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Data Supplement

Within-Subject Blood Pressure Level – Not Variability – Predicts Fatal and Nonfatal Outcomes in a General Population

Short title: Outcome and Blood Pressure Variability

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Table S1: **Variability by Quartiles of Mean Systolic Blood Pressure**

Characteristic	Categories of mean systolic blood pressure level				*P*
Limits					
Women	92.4–111.2	111.3–119.4	119.6–130.4	130.6–198.2	
Men	97.4–118.6	118.6–125.8	125.8–135.4	135.4–204.2	
Number of subjects	746	733	730	735	
Overall variability					
VIM (units)	5.50 (2.84)	5.33 (2.61)†	5.42 (2.86)	5.56 (2.95)	0.58
MMD (mm Hg)	12.93 (6.45)	14.33 (6.74)‡	16.02 (7.79)§	20.26 (10.11)§	<0.0001
ARV (mm Hg)	3.59 (1.73)	3.81 (1.79)*	3.99 (1.83)	4.93 (2.49)§	<0.0001
Within visit variability					
VIM (units)	3.63 (1.75)	3.44 (1.62)*	3.33 (1.51)	3.48 (1.80)	0.037
MMD (mm Hg)	7.28 (3.60)	7.55 (3.83)*	8.20 (3.96)*	10.43 (5.78)§	<0.0001
ARV (mm Hg)	5.22 (1.64)	3.35 (1.72)	3.45 (1.72)	4.24 (2.36)§	<0.0001
Between visit variability					
VIM (units)	4.75 (4.21)	4.79 (3.91)	5.08 (4.27)	5.07 (4.29)	0.067
MMD (mm Hg)	5.33 (4.74)	6.17 (5.06)†	7.36 (6.20)‡	9.33 (8.00)§	<0.0001

Values are arithmetic means (SD). Systolic blood pressure was based on 10 blood pressure readings, i.e., 5 consecutive blood pressure readings at each of 2 home visits at an interval of 2-4 weeks. VIM, MMD and ARV indicate variability independent of the mean, the difference between maximum and minimum blood pressure and average real variability, respectively. ARV for between visit variability is the same as MMD and is therefore not presented.
P-values are for linear trend across categories of systolic blood pressure level.
P-values for difference with adjacent lower quartile: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$; and § $P \leq 0.0001$.

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Table S2: **Correlates of the Within- and Between Visit Systolic Variability in 2944 Participants**

	Within visit			Between visits	
Label	**VIM** (units)	**MMD** (mm Hg)	**ARV** (mm Hg)	**VIM** (units)	**MMD** (mm Hg)
Variance explained					
Total	0.292	0.368	0.372	0.019	0.089
Pedigree	0.258	0.248	0.287	0.011	0.012
Fixed effects	0.034	0.120	0.086	0.009	0.078
Parameter estimates (±SE)					
Age (+10 years)	0.148 (0.022)§	0.354 (0.057)§	0.128 (0.024)§	…	…
Body mass index (+5 kg/m^2)	–0.135 (0.037)‡	–0.328 (0.096)†	–0.118 (0.041)†	0.139 (0.050)†	0.211 (0.081)†
Systolic blood pressure (+10 mm Hg)	–0.051 (0.022)*	0.877 (0.056)§	0.293 (0.024)§	…	0.895 (0.083)§
Heart rate (+5 beats per minute)	0.068 (0.017)§	0.155 (0.043)‡	0.061 (0.018)‡	2.189 (0.744)†	3.968 (1.088)‡
Total/HDL cholesterol (+1 unit)	–0.063 (0.018)‡	–0.162 (0.046)‡	–0.083 (0.020)§	0.732 (0.313)*	1.268 (0.462)†
Plasma glucose (+1 mmol/l)	0.048 (0.022)*	0.112 (0.058)	0.053 (0.024)*		…
Serum creatinine (+10 μmol/l)	–0.050 (0.017)†	–0.166 (0.045)‡	–0.061 (0.019)†		…
Treated with β-blockers	0.287 (0.123)*	0.745 (0.317)*	…		…
Treated with diuretics	–0.278 (0.134)*	–0.853 (0.344)*	…		…

Systolic blood pressure was based on 10 blood pressure readings, i.e., 5 consecutive blood pressure readings at each of 2 home visits at an interval of 2-4 weeks. VIM, MMD and ARV indicate variability independent of the mean, the difference between maximum and minimum blood pressure and average real variability, respectively. ARV for between visit variability is the same as MMD and is therefore not presented. The following variables were not related to any index of variability: energy expenditure in physical activity, triglycerides, serum potassium, history of cardiovascular disease, current smoking and alcohol intake, diabetes, and classes of antihypertensive drugs other than diuretics and β-blockers. Significance of the parameter estimates: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$; and § $P \leq 0.0001$.

