Archival Report

Biological Psychiatry

High Blood Pressure and Risk of Dementia: A Two-Sample Mendelian Randomization Study in the UK Biobank

William Sproviero, Laura Winchester, Danielle Newby, Marco Fernandes, Liu Shi, Sarah M. Goodday, Albert Prats-Uribe, Daniel P. Alhambra, Noel J. Buckley, and Alejo J. Nevado-Holgado

ABSTRACT

BACKGROUND: Findings from randomized controlled trials have yielded conflicting results on the association between blood pressure (BP) and dementia traits. We tested the hypothesis that a causal relationship exists between systolic BP (SBP) and/or diastolic BP (DBP) and risk of Alzheimer's disease (AD).

METHODS: We performed a generalized summary Mendelian randomization (GSMR) analysis using summary statistics of a genome-wide association study meta-analysis of 299,024 individuals of SBP or DBP as exposure variables against three different outcomes: 1) AD diagnosis (International Genomics of Alzheimer's Project), 2) maternal family history of AD (UK Biobank), and 3) paternal family history of AD (UK Biobank). Finally, a combined meta-analysis of 368,440 individuals that included these three summary statistics was used as final outcome.

RESULTS: GSMR applied to the International Genomics of Alzheimer's Project dataset revealed a significant effect of high SBP lowering the risk of AD ($\beta_{GSMR} = -0.19$, $p = .04$). GSMR applied to the maternal family history of AD UK Biobank dataset (SBP [$\beta_{GSMR} = -0.12$, $p = .02$], DBP [$\beta_{GSMR} = -0.10$, $p = .05$]) and to the paternal family history of AD UK Biobank dataset (SBP [$\beta_{GSMR} = -0.16$, $p = .02$], DBP [$\beta_{GSMR} = -0.24$, $p = 7.4 \times 10^{-4}$]) showed the same effect. A subsequent combined meta-analysis confirmed the overall significant effect for the other SBP analyses ($\beta_{GSMR} = -0.14$, $p = .03$). The DBP analysis in the combined meta-analysis also confirmed a DBP effect on AD ($\beta_{GSMR} = -0.14$, $p = .03$).

CONCLUSIONS: A causal effect exists between high BP and a reduced late-life risk of AD. The results were obtained through careful consideration of confounding factors and the application of complementary MR methods on independent cohorts.

https://doi.org/10.1016/j.biopsych.2020.12.015

Alzheimer's disease (AD) represents the most common form of dementia (1). Epidemiological studies have found that the earliest pathological event in disease progression is reduced cerebral blood flow (1). Hypertension is one of the most common conditions that degrade cerebral circulation, and it has been found that prolonged high blood pressure (BP) is a cause of vascular dementia in individuals under 85 years of age (2). This evidence points to a potential link between BP and AD, which would make BP an ideal target for early AD therapy, given that medications able to manipulate BP exist. However, despite several published studies including meta-analyses of randomized controlled trials (RCTs), this association between high BP and AD remains unclear, with many studies reporting discordant results (3).

Several publications have investigated the relationship between midlife hypertension and late-life risk of AD (4–9), and two meta-analyses of dementia risk factors published results in favor of an increased risk of AD driven by midlife high BP (10,11). However, other studies such as the World Alzheimer's Report and a meta-analysis conducted by the Alzheimer's Research Forum (alzrisk.org) reported weak and inconsistent evidence (3,12–15) to support the association of midlife hypertension and AD incidence (3). A recent RCT reported a beneficial effect of antihypertensive drug treatment on the occurrence of mild cognitive decline (mild cognitive impairment), which is a precursor of dementia (15). However, even RCTs, integrally designed to tackle study confounding, have failed to provide consistent results on the dementia outcome, either because of the long follow-up between hypertension manifestation and dementia onset or because of an early termination of the study (15,16).

