
Greater Blood Pressure Variability Is Associated With Lower Cognitive Performance - The Maastricht Study -

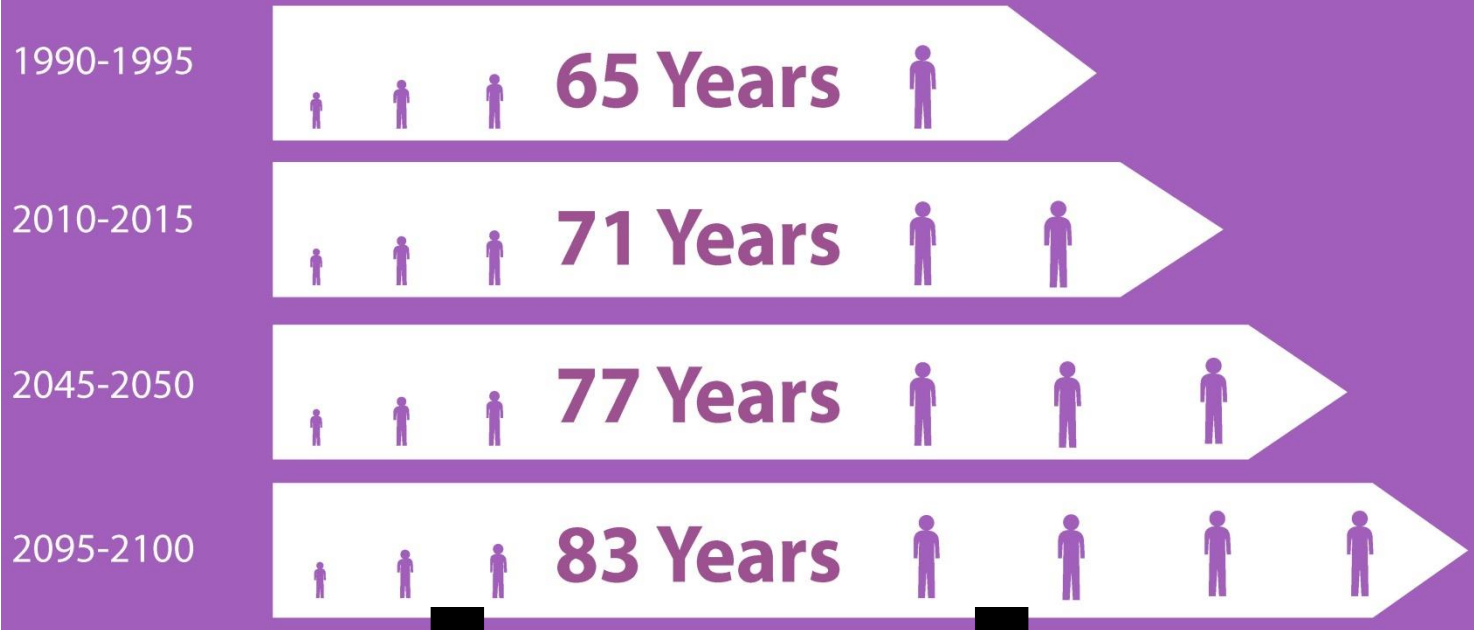
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Introduction

Global Life Expectancy

*Projected global life expectancy at birth**



Cognitive impairment
Blood pressure variability (BPV) as potential
modifiable risk factor?

Aim of study

To investigate the association between:

Blood pressure variability

(Within-visit, 24-hour and 7-day)

And

Cognitive performance

(Memory function, information processing speed and executive function)

Methods – The Maastricht Study



- Current study:
N = 3451
- N = 10,000
- 40-75 years
- Maastricht area
- Oversampling of T2DM
- Extensive phenotyping

