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- **Online Data Supplement**

Our objective is to characterize the development of the literature on hypertension and cognitive functioning from a historical perspective. This goal was stimulated by the review on "Historical Trends and Milestones in Hypertension Research" in the October 2012 issue of *Hypertension*.[1] Our specific aims are threefold: (1) to trace and describe the history of this area of research; (2) to identify milestones in knowledge and methods; and (3) to discuss briefly how this literature translates into patient care. The topic is of major relevance to research and practice because hypertension is a well-known risk factor for decline in cognitive performance within the normal range of cognitive functioning, mild cognitive impairment (MCI) and dementia. It is important to emphasize 3 features of the review: (1) it is not designed as a critical review of the literature, but rather to describe the historical influences on our current knowledge base (poor, mediocre and outstanding papers from the past have all shaped our present); (2) word-count limitations require that we omit statistical detail except to emphasize effect sizes in pivotal papers; and (3) each milestone topic is addressed by noting the earliest work then followed by examples of papers representing pivotal events. A number of comprehensive reviews of this literature are available,[2–6] including a seminal paper summarizing the formative years of this research.[7] Please see http://hyper.ahajournals.org for citations to additional reviews of the literature and papers published in *Hypertension*. We recognize the importance of the emerging literature on hypotension and cognitive function, but refer the readers to previous reviews which include this topic.[8–10]

Measurement of Cognitive Functioning

In this paper, the term *cognitive performance* is used to describe the outcome of studies measuring a full range of ability from low to high. The term *cognitive functioning* is used to describe, more generally, findings with respect to cognitive performance, MCI, or dementia. *Cognitive deficit* is used in a comparative sense, hypertensive individuals compared to some other group of subjects. The term *impairment* is used to indicate clinically significant cognitive dysfunction.

Lezak et al[11] provide a compendium of over 700 psychometric tests and subtests. They describe behaviors required to perform the test, the latent abilities that the tests purport to measure, eg, working memory, attention, and executive functioning. Classic neuropsychological texts describe how tests and the latent cognitive constructs they measure are used to make inferences about the hemisphere, locus, and extent of brain injury.[12] Figure 1 shows an example of a hypothetical study in which tests are being used to explore the hypothesis that hypertension is more strongly associated with executive functioning[13] and that this phenomenon is associated with reduced cerebral blood flow (CBF) to the frontal and prefrontal brain areas, but not to other brain areas.[14] *Executive functioning* (EF) can be defined as the ability to integrate and organize current knowledge to acquire new concepts and strategies that allow effective application of current information to new anticipated and unanticipated situations.[13] It is important to note that more than 1 test is used to identify a latent cognitive variable, eg, EF.[12,13] Tests that do and do not measure EF must be included in the test battery, and it is the pattern of results that provides evidence for or against the hypothesis. This hypothetical study includes measures of regional CBF and MRI. A paper by Haier et al[15] provides an example of this approach.

Details of the Literature Search

The online databases and search engines that we used initially to identify papers were PubMed, Medline, ScienceDirect, PsychINFO, PsyARTICLES, Psychology Abstracts, CINAHL, and the Cochrane Library. The basic requirement for a paper was that cognitive performance, MCI, or dementia had to be an outcome measure. Search terms relating to outcome measures were cognition, cognitive performance, cognitive functioning, MCI, cognitive dysfunction, dementia, Alzheimer's disease (AD), and vascular dementia (VaD). Search terms related to the predictor side were: hypertension, hypotension, orthostatic hypertension, orthostatic hypotension, high blood pressure (BP), low BP, pulse pressure, pulse

Catell Culture Fair Intelligence Test ⟶ General Intelligence ⟶ Unified Brain

Stroop Color Test
Category Word Fluency
Wisconsin Card Sorting
Trails B-A
⟶ *Executive Functioning (EF)* ⟶ Pre-Frontal/Frontal

WAIS Matrix Reasoning
WAIS Block Design
WAIS Object Assembly
Hooper Visual Organization
WMS Visual Memory
⟶ *Visual Memory, Construction and Organization and Integration* ⟶ Parietal
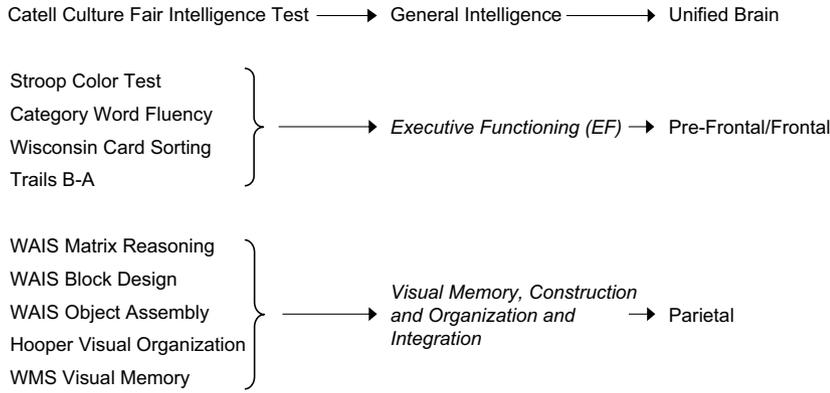
Figure 1. In this hypothetical example, objective scores on tests are used to index theoretical constructs that are in turn used as a basis for inferences about brain function. In this example, only 1 brain area other than the prefrontal/frontal is being considered. Test details may be found in Lezak et al.[11] WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale.

