7	26.7 (24.0 - 29.9)	-0.039 (-0.042; -0.035)	<0.001
Smoking (never, past, present)	never: 43.0% past: 39.4% present: 17.6%		past: -0.113 (-0.146; -0.079) present: -0.175 (-0.210; -0.132)	<0.001 <0.001
Alcohol intake (g/day)	12.2 \pm 18.4	5.35 (1.33 - 15.93)	0.0032 (0.0023; 0.0041)	<0.001
HbA1c (mmol/mol)	38.5 \pm 6.9	37 (35 - 40)	0.018 (0.016; 0.021)	<0.001
HDL cholesterol (mmol/l)	1.57 \pm 0.45	1.5 (1.24 - 1.84)	-0.066 (-0.106; -0.025)	0.001
LDL cholesterol (mmol/l)	3.56 \pm 0.92	3.52 (2.92 - 4.14)	0.048 (0.031; 0.066)	<0.001
Serum creatinine ($\mu\text{mol/l}$)	73.6 \pm 16.8	72 (63 - 82)	-0.001 (-0.002; 0.000)	0.029
Physical activity (MET-min/week)	8057 \pm 9535	4720 (1840 - 10800)	$1.46 \cdot 10^{-7}$ ($-1.41 \cdot 10^{-6}$; $1.70 \cdot 10^{-6}$)	0.853
Systolic blood pressure (mmHg)	132.9 \pm 17.4	131 (121 - 143)	0.046 (0.045; 0.047)	<0.001
Anti-hypertensive drugs (yes/no)	yes: 39.2% no: 60.8%		0.078 (0.044; 0.113)	<0.001
Lipid-lowering drugs (yes/no)	yes: 15.0% no: 85.0%		0.001 (-0.046; 0.048)	0.965
Urate-lowering drugs (yes/no)	yes: 3.6% no: 96.4%		0.264 (0.181; 0.347)	<0.001

Tab. S04a: Linear regression analyses relating serum urate concentrations (exposure variable) to pulse wave velocity (outcome variable), adjusting for relevant confounders restricted to individuals with normal serum urate levels (male:]180, 420] $\mu\text{mol/l}$; female:]140, 360] $\mu\text{mol/l}$) and age <31 years, n=5707; complete model: $r^2=0.250$. SD = standard deviation, IQR = interquartile range.

Variable	Mean \pm SD	Median (IQR)	Regression coefficient (confidence interval)	p-value
Arterial pulse wave velocity (m/s)	8.62 \pm 0.96	8.6 (8.0 - 9.2)		
Serum urate ($\mu\text{mol/l}$)	263 \pm 63	257 (214 - 309)	0.0007 (0.0002; 0.0012)	0.003
Sex (male, female)	male: 42.8% female: 57.2%		-0.173 (-0.247; -0.100)	<0.001
Age (years)	26.2 \pm 2.7	26 (24 - 28)	0.059 (0.051; 0.067)	<0.001
BMI (kg/m^2)	24 \pm 4.2	23.3 (21.1 - 26.0)	-0.022 (-0.028; -0.016)	<0.001
Smoking (never, past, present)	never: 58.1% past: 16.2% present: 25.7%		past: 0.015 (-0.048; 0.077) present: 0.052 (-0.001; 0.106)	0.644 0.057
Alcohol intake (g/day)	8 \pm 13	4.4 (1.48 - 9.42)	0.0003 (-0.0021; 0.0014)	0.723
HbA1c (mmol/mol)	32.7 \pm 3.8	33 (30 - 35)	0.002 (-0.004; 0.008)	0.445
HDL cholesterol (mmol/l)	1.58 \pm 0.41	1.53 (1.29 - 1.83)	0.029 (-0.033; 0.091)	0.361
LDL cholesterol (mmol/l)	2.66 \pm 0.73	2.59 (2.15 - 3.1)	0.096 (0.064; 0.127)	<0.001
Serum creatinine ($\mu\text{mol/l}$)	70.4 \pm 12.9	69 (61 - 79)	-0.003 (-0.006; -0.001)	0.003
Physical activity (MET-min/week)	7107 \pm 9052	3720 (1680 - 8720)	$-1.01 \cdot 10^{-6}$ ($-3.44 \cdot 10^{-6}$; $1.42 \cdot 10^{-6}$)	0.414
Systolic blood pressure (mmHg)	120.1 \pm 12.3	119 (111 - 128)	0.032 (0.030; 0.034)	<0.001
Anti-hypertensive drugs (yes/no)	yes: 1.7% no: 98.3%		0.175 (0.006; 0.344)	0.043
Lipid-lowering drugs (yes/no)	yes: 0.5% no: 99.5%		-0.156 (-0.469; 0.157)	0.329
Urate-lowering drugs (yes/no)	yes: 0.1% no: 99.9%		0.992 (0.165; 1.818)	0.019

