

RESEARCH ARTICLE

Higher systolic blood pressure in early-mid adulthood is associated with poorer cognitive performance in those with a dominantly inherited Alzheimer's disease mutation but not in non-carriers. Results from the DIAN study

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Abstract

BACKGROUND: The Dominantly Inherited Alzheimer Network (DIAN) is a longitudinal observational study that collects data on cognition, blood pressure (BP), and other variables from autosomal-dominant Alzheimer's disease mutation carriers (MCs) and non-carrier (NC) family members in early to mid-adulthood, providing a unique opportunity to evaluate BP and cognition relationships in these populations.

METHOD: We examined cross-sectional and longitudinal relationships between systolic and diastolic BP and cognition in DIAN MC and NC.

RESULTS: Data were available from 528 participants, who had a mean age of 38 (SD = 11) and were 42% male and 61% MCs, at a median follow-up of 2 years. Linear-multilevel models found only cross-sectional associations in the MC group between higher systolic BP and poorer performance on language ($\beta = -0.181 [-0.318, -0.044]$), episodic memory ($-0.212 [-0.375, -0.049]$), and a composite cognitive measure ($-0.146 [-0.276, -0.015]$). In NCs, the relationship was cross-sectional only and present for language alone.

DISCUSSION: Higher systolic BP was cross-sectionally but not longitudinally associated with poorer cognition, particularly in MCs. BP may influence cognition gradually, but further longitudinal research is needed.

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KEYWORDS

autosomal-dominant Alzheimer's disease, blood pressure, cognition

1 | BACKGROUND

Our understanding of dementia risk factors has expanded enormously over the last three decades.¹ Dementia can have a long prodromal phase. Consequently, a life-course understanding of dementia risk factors is needed. One of the leading modifiable risk factors for dementia is elevated blood pressure. Higher systolic blood pressure (SBP) in midlife is recognized as a risk factor for later cognitive decline and dementia. In later life, both higher and lower blood pressure have been associated with dementia risk.^{2,3} In earlier life, data are lacking. However, emerging evidence suggests that higher blood pressure in childhood, adolescence, and early adulthood (especially sustained or cumulative exposure to higher blood pressures) may increase the risk of poorer cognitive performance, particularly poorer executive function and memory.^{4–7}

Emerging data also show the potential for modifiable risk factors, such as higher blood pressure, impacting cognition or earlier age of dementia onset in those with young-onset dementia.^{8,9} However, the evidence for the role of raised blood pressure in this population is mixed. For example, higher blood pressure occurring more than 10 to 20 years before dementia diagnosis has been associated with early-onset dementia in an Australian case-control study population and a Swedish conscript population.^{8,10} Conversely, studies in self-reported early-onset Alzheimer's disease (AD)¹¹ or autosomal-dominant AD (ADAD)¹² have found no relationship between raised blood pressure and decline in domains of language, memory, executive function, or general cognition.

Understanding the relationship between blood pressure and cognition in early to midadult life and in an ADAD population is particularly important when we consider that the treatment of raised blood pressure in middle to late life may reduce the risk of later dementia.^{2,13} Additionally, antihypertensive drugs are safe and widely available.

We investigated the relationship between SBP and diastolic blood pressure (DBP), cumulative blood pressure, and cognition in an early adult to midlife population with separate analyses of those who have a genetic mutation causing them to develop ADAD and those without, but where these populations are drawn from the same environment. The Dominantly Inherited Alzheimer Network (DIAN) observational study population provides this vital and unique opportunity.

2 | METHODS

The DIAN observational study is a longitudinal cohort study established in 2008 that includes asymptomatic and symptomatic individ-

uals who have a parent or sibling with ADAD caused by a mutation in either the *PSEN1*, *PSEN2*, or *APP* genes and who can be classified as either ADAD mutation carriers (MCs) or non-carrier (NC) family members.¹⁴ Genotype confirmation of mutation status is undertaken; however, some participants and all investigators carrying out the assessments remain blind to mutation status. Study participants receive regular assessment by trained investigators, including blood and cerebrospinal fluid (CSF) sampling, the Clinical Dementia Rating (CDR), and cognitive assessment based on the Alzheimer's Disease Research Center (ADRC) Uniform Data Set.^{15,16} Longitudinal data are collected approximately every 3 years, rising to annual assessment on symptom onset or when the study participant is within 3 years of the age at which their parent began to show symptoms. Estimated years to onset (EYO) provide a way to evaluate the relationship between factors such as blood pressure and cognition in the context of the disease timeline. EYO are calculated using chronological age at study visit minus the mean age of decline for symptomatic individuals or minus the predicted age of decline based on the family mutation/parental age of symptom onset for asymptomatic individuals. They range from negative, that is, anticipated future onset, to positive, that is, past the age at which onset would have been expected.

2.1 | Neuropsychological assessment

Cognitive function was assessed using the ADRC Uniform Data Set, Neuropsychological Test Battery.¹⁷ The battery used in these analyses included 10 main tests: Forward Digit Span, Reverse Digit Span, Wechsler Adult Intelligence Scale-Revised (specifically the digit symbol substitution test), Trail Making Test Part A, Trail Making Test Part B, Logical Memory Story A, Immediate Recall and Delayed Recall, Animal List Generation, Vegetable List Generation, and the Boston Naming Test.¹⁸ Raw scores were first demographically corrected for age, sex, and education using published norms and transformed into z-scores.¹⁹ Next, cognitive domain z-scores were computed by averaging individual test z-scores: for the episodic memory domain, this used the Logical Memory Story A Immediate Recall and Delayed Recall tests; for the language domain score, Animal List Generation, Vegetable List Generation, and Boston Naming tests; the attention or working memory domain included the Forward and Reverse Digit Span tests; and finally for the executive function domain score the Trail Making Test A, Test B, and Symbol Digit Substitution Test. Finally, a composite cognitive z-score was computed by taking the average of the four cognitive domain z-scores.