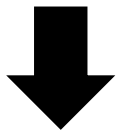


Methods – Blood pressure variability

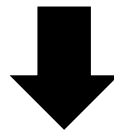
Within-visit BPV

24-hour BPV

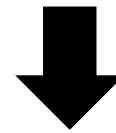
7-day BPV



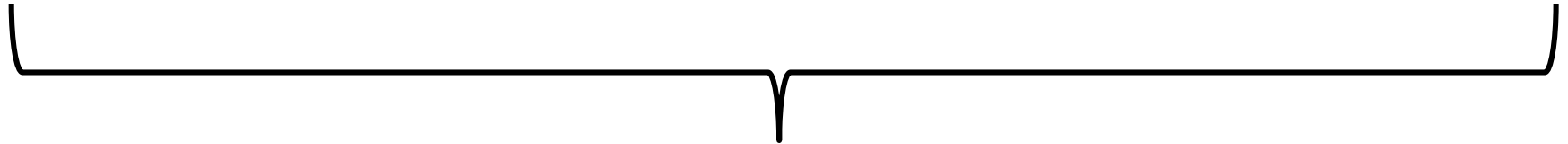
z-score



z-score

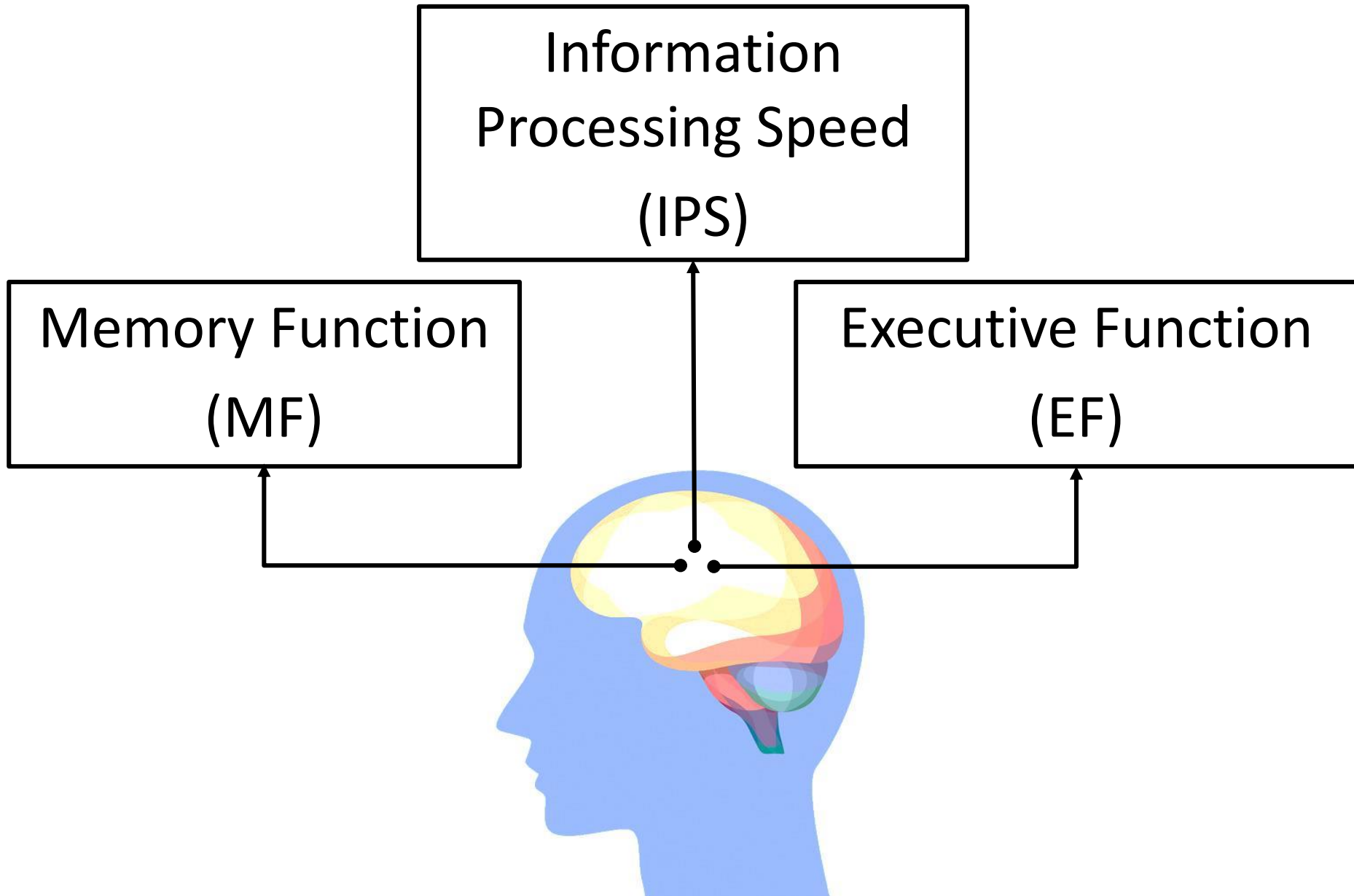


z-score



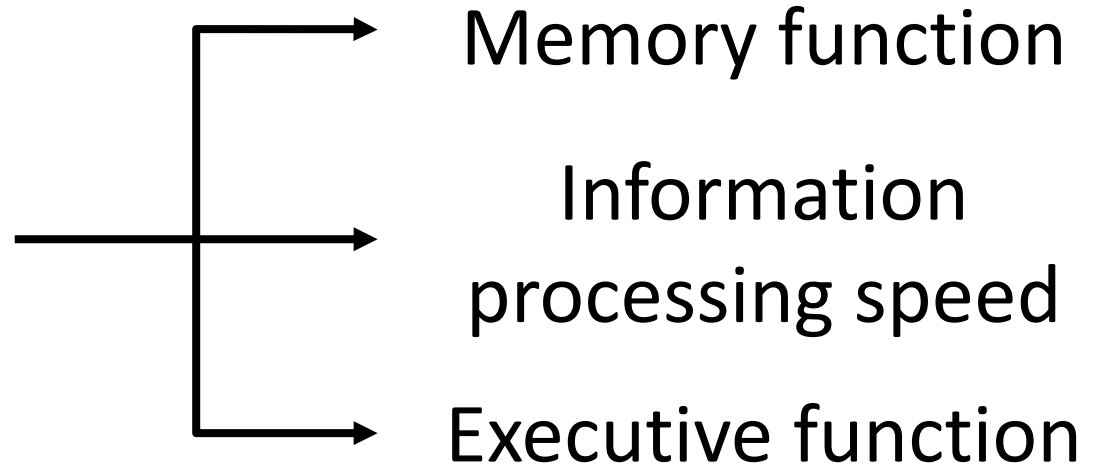
Summed and averaged to derive
a **composite index of BPV**

Methods – Cognitive performance



Methods – Statistical analysis

Tertiles of BPV
(Lowest tertile = reference)



Multiple linear regression with adjustments for, amongst others:
Age, sex, glucose metabolism status, mean 24-hour blood pressure,
educational level, and antihypertensive medication.

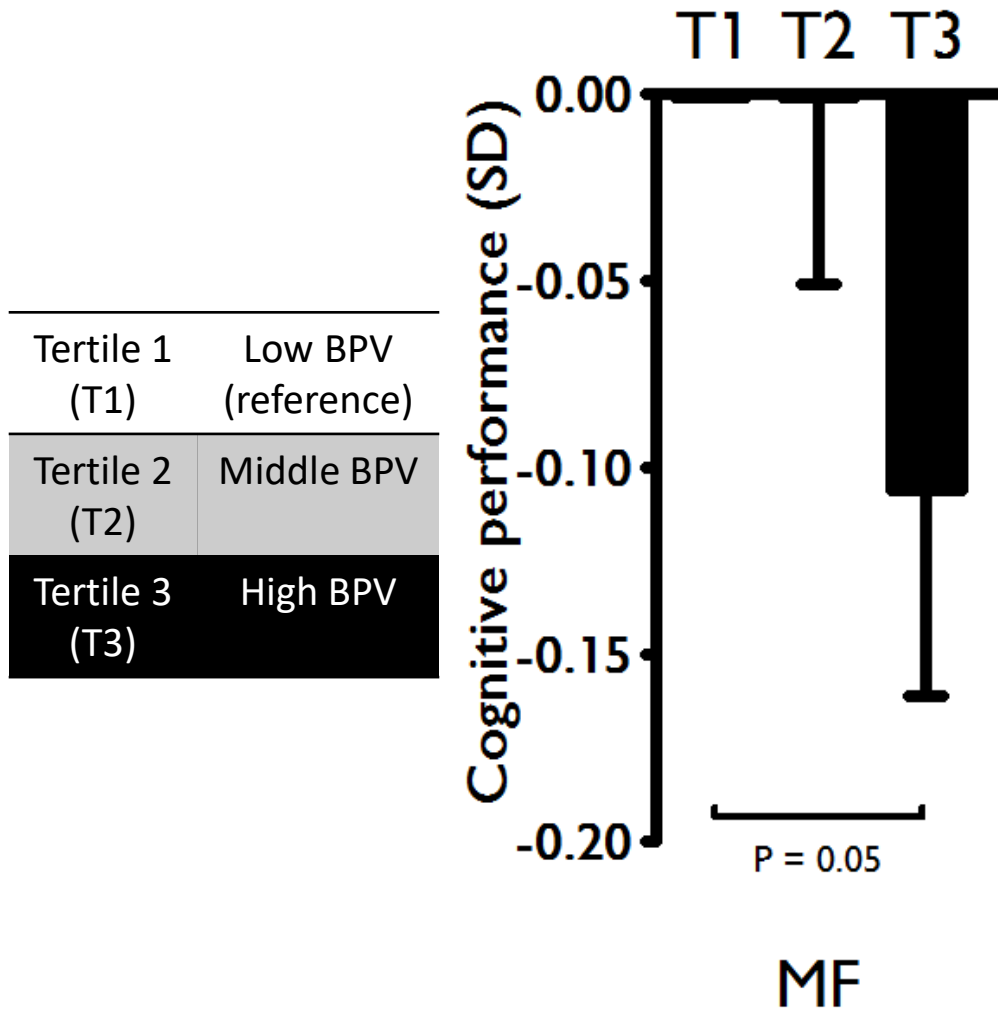
(Full model in supplemental slides)

Results – Clinical characteristics

Characteristic	Low BPV n=601	Middle BPV n=602	High BPV n=602
Age, years	58 ± 9	60 ± 8	62 ± 8
Men	323 (54%)	311 (52%)	302 (50%)
High educational level	257 (43%)	248 (41%)	226 (38%)
Type 2 diabetes mellitus	122 (20%)	159 (26%)	229 (38%)
Prior CVD	385 (14%)	109 (18%)	109 (18%)
Current depression	22 (4%)	16 (3%)	26 (4%)
Use of antihypertensives	183 (30%)	229 (38%)	294 (49 %)
24-hour systolic BP, mmHg	116 ± 9	120 ± 11	124 ± 13
24-hour diastolic BP, mmHg	73 ± 6	74 ± 7	76 ± 8