Tab. S04b: Linear regression analyses relating serum urate concentrations (exposure variable) to pulse wave velocity (outcome variable), adjusting for relevant confounders restricted to individuals with normal serum urate levels (male:]180, 420] $\mu\text{mol/l}$; female:]140, 360] $\mu\text{mol/l}$) and age 31-50 years, $n=22784$; complete model: $r^2=0.316$. SD = standard deviation, IQR = interquartile range.

Variable	Mean \pm SD	Median (IQR)	Regression coefficient (confidence interval)	p-value
Arterial pulse wave velocity (m/s)	9.76 \pm 1.43	9.6 (8.9 - 10.5)		
Serum urate ($\mu\text{mol/l}$)	266 \pm 65	260 (214 - 313)	0.0007 (0.0004; 0.0011)	<0.001
Sex (male, female)	male: 44.8% female: 55.2%		-0.149 (-0.198; -0.101)	<0.001
Age (years)	43.1 \pm 5.6	44 (39 - 48)	0.053 (0.050; 0.055)	<0.001
BMI (kg/m^2)	25.8 \pm 4.6	25.0 (22.6 - 28.0)	-0.019 (-0.023; -0.015)	<0.001
Smoking (never, past, present)	never: 47.1% past: 29.0% present: 23.9%		past: -0.024 (-0.061; 0.013) present: 0.026 (-0.014; 0.066)	0.1.97 0.200
Alcohol intake (g/day)	8.9 \pm 14.1	4.00 (1.18 - 10.87)	$-2.77 \cdot 10^{-5}$ (-0.0011; 0.0011)	0.963
HbA1c (mmol/mol)	34.9 \pm 5.1	35 (32 - 37)	0.018 (0.014; 0.021)	<0.001
HDL cholesterol (mmol/l)	1.55 \pm 0.42	1.5 (1.24 - 1.80)	-0.058 (-0.103; -0.013)	0.012
LDL cholesterol (mmol/l)	3.2 \pm 0.85	3.13 (2.61 - 3.72)	0.067 (0.047; 0.086)	<0.001
Serum creatinine ($\mu\text{mol/l}$)	71.3 \pm 13.1	70 (62 - 80)	-0.002 (-0.004; -0.001)	0.008
Physical activity (MET-min/week)	7074 \pm 9561	3280 (1240 - 9000)	$7.05 \cdot 10^{-7}$ ($-9.21 \cdot 10^{-7}$; $2.33 \cdot 10^{-6}$)	0.395
Systolic blood pressure (mmHg)	123.8 \pm 14.3	123 (114 - 132)	0.044 (0.043; 0.045)	<0.001
Anti-hypertensive drugs (yes/no)	yes: 9.8% no: 90.2%		0.194 (0.139; 0.249)	<0.001
Lipid-lowering drugs (yes/no)	yes: 2.4% no: 97.6%		0.197 (0.093; 0.302)	<0.001
Urate-lowering drugs (yes/no)	yes: 0.5% no: 99.5%		0.203 (-0.01; 0.417)	0.062

Tab. S04c: Linear regression analyses relating serum urate concentrations (exposure variable) to pulse wave velocity (outcome variable), adjusting for relevant confounders restricted to individuals with normal serum urate levels (male:]180, 420] $\mu\text{mol/l}$; female:]140, 360] $\mu\text{mol/l}$) and age >50 years, n=35604; complete model: $r^2=0.356$. SD = standard deviation, IQR = interquartile range.