Conversely, a recent longitudinal study on ~2.6 million individuals in the United Kingdom confirmed a moderate positive association between long-term high BP and vascular dementia, though, paradoxically, the study reported a weaker inverse association with AD (17). The inverse association between BP and AD first described by Gregson *et al.* (17) was reported as a causal association, but such inference should be interpreted

SEE COMMENTARY ON PAGE 742

ISSN: 0006-3223

Biological Psychiatry April 15, 2021; 89:817–824 www.sobp.org/journal

cautiously. These inconsistencies in the literature call for the use of alternative methods, for instance those that target causal effects and use complementary data sources, rather than single cohorts. Mendelian randomization (MR) is a causal inference methodology that can test the effect of a modifiable exposure on a disease by using genetic variants to provide evidence of robust associations and incorporates the advantage of summary statistics from large-cohort genome-wide association studies (GWASs) (18).

In this study, two-sample MR approaches were used to assess the potential causal relationship between high BP (systolic BP [SBP]/diastolic BP [DBP]) and AD risk. Data were obtained from a collection of complementary sources, including large-scale GWAS analyses on blood pressure (BP) (19) and Alzheimer's disease (AD) (20) and the UK Biobank (UKBB) (21), which is one of the largest genetic and phenotypic data resources available to researchers today (22).

METHODS

This study relied on de-identified summary-level data that have been made publicly available (the International Consortium for Blood Pressure [ICBP] GWAS and the International Genomics of Alzheimer's Project [IGAP] GWAS) and on the patient-level UKBB phenotypic and genetic data; ethical approval was obtained in all original studies and for the UKBB data usage (application No. 43309). Data were analyzed for this study from January 1, 2019, to June 30, 2019.

Data Sources

The analyses were performed using genetic instruments associated with BP selected from summary statistics of a recently published Stage 1 GWAS meta-analysis as part of the ICBP (19). The association estimates between BP genetic instruments and AD were obtained from four GWAS summary statistics: 1) the IGAP GWAS (20); 2) maternal UKBB family history of AD (MFH-UKBB); 3) paternal UKBB family history of AD (PFH-UKBB); and 4) a combined meta-analysis that used the IGAP, MFH-UKBB, and PFH-UKBB GWAS results (MA-AD) (21). The IGAP cohort uses AD diagnosis as an outcome measure. The UKBB cohort uses self-reported family history of AD/dementia as a proxy for AD diagnosis. The accuracy of this measure has been shown using genetic correlation analysis and reported by Marioni *et al.* (21). Full cohort and variable descriptions are provided in the Supplement.

Instrument Selection Criteria

We used the following selection criteria to choose the genetic instruments: a set of single nucleotide polymorphisms (SNPs) that reached GWAS significance ($p < 5 \times 10^{-8}$) (18) in association with DBP and/or SBP; all SNPs were confirmed in previous publications (19). In order to assess whether any genetic instrument was previously associated with AD as an outcome and remove possible confounding, we searched the PhenoScanner GWAS database (version 2; http://phenoscanner.medschl.cam.ac.uk) (23) and removed SNPs that reached genome-wide significance ($p < 5 \times 10^{-8}$) in published dementia GWASs. As part of the data harmonization process, we checked that all effect/reference alleles were in agreement with the dbSNP151 reference in all used summary statistics (19–21) and in the UKBB family history results from the paternal and maternal logistic regression analyses described below. All nonmatching alleles were switched (A1=A2 and A2=A1) and the sign of the beta estimates changed. For quality control, we checked for reciprocal strand alleles (e.g., C=G and T=A), excluding alleles with ambiguous SNPs and allele frequencies between 0.4 and 0.6. All instrument SNPs present in the UKBB were in Hardy-Weinberg equilibrium ($p > 1 \times 10^{-10}$), and they also had a minor allele frequency >1% and imputation quality info score >0.9. A list of genetic instruments is reported in Table S1. We retained a total of 81 genome-wide-significant SNP instruments from the ICBP summary statistics (DBP, $n = 61$; SBP, $n = 64$) (19), and a description of the SNP exclusion is reported in the Supplement.