wave velocity, augmentation index, central BP, and antihypertensive medication/drug/treatments. Additional qualifying papers were obtained by reading papers identified by these searches. Clinical trials of antihypertensive medications and lifestyle changes were included in the counts of research papers, as were nontrial studies comparing antihypertensive medications with respect to cognitive performance.

For the papers published in *Hypertension* we used the same search methods but also obtained a record of published papers from *Hypertension* staff. In this brief historical outline, we discuss some papers that relate hypertension/BP to structural and functional change in the brain, but that did not include cognitive measures. These papers were not included in the counts on Figure 2. We searched published articles between 1900 and 2011. We then used each article retrieved to trace back to the first published article on the topic and to find additional papers. Case studies were not included in the counts, and counts were not based on judgments as to adequate controls.

Growth in Publications
Figure 2 shows the growth in peer review publications beginning in 1962. There was slow initial growth and then, beginning

in 1997, a dramatic rise in published articles. Of the 683 papers included in Figure 2, 88 used dementia as a sole outcome and the balance used cognitive functioning, including or excluding dementia. The growth in publications on cognitive performance parallels the growth of publications in science, including hypertension research in general.[1] This profile rise in publications in general was paralleled by *Hypertension* (not shown) after a later beginning (1982). The lag reflects the fact that much of the earlier literature was published in psychology, neurology, and gerontology journals. Publication in journals on hypertension was important with respect to attracting the attention of the medical community to research on hypertension and cognitive functioning.

Milestone Events and Periods
Kotchen[1] compiled a list of noteworthy discoveries, authors, and papers in hypertension research using as a criterion recipients of the Annual Council for High Blood Pressure Awards. This was not possible for our purposes because hypertension-cognition research is multidisciplinary. No single organization gives awards for research on hypertension with this focus. Conse-
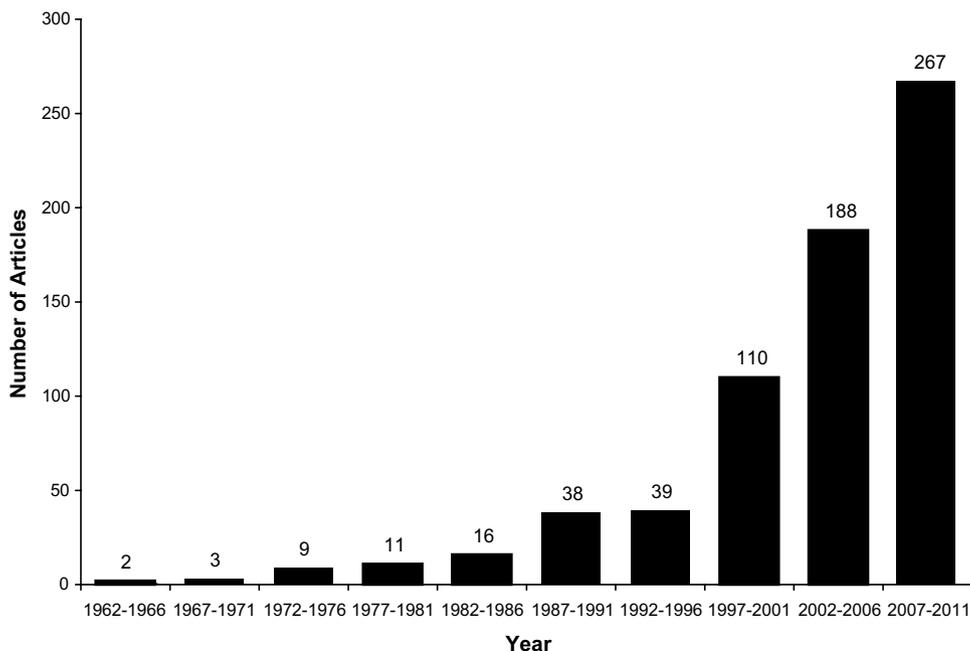
Figure 2. Estimated number of published papers (including clinical trials) on hypertension and cognitive function appearing in the literature between 1962 and 2011.

quently, we identify milestone events within research periods in terms of major research emphases during that period. Dates are approximate and the work beginning in one period continues into the next. The papers we cite are illustrative of research trends. Exclusion of published papers does not indicate that they are of secondary importance.

The Null Period (Pre-1928)

Hypertension was first measured in 1733.[1] The search for causes of hypertension was well underway by 1844,[1] but there was little specific concern about hypertension and cognition until 1928. Even then studies were observational and concerned with the brain.