Variable	Mean \pm SD	Median (IQR)	Regression coefficient (confidence interval)	p-value
Arterial pulse wave velocity (m/s)	11.57 \pm 1.87	11.4 (10.3 - 12.6)		
Serum urate ($\mu\text{mol/l}$)	284 \pm 63	283 (237 - 331)	0.0012 (0.0008; 0.0015)	<0.001
Sex (male, female)	male: 47.3% female: 52.7%		-0.130 (-0.174; -0.086)	<0.001
Age (years)	60.1 \pm 5.8	60 (55 - 65)	0.094 (0.091; 0.096)	<0.001
BMI (kg/m^2)	27 \pm 4.6	26.4 (23.8 - 29.5)	-0.039 (-0.043; -0.035)	<0.001
Smoking (never, past, present)	never: 43.7% past: 38.5% present: 17.8%		past: -0.124 (-0.159; -0.089) present: -0.170 (-0.215; -0.125)	<0.001 <0.001
Alcohol intake (g/day)	11.8 \pm 17.8	5.21 (1.33 - 14.99)	0.0029 (0.0019; 0.0038)	<0.001
HbA1c (mmol/mol)	38.3 \pm 6.8	37 (35 - 40)	0.020 (0.017; 0.022)	<0.001
HDL cholesterol (mmol/l)	1.59 \pm 0.45	1.53 (1.26 - 1.86)	-0.078 (-0.121; -0.036)	<0.001
LDL cholesterol (mmol/l)	3.55 \pm 0.91	3.51 (2.92 - 4.12)	0.050 (0.031; 0.068)	<0.001
Serum creatinine ($\mu\text{mol/l}$)	72.6 \pm 15.7	71 (62 - 81)	-0.001 (-0.002; 0.000)	0.137
Physical activity (MET-min/week)	8056 \pm 9548	4680 (1840 - 10800)	$-2.60 \cdot 10^{-7}$ ($-1.90 \cdot 10^{-6}$; $1.39 \cdot 10^{-6}$)	0.756
Systolic blood pressure (mmHg)	132.7 \pm 17.3	131 (121 - 143)	0.046 (0.045; 0.047)	<0.001
Anti-hypertensive drugs (yes/no)	yes: 36.3% no: 63.7%		0.088 (0.051; 0.124)	<0.001
Lipid-lowering drugs (yes/no)	yes: 14.2% no: 85.8%		0.026 (-0.024; 0.076)	0.310
Urate-lowering drugs (yes/no)	yes: 3.4% no: 96.6%		0.249 (0.159; 0.340)	<0.001

Tab. S05: Description of the model variables in persons included in the analysis (n=70649) and in the group excluded due to incomplete data sets. (SD = standard deviation, IQR = interquartile range).

Variable	Included cohort		Excluded cohort		
	Mean \pm SD	Median (IQR)	Mean \pm SD	Median (IQR)	n
Arterial pulse wave velocity (m/s)	10.72 \pm 1.97	10.5 (9.3 - 11.9)	10.93 \pm 2.04	10.7 (9.5 - 12.1)	19,638
Serum urate (μ mol/l)	286 \pm 80	279 (227 - 338)	286 \pm 81	280 (226 - 336.8)	25,468
Sex (male, female)	male: 47.1% female: 52.9%		male: 45.0% female: 55.0%		30,907
Age (years)	51.4 \pm 12.4	53 (44 - 62)	53.4 \pm 12.2	55 (46 - 64)	30,907
BMI (kg/m ²)	26.6 \pm 4.8	25.9 (23.1 - 29.1)	27.5 \pm 5.7	26.5 (23.5 - 30.3)	27,138
Smoking (never, past, present)	never: 45.6% past: 33.9% present: 20.5%		never: 43.6% past: 35.4% present: 21.0%		25,618
Alcohol intake (g/day)	10.8 \pm 16.8	4.67 (1.29 - 13.40)	10.8 \pm 18.1	4.25 (0.95 - 13.30)	24,842
HbA1c (mmol/mol)	36.7 \pm 6.5	36 (33 - 39)	37.8 \pm 7.7	37 (34 - 40)	25,082
HDL cholesterol (mmol/l)	1.56 \pm 0.44	1.50 (1.24 - 1.82)	1.54 \pm 0.45	1.48 (1.22 - 1.81)	24,810
LDL cholesterol (mmol/l)	3.36 \pm 0.92	3.31 (2.71 - 3.94)	3.34 \pm 0.94	3.29 (2.68 - 3.95)	20,288
Serum creatinine (μ mol/l)	72.7 \pm 15.9	71 (62 - 81)	73.2 \pm 21	71 (62 - 82)	25,550
Physical activity (MET-min/week)	7657 \pm 9541	4080 (1600 - 10080)	6198 \pm 9009	2800 (240 - 8120)	24,784
Systolic blood pressure (mmHg)	128.7 \pm 16.7	127 (117 - 139)	129.8 \pm 17.9	128 (117 - 140)	30,663
Anti-hypertensive drugs (yes/no)	yes: 26.1% no: 9.4%		yes: 32.4% no: 67.6%		28,468
Lipid-lowering drugs (yes/no)	yes: 26.1% no: 90.6%		yes: 11.9% no: 88.1%		30,907
Urate-lowering drugs (yes/no)	yes: 2.3% no: 97.7%		yes: 3.1% no: 96.9%		30,907