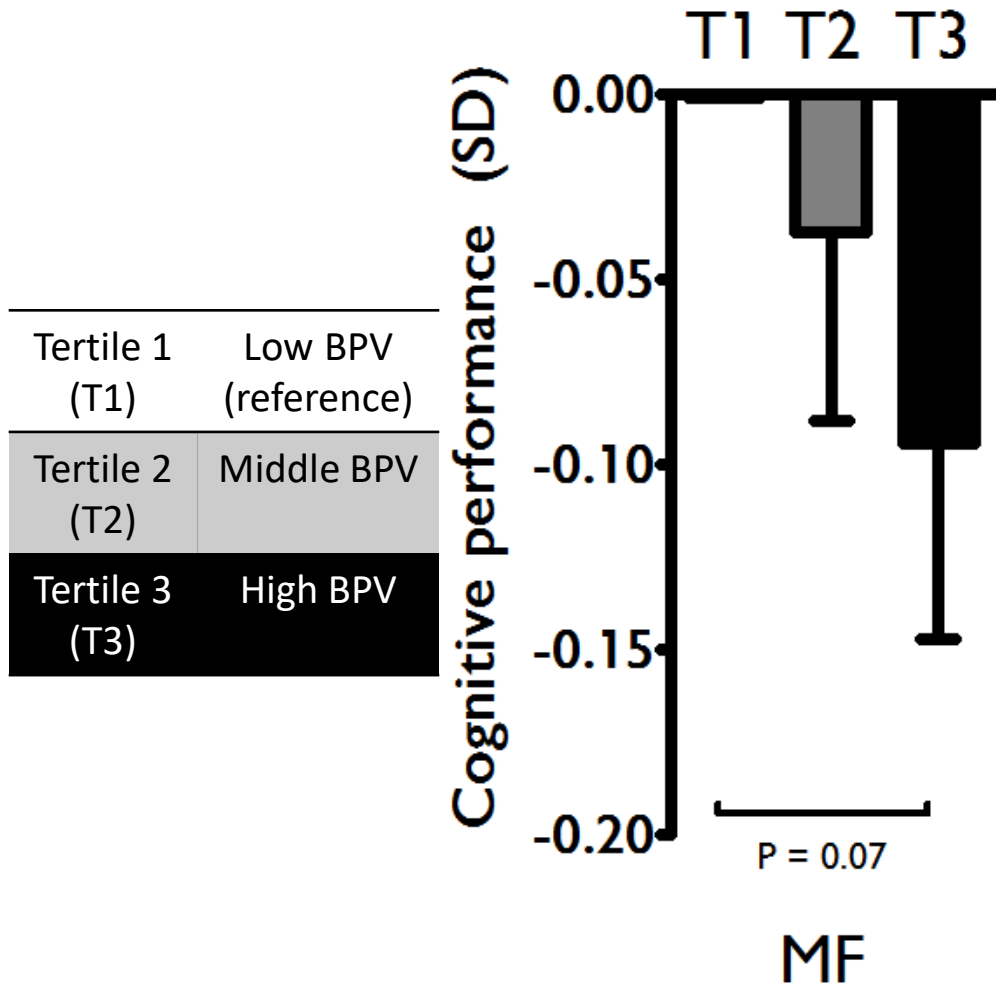
Data presented as mean ± SD or n (%)

Results – systolic BPV



Bars represent difference in cognitive performance (SD) as compared to tertile 1 of systolic BPV. Error bars represent standard error.

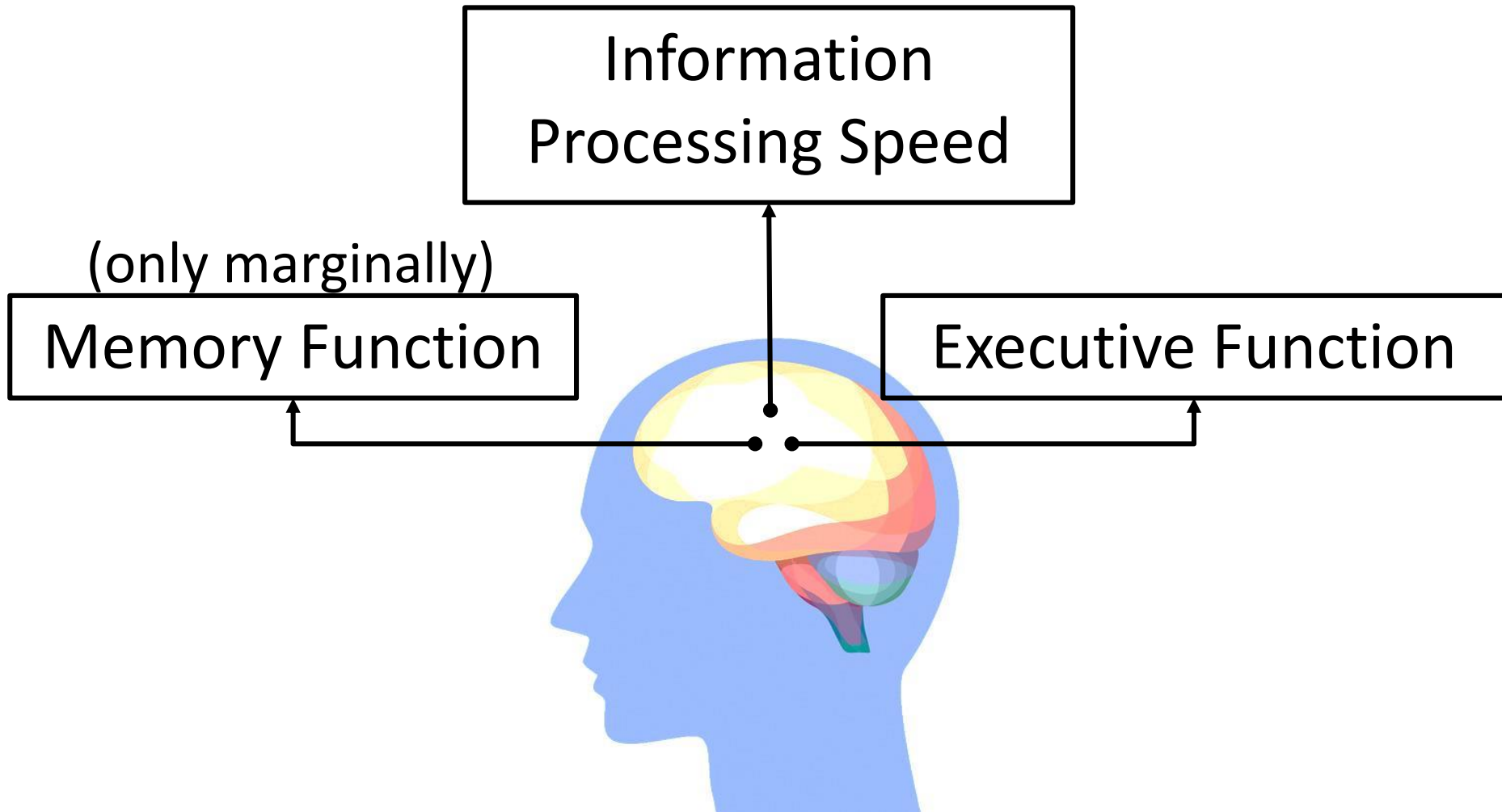
Results – diastolic BPV



Bars represent difference in cognitive performance (SD) as compared to tertile 1 of diastolic BPV. Error bars represent standard error.

Discussion

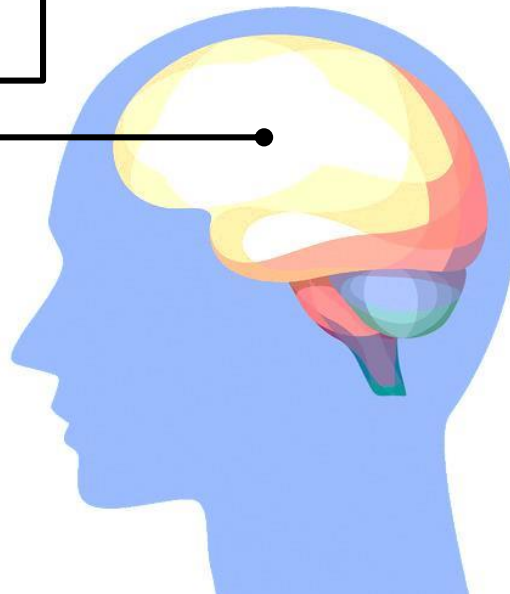
High diastolic BPV was statistically significantly associated with lower:



Discussion

High systolic BPV was marginally statistically significantly associated with lower:

Memory Function

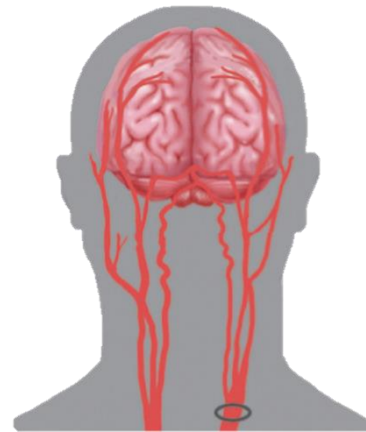


Discussion

In terms of ageing, these effects are equivalent to:

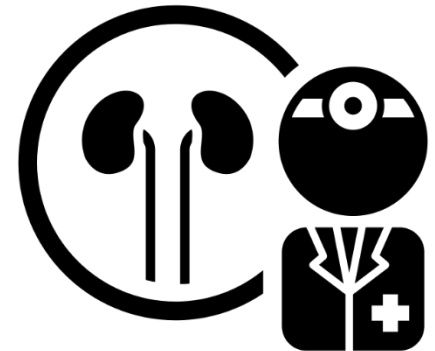
In terms of risk factors, effects are equivalent to:

3 years of ageing

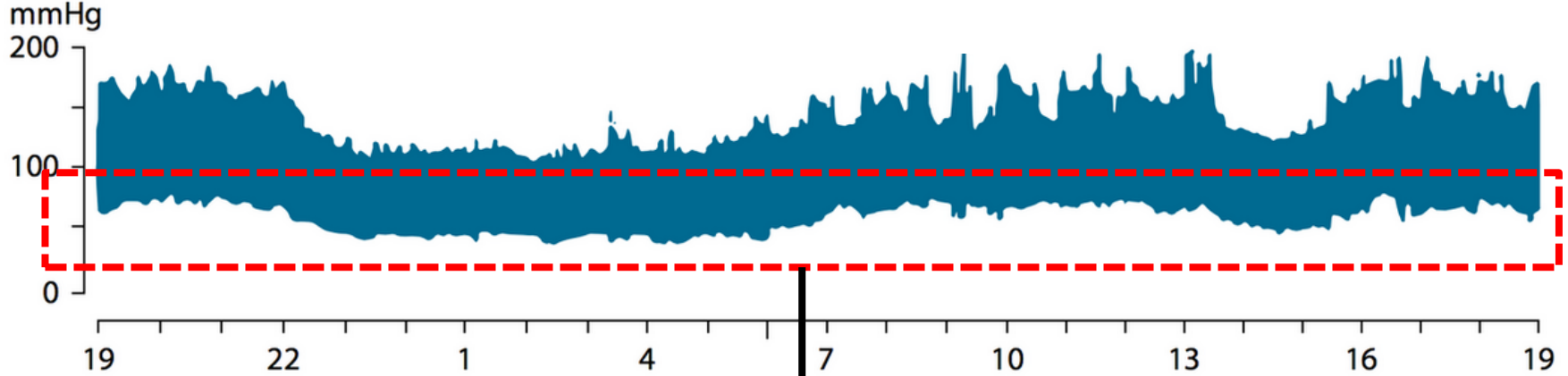


Carotid arterial stiffness

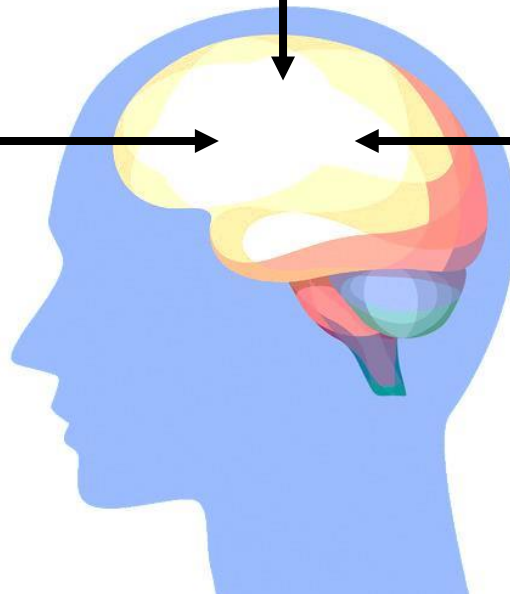
Micro-albuminuria



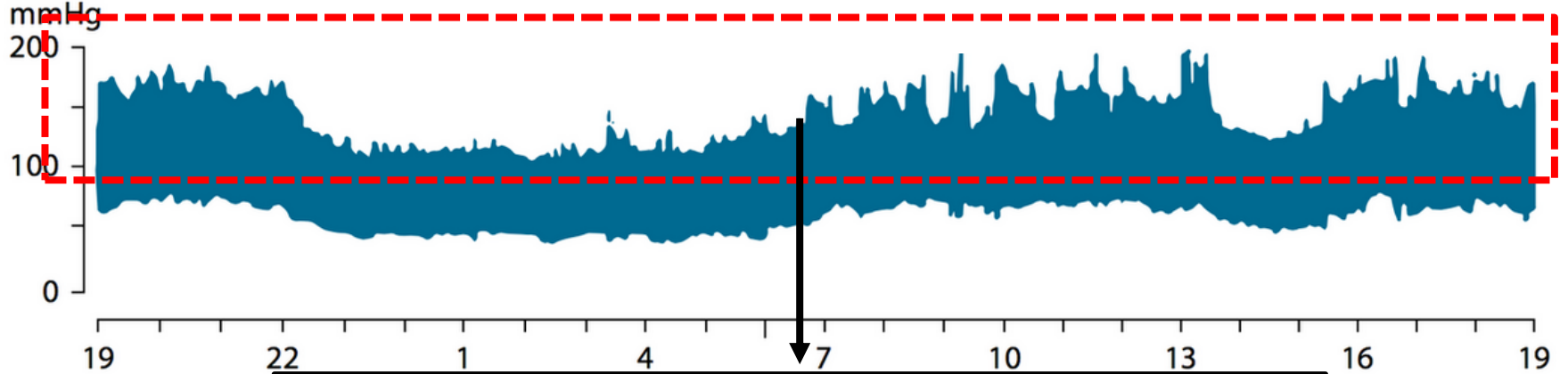
Discussion



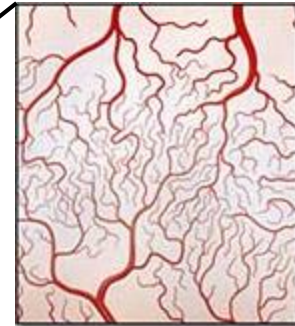
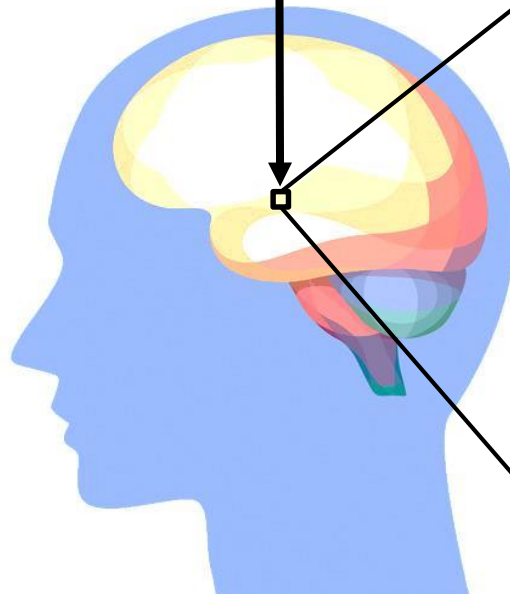
Lower perfusion pressure



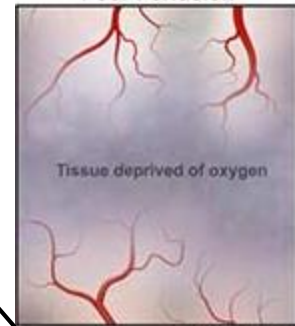
Discussion



Autoregulatory vasoconstriction



Poor Perfusion



Tissue deprived of oxygen

Conclusion

Greater very short- to mid-term diastolic, and to a lesser extent, systolic BPV may be a modifiable risk factor for cognitive impairment in 40- to 75-year old individuals.