Clinical Observation Period (1928–1947)

Observation in the clinic focused on hypertension as a possible reason for changes in brain structure and function in persons who came to clinics or hospitals with overt cognitive and psychiatric impairments and relatively high levels of sustained, untreated hypertension. Kotchen uses the term *therapeutic nihilism*[1] (p. 527) to describe attitudes toward treatment at this time. First-generation drugs were available, but despite mounting evidence that hypertension was related to risk of stroke and heart disease, there was a prevailing reservation about treating hypertension. Kotchen notes that in 1931, "Paul Dudley White, an eminent Boston cardiologist, wrote that hypertension may be an important compensatory mechanism which should not be tampered with, even where it is certain that we could control it"[1] (p. 527). In 1931, Hay wrote in the *British Medical Journal* that "the greatest danger to a man with high blood pressure lies in its discovery, because some fool is certain to try to reduce it"[1] (p. 527).

Clinical Case Study Period (1947–1962)

The first case studies on hypertension and cognitive functioning began circa 1947, at about the time when Page introduced "'mosaic theory' to explain the etiology of hypertension"[1] (p. 525). These studies involved blind clinical neuropsychological evaluation of small numbers of patients (eg, n=14)[16] with very high uncontrolled BP (157–202 mmHg systolic and 99–130 mmHg diastolic),[17] and symptoms of brain damage. Following several studies indirectly related to hypertension,[2] Apter et al[16] in 1951 and Reitan[17] in 1954 published several pioneering papers. They concluded that their hypertensive patients performed in a manner similar to brain-damaged individuals, particularly persons with EF disabilities, ie, the patients demonstrated an inability to integrate, organize, problem solve, and engage in meaningful and thoughtful action. Obviously this description mischaracterizes the cognitive functioning of hypertensive individuals typically seen in the office or clinic today. Indeed, subsequent work in 1987[18] found no evidence of clinically significant cognitive impairment in persons manifesting uncomplicated primary hypertension. This is a generally agreed on conclusion in reviews of this literature.[2–5,7]

Descriptive Study Period (1962–1972)

The first widely cited case-control study of hypertension and cognitive functioning was published in 1964.[19] Spieth reported that, compared to their normotensive counterparts

(n=560), hypertensive commercial air traffic controllers and aircraft pilots (n=17) performed at a lower level on multiple measures of speed of performance. There was some research indirectly related to hypertension done prior to this period,[2] but it was not focused on hypertension specifically. Spieth[19] concluded that the differences observed between cases and controls could be due to stress related to license recertification rather than brain injury. This caveat represents an early awareness that factors other than biological phenomena can explain relations between hypertension and cognitive ability, and that confounding by stress, anxiety, depression, and psychosocial variables are more likely to occur when hypertensive individuals are aware of their diagnosis and these confounders are not controlled.[2,7,8,20]

Possibly the event with the greatest impact on this period and the following decade of work was the publication of the Duke University Longitudinal Study of Hypertension in *Science* in 1971 by Wilkie and Eisdorfer.[21] The sample was small (total N=202), all subjects were being treated and controls for hypertension-related comorbidity and risk factors widely used in current research were not used. For persons 60 to 69 years of age at baseline, a major hypertension-associated longitudinal decline in Wechsler Adult Intelligence Scale (WAIS) Performance Scaled Scores was observed over 10 years. Hypertension was defined as diastolic BP >105 mmHg which is equivalent to Stage 2 hypertension by current definitions. In contrast, there was a trivial and nonsignificant decline in WAIS Performance Scaled Scores for study participants who exhibited "normal" BP, diastolic BP <95 mmHg. Change over 10 years was examined for subjects 70 to 79 years of age, but none of the Stage 2 hypertensive individuals returned to be tested after the 10-year follow-up. The first elements of the findings and methodological issues with longitudinal research were seen in this study. The hypertensive individuals showed decline on measures of fluid intellect, ie, solving of novel problems and tests of visual-spatial organization and constructional abilities under time constraints,[21] but subject attrition from baseline was observed for the poorest performing individuals in the poorest cardiovascular health. Findings reported for "borderline hypertension" were not replicated in later research with better controls[2] and thus are not described.

