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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 collecting data on cognition, blood pressure(BP) and other variables from Autosomal Dominant Alzheimer's Disease mutation carriers(MC) and non-carrier(NC) family

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members in early-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 mean age 38(SD=11), 42% male, 61% MCs, median follow-up two years. Linear-multilevel models found only cross-sectional associations in the MC group between higher systolic BP and poorer performance on language (β=−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 MC. BP may influence cognition gradually, further longitudinal research is needed.

Keywords

blood pressure; cognition; autosomal dominant Alzheimer's disease

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]

There is also emerging data to 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 10–20 years before dementia diagnosis has been associated with early onset dementia in an Australian case-control study population and a Swedish conscript population, respectively.[8, 10] Conversely, studies in self-reported early onset Alzheimer's disease (AD) [11] or Autosomal Dominant AD [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 mid-adult life and in a Autosomal Dominant AD population is particularly important when we consider that the treatment of raised blood pressure in mid-late life may reduce the risk of later dementia[13, 14] 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-mid adult population with separate analyses of those who have a genetic mutation causing them to develop Autosomal Dominant AD 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 which includes asymptomatic and symptomatic individuals who have a parent or sibling with Autosomal Dominant AD caused by a mutation in either the *PSEN1*, *PSEN2* or *APP* genes and who can be classified as either Autosomal Dominant AD mutation carriers (MC) or non-carrier (NC) family members.[15] 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. [16] [17] Longitudinal data is collected approximately every three years, rising to annual assessment on symptom onset or when the study participant is within three 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. [18] They range from negative, i.e. anticipated future onset, to positive, i.e. passed the age at which onset would have been expected.

2.1. Neuropsychological assessment

Cognitive function was assessed using the Alzheimer’s Disease Research Center (ADRC) Uniform Data Set, Neuropsychological Test Battery.[19] The battery used in these analyses included 10 main tests: Digit Span Forward, Digit Span Backward, Wechsler Adult Intelligence Scale-Revised (specifically the digit symbol substitution test), Trail Making Test A, Trail Making Test B, Logical Memory Story-A, Immediate Recall and Delayed Recall, Animal List Generation, Vegetable List Generation, and the Boston Naming Test.[20] Raw scores were first demographically-corrected for age, sex and education using published norms and transformed into z-scores.[21] 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 Digit Span Forward and Backward 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.

2.2. Blood pressure measures

Systolic and diastolic blood pressure 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.[22] 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 which suggests that cumulative exposure, similar to calculating 'pack years' for smoking', may be a better way of evaluating blood pressure impact).[4, 23] 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 blood pressure of 120 at time 0 and a subsequent pressure of 150 after 4 years and 160 after 8 years etc: would have a cumulative exposure of (120*4 year) + (150*4) + 160… etc. When analysing 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 is 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 at least one follow-up visit after baseline, at least two blood pressure measures and who had a baseline CDR <0.5 (minimising any potential impact of falling blood pressure close to dementia diagnosis[24])

The baseline characteristics of the sample were described, and the characteristics of those who carry an Autosomal Dominant AD mutation (MC), those who do not (NC), and those included 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 10mmHg) and baseline cognitive function (z-score), blood pressure (per 10mmHg) and cognitive function (z-score) over time and cumulative exposure to blood pressure (per 100mmHg) 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 $P < .05$ was used and statistical analyses were carried out using SAS statistical software v9.4

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). Multi-level 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 (Aβ) 42/40 ratio and processing lot number. Autosomal Dominant AD family identification code was included as a random intercept to allow for potential clustering of characteristics within families. Since missing data was 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, systolic and diastolic blood pressure (systolic and diastolic were centred around values of 100mmHg/70mmHg 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), 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, Aβ42/40 ratio and processing lot number. Systolic blood pressure was adjusted for diastolic pressure and vice versa. Linear multilevel models were run separately in MC and NC. 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 100mmHg increment in cumulative blood pressure accrued over follow-up. This was adjusted for age, sex, 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, 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, a standard deviation (SD) of 2.3 years, and a median of 2 years (interquartile range 0, 3.9).