Future research:

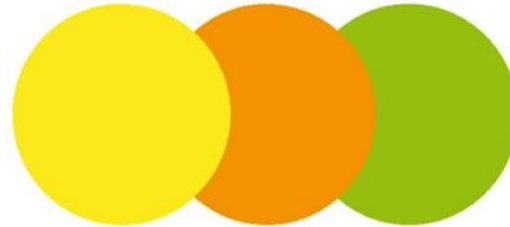
Differential effects of systolic and diastolic BPV?

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Maastricht Study participants
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THE MAASTRICHT STUDY

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Maastricht University

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Maastricht
Health Campus



dit onderzoek wordt ondersteund door de
Gemeente Maastricht

Diabetesonderzoekfonds
LIMBURG



Diabetes
Fonds

Thank you for your attention

Questions?

Full model

- Model 1: age, sex and glucose metabolism status (entered categorically).
- Model 2: 1 + 24-hour mean systolic or diastolic blood pressure (where appropriate).
- Model 3: 2+ lifestyle factors (i.e., BMI, alcohol consumption, smoking status and educational level).
- Model 4: 3 + cardiovascular risk factors (i.e., eGFR, TC/HDL-cholesterol ratio, triglycerides, lipid-modifying medication and antihypertensive medication classes [beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers and diuretics separately]).
- Model 5: 4 + prior CVD and current major depressive episode.

Strengths and limitations

- Strengths

- Multiple BPV indices
- Extensive cognitive test battery
- Well-characterized, large study population
- Adjusted for many confounders (overadjustment?)

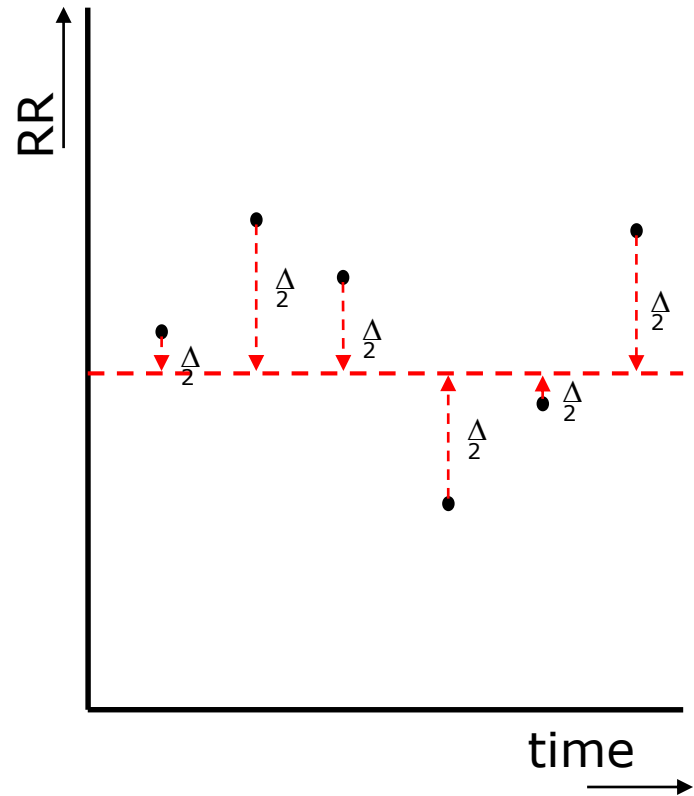
- Limitations

- Cross-sectional design
- Well-treated study population
- Possible overadjustment

Calculation of standard deviation

Standard deviation

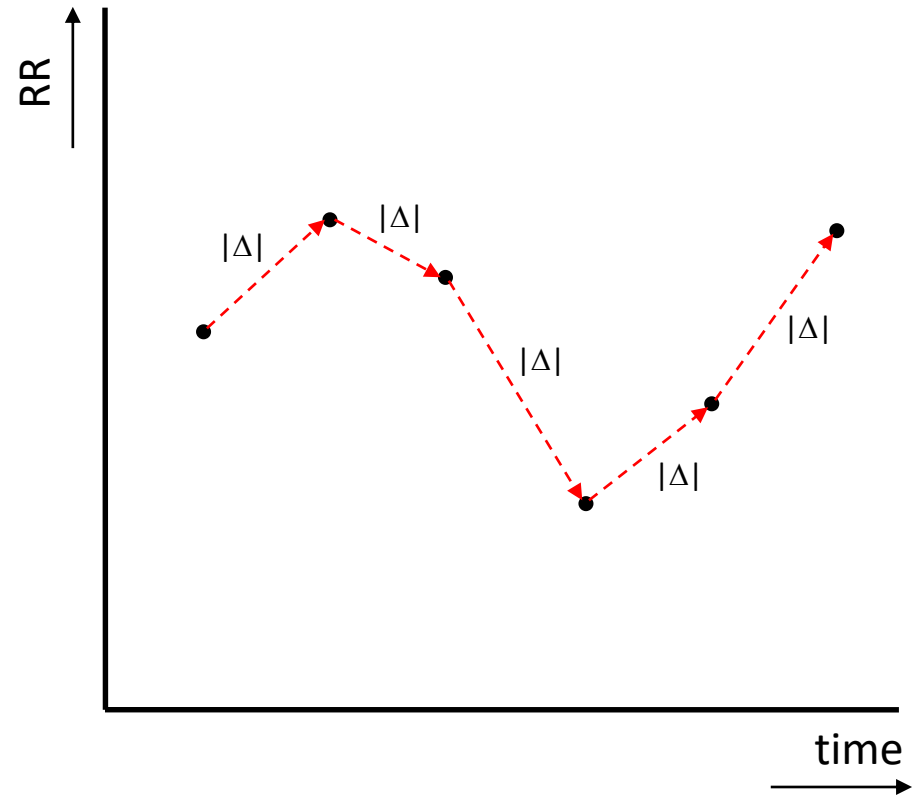
$$SD = \frac{\sqrt{\sum_{i=1}^N (x_i - \bar{x})^2}}{N}$$