Mendelian Randomization

We tested the hypothesis that high BP may have a causal effect on AD. We performed a two-sample MR analysis using beta estimates of the ICBP Stage 1 meta-analysis (Supplement) as exposure for BP in the MR design, and the following datasets as outcome for AD: 1) β estimates and standard errors (SEs) of AD from the IGAP (20) (see Supplement); 2) log-transformed odds ratios (ORs) and SEs obtained from analysis of MFH-UKBB and PFH-UKBB data (Supplement); and 3) β estimates and SEs of a combined meta-analysis summary statistics (MA-AD) (21) (Supplement) that used IGAP, MFH-UKBB, and PFH-UKBB data. Our main analysis comprised a generalized summary MR (GSMR) using the GSMR R package (24), which excludes SNPs that show evidence of pleiotropic effects by the heterogeneity in dependent instruments outlier analysis (HEIDI-outlier test < 0.01). We therefore estimated a causal association between the exposure and the outcomes using the GSMR method (24).

We used 10,000 randomly selected unrelated samples from the UKBB dataset as a reference to determine linkage disequilibrium patterns, and we clumped SNPs for independence if correlated at $r^2 > .001$. Only one representative SNP was retained.

We subsequently performed a sensitivity analysis for each dataset combination using the TwoSampleMR R (25) package to conduct MR analysis using inverse variance–weighted (IVW) meta-analysis with fixed/random effect and MR-Egger regression. The IVW is the equivalent of a weighted regression of exposure on outcome effects with the intercept constrained to zero. Owing to this constraint, the results can be biased if instrument SNPs show horizontal pleiotropy. This can be caused by the influence on the outcome through causal pathways other than the exposure (26). We therefore compared the IVW results with the MR-Egger regression, testing whether the MR-Egger intercept was different from zero. This was used as an indicator of average pleiotropic bias because this regression intercept is not constrained at the origin. Although the MR-Egger method's estimate is known to be relatively robust to the presence of pleiotropy, it is also affected by a reduced statistical power (18). Therefore, in presence of pleiotropy, an MR-Egger regression estimate was used; in case of no pleiotropy, an IVW-MR estimate was preferred. Moreover, in order to detect heterogeneous

outcomes, we further included leave-one-SNP-out analyses and the modified Cochran Q statistic, also implemented in the TwoSampleMR R package (25). In both SBP and DBP analyses, we scaled MR estimates per standard deviation difference of the risk factor.

IVW-MR estimates were also used to produce post hoc power calculations for each MR analysis using an online MR power calculation tool (https://sb452.shinyapps.io/power/) (27). The coefficient of determination (R^2) of exposure on genetic variants was calculated on the total allele score using the TwoSampleMR R package.

RESULTS

Mendelian Randomization

SNPs were used as instruments in GSMR on three different AD exposures: 1) AD risk from the IGAP, 2) MFH of AD (MFH-UKBB), and 3) PFH of AD (PFH-UKBB). Finally, subsequent meta-analysis (MA-AD) confirmed results by combining the IGAP, MFH-UKBB, and PFH-UKBB outcomes. We used sensitivity analyses to measure the effect of employing different types of MR methods, IVW-MR and MR-Egger, and of pleiotropy.

Results using the IGAP dataset showed a statistically significant protective causal effect of SBP on AD ($\beta_{GSMR} = -0.19$, $p = .04$) (Figure 1A). IVW-MR with random effect and MR-Egger confirmed the GSMR results for SBP ($\hat{\beta}_{xy\text{-}IVW} = -0.19$, $p = .03$; $\hat{\beta}_{xy\text{-}MR\text{-}Egger} = -0.72$, $p = .03$). No pleiotropy was detected in this case. The DBP analysis in the IGAP did not show evidence of a causal relationship ($\beta_{GSMR} = -0.06$, $p = .55$) (Figure 1B). We additionally performed the same analyses in IGAP excluding the ambiguous-strand SNPs that were included in the previous analysis. The alternative results did not deviate significantly from the original DBP analysis in the IGAP (data not shown). Sensitivity analysis detected a source of pleiotropy (MR-Egger intercept, $p < .01$), and the MR-Egger regression estimates confirmed an inverse causation in the DBP ($\hat{\beta}_{xy\text{-}MR\text{-}Egger} = -0.95$, $p = 3.9 \times 10^{-3}$) analysis. No evidence of confounding heterogeneity of effect sizes (leave-one-out; Cochran Q statistic, $p > .10$) was observed in either of these two analyses.

