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## Cognitive performance across the lifespan and domains

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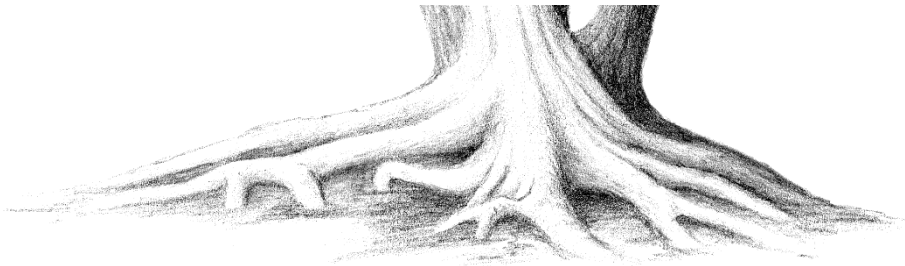
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# Chapter 7

## **No evidence of causal effects of blood pressure on cognition in the population at large**

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## Introduction

Healthy cognitive functioning is of high value to all members of society because it is important for general wellbeing, and predicts work performance and successful career paths. To promote cognitive health, a major strategy is to reduce the impact of the ‘usual suspects’: physical inactivity, smoking, diabetes and high blood pressure. However, for at least one of these risk factors, sustained high blood pressure, the relationship to cognitive functioning is complex. Reviews on this relationship have yielded mixed conclusions (Novak & Hajjar, 2010; Qiu, Winblad, & Fratiglioni, 2005; Reitz & Luchsinger, 2007), in keeping with the rather inconclusive findings in the primary studies (e.g., Harrington, Saxby, McKeith, Wesnes, & Ford, 2000; Lande, Kaczorowski, Auinger, Schwartz, & Weitzman, 2003; Lyngdoh et al., 2013; Tzourio, Dufouil, Ducimetiere, & Alperovitch, 1999). We here address the heterogeneity in these results. To date, whether cognitive functioning actually benefits from the reduction of high blood pressure remains an open question.

A limitation of the vast body of the studies done so far is that they mainly examine the association between blood pressure and cognition in older samples. This is understandable in view of the relatively large number of hypertensives among the elderly (Harrington et al., 2000), and the large societal burden caused not just by neurodegenerative disease but also by normal age-related cognitive decline. In the elderly, there are sensible mechanistic explanations for a negative association between high blood pressure and cognitive functioning. A currently high blood pressure level is the best predictor of prolonged past exposure to high blood pressure. Sustained exposure to high blood pressure increases the risk of atherosclerotic changes in intracerebrovascular vessels that result in a reduction of vessel number and diameter, leading to reduced vascular reserve and perfusion of the brain (Novak & Hajjar, 2010; Pires, Ramos, Matin, & Dorrance, 2013). On the neurological level this results in brain atrophy, white matter lesions, and possibly enhances Alzheimer-like pathology (Schmidt et al., 1995; Skoog, 1998; van Vliet, Westendorp, van Heemst, de Craen, & Oleksik, 2010; Waldstein, 2003).

In spite of the face validity of high blood pressure being detrimental for cognitive functioning, the actual association between blood pressure and cognitive functioning in the elderly is more complex. First, high blood pressure may be beneficial, possibly to compensate for loss of neural cell functioning (Anson & Paran, 2005; Novak & Hajjar, 2010). Second, in older people blood pressure may be lowered as a result of neurological disorders and brain lesions, which may have resulted from high blood pressure in the first place (van Vliet et al., 2010). Third, apart from high blood pressure, low blood pressure has also

been shown to have disadvantageous effects on cognitive functioning in elderly subjects (Hu, Li, Colditz, Willett, & Manson, 2003; Owen, Healy, Matthews, & Dunstan, 2010). Low blood pressure may compromise autoregulatory processes such that elderly are no longer capable of maintaining sufficient blood flow to neuronal tissue. This reduced perfusion causes reduced cortical activation, both during tonic states as well as when cognitive performance demands extra activation (Duschek & Schandry, 2007). Taken together, this indicates that the association between blood pressure and cognition is more complex, possibly because the relation is non-linear across the life span.

Despite the evidence for associations of blood pressure and atherosclerotic processes with cognition, generalization of these results is difficult, because most studies mainly involved elderly subjects. Much less is known about the association between blood pressure and cognitive functioning in samples that are representative of the population at large, which should include adolescent, young adult and middle-aged participants as well. Moreover, whereas general cognitive impairment (usually measured by the Mini-Mental State Examination, also known as MMSE) and memory loss have been the major focus of these studies in the elderly, other cognitive domains are relevant as well. Hypertension is related to brain function through reduced blood flow and metabolism, particularly in frontal, temporal and subcortical parts of the brain (Waldstein, 2003), suggesting possible different sensitivity of brain areas. This may explain why the majority of findings on specific cognitive domains find effects of blood pressure on functions like memory, attention, and executive functions (Duschek & Schandry, 2007; Gifford et al., 2013; Mitchell et al., 2011; Waldstein, 2003), but that learning, verbal, spatial and emotional abilities may be less affected. This means that different cognitive functions that depend on separate areas of the brain can be differentially susceptible to high BP, stressing the need to verify effects across cognitive domains (Birns, Morris, Donaldson, & Kalra, 2006).