Wilkie and Eisdorfer explained longitudinal decline for the Stage 2 hypertensive group in terms of cerebral ischemia and resulting hypoperfusion. Five years later (1976) Hagberg and Ingvar[22] reported that reduction in cognitive performance in dementia was associated with abnormalities in CBF, and it is now clear that regional CBF studies are central to the studies of blood flow mechanisms intervening between hypertension and performance deficits.[3,23,24]

Both systolic and diastolic BP mmHg were inversely associated with levels of performance on WAIS Performance Scale subtests and positively related to the amount of decline in these scores over 10 years. Consequently, a dose-response-relation between BP and cognitive performance, important for arguments with regard to causal associations, was established. Associations between higher BP and lower cognitive functioning were observed in many of the studies that followed over the years and these relations were robust when

adjusted for age, multiple other demographic factors, and hypertension-associated risk factors and comorbidity.[5,25,26–30]

The use of hypertension diagnostic categories and BP as predictor variables has been very important for the continuity of research in this area because cut values defining hypertension have progressively declined over the years. The emphasis on the diagnostic importance of BP has swung from diastolic to systolic BP and finally to a recognition of the importance of both measures.[31] In general, both have been related to cognitive functioning in the cognitive literature regardless of age at the time of BP assessment.[5,25,27] The importance of the Duke Longitudinal Study[21] was its originality and the fact that it stimulated many of the cross-sectional and longitudinal studies that followed. For example, in 1975 baseline data collection in the Maine Syracuse Longitudinal Study (MSLS) of hypertension and cognitive performance[2,28,29] began as a direct response to the Duke study.[21] Longitudinal MSLS data resulting from 2 very long follow-up periods, 14[28] and 19 years,[29] are summarized in a section on longitudinal studies which follows after our synopsis of the cross-sectional period of study.

Descriptive-Cross-Sectional Period (1973–1982)

After the Duke study, longitudinal data on cognitive performance did not appear again in the literature for 15 years. Published studies were predominantly cross-sectional,[2–7,15,25] and 3 research emphases were dominant: (1) descriptive studies designed to improve controls, ie, exclusion, adjustment for confounders, and sensitivity analyses; (2) further examination of age by hypertension interactions with regard to cognitive performance in young and middle-aged adults; and (3) determination of which specific cognitive abilities are vulnerable to hypertension. A majority of reports indicated that relations between hypertension/BP and cognition were robust regardless of additional controls.[5] It became clear that associations between hypertension/BP and cognition were seen for older as well as younger adults and that parental history of hypertension was a risk factor for poorer cognitive performance.[5]

Waldstein's argument for more attention to be paid to hypertension and cognition in young adults and children was reinforced by papers and reviews appearing between 2002 and 2010 that described deficits in attention and EF, among other cognitive abilities, in young children and adolescents,[32] and the adverse consequences of hypertension for the developing brain.[33]

With respect to hypertension-related cognitive abilities, the cross-sectional literature indicated hypertension/BP-associated performance deficits on psychometric tests measuring fluid intelligence, EF, learning and memory, attention, perceptual-motor skills, psychomotor speed, motor function, and visual-spatial-organizational skills with sparing of well-practiced verbal abilities such as information and vocabulary skills (crystallized ability) in nondemented individuals.[5,7,8] EF has been singled out as particularly vulnerable to hypertension and rise in BP in some studies,[4,14] but it is quite clear that EF is difficult to separate from fluid intelligence.[13]

In almost all studies there are significant individual differences in performance levels,[30] and cognitive deficits do not rise

to clinically significant cognitive impairment in uncomplicated primary hypertension.[2,18,34] This may seem inconsistent with findings of neurobiological changes in the brain based on positron emission tomography (PET), MRI and CBF, but it must be recognized that the compensatory capability of the brain and the individual is significant[12] as is indicated by recent regional CBF studies by Jennings et al.[24] The next time period marked a move from cross-sectional work to prospective designs with large community-based samples.

Prospective and Population Studies (1982–1996)

The Framingham Heart Study (FHS) began in 1950. The first FHS data on hypertension and cognition appeared in 1987.[35] This large-sample study (n=2132) by Farmer and colleagues[35] generated considerable attention because it reported no associations between BP and multiple measures of cognitive performance in persons 59 to 89 years of age. These negative findings were challenged because only one or two BP measurements were taken concurrently with the assessment of cognitive function.[36] In a second FHS study[37] with subjects of the same age, but stroke excluded (n=1993), BP was measured over a 26-year period that overlapped with the measurement of cognitive performance. Statistically significant inverse associations between BP and cognition were now observed and the longer the exposure to hypertension, the lower the cognitive performance. Given a significant graded relation between level of cognitive deficit and the probability of being on medication at the time of cognitive testing, Farmer et al[37] suggested that cognitive deficit may have been associated with reduced adherence to drug treatment regimens rather than subvascular disease.

This conclusion was challenged in a 1993 paper[36] by Elias et al who used the FHS sample using a prospective design and reaching back to a point in time when relatively fewer cases of hypertension were treated.[1] In the most important of 3 analyses, the independent variables were untreated systolic and diastolic BP averaged over the first 8 FHS biennial examinations (1950–1964) for a subsample of 1485 individuals with 18% defined as hypertensive (BP ≥160/95 mm Hg). BP ranged from 95 to 193 mm Hg systolic and 56 to 115 mm Hg diastolic. Averaged BP values were related to cognitive performance measured once 14 or 15 years after the BP surveillance period when participants were 55 to 88 years of age (1976–1978). The outcome variables, 8 cognitive test scores, were expressed in standardized (z) scores so that test results could be directly compared across tests. With exclusion of persons with acute stroke and adjustment for age, education, occupation, sex, alcohol consumption, and cigarette smoking, untreated systolic and diastolic BP values averaged over this 1950 to 1964 surveillance period were linearly and inversely associated with performance level, including scores on the composite of all cognitive performance levels and tests of episodic verbal memory-immediate recall, episodic verbal memory-delayed recall, working memory, and visual memory. The mean and standard deviation (SD) for the distribution of z scores were 0 and 1, respectively, and regression coefficients were expressed in SD units. Compared to participants with normal BP, the untreated