RESEARCH IN CONTEXT

1. **Systematic Review:** We reviewed the available literature through traditional sources (e.g., PubMed). Most of the studies on blood pressure and cognitive function are in middle to late life or in general populations. There is also a limited literature on blood pressure and early-onset dementia.
2. **Interpretation:** Our findings point to the potential importance of blood pressure for cognition in early to middle adulthood and particularly in an autosomal-dominant Alzheimer's disease population. However, the role of blood pressure in cognitive change over time remains unclear.
3. **Future Directions:** Our findings highlight a need for further longitudinal data to evaluate the relationship between blood pressure and cognitive change in early to midlife and in mutation carrier (MC) and non-carrier (NC) populations.

2.2 | Blood pressure measures

SBP and DBP were measured at each visit in accordance with local practice. Since even blood pressures classified as comparatively low by today's treatment standards may be associated with an increased risk of cardiovascular events, stroke, and poorer cognition, blood pressure measures were used as continuous variables. Furthermore, there is, as yet, no clear blood pressure threshold above which risk of cognitive decline or dementia begins to be incurred.²⁰ Blood pressure measures in mmHg were used in three ways, one cross-sectional and two longitudinal. These were (1) at baseline, to examine the relationship between baseline blood pressure and baseline cognitive function; (2) to examine the relationship between average blood pressure and cognitive function over time; and (3) between cumulative exposure to blood pressure and change in cognitive function over follow-up (following recent work that suggests that cumulative exposure, similar to calculating "pack years" for smoking, may be a better way of evaluating blood pressure impact).^{4,21} Cumulative or "summed exposure" was estimated in those with blood pressure and cognitive function measures at a minimum of two visits. Specifically, cumulative measures conservatively assumed blood pressure remained the same until a subsequent visit recorded a different blood pressure level. The blood pressure at each visit was then multiplied by the years between that visit and the next. The cumulative total exposure was obtained by summing the totals across the visits in each individual. For example, an individual with a baseline SBP of 120 at time 0, a subsequent pressure of 150 after 4 years, 160 after 8 years, and so on would have a cumulative exposure of $(120 \times 4 \text{ years}) + (150 \times 4) + 160$, and so on. When analyzing cumulative blood pressure, the longest duration of blood pressure exposure

and concomitant neuropsychological change was selected for each participant.

2.3 | Statistical analysis

Periodically a checked and approved copy of the live DIAN database is frozen and a copy is saved (referred to as a data freeze), no further data are entered into the frozen copy, and it is subsequently made available for analysis. Two analytical samples were used in the present analyses. The first encompassed all participants available at the DIAN study data freeze 13, where data were deemed useable, approved by study monitors, and passed all quality control measures. The second sample was a subset of the full sample and included only participants who had had at least one follow-up visit after baseline, at least two blood pressure measures, and a baseline CDR < 0.5 (minimizing any potential impact of falling blood pressure close to dementia diagnosis²²).

The baseline characteristics of the sample were described, and the characteristics of those who carry an ADAD mutation (MC), those who do not (NC), and those included in and excluded from the cumulative blood pressure sample were examined using *t*-tests, Wilcoxon, and chi-squared tests as appropriate. Regression was used to evaluate the relationship between baseline blood pressure (per 10 mmHg) and baseline cognitive function (z-score), blood pressure (per 10 mmHg) and cognitive function (z-score) over time, and cumulative exposure to blood pressure (per 100 mmHg) and concomitant change in cognition (change in z-score) over the same time period. Variance inflation factors for SBP and DBP were assessed prior to their inclusion in the models. A statistical significance threshold of $p < 0.05$ was used and statistical analyses were carried out using SAS statistical software version 9.4

2.4 | Baseline cross-sectional analyses

We conducted cross-sectional analyses to examine the relationship between baseline SBP and DBP (mmHg) and baseline cognitive performance (z-score) by carrier status (MC or NC). Multilevel linear regression was adjusted for age and sex and then additionally for factors known to influence dementia risk. These included years of education, total activity (minutes/week), body mass index (BMI), cardiovascular disease (any of heart attack, cardiac bypass procedure, pacemaker, angioplasty/endarterectomy/stent, congestive heart failure, atrial fibrillation), hypercholesterolemia, antihypertensive use, English as a first language, Alzheimer's biomarker amyloid ($A\beta$) 42/40 ratio, and processing lot number. ADAD family identification code was included as a random intercept to allow for potential clustering of characteristics within families. Since missing data were present for some of the confounding variables, both the minimally and fully adjusted results are presented. Analyses were run separately in MC and NC groups. Model fit was examined using residual plots. The relationship between blood pressure, cognitive domain, and mutation status was examined graphically by plotting the baseline SBP and DBP

against baseline cognitive performance. Cross-sectional analyses were carried out for the whole sample.

To examine possible relationships between blood pressure and estimated onset date, SBP and DBP were also plotted against EYO by mutation status adjusted for chronological age and allowing for potential quadratic relationships.