A final complication to take into account when studying the association between cognition and blood pressure is that both may be influenced by one or more 'third' factors, which could either have detrimental or beneficial effects on both, or have a detrimental effect on e.g., blood pressure but a beneficial effect on cognition. The latter could lead to the absence of a clear association even in the presence of true causal effects of for example blood pressure on cognition. A clear example of the former 'third' factor influencing both cognition and blood pressure in a detrimental way is age (Deary et al., 2009; Franklin, 1999). Hence, age effects need to be controlled for rigorously. An environmental third factor that could detrimentally impact on both cognitive functioning and blood pressure is parental SES.

As compared to individuals from high SES backgrounds, individuals from low SES backgrounds tend to more often exhibit lifestyles (e.g., smoking) that may influence both cognitive functioning and blood pressure negatively (Adler & Ostrove, 1999). Third factors may also be of genetic origin: pleiotropic genetic variation may impact on common neurobiological pathways that influence both blood pressure and cognitive functioning (Herrera, Pasion, Tan, Moran, & Ruiz-Opazo, 2013; Obisesan, 2009). This might reflect shared common neurobiological pathways, or may indicate there are independent effects on both blood pressure and cognitive functioning (Waldstein, 2003). A design that is optimally suited to address the influence of third factors is a monozygotic (MZ) twin pairs difference design. MZ twins have the same age and sex, share (nearly) 100% of their segregating genes and a large part of their childhood environment. If the MZ twin with a higher blood pressure than the co-twin also has reduced cognitive functioning, this would argue in favor of a detrimental effect of high blood pressure that is causal, as this design controls for the impact of age, shared environment, and genotype (e.g., de Moor et al., 2008).

In the present study, we systematically investigate the association between current levels of systolic and diastolic blood pressure on age-dependent normal cognitive functioning while taking into account the sources that may have led to mixed results across previous studies. We allow the association between blood pressure and cognitive functioning to be non-linear, such that both low and high blood pressure constitute a risk. We further allow the sensitivity to the effects of blood pressure to depend on the cognitive domains. Thirdly, we test the relation between blood pressure and cognition in a design that controls maximally for ‘third factors’, of genetic and / or environmental origin. To this end we assessed blood pressure and cognitive performance in participants from a large population-based twin-family sample ranging from children to elderly individuals across a wide range of well-defined neurocognitive domains. In a subsample of 123 monozygotic twin pairs, we ordered the twins within pairs according to blood pressure levels and tested if the twin with the higher BP differed from the co-twin on any of the cognitive domains. Because MZ twins share both their genomic information and part of their environment, this analysis controls for genetic pleiotropy and the influence of shared environmental factors, for example (parental) socio-economic status, on both traits.

## **Materials and Methods**

### **Participants**

In total there were 1140 participants, mainly ( $n = 1110$ ) recruited from 431 families from the Netherlands Twin Register (NTR, Boomsma et al., 2006; van

Beijsterveldt et al., 2013; Willemsen et al., 2013). The other 30 participants were university students. Age of the participants ranged from 10 to 86 years old (668 female, 472 male).

All participants took part in one of two studies in which measurements of blood pressure and cognitive performance were collected, referred to as the twin-family study and the twin-sibling study. The twin-family study sample consisted of 864 family members from 341 families. The majority of these participants were part of a twin pair (438) or siblings of twins (78). The rest were family of these twins and siblings, including parents (160 mothers, 126 fathers), children (9) and partners (53) of twins and siblings. In addition to this family sample, 30 university students participated in the pilot phase and were tested according to the twin-family protocol. The sample of the twin-sibling study consisted of 176 adolescent twins and 70 siblings from 89 families who participated in the third wave of assessment in a longitudinal study on development of brain and cognition (BrainScale study, van Soelen et al., 2012a).

## Procedure

Studies and procedures of the twin-family study were approved by the Medical Ethics Review Committee of the Vrije Universiteit Medical Center Amsterdam, and for the twin-sibling study were approved by the Central Committee on Research Involving Human Subjects. First, participants were approached by mail. In a structured phone call interview participants were asked if they were willing to participate, if necessary additional information about the study was provided, and possible exclusion criteria were explored. After establishing an appointment, confirmation letters were sent, which included written informed consent forms and questionnaires. Consent forms were signed and returned at the appointment, after participants were given a full explanation of the procedure. Medication use and demographic data like education were registered, and a reading test was administered.