hypertensive individuals performed 0.15 SD lower on the composite score ($\beta = -0.15$), and deficits ranged between 0.25 ($\beta = -0.25$) and 0.18 ($\beta = -0.18$) for the various measures of memory with the lowest performance on episodic verbal memory-immediate recall.

Although a prospective relation between BP and cognitive performance was observed, it could be argued that events during the 12- to 14-year interval between BP surveillance and measurement of cognitive performance could have influenced the cognitive findings. Consequently, the analysis was repeated with a smaller sample (n=1038; 7.5% hypertensive) that remained untreated from the beginning of the FHS (1950) through the neuropsychological examination period (1976–1978). Again, linear inverse associations were observed for systolic and diastolic BP averaged over the 15 biennial examinations and cognitive performance at a single occasion between examinations 14 or 15.

In a reanalysis of these data, poor performance was defined as a score in the lower 50th percentile of the distribution of test scores and risk of poor performance for each 10 mm Hg in diastolic BP was estimated. Each 10 mm Hg increment in diastolic BP was associated with a risk increment between 13% (OR, 1.13) and 14% (OR, 1.14) for the 4 memory tests. Similar results were obtained for systolic BP. In a further analysis, the never-treated hypertensive cohort was compared to the normal BP cohort. The hypertensive group was at 41% to 53% higher risk for poor performance across the episodic and visual memory tests.[25] The results cannot be explained in terms of nonadherence to antihypertensive medications. None of the hypertensive participants were treated and none had a treatment history when admitted to the study 26 to 28 years earlier.

The work with the FHS was followed by studies of midlife BP and late-life cognitive performance and dementia[38–40] using the Honolulu-Asia Aging Study population. Midlife BP was associated with lower cognitive performance and dementia assessed on 1 occasion later in life. In the dementia study with 3703 Japanese-American men, the risk of dementia was higher (OR, 4.8; 95% CI, 2.00–11.00), when subjects with systolic BP ≥160 mm Hg were compared to a reference group of persons with systolic BP of 110 to 139 mm Hg.[40]

These and other prospective studies[2,5,25,41] allow 4 generalizations: (1) relations between hypertension and cognition are seen when exposure to hypertension in various studies precedes the outcome by 10 to 20 years;[2,25,38–41] (2) length of exposure to hypertension is positively associated with the magnitude of cognitive deficit; (3) lower cognitive performance cannot be explained away as a phenomenon related to treatment with antihypertensive medications; and (4) relationships between hypertension and cognitive impairment are stronger in untreated persons. The limitation in a number of the studies summarized above was that cognitive performance and dementia were assessed only once after the prospective surveillance period, but a number of longitudinal studies of cognition that followed combined prospective designs (BP and hypertension) with longitudinal analysis of change over time.[28,29]

Expanding Knowledge and Improved Methods (1996–2011)

There were many new developments between 1996 and 2011, including studies relating higher pulse wave velocity (a gold standard index of arterial stiffness) to accelerated longitudinal decline in cognitive performance scores, eg.[42] We focus on what we consider to be the most important research trends among many other research advances during this period of time.[6,20,22–25]

New Effect Modifiers

Age has been a target of research on effect modifiers of the BP-cognition relationship since the Duke Longitudinal Study. A concern for other cardiovascular disease (CVD) risk factors that might modify relations between hypertension and cognitive functioning began in 1997 with the finding of significant multiplicative interactions between hypertension/BP and diabetes mellitus in the FHS.[26] The combined presence of these risk factors was associated with lower cognitive performance than the presence of either alone. The same effect modification result was reported in an FHS study of hypertension, obesity, and cognitive performance where the statistical effects of these risk factors were additive.[43] Additive and interactive risk factor effects have been seen in many studies involving other CVD risk factors, including ApoE-$\varepsilon 4$ genotype.[44] Clearly hypertension plays a role in concert with other major CVD risk factors in the association between metabolic syndrome and cognitive performance.[44]

In the Kungsholmen study of APOE, antihypertensive medications served as modifiers of other important risk factors for dementia.[45] Compared with the presence of the $\varepsilon 3/\varepsilon 3$ allele, presence of 1 or 2 APOE-$\varepsilon 4$ alleles increased the risk of developing dementia, risk ratio (RR), 1.5; 95% CI, 1.1 to 2.1. For hypertensive individuals not using antihypertensive medications, the relative risk of dementia for APOE-$\varepsilon 4$ carriers was raised (RR, 2.2; 95% CI, 1.4–3.4), but antihypertensive treatment was protective (RR, 0.9; 95% CI=, 0.5–1.6). The same pattern of results was observed when AD was the outcome variable.