2.5 | Longitudinal analyses

Longitudinal analyses in those with at least one follow-up assessment, at least two blood pressure measures, and baseline cognition CDR < 0.5 were carried out in two ways. The first used linear multilevel models and z-scores for each cognitive domain to examine the relationship between cognition, SBP, and DBP (systolic and diastolic were centered around values of 100 mmHg/70 mmHg, respectively) with a random intercept for the DIAN family identification code. This allowed us to derive an estimate of the average blood pressure on cognition using a meaningful reference point and with varied visit frequency and

repeated measurements within participants over time. Analyses were first run adjusted for age, sex, and time and then additionally adjusted for years of education, total activity (minutes/week), BMI, cardiovascular disease (any of heart attack, cardiac bypass procedure, pacemaker, angioplasty/endarterectomy/stent, congestive heart failure, atrial fibrillation), hypercholesterolemia, antihypertensive use, English as a first language, A β 42/40 ratio, and processing lot number. SBP was adjusted for DBP and vice versa. Linear multilevel models were run separately in MCs and NCs. Model fit was examined using residual plots.

2.6 | Cumulative blood pressure

The second longitudinal analysis used linear multilevel models to examine the relationship between cumulative blood pressure in mmHg and cognitive change in the NC group. This allowed us to derive an estimate for each 100-mmHg increment in cumulative blood pressure accrued over follow-up. This was adjusted for age, sex, years of education, total activity (minutes/week), BMI, cardiovascular disease (any

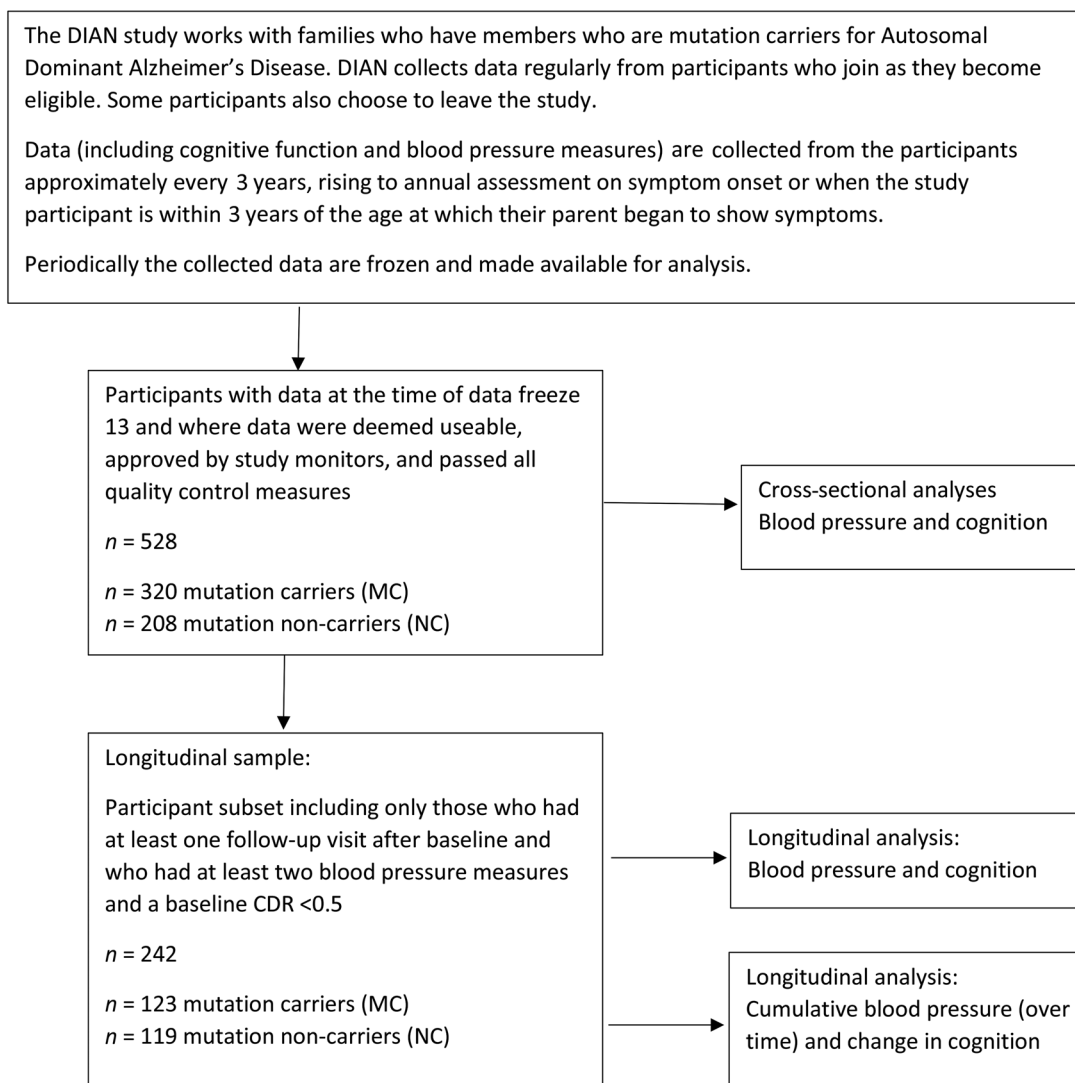


FIGURE 1 Flow chart.

TABLE 1 Baseline characteristics of study participants.