In the twin-family study, testing took place at the Vrije Universiteit Amsterdam laboratory ( $n = 358$ ) or at the participants' home ( $n = 536$ ). A baseline measurement of blood pressure was taken for all participants during the first ( $n = 885$ ) and second ( $n = 883$ ) designated break point of the cognitive test battery, and for the more recent and largest part of the participants an additional measurement was taken prior to the start of cognitive testing ( $n = 764$ ).

In the twin-sibling study, testing took place in the University Medical Center Utrecht. As part of an extensive study which included MRI scans of the brain, the same cognitive test protocol was assessed as in the twin-family study, but only a single measurement of blood pressure was taken.

The administration procedure of the Computerized Neuropsychological Battery was kept similar across studies and locations. The battery was installed on Macbooks to enable offline administration during home visits. The test administrator would read the instructions to the participant (who could read them along on the screen), and monitored whether the participant understood the instructions and practice trials. Test scores were later uploaded to the Pennsylvania servers for data storage and automated validation. Breakpoints were at specific moments, for example after cognitively demanding tests (also shown in Table 1). Test administration was not interrupted at other moments.

## **Materials**

### ***Blood pressure***

Blood pressure (BP) was measured from the brachial artery in the arm by a digital blood pressure monitor (Omron). Participants were in a sitting position. Both systolic (SBP) and diastolic (DBP) BP was recorded. Depending on the study sample and study phase (see procedure), BP was measured one, two, or three times. The intercorrelations between DBP measurements ranged from 0.78 to 0.85 and between SBP measurements from 0.87 to 0.91, indicating the reliability of both BP measures.

### ***Cognitive performance***

Cognitive performance was assessed through the Dutch translation of the web-based Computerized Neuropsychological Battery (CNB, Gur et al., 2010). In short, the CNB includes a total of 17 cognitive tests, generating 33 measures of cognitive performance in five broad domains (Table 1): 16 measures of accuracy (the number or percentage of correct responses on the cognitive tests), 16 measures of reaction time (median response time in milliseconds for those correct responses), and one measure of motor speed (number of taps on the finger tapping test, TAP). Reaction times were multiplied by -1 so that high cognitive performance was always denoted by a high test score. We refer to Swagerman et al., (2015a) for a more extensive description of the battery and full descriptives for the performance data.

## **Statistical analyses**

Invalid scores (~0.9%) and data from children under age 13 ( $n = 4$ ) were excluded from the present analysis, which comprised two sets of statistical analyses: the first set involved data from the complete sample, the other the data from monozygotic twin pairs only. In both sets of analyses, DBP values were averaged over the (one, two or three) measurements. The same held for SBP.

**Table 1.** Tests and their cognitive measure and domain, given in order of assessment.

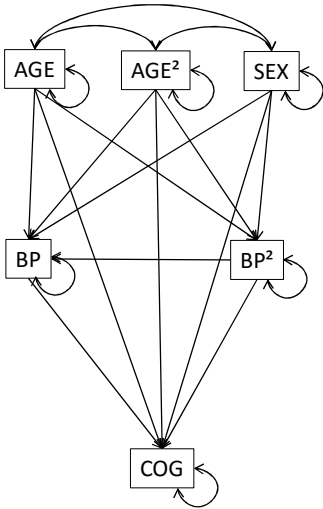
Test name	Label	Cognitive measure	Cognitive domain
Motor Praxis Test	MP	sensorimotor speed	sensorimotor
Penn Emotion Identification Test	EI	emotion identification	social cognition
Penn Continuous Performance Test	CPT	attention	executive control
Breakpoint 1			
Penn Facial Memory Test	CPFi	face memory	memory
Penn Word Memory Test	CPWi	verbal memory	memory
Letter-N-Back Test	LNB	working memory	executive control
Penn Facial Memory Test – delayed	CPFd	face memory	memory
Penn Word Memory Test – delayed	CPWd	verbal memory	memory
Breakpoint 2			
Penn Conditional Exclusion Test	CET	abstraction / flexibility	executive control
Measured Emotion Differentiation Test	EDT	emotion differentiation	social cognition
Computerized Finger-Tapping Test	TAP	motor speed	sensorimotor
Penn Matrix Reasoning Test	MAT	nonverbal reasoning	complex cognition
Breakpoint 3			
Visual Object Learning Test	VOLTi	spatial memory	memory
Penn Logical Reasoning Test	VRT	language reasoning	complex cognition
Age Differentiation Test	ADT	age differentiation	social cognition
Variable Penn Line Orientation Test	LOT	spatial ability	complex cognition
Visual Object Learning Test – delayed	VOLTd	spatial memory	memory