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Table S3: **Adjusted Standardized Hazard Ratios for Endpoints in Relation to the Mean and Within Visit Variability of Systolic Pressure**

Endpoint (number)	Basic model		Full model					
	Mean SBP		VIM		MMD		ARV	
	HR (95% CI)	R^2 (%)	HR (95% CI)	R^2 (%)	HR (95% CI)	R^2 (%)	HR (95% CI)	R^2 (%)
Mortality								
Total (401)	1.18 (1.08–1.30)‡	28.6	0.95 (0.86–1.05)	<0.01	0.97 (0.88–1.06)	<0.01	0.98 (0.89–1.07)	<0.01
Cardiovascular (164)	1.37 (1.18–1.59)§	18.4	0.97 (0.84–1.13)	<0.01	0.99 (0.87–1.14)	<0.01	0.98 (0.85–1.12)	<0.01
Cardiac (112)	1.44 (1.22–1.70)§	13.5	0.95 (0.79–1.13)	<0.01	0.96 (0.81–1.13)	<0.01	0.98 (0.83–1.15)	<0.01
Cardiovascular events								
All (311)	1.25 (1.12–1.40)‡	16.8	1.07 (0.97–1.18)	<0.01	1.08 (0.98–1.18)	<0.01	1.04 (0.95–1.15)	<0.01
Cardiac (164)	1.29 (1.13–1.46)‡	12.4	1.06 (0.95–1.19)	0.10	1.07 (0.96–1.19)	0.10	1.05 (0.94–1.17)	0.10
Coronary (133)	1.21 (1.03–1.41)*	8.5	1.04 (0.90–1.20)	<0.10	1.06 (0.92–1.22)	<0.01	0.99 (0.85–1.15)	<0.01
Stroke (49)	1.44 (1.04–1.98)*	4.9	1.09 (0.84–1.43)	<0.01	1.12 (0.88–1.44)	<0.01	0.96 (0.71–1.29)	<0.01

Systolic blood pressure (SBP) level and variability were based on 10 blood pressure readings, i.e., 5 consecutive blood pressure readings at each of 2 home visits, 2-4 weeks apart. VIM, MMD and ARV indicate variability independent of the mean, the difference between maximum and minimum blood pressure and average real variability, respectively. The basic model accounts for relatedness and includes in addition to mean SBP, sex, age, body mass index, heart rate, smoking and drinking, total-to-HDL serum cholesterol ratio, plasma glucose, history of cardiovascular disease and use of β-blockers accounts as covariables. Full models include the aforementioned covariables and both mean SBP and an index of SBP variability. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-SD increase in the explanatory variables: 15.6 mm Hg for level of blood pressure and 2.82 units, 8.36 mm Hg, 2.05 mm Hg for VIM, MMD and ARV, respectively. The R^2 statistic is a measure for the risk prediction provided by the basic model including mean SBP and the additive contribution of the indexes of variability.
The cause of death was renal in 6 cases and unknown in 31 cases.
Significance of the hazard ratios: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$; and § $P \leq 0.0001$.

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Table S4: **Adjusted Standardized Hazard Ratios for Endpoints in Relation to the Mean and Between Visit Variability of Systolic Pressure**

Endpoint (number)	Basic model		Full model			
	Mean SBP		VIM		MMD	
	HR (95% CI)	R^2 (%)	HR (95% CI)	R^2 (%)	HR (95% CI)	R^2 (%)
Mortality						
Total (401)	1.18 (1.08–1.30)‡	28.6	1.02 (0.93–1.12)	<0.01	1.02 (0.94–1.11)	<0.01
Cardiovascular (164)	1.37 (1.18–1.59)§	18.4	1.14 (0.99–1.30)	0.10	1.11 (0.98–1.25)	<0.01
Cardiac (112)	1.44 (1.22–1.70)§	13.5	1.09 (0.93–1.29)	<0.01	1.08 (0.93–1.24)	<0.01
Cardiovascular events						
All (311)	1.25 (1.12–1.40)‡	16.8	1.03 (0.94–1.13)	<0.01	1.03 (0.95–1.13)	<0.01
Cardiac (164)	1.29 (1.13–1.46)‡	12.4	1.01 (0.90–1.14)	<0.01	1.02 (0.91–1.13)	<0.01
Coronary (133)	1.21 (1.03–1.41)*	8.5	0.92 (0.78–1.08)	0.10	0.92 (0.79–1.07)	<0.01
Stroke (49)	1.44 (1.04–1.98)*	4.9	1.14 (0.89–1.45)	<0.01	1.09 (0.89–1.35)	<0.01