	Cross-sectional sample (total cohort <i>n</i> = 528)			Longitudinal sample (<i>n</i> = 242)		
	Mutation Carriers (<i>n</i> = 320)	Non-carriers (<i>n</i> = 208)	<i>p</i> value	Mutation carriers (<i>n</i> = 123)	Non-carriers (<i>n</i> = 119)	<i>p</i> value
Age (years)	38.2 (10.9) Range 18 to 67	37.9 (11.4) Range 18 to 69	0.734	34.5 (9.6) Range 18 to 61	37.8 (10.3) Range 19 to 61	0.011
Male	140 (44%)	84 (40%)	0.422	47 (38.5%)	47 (39.5%)	0.896
Years of education	14.3 (3.1)	14.7 (2.9)	0.092	14.6 (2.8)	15.0 (2.6)	0.187
Systolic blood pressure (mmHg)	121.9 (13.2)	123 (16.9)	0.434	121.1 (13.8)	120.0 (15.4)	0.2
Diastolic blood pressure (mmHg)	75.1 (9.7)	75.5 (10.5)	0.114	73.8 (9.5)	75.8 (9.9)	0.11
Pulse rate	69.1 (12.5)	70.8 (11.4)	0.119	71.0 (11.2)	69.3 (10.0)	0.233
Body Mass Index	27.4 (5.8)	28.3 (6.6)	0.118	27.5 (5.3)	28.5 (6.8)	0.211
Hypertension	26 (8%)	32 (15%)	0.025	8 (6.6%)	16 (13.8%)	0.097
Anti-hypertensive	19 (6%)	23 (11%)	0.047	5 (4.1)	14 (11.8)	0.032
Cardiovascular disease ^a	25 (8%)	13 (6%)	0.606	10 (8.2)	9 (7.6)	1.000
Hypercholesterolemia	43 (13%)	26 (13%)	0.859	18 (14.8%)	14 (11.8%)	0.743
Eversmoker	136 (43%)	89 (43%)	<0.001	50 (40.9%)	54 (45.4%)	0.743
MMSE score	26.7 (5.2)	29 (1.3)	<0.001	29.1 (1.2)	29.2 (1.2)	0.475

Values are presented in mean (standard deviation) for continuous variables and absolute count (percentage) for categorical variables.

^aCardiovascular disease (any of the following conditions: heart attack, cardiac bypass procedure, pacemaker, angioplasty/endarterectomy/stent, congestive heart failure, atrial fibrillation).

of heart attack, cardiac bypass procedure, pacemaker, angioplasty/endarterectomy/ stent, congestive heart failure, atrial fibrillation), hypercholesterolemia, English as a first language, antihypertensive use, Aβ42/40 ratio, and processing lot number, and additionally for baseline cognitive performance and baseline blood pressure (cumulative SBP was adjusted for baseline DBP and vice versa). Model fit was examined using residual plots. As cumulative exposure is calculated based on length of follow-up (higher values for longer follow-up), this is not reported for the MC group, where duration of study follow-up may be influenced by decline.

The DIAN study was approved by the relevant Institutional review boards for all of the participating institutions. Informed written consent was obtained from all participants at each site. The data analyses undertaken in this study were approved by the University of New South Wales Human Research Advisory Panel HC3378.

3 | RESULTS

Baseline data were available for a total of 528 participants. The median number of visits was two, and there were 329 who had at least one follow-up visit after baseline. The mean number of blood pressure measures was 1.9 (standard deviation [SD] 1.1), median 2.0. Of the 528, 46% (242) had baseline blood pressure measures, at least one follow-up visit with at least one repeat blood pressure measurement, repeat assessment of cognitive function, and a baseline CDR score of less than

0.5) (see Figure 1 for a flow chart and Table 1 for details). Overall, time spent in the study (*n* = 528) ranged from 0 to 8.2 years, with a mean of 2.2, SD of 2.3 years, and median of 2 years (interquartile range 0, 3.9).

3.1 | Baseline characteristics (Table 1)

The cohort of 528 were predominantly in early to middle adulthood, with a mean age of 38 years (SD 11), under half (42%) were male, and over half (61%) of the sample were MCs. Data for the MC and NC groups were comparable. The two groups were similar in age with similar levels of educational attainment. They also had similar baseline blood pressure and baseline cardiovascular disease.

CSF biomarkers for AD-related amyloid at baseline were available for 420 participants and differed between the MC and NC groups for the ratio of Aβ42/40 (*p* < 0.0001) and for Aβ42 (*p* < 0.0001) but not Aβ40 (*p* = 0.19). The Aβ42/40 ratio had a mean value of 0.08 (SD = 0.05) in the MC group and 0.11 (SD = 0.04) in the NC group. For Aβ40 the values were 8342 pg/ml (SD3308) for the MC and 8788 pg/ml (SD3450) for the NC group, and for Aβ42 642 pg/ml (SD381) for the MC and 875 pg/ml (SD277) for the NC group. These results were in the anticipated direction.²⁴

Baseline Mini-Mental State Examination (MMSE) score was higher in NCs, with a mean score of 29 (SD = 1.3) versus 26.7 (SD = 5.2) in MCs. The NCs were also more likely to have been diagnosed with hypertension and to be taking antihypertensives.

TABLE 2 Linear regression results showing cross-sectional relationships between baseline blood pressure and baseline cognitive function (z-score) by mutation status.