### ***Whole sample analyses***

For each of the 33 cognitive measures, the association of cognitive performance with BP was estimated by fitting the path model that is diagrammed in Figure 1. That is, each cognitive performance measure was regressed on DBP or SBP and its mean centered square (DBP<sup>2</sup> or SBP<sup>2</sup>), while regressing out the possible confounding effects of sex, age, and the (mean centered) square of age (age<sup>2</sup>). The coefficients of the direct paths from the BP variables to the cognitive measure were the parameters of interest. Hence, the entire set of analyses yielded 2 (linear and quadratic)\*2 (systolic and diastolic)\*33 (cognitive variables) = 132 path coefficient estimates, so 132 test statistics. In view of chance capitalization, while acknowledging Bonferroni correction for multiple testing may be too conservative, we corrected the original significance level (0.05) via Matrix Spectral Decomposition (Li & Ji, 2005), which indicated that the data could be described along 23 statistically independent dimensions. This yielded a corrected significance level of:  $\alpha = 0.05/23 \approx 0.002$  (see also Swagerman et al., 2015a).



**Figure 1.** Graphical representation of the path model fitted to the data of the whole sample, showing that cognitive test performance (COG) depends on blood pressure (BP) and (mean centered) blood pressure squared ( $BP^2$ ), while regressing out the effects of sex, age, and the mean centered square of age ( $AGE^2$ ).



The path modeling was performed in R using packages lavaan (Rosseel, 2012) and lavaan.survey (Oberski, 2014). We opted for robust sandwich estimation (in view of the data being skewed) and included family number as a cluster variable (in view of the data being family clustered). To estimate the sensitivity of the effects to antihypertensive medication, all analyses were rerun after excluding all individuals who take any type of antihypertensive medication (60 females, 58 males, mean age 69.08).

### *Monozygotic twin pairs difference analyses*

To control for possible confounding effects other than those of age and sex, including shared environmental and genetic factors, additional analyses were performed using the data from the monozygotic (MZ) twins only. Within twin pairs, the MZ twins were ranked on the basis of their blood pressure, such that two groups were formed: a high BP group, consisting of the twins with the relatively high BP, and a low BP group, consisting of the twins with the relatively low BP. Next, we investigated the mean difference in cognitive performance between those groups.

The rationale behind such analyses is as follows. As MZ twin pairs are not only of the same age and sex, but also matched on their genotype (since they are 100% genetically identical) and many environmental variables, mean group differences in cognitive performance between the MZ twins cannot be explained

by the variables on which they are matched. Any mean group differences in cognitive performance between the groups can thus be attributed to the between pair differences in blood pressure (or nonshared causes thereof). If high blood pressure has a negative effect on cognition, the high BP group is expected to display significantly lower cognitive performance scores (on average) as compared to the low BP group; if BP has a positive effect, the high BP group is expected to score higher than the low BP group. If, despite differences in blood pressure, mean differences between cognitive scores are insignificant, one is allowed to conclude that BP does not influence cognitive performance. The ranking, grouping, and subsequent analysis of mean scores was done for SBP and DBP separately.

Two-sided paired t-tests were performed in SPSS version 21 (IBM Corp., 2011) separately for DBP and SBP on the 33 cognitive performance scores. In line with the whole sample analysis, we used a corrected significance level of 0.002 to account for the multiple testing in a set of correlated dependent variables. The 287 MZ twins in total formed 132 pairs of whom data were complete for both twins. Ranks of mean SBP and DBP were consistent in 96 of these pairs. If both twins had exactly equal mean BP values (3 twin pairs had equal mean DBP, 1 pair equal mean SBP), twins were assigned to the high and low BP groups randomly. If one or both twins of a pair used antihypertensive medication, both twins were excluded from the analyses (five pairs concordant, four pairs discordant for medication use). Ultimately, in total the analyses included 123 complete twin pairs.

## Results

### Descriptive statistics

The mean DBP was 75.49 (SD = 10.98) and the mean SBP 129.51 (SD = 17.02). Mean sex differences in DBP (males:  $M = 75.83$ ,  $SD = 11.08$ ; females:  $M = 75.25$ ,  $SD = 10.91$ ) were not significant ( $\beta = -0.04$ ,  $se = 0.03$ ,  $p = 0.23$ ). Mean sex differences in SBP (males:  $M = 134.87$ ,  $SD = 15.87$ ; females:  $M = 125.76$ ,  $SD = 16.80$ ) were however significant ( $\beta = 0.25$ ,  $se = 0.03$ ,  $p < .001$ ). Both DBP and SBP related significantly with age ( $\beta = 0.49$ ,  $se = 0.03$ ,  $p < .001$ ;  $\beta = 0.48$ ,  $se = 0.03$ ,  $p < .001$ , respectively).

### Whole sample analyses

The standardized results of the path modeling, i.e., the direct path coefficients of both the linear and quadratic terms of SBP and DBP on cognitive performance and their test statistics, are provided in Table 2 and summarized graphically in Figure 2. These coefficients can be interpreted as age and sex corrected effects of current blood pressure on current cognitive performance.