In the UKBB cohort, estimates confirmed a protective causal relationship between both SBP and DBP with AD family history: MFH-UKBB (SBP [$\beta_{GSMR} = -0.12$, $p = .02$], DBP [$\beta_{GSMR} = -0.10$, $p = .05$], PFH-UKBB (SBP [$\beta_{GSMR} = -0.16$, $p = .02$], DBP [$\beta_{GSMR} = -0.24$, $p = 7.4 \times 10^{-4}$]) (Figure 1C–F). Sensitivity analyses found no evidence of confounding heterogeneity of effect sizes (leave-one-out; Cochran Q statistic, $p > .10$) or from pleiotropy (MR-Egger intercept, $p > .05$). Furthermore, IVW-MR with random effect confirmed the GSMR results: SBP (MFH-UKBB [$\hat{\beta}_{xy\text{-}IVW} = -0.12$, $p = .02$], PFH-UKBB [$\hat{\beta}_{xy\text{-}IVW} = -0.17$, $p = .03$]), DBP (MFH-UKBB [$\hat{\beta}_{xy\text{-}IVW} = -0.10$, $p = .03$], PFH-UKBB [$\hat{\beta}_{xy\text{-}IVW} = -0.24$, $p = 3.1 \times 10^{-4}$]) (Table 1).

We subsequently estimated an overall estimate between BP and the combined meta-analysis (MA-AD) (24). A total of 64 SNPs for SBP and 59 SNPs for DBP overlapped between the UKBB and IGAP datasets. For SBP, we confirmed the overall significant causal effect ($\beta_{GSMR} = -0.14$, $p = .03$; $\hat{\beta}_{xy\text{-}IVW} = -0.14$, $p = .03$) (Figure 1G; Table 1). For DBP, we also confirmed a protective effect of high DBP and AD ($\beta_{GSMR} = -0.14$, $p = .03$; $\hat{\beta}_{xy\text{-}IVW} = -0.14$, $p = .03$; $\hat{\beta}_{xy\text{-}MR\text{-}Egger} = -0.50$, $p = .02$) (Figure 1H; Table 1). No evidence of pleiotropy (MR-Egger intercept, $p > .05$) or heterogeneity of effect sizes was found in either of these two analyses (leave-one-out; Cochran Q statistic, $p > .10$).

Both the MFH-UKBB and PFH-UKBB datasets reached a moderate power to detect a causal effect both in SBP analyses (MFH-UKBB, 51.6%; PFH-UKBB, 53.3%) and in DBP analyses (MFH-UKBB, 46.7%; PFH-UKBB, 86.7%). Also, statistical power of 63.1% was reached using the IGAP dataset in the SBP analysis, but reduced power of 12.1% was evident when using DBP genetic instruments. The overall analysis using the MA-AD results reached a minimum of 94.2% power in the SBP analyses and a maximum of 95.6% power in the DBP analyses (Table S2).

Observational analyses of the relationship between BP measurements and family history of AD were estimated in the UKBB dataset (methods reported in the Supplement; cohort summary statistics in Table S3). Logistic regression analyses adjusting for age, sex, body mass index, smoking, hypertension medication, 40 principal components, genotype array, and genetic batch were performed. Results showed that SBP was associated with a protective effect on family history of AD (Figure 2; Supplement), which was detectable after both causal and observational estimates were scaled to a genetically predicted 10-mm Hg difference in BP. This protective effect was unchanged when the observational model was adjusted for antihypertensive drugs (Figure 2).

DISCUSSION

Several publications suggest that high BP manifested in midlife may contribute to an increased risk of AD in late life (4–9), and two meta-analyses supported this result (10,11). However, a meta-analysis published by the Alzheimer's Research Forum suggested that no association exists between midlife high SBP or high DBP and the incidence of AD but suggested that an inverse association between late-life hypertension and AD does exist (12). Similar contradictory results have been reported by other meta-analyses including observational studies or meta-analyses of RCT studies that had not been able to determine a clear effect of midlife use of antihypertensive drugs and late-life risk of dementia (Supplement and Table S4). A possible cause of these contradictory results might be that observational studies analyze correlation, rather than causation, and that RCT studies did not reach statistical power. In this study, we performed two-sample MR analysis, using publicly available GWAS summary statistics and the UKBB dataset, to test for a causal association between higher levels of BP due to genetic predisposition and lower AD risk. Using family history of AD as a proxy for AD status, we report evidence of a protective effect of genetically inherited higher levels of BP and a lower chance of having PFH or MFH of AD. A logistic regression analysis of family history of AD and BP was also performed in the UKBB, reporting an association between high BP levels and reduced risk of AD. Findings from the MR and logistic regression analyses showed similar standardized ORs (Figure 2). Our data confirm previous findings (27), and by selecting larger sample