Systolic blood pressure (SBP) level and variability were based on 10 blood pressure readings, i.e., 5 consecutive blood pressure readings at each of 2 home visits, 2-4 weeks apart. VIM, MMD and ARV indicate variability independent of the mean, the difference between maximum and minimum blood pressure and average real variability, respectively. The basic model accounts for relatedness and includes in addition to mean SBP, sex, age, body mass index, heart rate, smoking and drinking, total-to-HDL serum cholesterol ratio, plasma glucose, history of cardiovascular disease and use of β-blockers accounts as covariables. Full models include the aforementioned covariables and both mean SBP and an index of SBP variability. Hazard ratios (HR) given with 95% confidence interval (CI) express the risk associated with a 1-SD increase in the explanatory variables: 15.6 mm Hg for level of blood pressure and 2.82 units, 8.36 mm Hg, 2.05 mm Hg for VIM, MMD and ARV, respectively. The R^2 statistic is a measure for the risk prediction provided by the basic model including mean SBP and the additive contribution of the indexes of variability.
The cause of death was renal in 6 cases and unknown in 31 cases.
Significance of the hazard ratios: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$; and § $P \leq 0.0001$.

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Table S5: **Adjusted Standardized Hazard Ratios for Total Mortality and All Cardiovascular Events in Relation to Mean and Overall Variability of Systolic Pressure in Different Strata**

	At risk	Events	Mean SBP	VIM	R^2 (%)
Total mortality					
All participants	2944	401	1.18 (1.08–1.30)‡	1.00 (0.91–1.10)	<0.01
Women	1494 (51%)	173 (43%)	1.35 (1.16–1.57)‡	1.01 (0.88–1.16)	<0.01
Men	1450 (49%)	228 (57%)	1.09 (0.96–1.22)	1.00 (0.89–1.12)	<0.01
<60 years	2365 (80%)	116 (29%)	1.19 (0.98–1.44)	1.02 (0.83–1.25)	<0.01
≥60 years	579 (20%)	285 (71%)	1.17 (1.05–1.31)†	1.02 (0.91–1.13)	<0.01
No history of CVD	2739 (93%)	310 (77%)	1.21 (1.08–1.35)‡	1.02 (0.91–1.15)	<0.01
History of CVD	205 (7%)	91 (23%)	1.01 (0.80–1.27)	0.92 (0.78–1.08)	0.20
Untreated	2578 (88%)	291 (73%)	1.11 (0.99–1.25)	0.97 (0.87–1.10)	<0.01
Treated	366 (12%)	110 (27%)	1.41 (1.18–1.67)‡	1.09 (0.95–1.25)	0.20
Normotensive	2227 (76%)	182 (45%)	1.19 (0.93–1.54)	0.94 (0.81–1.10)	<0.01
Hypertensive	717 (24%)	219 (55%)	1.21 (1.06–1.39)†	1.03 (0.92–1.16)	<0.01
All cardiovascular events					
All participants	2944	311	1.26 (1.12–1.41)‡	1.05 (0.96–1.15)	<0.01
Women	1494 (51%)	130 (42%)	1.43 (1.21–1.69)§	1.21 (1.06–1.39)†	0.40
Men	1450 (49%)	180 (58%)	1.16 (0.99–1.36)	0.96 (0.84–1.09)	0.10
<60 years	2365 (80%)	127 (41%)	1.27 (1.04–1.55)*	1.02 (0.87–1.19)	<0.01
≥60 years	579 (20%)	184 (59%)	1.25 (1.09–1.44)†	1.11 (0.98–1.25)	0.40
No history of CVD	2739 (93%)	236 (76%)	1.37 (1.21–1.56)§	1.08 (0.96–1.21)	0.10
History of CVD	205 (7%)	75 (24%)	0.97 (0.76–1.25)	1.04 (0.91–1.19)	<0.01
Untreated	2578 (88%)	223 (72%)	1.21 (1.11–1.49)‡	0.99 (0.87–1.12)	<0.01
Treated	366 (12%)	88 (28%)	1.20 (1.00–1.43)*	1.21 (1.06–1.38)†	1.00
Normotensive	2227 (76%)	143 (46%)	1.31 (0.99–1.74)	1.03 (0.89–1.19)	<0.01
Hypertensive	717 (24%)	168 (54%)	1.15 (0.99–1.33)	1.07 (0.95–1.20)	0.10

Systolic blood pressure (SBP) level and variability independent of the mean (VIM) were based on 10 blood pressure readings, i.e., 5 consecutive blood pressure readings at each of 2 home visits, 2-4 weeks apart. CVD indicates cardiovascular disease. The R^2 statistic is a measure for the refinement of the risk prediction by adding VIM to models already including mean SBP and other covariables. Hypertension was a blood pressure (average of 10 readings) equal to or exceeding 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs. Significance of the hazard ratios: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$; and § $P \leq 0.0001$.