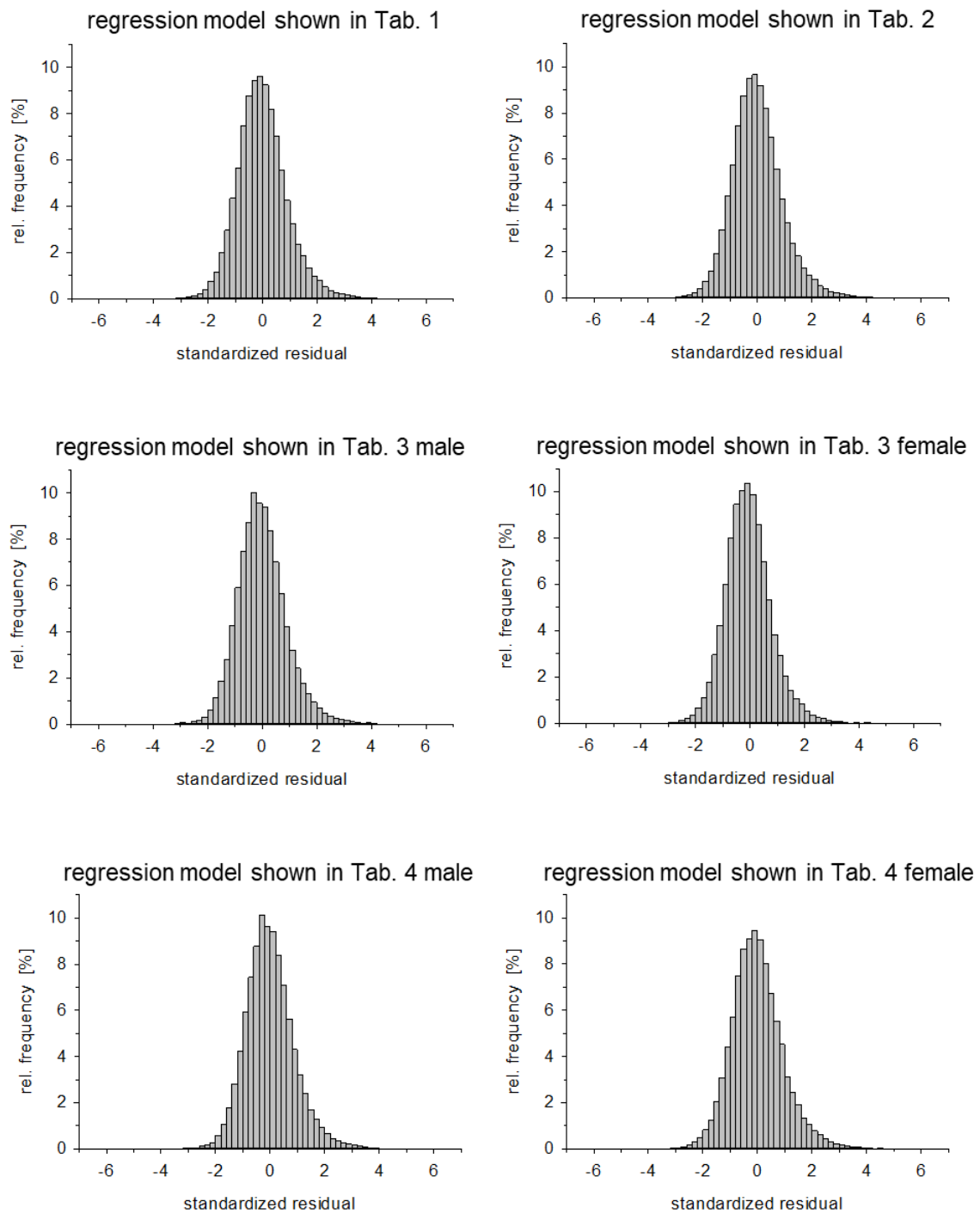


Fig. S03: Distributions of the standardized residuals of the regression models described in Tabs. 1-4.