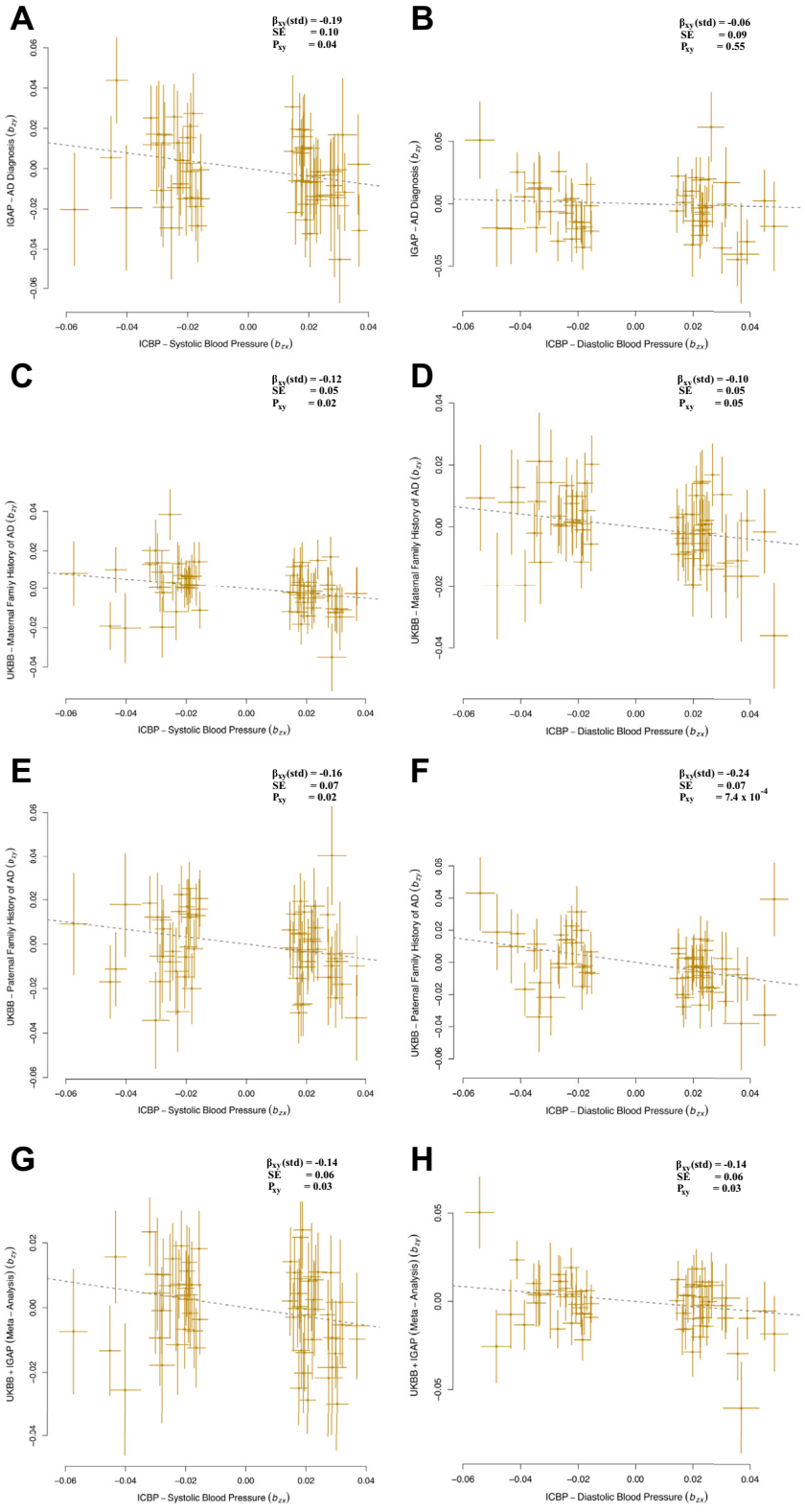

Figure 1. Generalized summary Mendelian randomization (GSMR) analysis of systolic blood pressure (SBP)/diastolic blood pressure (DBP) with Alzheimer's disease (AD) diagnosis and family history of AD. GSMR analysis was performed to test the effect of BP on AD. Family history of AD (either paternal or maternal) was used as a proxy for AD diagnosis (21). GSMR–HEIDI-outlier analysis was applied to all analyses to detect and eliminate the instruments that showed significant pleiotropic effects on both exposure factor (standardized beta estimate [$\beta_{zx(std)}$]) and outcome (log-transformed odds ratio [β_{zy}]). $\beta_{zx(std)}$ is the standardized estimate representing the change in outcome for a 1-unit increase in the exposure variable; SE is the standard error of the $\beta_{zx(std)}$ coefficient; P_{xy} is the *p* value of the $\beta_{zx(std)}$ coefficient. The plots report the linear relationship between the standardized exposure estimates ($\beta_{zx(std)}$) and the outcome estimates (β_{zy}). **(A, B)** The causal relationship ($\beta_{xy(std)}$) between SBP and DBP (exposure; International Consortium for Blood Pressure [ICBP] Stage 1 meta-analysis) (19) and diagnosis of AD (International Genomics of Alzheimer's Project [IGAP] Stage 1 meta-analysis summary statistics) (20). **(C, D)** The causal relationship ($\beta_{xy(std)}$) between SBP and DBP (exposure; ICBP Stage 1 meta-analysis) (19) and maternal family history of AD (UK Biobank [UKBB]). **(E, F)** The causal relationship ($\beta_{xy(std)}$) between SBP and DBP (exposure; ICBP Stage 1 meta-analysis) (19) and paternal family