Mutation status	Blood pressure per 10 mmHg	Composite cognitive function coefficient (95% confidence interval [CI])	Working memory and attention coefficient (95% CI)	Language coefficient (95% CI)	Episodic memory coefficient (95% CI)	Executive function coefficient (95% CI)
MC	Systolic	−0.146 (−0.276, −0.015)	−0.101 (−0.235, 0.033)	−0.181 (−0.318, −0.044)	−0.212 (−0.375, −0.049)	−0.058 (−0.295, 0.178)
	<i>p</i> value	.029	.138	.01	.012	.623
	Diastolic	0.077 (−0.092, 0.246)	0.081 (−0.094, 0.256)	0.154 (−0.025, 0.333)	0.115 (−0.097, 0.326)	−0.123 (−0.432, 0.186)
	<i>p</i> value	.367	.359	.09	.383	.43
NC	Systolic	−0.064 (−0.138, 0.010)	0.026 (−0.092, 0.143)	−0.094 (−0.182, −0.006)	−0.153 (−0.314, 0.007)	−0.050 (−0.125, 0.026)
	<i>p</i> value	.087	.66	.037	.06	.188
	Diastolic	0.088 (−0.033, 0.209)	0.059 (−0.135, 0.252)	0.095 (−0.050, 0.240)	0.194 (−0.071, 0.459)	−0.007 (−0.132, 0.118)
	<i>p</i> value	.149	.54	.19	.145	.915

Adjusted for baseline age, sex, years of education, total activity (minutes/week), body mass index, history of cardiovascular disease (heart attack, or cardiac bypass procedure, or pacemaker, or angioplasty/endarterectomy/stent, or congestive heart failure, or atrial fibrillation), hypercholesterolemia, English as a first language, systolic or diastolic blood pressure, antihypertensive use, cerebrospinal fluid (CSF) ABeta42/40 ratio, and for CSF sample processing lot number. Estimates are unstandardised.

NCs included in the longitudinal analyses were similar to NCs in the full baseline sample. MCs in the longitudinal sample were younger, were less likely to be male, and had a higher baseline MMSE score.

3.2 | Blood pressure and cognition—Cross-sectional analyses (Table 2)

In the MC group, results were consistent for the models with minimal ($n = 285$, NC $n = 207$) and full adjustment ($n = 224$ MC $n = 160$ NC). In the fully adjusted model, there was a relationship between higher SBP at baseline and poorer cognitive performance on the composite measure (baseline z-score β coefficient -0.146 [95% confidence interval, CI] -0.276 , -0.015) per 10 mmHg increase $p = 0.029$). Patterns were similar for episodic memory (-0.212 [-0.375 , -0.049] $p = 0.012$), and language (-0.181 [-0.318 , -0.044] $p = 0.01$). There were no relationships between DBP and cognition.

For the NC group, point estimates were negative for SBP for four of the five domains, and there was a relationship between higher SBP and poorer performance on the language measure (-0.094 [-0.182 , -0.006] $p = 0.037$) and significant relationships between higher SBP and poorer performance on the composite and episodic measures in the minimally adjusted model that were no longer present with full adjustment. See Figure S1 for a graphical representation of the baseline relationship between cognition and blood pressure. Because there were executive function scores that were low in the MCs, sensitivity analyses were carried out excluding those with low executive function

scores (z-score less than -4) in the MC group, but they did not change the significance of the results (SBP 0.017 [-0.121 , 0.155] and DBP -0.062 [-0.233 , 0.109]).

Examining the relationship between baseline SBP and DBP and estimated years to onset in the MC and NC groups separately revealed no differing patterns by group (Figure 2, Table S1).

3.3 | Blood pressure and cognition—Longitudinal analyses

Longitudinal analysis using linear multilevel models examining the relationship between repeated measures of cognition and blood pressure found no relationships between SBP or DBP and any of the cognitive outcomes for either the MC or NC group. (Table S2). Minimally adjusted model: MC $n = 123$, NC $n = 119$. Fully adjusted model: MC $n = 93$, NC $n = 87$.

Examining the relationship between cumulative blood pressure in the NC group found no statistically significant relationships between greater cumulative exposure to SBP or DBP over time and change in cognitive performance over the same time period. There were significant relationships between greater cumulative exposure and less decline in executive function, but these were not present in the fully adjusted model. Since cumulative measures can yield large numbers, results are reported per 100 mmHg (Table S3).

Additional results from minimally adjusted analyses are shown in Tables S4–6.