**Table 2.** The age and sex corrected linear and quadratic effects ( $\beta$ ; direct path coefficients in Figure 1) of diastolic and systolic blood pressure on cognitive accuracy and speed performance including their standard errors (SE) and p-values ( $n$ ).

Domain (accuracy)	Diastolic blood pressure						Systolic blood pressure					
	Linear			Quadratic			Linear			Quadratic		
	$\beta$	SE	$p$	$\beta$	SE	$p$	$\beta$	SE	$p$	$\beta$	SE	$p$
<i>Executive control</i>												
Abstraction & flexibility	-.005	.032	.876	-.020	.036	.568	.043	.034	.210	-.004	.034	.915
Attention	.030	.031	.325	-.011	.027	.685	.053	.035	.128	-.049	.033	.147
Working Memory	.012	.030	.697	.013	.029	.657	.050	.035	.157	-.016	.035	.651
<i>Memory</i>												
Verbal Memory	.027	.034	.421	-.072	.038	.058	.002	.038	.958	-.012	.035	.737
delayed	.037	.032	.251	-.057	.029	.049*	-.005	.034	.885	-.044	.032	.170
Facial Memory	-.029	.036	.423	-.039	.032	.215	-.018	.036	.616	-.003	.031	.916
delayed	.002	.033	.960	-.029	.030	.336	.010	.036	.786	.017	.035	.633
Spatial Memory	-.053	.032	.092	-.006	.028	.819	-.061	.034	.071	.015	.031	.630
delayed	-.061	.033	.067	-.018	.034	.601	-.020	.036	.568	-.015	.035	.672
<i>Complex Cognition</i>												
Nonverbal Reasoning	-.056	.029	.053	-.021	.024	.377	-.027	.033	.421	-.005	.029	.878
Language Reasoning	-.003	.034	.928	-.034	.029	.240	-.035	.037	.334	.026	.034	.445
Spatial Ability	-.053	.034	.118	.031	.033	.339	.007	.036	.850	.003	.032	.922
<i>Social Cognition</i>												
Emotion Identification	.041	.035	.234	-.040	.031	.186	.060	.035	.085	.001	.029	.981
Emotion Differentiation	.005	.033	.890	.002	.028	.953	.056	.036	.121	-.043	.035	.215
Age differentiation	.053	.032	.100	-.064	.035	.070	.092	.036	.011*	-.073	.036	.043*
<i>Sensorimotor</i>												
Sensorimotor Speed	-.001	.035	.988	-.003	.027	.915	-.030	.033	.359	.032	.030	.290

\* = significant at  $\alpha = .05$ .

**Table 2 - continued.**

Domain (speed)	<u>Diastolic blood pressure</u>						<u>Systolic blood pressure</u>					
	Linear			Quadratic			Linear			Quadratic		
	$\beta$	<i>SE</i>	<i>p</i>	$\beta$	<i>SE</i>	<i>p</i>	$\beta$	<i>SE</i>	<i>p</i>	$\beta$	<i>SE</i>	<i>p</i>
<i>Executive control</i>												
Abstraction & flexibility	-.060	.030	.048*	.003	.034	.923	-.059	.03	.052	.001	.038	.979
Attention	.023	.034	.501	.013	.027	.634	-.020	.037	.591	.061	.036	.087
Working Memory	.055	.033	.095	-.026	.035	.448	-.008	.038	.822	.037	.037	.320
<i>Memory</i>												
Verbal Memory	.065	.031	.034*	-.037	.025	.136	.061	.032	.061	.001	.025	.967
delayed	.033	.030	.264	-.021	.024	.380	.020	.031	.524	.025	.025	.315
Facial Memory	.071	.036	.045*	-.02	.030	.495	.044	.035	.209	.007	.026	.798
delayed	.048	.034	.162	.003	.031	.915	.017	.035	.628	.031	.027	.238
Spatial Memory	.006	.033	.849	-.006	.030	.849	.013	.033	.693	.020	.026	.449
delayed	.013	.029	.659	.008	.028	.786	-.008	.029	.782	.026	.026	.326
<i>Complex Cognition</i>												
Nonverbal Reasoning	.078	.031	.013*	.034	.026	.189	.049	.038	.194	-.001	.034	.986
Language Reasoning	.107	.035	.002*	.005	.023	.818	.062	.037	.093	.003	.029	.915
Spatial Ability	.033	.028	.242	-.005	.024	.819	-.043	.030	.151	.038	.027	.150
<i>Social Cognition</i>												
Emotion Identification	.114	.037	.002*	-.025	.033	.440	.070	.035	.045*	.033	.022	.145
Emotion Differentiation	.034	.027	.213	.018	.020	.358	-.018	.028	.527	.043	.022	.056
Age differentiation	.030	.027	.267	-.005	.020	.809	-.004	.028	.893	.012	.025	.640
<i>Sensorimotor</i>												
Sensorimotor Speed	.036	.035	.298	-.007	.032	.815	.033	.034	.321	.043	.025	.076
Motor Speed	.016	.027	.560	-.016	.020	.425	.014	.028	.624	.056	.022	.013*

\* = significant at  $\alpha = .05$ .