history of AD (UKBB). **(G, H)** The causal relationship ($\beta_{xy(std)}$) between SBP or DBP (exposure; ICBP Stage 1 meta-analysis) (19) and the summary statistics of the combined meta-analysis that used maternal family history of AD (UKBB), paternal family history of AD (UKBB), and the results from the IGAP Stage 1 meta-analysis (21). All MR estimates are standardized and expressed as a 1-SD increase in SBP (SD = 22.1 mm Hg) and a 1-SD increase in DBP (SD = 12.4 mm Hg).

Table 1. Summary of the MR-Based Analysis of Blood Pressure and Dementia

	Systolic Blood Pressure																Diastolic Blood Pressure											
	ICBP–IGAP			ICBP–MFH-UKBB			ICBP–PFH-UKBB			ICBP–MA-AD			ICBP–IGAP			ICBP–MFH-UKBB			ICBP–PFH-UKBB			ICBP–MA-AD		
Method	SNPs	β (SE)	*p* Value	SNPs	β (SE)	*p* Value	SNPs	β (SE)	*p* Value	SNPs	β (SE)	*p* Value	SNPs	β (SE)	*p* Value	SNPs	β (SE)	*p* Value	SNPs	β (SE)	*p* Value	SNPs	β (SE)	*p* Value
GSMR	63	−0.19 (0.10)	.04	64	−0.12 (0.05)	.02	64	−0.16 (0.07)	.02	64	−0.14 (0.06)	.03	56	−0.06 (0.09)	.55	61	−0.10 (0.05)	.05	61	−0.24 (0.07)	7.4×10^{-4}	59	−0.14 (0.06)	.03
IVW (Fixed Effects)	63	−0.19 (0.10)	.04	64	−0.12 (0.05)	.02	64	−0.17 (0.08)	.03	64	−0.14 (0.06)	.03	56	−0.06 (0.10)	.56	61	−0.10 (0.05)	.05	61	−0.24 (0.07)	7.3×10^{-4}	59	−0.14 (0.06)	.03
IVW (Random Effects)	63	−0.19 (0.09)	.03	64	−0.12 (0.05)	.02	64	−0.17 (0.08)	.03	64	−0.14 (0.06)	.03	56	−0.06 (0.10)	.56	61	−0.10 (0.05)	.03	61	−0.24 (0.07)	3.1×10^{-4}	59	−0.14 (0.06)	.03
MR-Egger	63	−0.72 (0.32)	.03	64	−0.04 (0.19)	.82	64	0.04 (0.26)	.87	64	−0.22 (0.22)	.31	56	−0.95 (0.32)	3.9×10^{-3}[a]	61	−0.02 (0.17)	.89	61	−0.19 (0.07)	.42	59	−0.50 (0.21)	.02