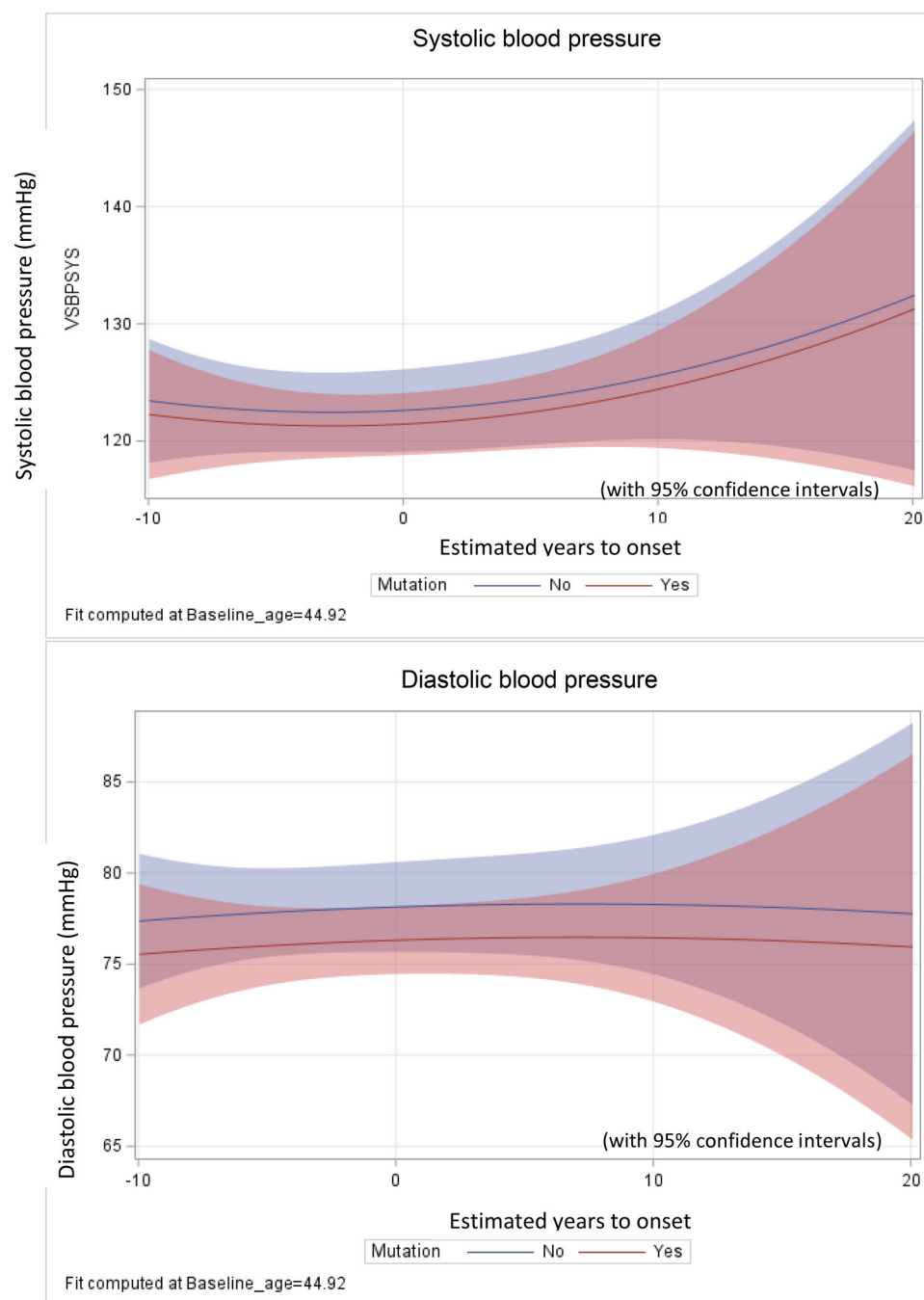


FIGURE 2 Relationship between baseline blood pressure and estimated years to onset in sample 1.

4 | DISCUSSION

In these analyses of participants in the DIAN study, with and without an ADAD mutation, we found a cross-sectional relationship between higher SBP and poorer performance on cognitive domains of language, episodic memory, and a composite cognitive measure at baseline in ADAD MCs. Importantly, these associations were present after adjusting for levels of CSF amyloid biomarkers. In first-degree relatives who were NCs, the point estimates were broadly in the same direction as for MCs, but only the relationship between higher SBP and poorer

performance on language was statistically significant. There was no clear relationship between blood pressure and estimated onset date of dementia. Longitudinal analyses examining the relationship between blood pressure and cognition and cumulative blood pressure and cognition found no statistically significant relationships with cognitive performance in either the MC or NC groups.

Cross-sectional relationships between raised SBP and poorer cognitive function were shown previously in early to midlife NC populations. Analyses of the National Health and Nutrition Examination Survey (NHANES III) data found associations between higher SBP and poorer

performance on a working memory task in 1773 participants aged 20 to 39 years.²⁴ Since NHANES was reporting on a subsample of a general population, it is unlikely to have contained any participants with an ADAD mutation, which represent a very small proportion (i.e., <5%) of all AD cases.²⁵ Other early adulthood cohort studies in general populations have also demonstrated a relationship between greater cumulative blood pressure and poorer cognition, with cross-temporal analyses reporting on longitudinal risk factor data but a single measure of cognition at follow-up.^{4,26,27} Specifically, the Young Finns⁴ and Coronary Artery Risk Development in Young Adults (CARDIA)^{6,26,27} studies have reported relationships between higher cumulative exposure to both SBP and DBP as associated with increased risk of poorer cognitive performance with around 20 years of follow-up. Such prior population studies like these differ from our analyses. They were able to include larger numbers of participants over longer exposure times and as such may have greater power to show relationships where we only saw a cross-sectional relationship between higher SBP and poorer performance on language in the NC population.