Mechanisms and Brain Regions

A continued expanding interest in mechanisms was accompanied by a major trend away from emphasis on the special vulnerability of the prefrontal-brain regions to BP extremes,[4,14] to a focus on structural and functional change over a wide range of brain regions, ie, brain regions affected by hypertension.[46] Jagust et al,[23] Jennings et al,[3] Raz et al,[14] and Manolio et al[4] provide reviews of the brain mechanism and brain region literature in more depth than is possible here. Studies by Kochunov et al[47] and Gunstad et al[48] illustrate a renewed interest in genetic mechanism as intervening between BP and cognitive functioning.

Longitudinal Studies

Improvement in longitudinal methods may have been one of the most important methodological advances in this time period. Beginning in the mid-1980s, a wave of "post-Duke" longitudinal studies of cognitive performance with 2 times of measurement designs appeared in the literature,[2,5,7,8,20] but

Table 1.   Longitudinal Studies With Three or More Examinations*

Study	Age at Baseline	No. of Examinations	Result	Outcome Improving, Declining, or No Change If Not Significant Change	Study Sample
Skoog et al (1996)[55]	70	Baseline+3 ages groups with dementia over 15 y	Higher BP at age 70 was a risk factor for dementia at age 79–85 y	BP related risk for dementia was seen for persons over 79 y of age	Göteborg (Sweden) Longitudinal/n=382
Elias MF et al (1998)[28]	40–70	3 over 18 y	Individuals with higher BP at baseline and over the entire study period showed more decline in fluid cognitive performance measures over time	Visualization/Fluid Subtests of the WAIS	Maine Syracuse Longitudinal Study/n=150
Swan et al (1998)[50]	39–59	At least 10 exams over 20–30 y	Persons who maintained elevated BP over the 20–30 y tracking period were at higher risk for lower performance levels	Verbal Learning and Memory Function on the Iowa Screening Battery	Western Collaborative Group Study/n=717
Hassing et al (2004)[56]	Mean=83 (SD=2.3)	4 exams over 8 y	Diabetes related to decline- not hypertension, but greatest decline for both diabetic and hypertensive groups	Mental Status Evaluation with MMSE	Origins of Variance in the Old-Old Study/n=258
Elias PK et al (2004)[29]	18–47 47–83	2–5 examinations over 19 y	Higher levels of baseline systolic and diastolic BP and hypertension related to longitudinal decline in a composite of fluid ability scores but not crystallized ability	A composite of fluid ability measures from the WAIS including visualization spatial ability	Maine Syracuse Longitudinal Study/n=529
Hebert et al (2004)[57]	≥65	4 exams over 7 y	No hypertension-associated decline	3-brief form tests of the MMSE	Biracial Study Chicago/n=428
Insel et al (2005)[51]	≥65	4 exams over 7 y	Increasing BP (19 mm Hg systolic) related to decline in performance in normal BP group	MMSE and the clock drawing test	Hispanic Established Population for Epidemiologic Study for the Elderly/n=2859
Waldstein et al (2005)[49]	Mean=70.6 (SD=8.3)	1 to 7 exams over 10 y	U-shaped relation between BP and decline	Multiple cognitive abilities	Baltimore Longitudinal Study/n=847
Kuo et al (2005)[52]	65–94	3 annual exams over 3 y	Hypertension associated with more rapid cognitive decline over time, logical reasoning ability	Logical reasoning interpreted as measuring executive functioning	Advanced Cognitive Training for Independent and Vital Elderly trial/n=2802
Hajjar et al (2005)[53]	76.8 (0.03)	1 to 58 mo	Nondemented and demented status at baseline—antihypertensive medications were associated with lower rate of decrement over time for MMSE and measures of executive functioning	MMSE and measures of executive functioning	Hispanic Established Population Study of the Elderly/n=258
Knopman et al (2009)[54]	45–64	4 cognitive assessments over 14 y beginning in 1990–1992 and 2004–2006	Hypertension associated with cognitive decline	Word fluency delayed (executive function), word recall and digit symbol substitution for both groups	ARIC cohort/n=1130

*Other incident dementia studies are cited in text. Skoog et al[55] are cited in the table because there was a follow-up with 3 distinct age groups.