**Table 3.** Showing the mean cognitive performance scores of the high and low diastolic and systolic monozygotic twin groups, the mean differences ( $\Delta$ ) with their standard deviations, and the results of the paired t-tests (t-statistic, t; and p-value, p).

Variable	Diastolic blood pressure				Systolic blood pressure							
	Mean high	Mean low	$\Delta$	$\Delta$ (SD)	t	p	Mean high	Mean low	$\Delta$	$\Delta$ (SD)	t	p
Blood Pressure	77.2	69.0	7.9	6.2	14.141	.000**	129.0	119.2	9.8	8.4	12.995	.000**
Domain (accuracy)												
<i>Executive Control</i>												
Abstraction & flexibility	1.9	2.0	-0.2	0.9	-1.864	.065	1.8	2.0	-0.2	0.9	-2.265	.025*
Attention	55.8	56.3	-0.5	4.2	-1.395	.165	56.2	56.0	0.2	4.2	.576	.566
Working Memory	19.0	19.2	-0.2	1.4	-1.323	.188	19.1	19.1	-0.2	1.4	-1.189	.237
<i>Memory</i>												
Verbal Memory	1.86	2.01	-0.2	0.9	1.376	.171	36.8	36.4	0.4	2.9	1.626	.107
delayed	55.8	56.3	-0.5	4.2	1.122	.264	35.8	35.4	0.3	3.5	1.017	.311
Facial Memory	19.0	19.2	-0.2	1.4	-1.974	.051	31.8	32.0	-0.2	3.7	-.714	.476
delayed	1.86	2.01	-0.2	0.9	-.760	.449	33.0	33.1	-0.1	3.6	-.253	.801
Spatial Memory	55.8	56.3	-0.5	4.2	-1.082	.281	16.1	16.3	-0.2	2.4	-.857	.393
delayed	19.0	19.2	-0.2	1.4	-1.029	.306	15.4	15.7	-0.3	2.6	-1.100	.273
<i>Complex Cognition</i>												
Nonverbal Reasoning	15.1	14.9	0.1	4.3	.233	.817	15.1	14.9	0.2	4.3	.444	.658
Language Reasoning	69.2	65.2	3.6	21.4	1.850	.067	69.3	65.1	3.8	21.4	1.959	.052
Spatial Ability	13.2	13.5	-0.3	3.5	-.978	.330	13.2	13.5	-0.4	3.5	-1.186	.238
<i>Social Cognition</i>												
Emotion Identification	32.8	33.3	-0.4	3.3	-1.423	.157	32.9	33.2	-0.3	3.3	-.871	.385
Emotion Differentiation	28.5	28.4	0.2	4.2	.425	.671	28.4	28.5	-0.1	4.2	-.128	.899
Age differentiation	27.6	27.4	0.2	4.7	.478	.633	27.5	27.5	0.0	4.7	-.057	.954
<i>Sensorimotor</i>												
Sensorimotor Speed	20.0	20.0	0.0	0.2	1.000	.319	20.0	20.0	0.0	0.2	1.000	.319

\* = significant at  $\alpha = .05$ , \*\* = significant at  $\alpha = .01$ .