To our knowledge, our work is the first to show such cross-sectional relationships between raised SBP and poorer cognitive performance across domains in an early adult to midlife MC group. That these relationships were found to be sustained after adjustment for AD-related amyloid biomarkers and other dementia risk factors is important as it implies a potential role for raised blood pressure acting independently of the underlying amyloid-related processes. This is plausible since there are multiple vascular structural and functional pathways linking raised blood pressure to poorer cognitive function and incident dementia.²⁹ A detailed review is beyond the scope of this article, but these include clinical and subclinical stroke, vascular remodeling and stiffening, extra/intracranial atherosclerosis, small-vessel disease, and microvascular rarefaction. Functional impacts may also include disruption in endothelial cell function, disruption in neurovascular coupling, disruption in autoregulation, and damage to blood-brain barrier integrity. This is particularly important for vulnerable groups such as MCs and those with cerebral amyloid angiopathy since opportunities to reduce risk are very few and blood pressure is a modifiable risk factor. Furthermore, recent research shows that blood pressure lowering may reduce the risk of late onset dementia. This raises important questions about the possibility of moderating risk, even slightly, in this MC group.^{30,31} Our findings highlight the need for further investigation. Since our findings are from observational data, we cannot demonstrate causality. Furthermore, our longitudinal analyses did not show the same results, although we were limited by only being able to include short follow-up periods from a subset of the DIAN cohort for whom repeat blood pressure measures were available.

While the exposure time needed for high blood pressure to have an impact on cognitive performance is not currently known, data from the Atherosclerosis Risk In the Community (ARIC) study reported a decline of just 0.056 global cognition z-score points (95% CI, -0.1 to -0.012)³¹ over 20 years in those with hypertension at baseline (aged 48 to 67 years) compared to normotensives. This implies that longer exposures to raised blood pressure than those observed in these analyses are needed for any impact on cognition to be of sufficient size to

be measurable and represents a limitation to our study. Such long exposures are also less likely to occur in MC rather than NC populations, given the rise in SBP with aging and earlier mortality in MCs.

Interestingly, our analyses showed stronger cross-sectional relationships between higher SBP and poorer cognition in the MC but not in the NC group. This may reflect a greater vulnerability in the MC group. In particular the MC group may have greater cognitive vulnerability and or lower resilience to risk factor exposure due to the inheritance of a gene mutation that causes AD, despite the fact that neither group shows any difference in their overall blood pressure levels. Conversely, we cannot exclude the possibility that the gene mutation itself may also give rise to higher blood pressure.³²

There are unavoidable limitations to our study. Our results must be considered in the context of the population we chosen to study, which, while unique in having ADAD (a rare condition) and a family-based comparison population, is inevitably small, which restricts our statistical power. The prevalence of young-onset dementia is estimated at 119/100,000 population,³³ and the DIAN study includes one particular subset of this population based on their inheritance of an AD-causing mutation. The genetic etiology for most young-onset dementia outside of DIAN is unclear²⁵ and could be due to a combination of factors. Examples of such factors could include cases arising from carrying multiple AD risk alleles, such as two copies of the $\epsilon 4$ allele of the apolipoprotein E (APOE) gene, mutations that may be recessive or have incomplete penetrance, or de novo causative mutations in known or as yet to be determined genes or combinations of genes.²⁵ Nevertheless, the size of the DIAN study and use of confirmatory genotyping in such a rare disorder, alongside a similarly sized group of individuals drawn from the same families in the same population, represent as rigorous a paradigm as possible and, thus, an ideal opportunity to evaluate the impact of a risk factor such as blood pressure.

Both the MC and NC groups from the DIAN study also had blood pressure measures that were not especially high by current treatment threshold standards, although greater numbers of those in the NC group had a diagnosis of hypertension and were taking antihypertensive medication. While the level of blood pressure is thought to be most important for cognition, rather than either the diagnostic threshold for hypertension or class of antihypertensive,^{13,34} it is not clear why such a difference between the groups would exist. Given the sample size, however, even a relatively small difference in the absolute number with hypertension would be reflected in the percentage with a diagnosis. The level of blood pressure in the two groups may have limited the potential for relationships between blood pressure and cognition to be observed; on the other hand, these blood pressures are likely to be similar to or even slightly higher than those of the general population at equivalent ages.³⁵ Finally, the included population may not be representative of similarly aged populations elsewhere, and while we adjusted for BMI and other factors known to impact cognitive function, there remains the possibility of unmeasured confounding.

Finally, our results do not infer causality, and the clinical relevance of the relationship may be limited given the size of the cognitive differences by level of blood pressure difference. Nevertheless, despite these limitations, our results provide an important addition to our

understanding of the potential role of blood pressure in cognition, especially in a particularly vulnerable MC population. Our study also adds data to our growing knowledge of longitudinal relationships between blood pressure and cognitive change in early to midlife NC populations.

4.1 | Conclusion and next steps

Using the DIAN study population of families with an ADAD mutation, we found cross-sectional relationships between higher SBP and poorer cognitive performance in those with the autosomal AD mutation. Overall, these data highlight a need for further research with longer follow-up to identify blood pressure ranges that may be optimal for healthier cognition in early to midlife populations and to gain a better understanding of whether new or additional blood pressure control would be beneficial to protect cognition in this age group, particularly in a vulnerable population carrying causative mutations.

ACKNOWLEDGMENTS

Data collection and sharing for this project was supported by the Dominantly Inherited Alzheimer Network (DIAN, U19AG032438), funded by the National Institute on Aging (NIA), the Alzheimer's Association (SG-20-690363-DIAN), the German Center for Neurodegenerative Diseases (DZNE), Raul Carrea Institute for Neurological Research (FLENI), partial support by Research and Development Grants for Dementia from Japan Agency for Medical Research and Development, (AMED), and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), Spanish Institute of Health Carlos III (ISCIII), Canadian Institutes of Health Research (CIHR), Canadian Consortium of Neurodegeneration and Aging, Brain Canada Foundation, and Fonds de Recherche du Québec – Santé. This manuscript was reviewed by DIAN study investigators for scientific content and consistency of data interpretation with previous DIAN study publications. We acknowledge the altruism of the participants and their families and the contributions of the DIAN research and support staff at each of the participating sites for their contributions to this study. This work was not separately funded.