Calculation of average real variability

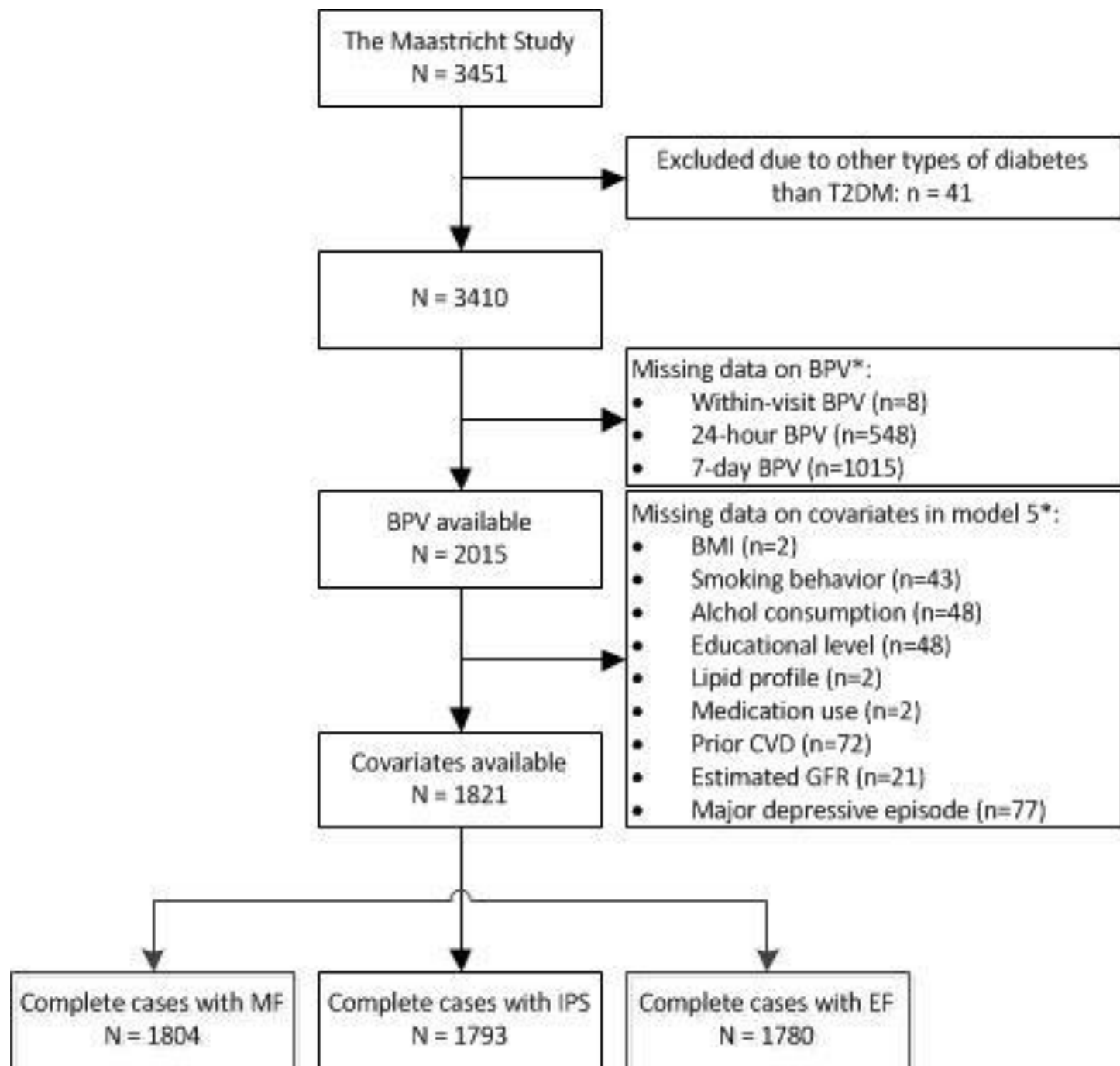
'Average real variability'

$$ARV = \frac{\sqrt{\sum_{i=1}^{N-1} |x_{i+1} - x_i|^2}}{N - 1}$$



Defining glucose metabolism status

	2h post OGTT glucose (mmol/L)		
Fasting plasma glucose (mmol/L)	< 7.8	7.8 - 11.1	≥ 11.1
< 6.1	Normal (NGM)	IGT (Prediabetes)	Type 2 diabetes (T2DM)
6.1 - 7.0	IFG (Prediabetes)	IFG + IGT (Prediabetes)	Type 2 diabetes (T2DM)
≥ 7.0	Type 2 diabetes (T2DM)	Type 2 diabetes (T2DM)	Type 2 diabetes (T2DM)



Clinical characteristics

	Tertile 1 (low) n = 601	Tertile 2 (middle) n = 602	Tertile 3 (high) n = 601
Demographics			
Age, years	57.7 ± 8.6	60.1 ± 7.6	61.5 ± 7.6
Men	323 (53.7%)	311 (51.7%)	302 (50.2%)
Educational level			
Low	84 (14.0%)	105 (17.4%)	98 (16.3%)
Intermediate	260 (43.3%)	249 (41.4%)	277 (46.1%)
High	257 (42.8%)	248 (41.2%)	226 (37.6%)
Cardiovascular risk factors			
BMI, kg/m ²	26.3 ± 4.2	26.9 ± 4.1	27.7 ± 4.4
Waist circumference, cm ^a	93.5 ± 13.1	95.5 ± 12.9	97.9 ± 13.0
Glucose metabolism status			
NGM	395 (65.7%)	354 (58.8%)	276 (45.9%)
Prediabetes	84 (14.0%)	89 (14.8%)	96 (16.0%)
Type 2 diabetes	122 (20.3%)	159 (26.4%)	229 (38.1%)

Clinical characteristics

	Tertile 1 (low) n = 601	Tertile 2 (middle) n = 602	Tertile 3 (high) n = 601
Fasting plasma glucose, mmol/l	5.1 ± 0.4	5.2 ± 0.4	5.2 ± 0.4
Normal glucose metabolism	6.0 ± 0.6	5.9 ± 0.6	5.9 ± 0.6
Prediabetes	8.0 ± 2.2	7.7 ± 1.6	8.0 ± 2.2
Type 2 diabetes			
HbA1c (mmol/mol) ^a			
NGM	36.0 ± 3.6	36.5 ± 3.8	36.7 ± 3.3
Prediabetes	38.6 ± 4.9	39.0 ± 4.3	38.4 ± 3.9
Type 2 diabetes	50.5 ± 10.1	50.4 ± 9.6	53.2 ± 12.7
Total cholesterol, mmol/l	5.2 ± 1.2	5.2 ± 1.1	5.3 ± 1.2
HDL cholesterol, mmol/l	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5
LDL cholesterol, mmol/l	3.1 ± 1.0	3.1 ± 1.0	3.1 ± 1.1
Triglycerides, mmol/l	1.1 [0.8 – 1.5]	1.2 [0.9 – 1.7]	1.3 [1.0 – 1.9]
Total-to-HDL cholesterol ratio	3.7 ± 1.2	3.7 ± 1.1	3.8 ± 1.2
eGFR, ml/min/1.73m ²	90.6 ± 14.4	87.8 ± 14.1	86.6 ± 15.1

Clinical characteristics

	Tertile 1 (low) n = 601	Tertile 2 (middle) n = 602	Tertile 3 (high) n = 601
Lifestyle variables			
Smoking behavior			
Never	646 (35.8%)	247 (41.1%)	186 (30.9%)
Former	937 (51.9%)	286 (47.6%)	336 (55.8%)
Current	221 (12.3%)	68 (11.3%)	80 (13.3%)
Alcohol consumption			
None	342 (19.0%)	93 (15.5%)	116 (19.3%)
Low	993 (55.0%)	377 (62.7%)	329 (54.7%)
High	469 (26.0%)	131 (21.8%)	157 (26.1%)
Moderate-to-vigorous physical activity (h/wk) ^a	4.5 [2.3 – 8.0]	4.5 [2.3 – 7.6]	4.8 [3.0 – 8.3]

Clinical characteristics

	Tertile 1 (low) n = 601	Tertile 2 (middle) n = 602	Tertile 3 (high) n = 601
Medication			
Use of antihypertensive medication	183 (30.4%)	229 (38.0%)	294 (48.9%)
Beta-blockers	91 (13.5%)	99 (15.8%)	133 (22.1%)
Calcium channel blockers	49 (8.2%)	57 (9.5%)	57 (9.5%)
ACE inhibitors	40 (6.7%)	69 (11.5%)	115 (19.1%)
Angiotensin II receptor blockers	86 (14.3%)	112 (18.6%)	117 (19.5%)
Diuretics	68 (11.3%)	98 (16.3%)	119 (19.8%)
Lipid-modifying medication	186 (30.9%)	205 (34.1%)	260 (43.3%)

Clinical characteristics

	Tertile 1 (low) n = 601	Tertile 2 (middle) n = 602	Tertile 3 (high) n = 601
Blood pressure measurements			
Office SBP, mmHg	127.6 ± 14.9	134.3 ± 17.7	142.3 ± 18.0
Office DBP, mmHg	73.9 ± 9.1	76.0 ± 9.5	78.3 ± 10.1
24-hour SBP, mmHg	116.1 ± 9.3	119.6 ± 11.1	124.4 ± 12.8
24-hour DBP, mmHg	72.8 ± 6.3	74.2 ± 6.9	76.0 ± 7.7
7-day home SBP, mmHg ^a	120.7 ± 10.4	126.8 ± 12.1	134.6 ± 13.7
7-day home DBP, mmHg ^a	75.1 ± 7.2	77.3 ± 7.8	79.5 ± 9.1