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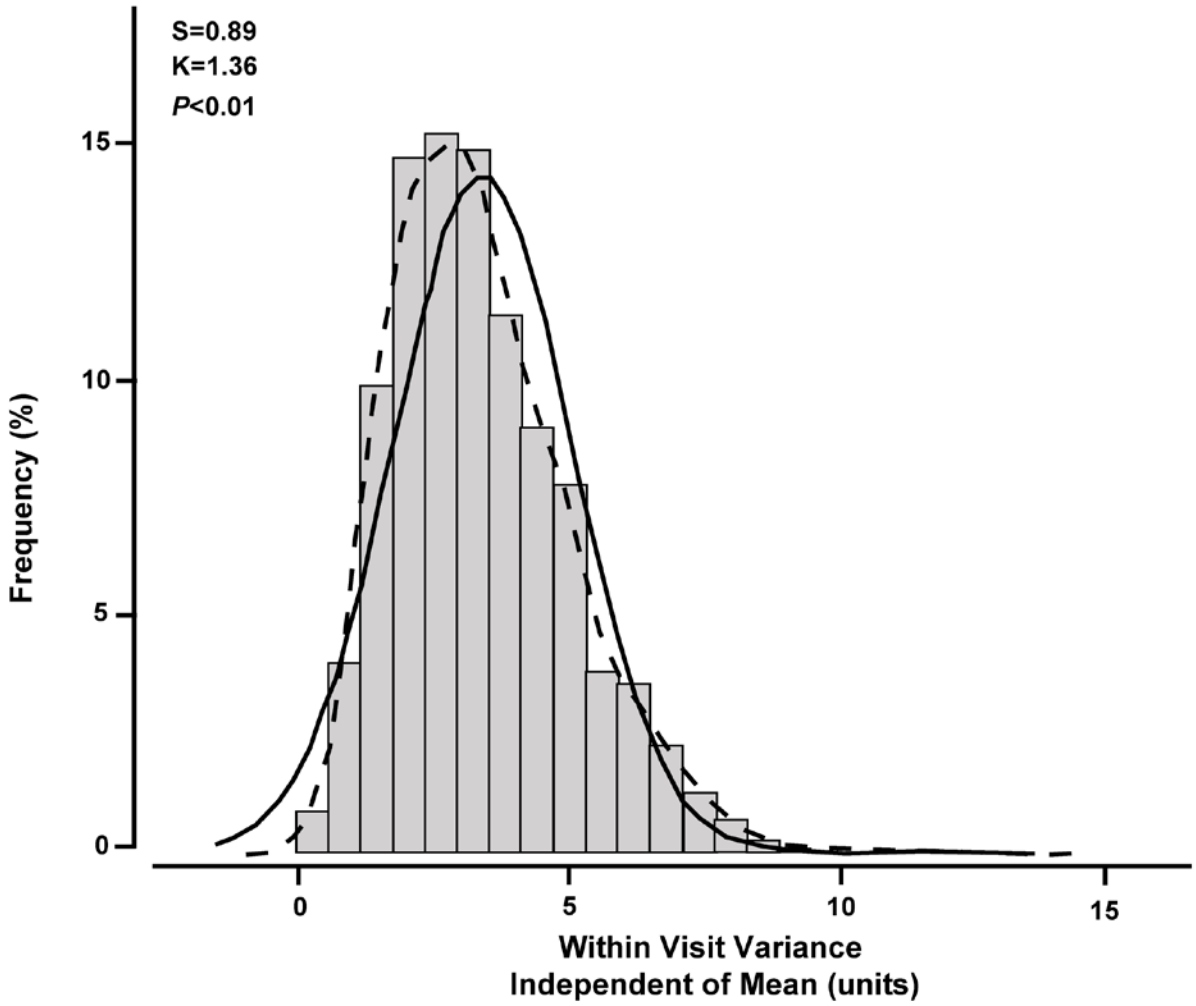

Figure S1: **Frequency Distribution of Within Visit Variability of Systolic Blood Pressure Independent of the Mean**

Within visit variability was computed for both sets of 5 blood pressure readings at a single visit and the so obtained parameters expressing variability were averaged over the 2 home visits. S and K are the coefficients of skewness and kurtosis, respectively; the *P* value is for departure of the actually observed distribution (full line) from normality (dotted line).