3.1. Baseline characteristics (Table 1)

The cohort of 528 were predominantly in early-mid adulthood with a mean age of 38 years (standard deviation (SD) 11), under half (42%) were male, and over half (61%) of the sample were mutation carriers. Data for MC and NC groups were comparable. The two groups were similar in age with similar educational level. 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 ($P < .0001$) and for Aβ42 ($P < .0001$) but not Aβ40 ($P = .19$). 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.[25]

Baseline MMSE score was higher in NCs, with mean scores 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.

NC included in the longitudinal analyses were similar to NC in the full baseline sample. MC in the longitudinal sample were younger, 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 Intervals (CI) −0.276, −0.015) per 10mmHg increase P=.029). Patterns were similar for episodic memory (−0.212 (−0.375, −0.049) P = .012), and language (−0.181 (−0.318, −0.044) P = .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 = .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 supplementary figure 1 for a graphical representation of the baseline relationship between cognition and blood pressure. Because there were executive function scores that were low in the MC sensitivity analyses were carried out excluding those with low executive function scores (z-score less than −4) in the MC group but did not change the significance of the results (systolic 0.017 (−0.121, 0.155) and diastolic −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, Supplementary Table 1).

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. (Supplementary Table 2). 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 100mmHg. (Supplementary Tables 3).

Additional results from minimally adjusted analyses are shown in Supplementary Tables 4–6.

4. Discussion

In these analyses of participants in the DIAN study, with and without an Autosomal Dominant AD 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 Autosomal Dominant AD 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 have been shown previously in early-mid-life 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 20–39 years.[26] Since NHANES reports on a subsample of a general population, it is unlikely to have contained any participants with an Autosomal Dominant AD mutation, which represent a very small proportion (i.e. <5%) of all AD cases.[27] 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, 28, 29] Specifically, the Young Finns[4] and Coronary Artery Risk Development in Young Adults (CARDIA)[6, 28, 29] 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 have been 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-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.[30] Detailed review is beyond the scope of this article but these include; clinical and sub-clinical stroke, vascular remodelling and stiffening, extra/intracranial atherosclerosis, small vessel disease, 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 MC 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 poses important questions about the possibility of moderating risk, even a little, in this MC group[31, 32]. 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.

Whilst 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),[33] over 20 years in those with hypertension at baseline (aged 48–67 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 ageing and earlier mortality in MC.

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 both groups having no 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.[34]

There are unavoidable limitations to our study. Our results must be considered in the context of the population we have chosen to study, which, whilst unique in having Autosomal Dominant AD (a rare condition) and a family-based comparison population, is inevitably small thus restricting our statistical power. The prevalence of young onset dementia is estimated at 119/100,000 population[35], and the DIAN study includes one particular subset of this population based on their inheritance of an AD-causing mutation. The genetic aetiology for most young onset dementia outside of DIAN is unclear[27] 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 ε4 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.[27] 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, represents 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. Whilst 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, [14, 36] 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 the general population at equivalent ages.[37] Finally, the included population may not be representative of similarly aged populations elsewhere, and whilst 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 mid-life NC populations.

4.1. Conclusion and next steps

Using the DIAN study population of families with an Autosomal Dominant AD 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 mid-life 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix - Collaborators