Clinical characteristics

	Tertile 1 (low) n = 601	Tertile 2 (middle) n = 602	Tertile 3 (high) n = 601
Blood pressure measurements			
Within-visit systolic BPV, mmHg	2.8 ± 1.5	4.4 ± 2.0	6.6 ± 3.1
Within-visit diastolic BPV, mmHg	2.1 ± 1.3	2.4 ± 1.5	2.9 ± 2.1
24-hour systolic BPV, mmHg	8.2 ± 1.4	9.9 ± 1.5	12.0 ± 2.7
24-hour diastolic BPV, mmHg	6.2 ± 1.4	6.8 ± 1.6	7.8 ± 2.1
7-day systolic BPV, mmHg	6.9 ± 1.7	8.7 ± 2.2	12.0 ± 4.7
7-day diastolic BPV, mmHg	4.8 ± 1.7	5.4 ± 1.8	7.1 ± 4.1

Clinical characteristics

	Tertile 1 (low) n = 601	Tertile 2 (middle) n = 602	Tertile 3 (high) n = 601
Mental health and cognitive performance			
Current major depressive episode	64 (3.6%)	22 (3.7%)	16 (2.7%)
Memory function	0.00 ± 1.00 ^d	0.11 ± 0.93	0.03 ± 0.98
Information processing speed^b	0.00 ± 1.00 ^d	0.13 ± 0.99	-0.01 ± 0.97
Executive function^c	0.00 ± 1.00 ^d	0.17 ± 1.04	-0.03 ± 0.96

Within-visit systolic BPV

		Cognitive performance domains					
		Memory function		Information processing speed		Executive function	
Model	Within-visit sBPV	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value
Crude	Low	Reference		Reference		Reference	
	Middle	-0.005 (-0.118; 0.109)	0.94	0.023 (-0.091; 0.136)	0.51	0.003 (-0.111; 0.117)	0.96
	High	-0.052 (-0.167; 0.062)	0.37	-0.003 (-0.118; 0.112)	0.95	-0.091 (-0.207; 0.024)	0.12
1	Low	Reference		Reference		Reference	
	Middle	0.003 (-0.097; 0.103)	0.95	0.048 (-0.052; 0.147)	0.25	0.022 (-0.082; 0.126)	0.68
	High	0.013 (-0.089; 0.114)	0.81	0.101 (0.000; 0.203)	0.05	-0.002 (-0.107; 0.104)	0.98
2	Low	Reference		Reference		Reference	
	Middle	-0.002 (-0.102; 0.098)	0.97	0.042 (-0.058; 0.142)	0.30	0.020 (-0.084; 0.125)	0.71
	High	-0.001 (-0.096; 0.108)	0.91	0.095 (-0.007; 0.197)	0.07	-0.004 (-0.110; 0.103)	0.95
3	Low	Reference		Reference		Reference	
	Middle	-0.025 (-0.123; 0.073)	0.61	0.011 (-0.084; 0.107)	0.64	-0.010 (-0.110; 0.090)	0.85
	High	-0.001 (-0.100; 0.099)	0.99	0.084 (-0.014; 0.182)	0.10	-0.012 (-0.114; 0.090)	0.82
4	Low	Reference		Reference		Reference	
	Middle	-0.021 (-0.119; 0.077)	0.67	0.015 (-0.081; 0.111)	0.59	-0.009 (-0.109; 0.091)	0.86
	High	0.005 (-0.095; 0.105)	0.92	0.084 (-0.014; 0.182)	0.09	-0.012 (-0.114; 0.090)	0.82
5	Low	Reference		Reference		Reference	
	Middle	-0.019 (-0.117; 0.079)	0.71	0.020 (-0.075; 0.116)	0.68	-0.005 (-0.105; 0.095)	0.92
	High	0.003 (-0.097; 0.103)	0.95	0.080 (-0.018; 0.177)	0.11	-0.015 (-0.117; 0.087)	0.77

Within-visit diastolic BPV

		Cognitive performance domains					
		Memory function		Information processing speed		Executive function	
Model	Within-visit dBPV	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value
Crude	Low	Reference		Reference		Reference	
	Middle	-0.062 (-0.176; 0.051)	0.28	-0.070 (-0.184; 0.044)	0.23	-0.099 (-0.213; 0.015)	0.09
	High	-0.064 (-0.176; 0.049)	0.27	-0.073 (-0.186; 0.039)	0.20	-0.095 (-0.207; 0.018)	0.10
1	Low	Reference		Reference		Reference	
	Middle	-0.052 (-0.152; 0.048)	0.31	-0.059 (-0.159; 0.041)	0.25	-0.090 (-0.194; 0.014)	0.09
	High	-0.012 (-0.112; 0.087)	0.81	0.002 (-0.097; 0.102)	0.96	-0.030 (-0.134; 0.073)	0.57
2	Low	Reference		Reference		Reference	
	Middle	-0.053 (-0.153; 0.047)	0.30	-0.061 (-0.161; 0.039)	0.23	-0.090 (-0.195; 0.014)	0.09
	High	-0.016 (-0.116; 0.084)	0.75	-0.008 (-0.107; 0.092)	0.88	-0.031 (-0.135; 0.073)	0.56
3	Low	Reference		Reference		Reference	
	Middle	-0.064 (-0.162; 0.033)	0.20	-0.072 (-0.167; 0.024)	0.14	-0.101 (-0.200; -0.001)	0.047
	High	-0.021 (-0.118; 0.076)	0.67	-0.015 (-0.111; 0.080)	0.75	-0.038 (-0.137; 0.061)	0.45
4	Low	Reference		Reference		Reference	
	Middle	-0.068 (-0.162; 0.030)	0.17	-0.076 (-0.172; 0.019)	0.12	-0.101 (-0.200; -0.001)	0.048
	High	-0.018 (-0.118; 0.080)	0.72	-0.010 (-0.105; 0.086)	0.84	-0.039 (-0.139; 0.060)	0.44
5	Low	Reference		Reference		Reference	
	Middle	-0.070 (-0.168; 0.028)	0.16	-0.080 (-0.176; 0.015)	0.10	-0.103 (-0.202; -0.003)	0.043
	High	-0.019 (-0.116; 0.079)	0.71	-0.011 (-0.107; 0.084)	0.82	-0.042 (-0.141; 0.058)	0.41

24-hour systolic BPV

		Cognitive performance domains					
		Memory function		Information processing speed		Executive function	
Model	24-hour sBPV	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value
Crude	Low	Reference		Reference		Reference	
	Middle	-0.045 (-0.158; 0.068)	0.43	-0.172 (-0.285; -0.059)	0.003	-0.173 (-0.186; -0.059)	0.003
	High	-0.157 (-0.270; -0.044)	0.006	-0.267 (-0.380; -0.155)	<0.001	-0.220 (-0.333; -0.106)	<0.001
1	Low	Reference		Reference		Reference	
	Middle	0.038 (-0.062; 0.139)	0.45	-0.047 (-0.147; 0.054)	0.36	-0.063 (-0.168; 0.042)	0.24
	High	-0.026 (-0.128; 0.077)	0.62	-0.048 (-0.151; 0.054)	0.35	-0.022 (-0.128; 0.085)	0.69
2	Low	Reference		Reference		Reference	
	Middle	0.028 (-0.073; 0.129)	0.59	-0.060 (-0.161; 0.042)	0.25	-0.067 (-0.172; 0.039)	0.22
	High	-0.050 (-0.157; 0.058)	0.36	-0.079 (-0.151; 0.029)	0.15	-0.031 (-0.143; 0.081)	0.59
3	Low	Reference		Reference		Reference	
	Middle	0.026 (-0.073; 0.125)	0.60	-0.063 (-0.161; 0.034)	0.21	-0.072 (-0.173; 0.030)	0.17
	High	-0.048 (-0.153; 0.058)	0.38	-0.074 (-0.186; 0.029)	0.16	-0.038 (-0.146; 0.070)	0.49
4	Low	Reference		Reference		Reference	
	Middle	0.029 (-0.070; 0.127)	0.57	-0.065 (-0.160; 0.032)	0.19	-0.072 (-0.173; 0.029)	0.16
	High	-0.041 (-0.147; 0.065)	0.45	-0.076 (-0.178; 0.029)	0.16	-0.036 (-0.144; 0.073)	0.52
5	Low	Reference		Reference		Reference	
	Middle	0.030 (-0.069; 0.129)	0.56	-0.062 (-0.159; 0.034)	0.21	-0.068 (-0.169; 0.033)	0.19
	High	-0.039 (-0.145; 0.067)	0.47	-0.072 (-0.175; 0.032)	0.18	-0.033 (-0.142; 0.075)	0.55