CONFLICT OF INTEREST STATEMENT

Randall Bateman reports grant support from the National Institute on Aging UFAG032438, R01AG068319, RF1AG061900, R56AG061900, R21AG067559, and R01AG53627/R56AG53627, from the Alzheimer's Association DIAN-TU-OLE-21-725093 and DIAN-TU-TAU-21-822987, investigator initiated grants from the Centene Corporation, Rainwater Foundation, Association for Frontotemporal Degeneration Biomarkers Initiative, Borden, BrightFocus Foundation, Cure Alzheimer's Fund, Coins for Alzheimer's Research Trust Fund, Eisai, The Foundation for Barnes-Jewish Hospital, TargetALS, Good Ventures Foundation, DIAN-TU Pharma Consortium, support from Biogen, AbbVie, Bristol Myers Squibbs, Novartis, Eli Lilly and Co., Hoffman-La-Roche, CogState, Signant, Eisai, Janssen, consulting fees from Amgen, Hoffman-La-Roche, honoraria or speakers fees

from the Korean Dementia Association, the American Neurological Association, Weill Cornell Medical College, leadership or committee roles and royalties from C2N Diagnostics, unpaid committee roles for Hoffman-La-Roche/Genentech, Borden, UK Dementia Research Institute at University College London, Stanford University, travel expenses from Hoffman-La-Roche, Alzheimer's Association Roundtable, Duke-Margolis Alzheimer's Roundtable, BrightFocus Foundation, Tau Consortium Investigator's Meeting, NAPA Advisory Council on Alzheimer's Research and US nonprovisional patent applications 12/267,974, 13/005,233, 62/492,718, 16/610,428, 17/015,985, and 15/515,909. William Brooks reports nothing to disclose. Jasmeer Chhatwal reports nothing to disclose. Gregory S Day's research is supported by NIH (K23AG064029, U01AG057195, U19AG032438), the Alzheimer's Association, and Chan Zuckerberg Initiative. He serves as a consultant for Parabon Nanolabs Inc., as a Topic Editor (Dementia) for DynaMed (EBSCO), and as the Clinical Director of the Anti-NMDA Receptor Encephalitis Foundation (Canada; uncompensated). He is the co-Project PI for a clinical trial in anti-NMDAR encephalitis, which receives support from Horizon Pharmaceuticals. He has developed educational materials for PeerView Media, Inc., and Continuing Education Inc. He owns stock in ANI Pharmaceuticals. Dr. Day's institution has received support from Eli Lilly for Dr. Day's development and participation in an educational event promoting early diagnosis of symptomatic Alzheimer's disease. Anne Fagan reports grants paid to her institution from NIH, scientific advisory board roles for Roche, Diagnostics, Genentech, and DiademRes, consulting for DiamiR and Siemens Healthcare Diagnostics Inc., and travel support for conference attendance and for in-person participation at a scientific advisory board meeting for South Texas Alzheimer's Disease Research Center. Peter Humburg reports nothing to disclose. Patrick G. Kehoe has received grants paid to his institution from the Sigmund Gestetner Foundation Fellowship, the Alzheimer's Society, Alzheimer's Research UK, BRACE, the Bright Focus Foundation, the British Heart Foundation, the UK Medical Research Council, and the UK National Institute of Health Research (NIHR-EME) in the last 36 months. Leadership roles in the last 36 months include membership of the Alzheimer's Society UK Research Advisory Council and as a trustee to the Research into Care of the Elderly (RICE) Centre, Bath, UK (unpaid). Johannes Levin reports speaker fees from Bayer Vital, Biogen, and Roche, consulting fees from Axon Neuroscience and Biogen, author fees from Thieme Medical Publishers and W. Kohlhammer GmbH medical publishers. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is beneficiary of the phantom share program of MODAG GmbH, and is inventor on the patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside the submitted work. Htein Linn Aung reports nothing to disclose. Hiroshi Mori reports nothing to disclose. Brian Gordon reports nothing to disclose. John C. Morris is funded by NIH grants P30 AG066444, P01AG003991, P01AG026276, U19 AG032438, and U19 AG024904. Neither Dr. Morris nor his family owns stock or has an equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. Ruth Peters reports grant funding paid to her institution

from the Australian National Health and Medical Research Council (NHMRC) and salary support from the NHMRC Dementia Centre for Research Collaboration. Leadership roles in the last 36 months include immediate past chair of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) Clinical Trials and Methodology Professional Interest Area (chair 2020 to 2022) (unpaid). Peter Schofield reports funding from the Roth Charitable Foundation and from NIH and an anonymous foundation paid through Washington University. Whitney Wharton reports funding NIA 1R01AG066203-02. Ying Xu reports nothing to disclose.

CONSENT STATEMENT

All human subjects provided informed consent.

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ischaemic heart disease mortality: a cross-sectional study. *BMJ Open*. 2013;3(8):e003423.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Xu Y, Aung HL, Bateman RJ, et al. Higher systolic blood pressure in early-mid adulthood is associated with poorer cognitive performance in those with a dominantly inherited Alzheimer's disease mutation but not in non-carriers. Results from the DIAN study. *Alzheimer's Dement*. 2023;1-11. <https://doi.org/10.1002/alz.13082>

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