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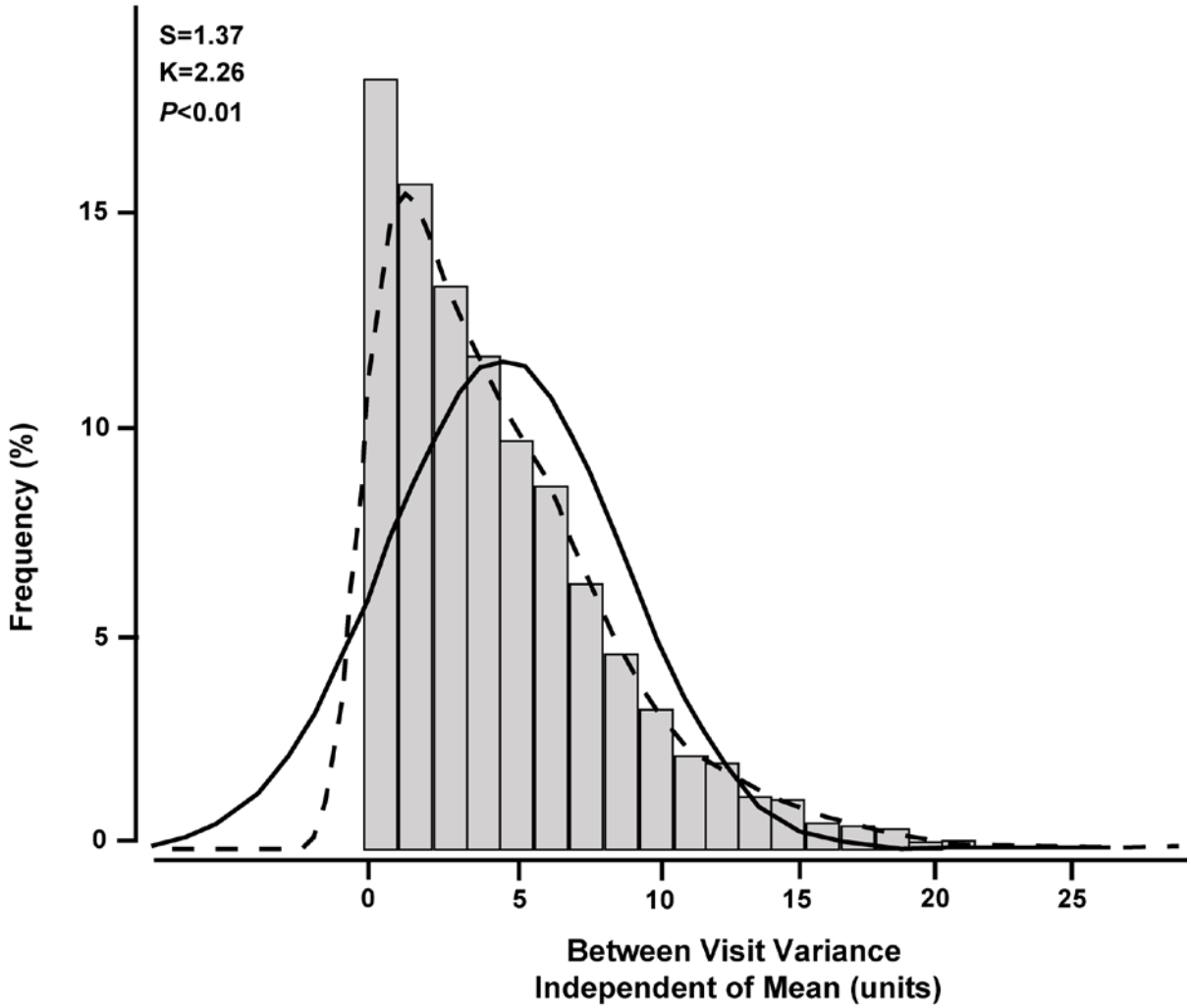

Figure S2: **Frequency Distribution of Between Visit Variability of Systolic Blood Pressure Independent of the Mean**

Between visit variability considered the variability (difference) between the mean blood pressure values at the 2 home visits. S and K are the coefficients of skewness and kurtosis, respectively; the *P* value is for departure of the actually observed distribution (full line) from normality (dotted line).

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