BP indicates blood pressure; MMSE, Mini-Mental State Examination; WAIS, Wechsler Adult Intelligence Scale.

this design does not allow the examination of possible nonlinear change in cognitive performance over time.[49] A pivotal set of longitudinal studies (Table) with at least 3 times (waves) of measurement began to appear in 1996.[2] In 9[28,29,49–55] of these 11[28,29,49–57] studies, hypertension and/or increments in BP (systolic, diastolic, or MAP) were statistically significant predictors of progressive decline in performance (linear and nonlinear) over time. This was true for predictions of decline in cognitive function from baseline BP (systolic and diastolic) and hypertension where follow-up of cognitive functioning ranged from a total of 3[52] to 30 years.[50] The hypertension and BP-associated decline in cognitive performance reported in these studies (Table) was seen with control for stroke, dementia, CVD risk factors, comorbidity, and antihypertensive treatment. Controls (including for treatment) involved exclusion, stratification, and statistical adjustment depending on the specific study.

The cognitive domains for which decline was reported paralleled those identified in cross-sectional work, ie, global performance and multiple specific cognitive abilities with the exception of overlearned and well-practiced verbal abilities (crystallized ability).[2,5,25] Concern for at least 3 times of serial measurement is reinforced by the Baltimore Longitudinal Study of Aging.[49] Waldstein and colleagues reported nonlinear relations between hypertension/BP and cognitive performance and a J-shaped relation between BP and performance,[49] thus confirming the importance of studies with more than 2 times of measurement.

The longitudinal study by Skoog et al[55] was particularly important to a swing from an emphasis on hypertension in VaD to a recognition of its importance in AD. In 1983, St. Clair and Whalley[58] published their now classic paper on the importance of hypertension in multi-infarct disease. At this time the presence of vascular disease, including hypertension, was an exclusion for the diagnosis of AD.[59] A study by Skoog et al[55] in 1996 and a second by Hoffman et al[60] in 1997 with the Rotterdam sample played pivotal roles in revisions of the recognition of hypertension and associated CVD risk factors as important predictors of AD. Skoog et al[55] followed 382 participants free from dementia at age 70 through the age intervals of 70 to 75, 75 to 79, and 79 to 85. Those who developed dementia from age 70 to 85 years exhibited higher systolic BP and diastolic BP at age 70. In 10 of the 18 participants who developed dementia between 79 and 85, high BP at age 70 was associated with AD. In the Rotterdam study (n=1982) published 1 year later, indices of atherosclerosis, including ankle-brachial systolic BP levels, were associated with VaD and AD.[60] Moreover, the prevalence of each increased with the severity of atherosclerotic disease. These studies had a significant impact on revision of definition of VaD[59] and recognition of the importance of hypertension in AD.

Although changes in cognitive performance over time and dementia have been studied longitudinally, there has been much less work on clinically recognized cognitive impairment that falls short of dementia. In 2007, Reitz et al[61] addressed the question of whether the risk of MCI is increased by hypertension. Baseline data were obtained for 918 individuals (mean age=76 years) between 1992 and 1994 and followed by data collection at the following periods: 1994 to 1996; 1996 to 1997; 1997 to 1999. During the longitudinal surveillance period, 160 cases of amnestic MCI and 174 cases of nonamnestic MCI were diagnosed. Hypertension was associated with increased risk of all-cause MCI (hazard ratio, 1.40; 95% CI, 1.06 to 1.77) and nonamnesic MCI (hazard ratio, 1.70; 95% CI, 1.13 to 2.42), after adjusting for age and sex and remained similar with additional adjustment for education and APOE-ε4 genotype. These associations were modestly attenuated when adjusted for stroke, diabetes, LDL cholesterol, smoking or heart disease, and use of antihypertensive medications. Alcohol consumption and depressed mood were not included in the covariate sets. After adjusting for stroke and other CVD risk factors there was no significant association between hypertension and amnestic MCI.

Four years later, using the Canadian Study of Health and Aging study population, Oveisgharan and colleagues,[62] using 2 waves of assessment (1991, 1991–1996), examined incident dementia for 990 elderly (mean age=83 years at baseline) participants defined as cognitively impaired but no dementia. No association between hypertension and progression to dementia was found for participants with memory dysfunction alone or in combination with executive dysfunction. However, among subjects with executive dysfunction alone, 58% with hypertension, as compared to 28% with normal BP, progressed to dementia. The authors speculated that control of hypertension might prevent progression to dementia in one-third of individuals with cognitive impairment but no dementia. Clinical trials are needed to verify this conclusion but taken together the studies are pivotal with regard to studying hypertension-related change in cognitive performance as it progresses from nonclinical deficit, to MCI, and then to dementia.