**Table 3 - continued.**

Domain (speed)	Diastolic blood pressure				<i>t</i>	<i>p</i>	Systolic blood pressure				<i>t</i>	<i>p</i>
	Mean high	Mean low	$\Delta$	$\Delta$ (SD)			Mean high	Mean low	$\Delta$	$\Delta$ (SD)		
<i>Executive Control</i>												
Abstraction & flexibility	-2547.3	-2472.5	-74.8	1081.7	-.764	.447	-2466.7	-2553.1	86.4	108.8	.883	.379
Attention	-483.7	-483.2	-0.5	52.2	-.106	.916	-485.2	-481.8	-3.4	52.1	-.714	.476
Working Memory	-529.1	-526.7	-3.7	122.3	-.334	.739	-529.1	-526.7	-3.3	122.3	-.296	.768
<i>Memory</i>												
Verbal Memory	-1478.0	-1453.9	-24.1	237.4	-1.124	.263	-1467.3	-1464.6	-2.8	238.6	-.128	.898
delayed	-1457.0	-1441.3	-15.8	281.3	-.622	.535	-1434.8	-1463.5	28.7	28.2	1.137	.258
Facial Memory	-1957.5	-1864.8	-9.3	498.7	-1.976	.050	-196.2	-1862.9	-1.1	496.8	-2.199	.030*
delayed	-1765.8	-1715.6	-47.7	44.3	-1.183	.239	-1747.1	-1734.6	-11.0	442.8	-.271	.787
Spatial Memory	-184.1	-1862.8	18.2	5.2	.402	.688	-1856.4	-1846.7	-14.3	5.4	-.315	.753
delayed	-1681.5	-1697.3	12.3	426.9	.317	.752	-1701.0	-1678.0	-31.1	425.9	-.803	.424
<i>Complex Cognition</i>												
Nonverbal Reasoning	-1026.5	-11038.6	815.5	6553.9	1.374	.172	-10629.1	-10672.9	78.1	6604.3	.131	.896
Language Reasoning	-9052.8	-8903.5	-136.6	3931.5	-.384	.702	-8955.0	-90.5	59.1	3933.4	.166	.869
Spatial Ability	-9459.6	-997.4	549.5	3126.1	1.933	.056	-9607.3	-9822.8	251.8	3164.3	.875	.383
<i>Social Cognition</i>												
Emotion Identification	-2056.3	-2116.7	6.4	492.1	1.361	.176	-2082.1	-209.9	8.8	495.7	.197	.844
Emotion Differentiation	-3409.1	-3314.1	-95.1	1085.2	-.972	.333	-3415.0	-3308.2	-106.8	1084.1	-1.093	.277
Age differentiation	-2838.5	-2769.3	-69.3	1052.4	-.730	.467	-2815.2	-2792.6	-22.7	1054.5	-.239	.812
<i>Sensorimotor</i>												
Sensorimotor Speed	-712.6	-712.8	0.2	132.8	.019	.985	-722.1	-703.3	-18.7	131.5	-1.580	.117
Motor Speed	114.9	113.2	1.9	12.9	1.574	.118	113.7	114.4	-.6	13.0	-.521	.603

\* = significant at  $\alpha = .05$ , \*\* = significant at  $\alpha = .01$ .

### ***Accuracy***

The effects of BP on accuracy were small and distributed around 0. Linear effects of DBP ranged from -0.061 (spatial memory delayed test) to 0.053 (age differentiation test) with a median of 0.002, and those of SBP ranged from -0.061 (spatial memory test) to 0.092 (age differentiation test) with a median of 0.007. Quadratic effects of DBP ranged from -0.072 (verbal memory test) to 0.031 (spatial ability test) with a median of -0.02 and those of SBP ranged from -0.073 (age differentiation test) to 0.032 (sensorimotor test) with a median of -0.004. None of these effects reached the level of significance ( $\alpha = 0.002$ ). Medication status did not influence the results: nearly identical effect sizes were obtained when the analyses were repeated after removing the 118 individuals taking antihypertensive medication and are therefore not reported.

### ***Speed***

Like the effects of BP on accuracy, the effects of BP on speed were small. Linear effects of DBP ranged from -0.060 (abstraction and mental flexibility) to 0.114 (emotion identification test) and were mostly positive with a median of 0.036. Yet of those effects, only the linear effects on language reasoning and emotion identification were significant ( $\alpha = 0.002$ ). This was also true in the repeated analyses after removing individuals taking antihypertensive medication.

Linear effects of SBP were centered around 0 again and ranged from -0.059 (abstraction and mental flexibility) to 0.070 (emotion identification test) with a median of 0.017. None of these coefficients were significant.

Quadratic effects of DBP ranged from -0.037 (verbal memory test) to 0.034 (nonverbal reasoning test) with a median of -0.005, and those of SBP ranged from -0.001 (nonverbal reasoning) to 0.061 (attention) with a median of 0.026. These were insignificant as well.

In conclusion, no systematic linear or quadratic association between blood pressure and cognitive functioning was found. There is some evidence of a linear effect of diastolic blood pressure on the speed of language reasoning and emotion identification, but the DBP effects on cognitive speed were not replicated in other tasks that measure performance in the same domain.

### ***Monozygotic twin pairs difference analyses***

The results of the additional MZ twin pair analysis are provided in Table 3. The mean BP of the high DBP and SBP groups were significantly higher than mean BP in the group with their co-twins with low DBP and SBP. The mean differences in cognitive performance were small and for about half of all test scores, the differences were in the positive direction and for the other half in the negative

direction. None of these intrapair MZ differences in cognitive performance remained significant after correction for multiple testing.

From the combined sets of analyses, we may derive that in the population at large associations between blood pressure and cognitive performance are absent when effects of confounding factors like age, sex, genetic pleiotropic and shared environmental factors are taken into account. We conclude that our analyses show no evidence for a causal relationship between (current) level of blood pressure on (current) cognitive functioning.