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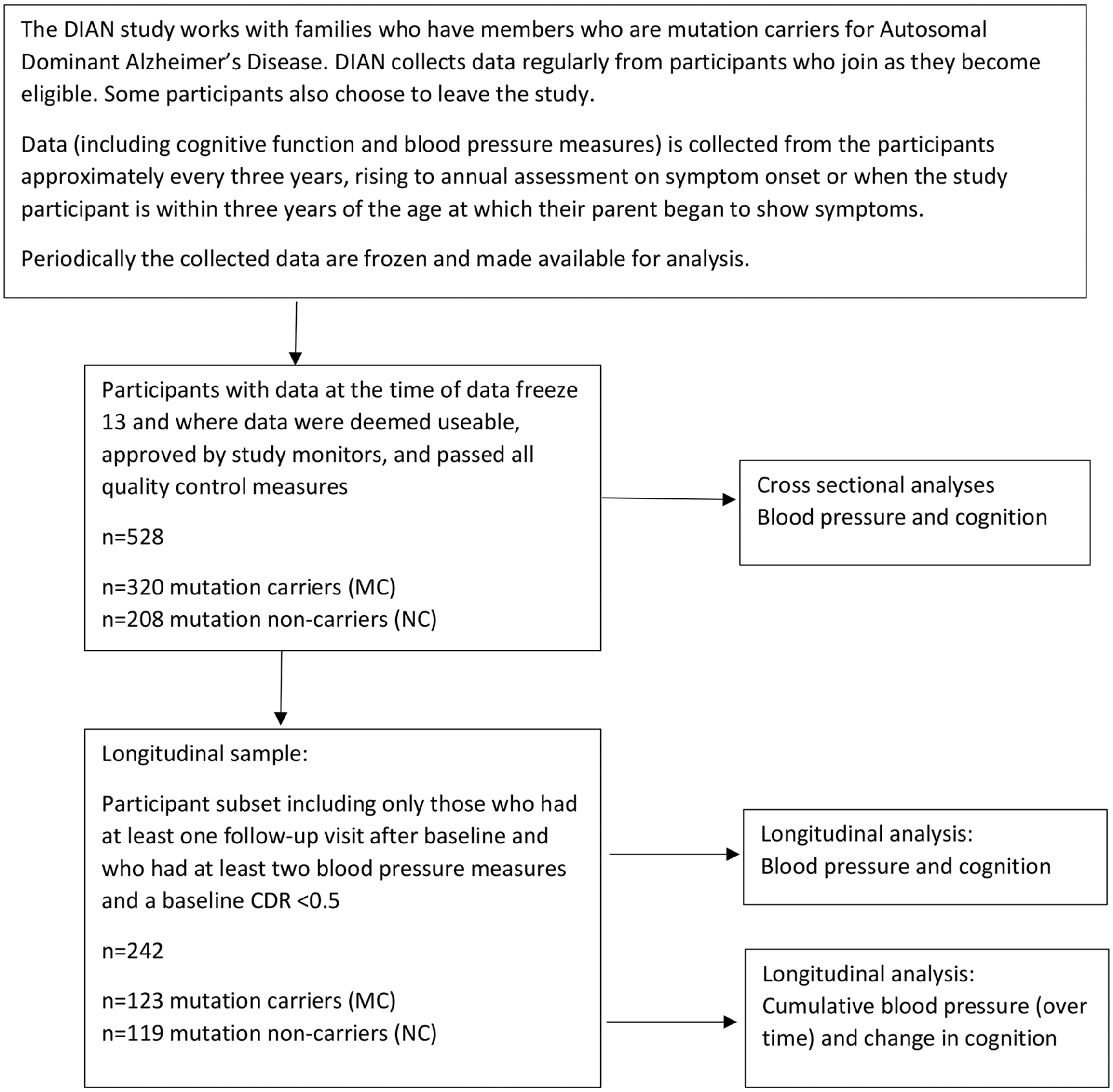

Figure 1.