24-hour diastolic BPV

		Cognitive performance domains					
		Memory function		Information processing speed		Executive function	
Model	24-hour dBPV	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value
Crude	Low	Reference		Reference		Reference	
	Middle	-0.076 (-0.189; 0.037)	0.19	-0.126 (-0.239; -0.013)	0.029	-0.088 (-0.201; 0.023)	0.13
	High	-0.182 (-0.295; -0.070)	0.002	-0.234 (-0.347; -0.121)	<0.001	-0.219 (-0.332; -0.105)	<0.001
1	Low	Reference		Reference		Reference	
	Middle	-0.026 (-0.126; 0.074)	0.61	-0.089 (-0.188; -0.002)	0.08	-0.054 (-0.158; 0.050)	0.31
	High	-0.117 (-0.217; -0.016)	0.022	-0.145 (-0.244; -0.066)	0.005	-0.136 (-0.241; -0.032)	0.011
2	Low	Reference		Reference		Reference	
	Middle	-0.032 (-0.132; 0.068)	0.53	-0.101 (-0.201; -0.011)	0.047	-0.056 (-0.161; 0.048)	0.29
	High	-0.127 (-0.228; -0.026)	0.014	-0.167 (-0.267; -0.037)	0.001	-0.141 (-0.246; -0.035)	0.009
3	Low	Reference		Reference		Reference	
	Middle	-0.037 (-0.135; 0.061)	0.46	-0.107 (-0.203; -0.001)	0.029	-0.066 (-0.166; 0.034)	0.20
	High	-0.104 (-0.204; -0.005)	0.040	-0.135 (-0.232; -0.030)	0.007	-0.116 (-0.2018 -0.014)	0.026
4	Low	Reference		Reference		Reference	
	Middle	-0.031 (-0.130; 0.067)	0.53	-0.097 (-0.193; 0.006)	0.015	-0.060 (-0.160; 0.040)	0.24
	High	-0.095 (-0.195; 0.005)	0.06	-0.128 (-0.225; -0.023)	0.011	-0.112 (-0.214; -0.009)	0.032
5	Low	Reference		Reference		Reference	
	Middle	-0.028 (-0.127; 0.070)	0.44	-0.089 (-0.185; 0.007)	0.07	-0.057 (-0.157; 0.044)	0.27
	High	-0.092 (-0.192; 0.008)	0.07	-0.120 (-0.218; -0.023)	0.015	-0.109 (-0.211; -0.006)	0.037

7-day systolic BPV

		Cognitive performance domains					
		Memory function		Information processing speed		Executive function	
Model	7-day sBPV	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value
Crude	Low	Reference		Reference		Reference	
	Middle	-0.134 (-0.247; -0.022)	0.019	-0.150 (-0.263; -0.038)	0.005	-0.194 (-0.307; -0.081)	0.001
	High	-0.297 (-0.410; -0.185)	<0.001	-0.269 (-0.482; -0.257)	<0.001	-0.345 (-0.457; -0.232)	<0.001
1	Low	Reference		Reference		Reference	
	Middle	-0.060 (-0.161; 0.040)	0.24	0.008 (-0.108; 0.093)	0.88	-0.063 (-0.168; 0.042)	0.24
	High	-0.130 (-0.233; -0.027)	0.013	-0.122 (-0.224; -0.019)	0.020	-0.127 (-0.234; -0.020)	0.020
2	Low	Reference		Reference		Reference	
	Middle	-0.070 (-0.171; 0.032)	0.18	-0.018 (-0.119; 0.083)	0.73	-0.068 (-0.174; 0.038)	0.21
	High	-0.148 (-0.253; -0.043)	0.006	-0.142 (-0.246; -0.037)	0.008	-0.137 (-0.247; -0.028)	0.014
3	Low	Reference		Reference		Reference	
	Middle	-0.052 (-0.151; 0.047)	0.30	0.004 (-0.093; 0.102)	0.93	-0.051 (-0.152; 0.051)	0.33
	High	-0.149 (-0.252; -0.046)	0.005	-0.132 (-0.233; -0.032)	0.010	-0.140 (-0.245; -0.035)	0.009
4	Low	Reference		Reference		Reference	
	Middle	-0.047 (-0.146; 0.053)	0.36	0.002 (-0.095; 0.100)	0.96	-0.056 (-0.158; 0.045)	0.28
	High	-0.138 (-0.241; -0.034)	0.009	-0.122 (-0.224; -0.021)	0.019	-0.138 (-0.244; -0.032)	0.011
5	Low	Reference		Reference		Reference	
	Middle	-0.048 (-0.148; 0.051)	0.34	-0.001 (-0.098; 0.096)	0.98	-0.060 (-0.161; 0.041)	0.25
	High	-0.138 (-0.242; -0.034)	0.009	-0.122 (-0.223; -0.020)	0.018	-0.138 (-0.244; -0.032)	0.011

7-day diastolic BPV

		Cognitive performance domains					
		Memory function		Information processing speed		Executive function	
Model	7-day dBPV	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value
Crude	Low	Reference		Reference		Reference	
	Middle	-0.087 (-0.200; 0.026)	0.13	-0.174 (-0.286; -0.061)	0.002	-0.126 (-0.239; -0.013)	0.029
	High	-0.217 (-0.330; -0.104)	0.001	-0.352 (-0.464; -0.240)	<0.001	-0.289 (-0.402; -0.175)	<0.001
1	Low	Reference		Reference		Reference	
	Middle	-0.057 (-0.157; 0.042)	0.26	-0.116 (-0.216; -0.017)	0.022	-0.075 (-0.179; 0.029)	0.16
	High	-0.068 (-0.169; 0.034)	0.19	-0.162 (-0.263; -0.061)	0.002	-0.125 (-0.231; -0.019)	0.021
2	Low	Reference		Reference		Reference	
	Middle	-0.062 (-0.163; 0.038)	0.22	-0.128 (-0.228; -0.028)	0.012	-0.077 (-0.181; 0.028)	0.15
	High	-0.075 (-0.177; 0.027)	0.15	-0.181 (-0.282; -0.079)	0.001	-0.128 (-0.235; -0.021)	0.019
3	Low	Reference		Reference		Reference	
	Middle	-0.059 (-0.157; 0.039)	0.24	-0.122 (-0.218; -0.027)	0.012	-0.075 (-0.175; 0.025)	0.14
	High	-0.074 (-0.174; 0.027)	0.15	-0.171 (-0.269; -0.073)	0.001	-0.131 (-0.233; -0.028)	0.012
4	Low	Reference		Reference		Reference	
	Middle	-0.058 (-0.156; 0.040)	0.25	-0.119 (-0.215; -0.023)	0.015	-0.076 (-0.176; 0.024)	0.14
	High	-0.065 (-0.166; 0.037)	0.21	-0.167 (-0.266; -0.068)	0.001	-0.141 (-0.244; -0.037)	0.008
5	Low	Reference		Reference		Reference	
	Middle	-0.057 (-0.156; 0.041)	0.25	-0.118 (-0.214; -0.022)	0.016	-0.077 (-0.177; 0.023)	0.13
	High	-0.064 (-0.165; 0.038)	0.22	-0.164 (-0.263 -0.066)	0.001	-0.140 (-0.243; -0.037)	0.008