Randomized to Treatment and Placebo Clinical Trials

Excluding trials with no placebo and crossover designs, the first clinical trials designed for the dual purpose of lowering BP and improving cognitive performance using a battery of psychometric test scores were seen in 1996. In a trial published by the Medical Research Council in older adults (65–75 years),[63] participants were randomly assigned to diuretic (hydrochlorothiazide plus amiloride), beta blocker (atenolol), or placebo arms. For a period of 54 months, 2584 participants were administered a battery of 4 psychometric tests. No statistically significant differences among active arms were observed. However, a follow-up of 387 surviving participants for 9 to 12 years indicated that less decline in systolic BP was associated with poorer cognitive performance on multiple cognitive performance tests with adjust-

ment for family history of dementia, cognitive performance at baseline, age, and alcohol consumption.[64]

The first large sample (n=4736; mean age 72 years) randomized to treatment and placebo clinical trials with a dementia outcome, the Systolic Hypertension in the Elderly Program (SHEP), was published in 1994.[65] Active treatment with a diuretic (Chlorthalidone), and addition of Atenolol or Reserpine if necessary to achieve BP lowering goals, had no statistically significant effect on incident dementia. The SHEP study was followed by the double-blind placebo controlled Syst-Eur study with 2418 participants (mean age=70).[66] Active treatment consisted of the dihydropyridine calcium channel blocker nitrendipine, which could be combined with enalapril, hydrochlorothiazide, or both to achieve BP control. This trial was terminated after a median of 2 years because active treatment was associated with a 42% decrease in fatal and nonfatal stroke. Active treatment reduced diastolic BP by 3.8 mmHg, systolic BP by 8.3 mmHg and incident dementia by 50%, from 7.7 to 3.8 dementia cases per 1000 patient years ($P=0.05$). After termination of the trial, all of the participants were offered open label treatment with the same active medication, thus lengthening follow-up to 3.9 years and increasing the number of AD cases from 32 to 64.[67] Immediate versus delayed antihypertensive therapy reduced the risk of dementia by 55%, and from 7.4 to 3.3 cases per 1000 patient years ($P<0.05$). Recent meta-analyses place positive results for these studies in the context of multiple studies that followed. For example, a 2007 meta-analysis, including 4 placebo-controlled trials for prevention of dementia, SHEP, Syst-Eur, PROGRESS, and SCOPE, reported a common OR of 0.89 (95% CI, 0.75–1.04; $P=0.15$).[7] In 2011 the meta analysis was updated and included ADVANCE, HYVET-COG, PRoFESS, and TRANSCEND trials.[68] In all trials combined there was no significant reduction in risk of dementia (approximately 5%), but for trials involving a diuretic or dihydropyridine calcium channel blocker as part of treatment, the reduction was significant (approximately 18%). Authors of the 2011 meta-analysis point out that differences between drug classes may be explained by the amount of BP reduction. Weighted meta-regression analysis indicted that lowering of systolic BP accounted for 41% of the variance in risk reduction. It is clear from these studies and other meta-analyses and reviews of the literature[69] that the issue of whether BP lowering with antihypertensive medications improves cognitive performance or decreases the risk of dementia has not been resolved.

Trials of Nondrug Therapies

A small trial by Smith et al[70] provides preliminary evidence that a combination of structured diet, exercise, and counseling, compared to treatment as usual, lowers BP and is associated with a parallel modest improvement in cognitive performance in younger and middle-aged adults presenting with either prehypertension BP values or modestly elevated BP values.[70]

Translation and Perspectives

The literature on hypertension and cognition strongly supports the need to treat hypertension early and aggressively, ie,

the brain is a target organ for hypertension and once morphological and functional changes have begun, restoration of cognitive functioning may be more difficult.[3] Lowered cognitive performance has serious implications for quality of life and healthcare costs at all ages. Sustaining one's level of cognitive performance over the lifespan may be an important motivation for patients to engage in preventive measures and adherence to drug treatment protocols. Results of clinical trials of antihypertensive medications are mixed. Positive changes in performance are modest when reported, but the progress of dementia has been slowed in a few major trials. The modest results obtained must be considered in relation to the fact that hypertension works its influence on cognitive performance in concert with other CVD risk factors,[44] and trials are conducted for relatively short periods of time relative to the long period of time involved in the progression from hypertension to dementia.

The termination of trials once BP lowering goals are reached does not allow the opportunity to examine success rates for cognitive restoration over longer and more meaningful periods of time, albeit ethical issue concerns do require a more sophisticated design. Clearly, adding a limited cognitive test battery in a study designed primarily to examine BP lowering is insufficient. The meta-analyses and reviews suggest the need to focus more on specific antihypertensive medications and drug classes in future studies, and to consider the extent to which medications lower BP.[6,68,70] Cognition must take on more importance as a hypertension-related outcome given the dramatic rise in prevalence and incidence of dementia projected for developed and developing countries.[68]

History teaches us that hypertension-related cognitive impairment is not a problem of old age, but a problem at all ages. There is a legitimate concern for initiating antihypertensive therapy in young adults who then must face a lifetime of treatment with antihypertensive medication. Preliminary studies indicate that structured diet and exercise programs may be effective in lowering mild and prehypertensive BP values and improving cognitive performance[70]; major clinical trials of lifestyle interventions are needed. *Sine remediis medicina debilis est.* Without remedies medicine is powerless.

Disclosures

Acknowledgments

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ONLINE SUPPLEMENT

HYPERTENSION AND COGNITIVE FUNCTIONING: A PERSPECTIVE IN
HISTORICAL CONTEXT

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Short Title: Historical Context of Hypertension and Cognition

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