In order to compare the results between the GSMR analysis and the other MR analysis, the same SNPs were used in each MR method. MR-Egger meta-regression intercept different from zero (p value $< .05$) was tested as an indication of directional horizontal pleiotropy driving the results. An MR-Egger test intercept different from zero was observed in the DBP-IGAP analysis. In this case, MR-Egger was chosen to estimate the causal relationship between BP and AD. In all the other analyses, no horizontal pleiotropy was detected (pleiotropy $p > .05$) and an IVW method was used to estimate a causal effect. A Cochran's Q heterogeneity p value $> .10$ was observed in all analyses. All analyses used the ICBP GWAS summary statistics (19) of SNPs strongly associated with hypertension ($p < 5 \times 10^{-8}$) as the exposure. As outcome, we used either diagnosis of AD (IGAP Stage 1 summary statistics) (20) or family history of AD as proxy for AD or dementia (UKBB logistic regression; family history of AD ~ SNPs + batch effect + array + center + 40 principal components). MA-AD [Marioni *et al.* (21)] analysis used two-stage meta-analysis that combined PFH and MFH of AD and the IGAP study summary statistics (21).

AD, Alzheimer's disease; BP, blood pressure; GSMR, generalized summary Mendelian randomization; GWAS, genome-wide association study; ICBP, International Consortium for Blood Pressure; IGAP, International Genomics of Alzheimer's Project; IVW, inverse variance weighted; MA-AD, combined meta-analysis; MFH, maternal family history; MR, Mendelian randomization; PFH, paternal family history; SNP, single nucleotide polymorphism; UKBB, UK Biobank.

[a]Intercept different from zero.

sets we showed how increased power can provide more conclusive results when using MR methods. For this study, we used systolic and diastolic measures of BP that have a shared genetic component. Even though two-thirds of the SNPs used in this study were associated with both SBP and DBP (Table S1), a slightly stronger association was detected with DBP (Table 1).

This study included only genetic instruments that showed the strongest association with high BP and that were recently published in a large meta-analysis (~1 million individuals). We applied stringent filters to include only SNPs that confirmed previous findings to avoid weaknesses often found in instrument selection (19). Three previous publications (28–30) used causal inference, performing MR with genetic instruments selected from large-scale GWASs. However, the analyses reported contradictory results. First, Østergaard *et al.* (28) reported a protective causal relationship of SBP with AD (OR of 0.83 [95% confidence interval (CI), 0.73–0.94] per genetically predicted 10-mm Hg increase in SBP) and included 24 SNPs using the IGAP summary statistics. Second, Larsson *et al.* (29) found no association between SBP (OR of 0.94 [95% CI, 0.77–1.14] per genetically predicted 10-mm Hg increase in SBP) or DBP (OR of 0.96 [95% CI, 0.79–1.16] per genetically predicted 10-mm Hg increase in DBP) with AD, retaining 100 SNPs and using, also, the IGAP summary statistics. Third, Andrews *et al.* (30) also found a moderate protective effect of both SBP (OR of 0.99 [95% CI, 0.99–1.00] per genetically predicted 10-mm Hg increase in SBP) and DBP (OR of 0.99 [95% CI, 0.98–0.99] per genetically predicted 10-mm Hg increase in SBP) using both novel and replicated SNPs associated with BP (435 SNPs for SBP analyses and 450 SNPs for DBP analyses) published by Evangelou *et al.* (19) and using a recent meta-analysis of AD diagnosis as MR outcome published by Kunkle *et al.* (31). Owing to the common outcome GWAS dataset used (IGAP), the different results detected in the MR analyses reported by Larsson *et al.* (29) compared with the results published by Østergaard *et al.* (28) depend exclusively on the choice of the genetic instruments. The discordant results reported by these two studies may be due to a greater number of SNPs used by Larsson *et al.* (29), giving a greater power to detect a larger proportion of variance, hence the detection of a true null association. However, there is also a possibility of a dilution of the association due to a greater pleiotropy caused by the higher number of instruments. Our study also used the IGAP results, but we included a more powerful combined meta-analysis including the IGAP and UKBB together (21), which reached a significant statistical power to detect a causal effect of ~96% in the DBP analyses and 94% in the SBP analyses (Table S2). Our results were consistent both at the single-study level (PFH/MFH; IGAP) and when using summary statistics from the AD meta-analysis published by Marioni *et al.* (21). Moreover, the uncertainty in the SNP-exposure and SNP-outcome association estimates is independent, and if weak instrument bias were an issue, effects would be in the direction toward the null and, therefore, would not be the cause of overestimation of the MR estimates (18). It is also important to note that the overlap of SNPs between these two previous MR studies (28,29) and our results is marginal (Table S1).