Flow chart

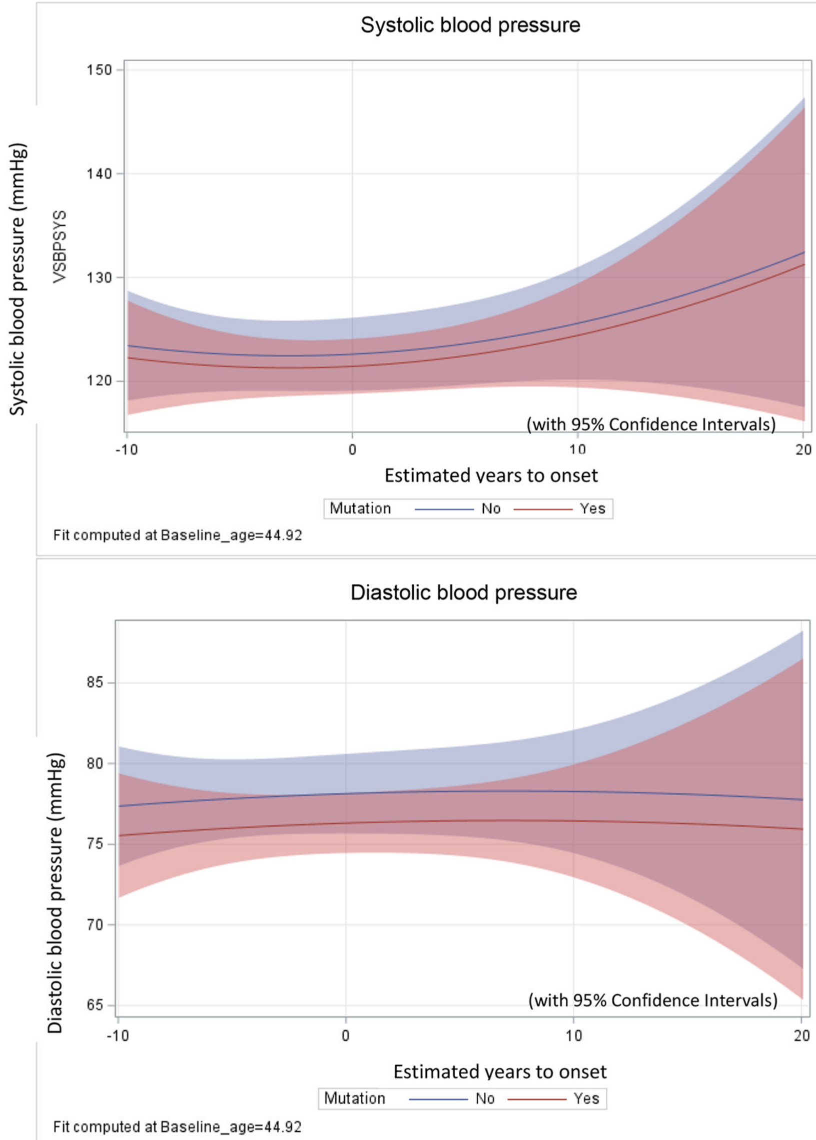

Figure 2.

Showing the relationship between baseline blood pressure and estimated years to onset in sample 1

For Estimated years to onset, negative values indicate time prior to expected age of onset, positive values indicate time beyond expected age of onset.

Graphs truncated at −10 and +20 due to small numbers of data points.

Table 1

Baseline characteristics of study participants

	Cross sectional sample (Total cohort n=528)			Longitudinal sample (n=242)		
	Mutation Carriers (n=320)	Non-Carriers (n=208)	P value	Mutation Carriers (n=123)	Non-Carriers (n=119)	P value
Age (years)	38.2 (10.9) Range 18–67	37.9 (11.4) Range 18–69	.734	34.5 (9.6) Range 18–61	37.8 (10.3) Range 19–61	.011
Male	140 (44%)	84 (40%)	.422	47 (38.5%)	47 (39.5%)	.896
Years of education	14.3 (3.1)	14.7 (2.9)	.092	14.6 (2.8)	15.0 (2.6)	.187
Systolic blood pressure (mmHg)	121.9 (13.2)	123 (16.9)	.434	121.1 (13.8)	120.0 (15.4)	.2
Diastolic blood pressure (mmHg)	75.1 (9.7)	75.5 (10.5)	.114	73.8 (9.5)	75.8 (9.9)	.11
Pulse rate	69.1 (12.5)	70.8 (11.4)	.119	71.0 (11.2)	69.3 (10.0)	.233
Body Mass Index	27.4 (5.8)	28.3 (6.6)	.118	27.5 (5.3)	28.5 (6.8)	.211
Hypertension	26 (8%)	32 (15%)	.025	8 (6.6%)	16 (13.8%)	.097
Anti-hypertensive	19 (6%)	23 (11%)	.047	5 (4.1)	14 (11.8)	.032
Cardiovascular disease[a]	25 (8%)	13 (6%)	.606	10 (8.2)	9 (7.6)	1.000
Hypercholesterolemia	43 (13%)	26 (13%)	.859	18 (14.8%)	14 (11.8%)	.743
Eversmoker	136 (43%)	89 (43%)	<.001	50 (40.9%)	54 (45.4%)	.743
MMSE score	26.7 (5.2)	29 (1.3)	<.001	29.1 (1.2)	29.2 (1.2)	.475

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

[a]Cardiovascular disease (Any of the following conditions: heart attack, cardiac bypass procedure, pacemaker, angioplasty/endarterectomy/stent, congestive heart failure, atrial fibrillation)

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 10mmHg	Composite cognitive function (coefficient (95% Confidence Intervals (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)
	P 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)
	P 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)
	P 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)
	P 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