## Discussion

We set out to explore the effects of diastolic and systolic blood pressure on cognitive functioning in a population-based sample with a wide age range. We attempted to explain the inconsistencies in studies thus far by allowing blood pressure effects to be curvilinear and to be different across accuracy and speed measures of five cognitive domains. We accounted for confounding of any association by genetic factors and by many shared environmental factors including parental SES. Our whole sample analyses showed that for the majority of the cognitive tests very little indication was found that, after correction for substantial age-effects, blood pressure was associated with cognitive test performance. The MZ twin pair analyses also did not suggest any effect of DBP or SBP on cognitive performance.

When we look at the analyses in the whole sample in a liberal way, i.e. without any correction for multiple testing, two instances of a possible adverse effect of BP on cognition were found, suggesting a detrimental effect of higher BP on the speed of emotion identification and verbal reasoning. The association with emotion identification is an isolated one as no other studies that we could identify have been conducted on blood pressure and tests of social cognition. Previous findings for blood pressure and language skills have been far from consistent but a meta-analysis of 12 studies found a possible trend that was in keeping with our result (Gifford et al., 2013). In view of the large number of cognitive domains tested, these two nominally significant associations most likely reflect false positives. They were not seen for other tasks within the relevant cognitive domains, and none were replicated for SBP.

Our findings were based on a large dataset of participants spanning a large age range, drawn from the general population. This differs from the bulk of the existing literature that focused on either children but mostly on the elderly. Studies in children are limited by the relatively few children showing hypertension, which is then often complicated in those children by comorbid disorders and congenital disease (Cha, Patel, Hains, & Mahan, 2012; Lande et



al., 2003; Lyngdoh et al., 2013). Studies in the elderly are complicated by comorbidity of high blood pressure with other atherosclerotic risk factors like cholesterol, diabetes, BMI, immune parameters, and medical or psychiatric disorders which can all assert an influence on cognitive functioning (Spauwen et al., 2015; van Vliet et al., 2010; Waldstein, 2003; Walther, Birdsill, Glisky, & Ryan, 2010). These factors can also cause cardiac pathology that itself reduces blood pressure, as seen in heart failure patients, further complicating the association between blood pressure and cognition because too low blood pressure also has disadvantageous effects on cognitive functioning in elderly subjects (Hu et al., 2003; Owen et al., 2010). Moreover, the effects of neurodegeneration and dementia are hard to separate from normal cognitive aging. The Institute of Medicine recently defined cognitive aging as a lifelong process of gradual changes in cognitive function that is highly variable across individuals and within individuals, and across cognitive domains (Blazer et al., 2015). Animal models show that, in contrast to Alzheimer disease or other neurodegenerative disorders, there is no loss of neurons with normal aging, but a gradual change in synaptic structure and function. The distinction is relevant because high blood pressure can compensate the loss of neural cell functioning (Anson & Paran, 2005; Novak & Hajjar, 2010) and this may have a different impact on normal and neurodegenerative cognitive aging. In view of these complexities it is perhaps not surprising that meta-analyses of large randomized controlled trials have not uniformly concluded that antihypertensive medication improves cognitive performance in the elderly (McGuinness, Todd, Passmore, & Bullock, 2009; Novak & Hajjar, 2010).

As a large part of our study sample consisted of adolescents, or young and middle-aged adults, atherosclerotic or neurodegenerative damage will not have been a major confounder, which is a strength of the current study. Repeating analyses in age groups under 30 or over 50 showed virtually the same results (analyses not shown). However, our study also suffered some limitations. The absence of curvilinear effects of blood pressure may mean that we overly complicated our analyses. We still recommend modeling them in future studies, since strong non-linear effects might be present in specific patient groups, as for example found in a subsample of diabetes patients (Spauwen et al., 2015). The largest limitation is the use of only one to three measurements of blood pressure in a sitting condition to characterize blood pressure. This may not be sensitive to detect effects of more complex aspects of blood pressure regulation. A more extensive assessment of blood pressure, for example also taken while lying down or while standing up to test for postural hypotension (e.g., Kuo et al., 2004) might have revealed different results for cognition. Finally, our twin design capitalized

on intra-pair differences in BP in genetically identical individuals, which were modest in size due to the substantial heritability of BP (Hottenga et al., 2005).

In summary, associations between cognitive functioning and DBP and SBP were absent for the vast majority of the 33 cognitive accuracy or speed measures, most notably in a well-matched within-twin pair comparison of MZ twins. The few nominally significant associations between specific test scores and blood pressure most likely reflect chance findings. We conclude that across a wide age range in the population at large, blood pressure level is not associated with cognitive functioning in a clinically meaningful way. This does not detract from the possible value of treating blood pressure to prevent atherosclerotic and neurodegenerative disease in older age, but it also suggests that there are no immediate cognitive benefits from lowering blood pressure per se.

**Figure 2.** Standardized effect size of linear and nonlinear effects of diastolic blood pressure and systolic blood pressure on cognitive accuracy and speed, ordered by cognitive domain.