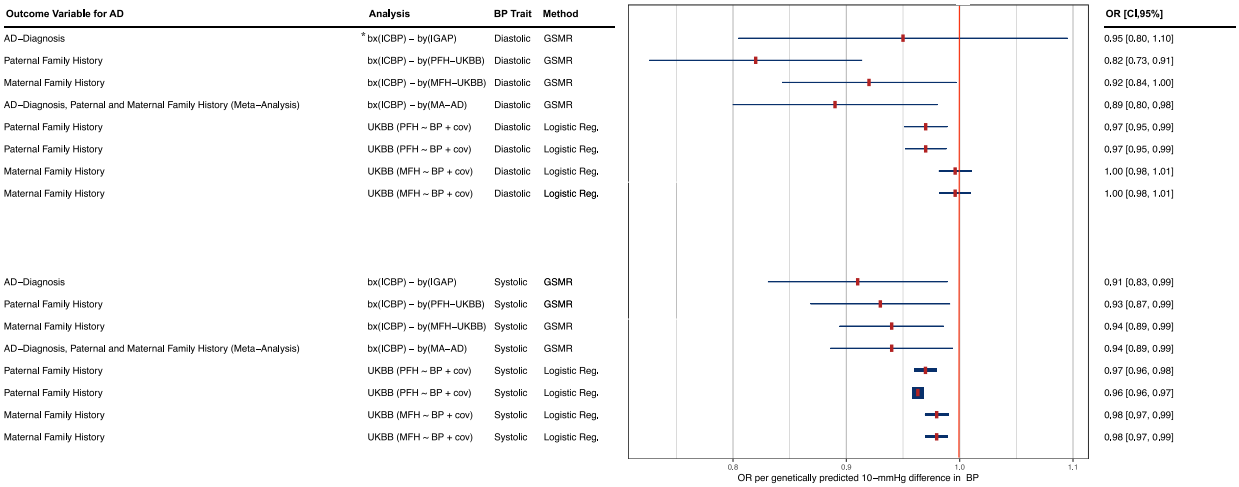

Figure 2. Forest plot of Mendelian randomization (MR) and logistic regression estimates of the relationship between systolic blood pressure (SBP)/diastolic blood pressure (DBP) and family history of Alzheimer's disease (AD) or AD diagnosis. The forest plot figure reports both observational and generalized summary Mendelian randomization (GSMR) estimates of the relationship between DBP and SBP and dementia outcome. The MR outcome variable used genome-wide association study summary statistics from the following: BP exposure, using the International Consortium for Blood Pressure (ICBP) meta-analysis (19); AD diagnosis, using the International Genomics of Alzheimer's Project [IGAP] Stage 1 meta-analysis (19); paternal family history (PFH) of AD and maternal family history (MFH) of AD, using the UK Biobank (UKBB) database; and a combined meta-analysis (MA-AD) including PFH-UKBB/MFH-UKBB data and the IGAP meta-analysis (21). A separate logistic regression analysis used family history of AD and either the first or the second BP measurement, adjusting the model for population stratification, genetic batch, array, assessment center, body mass index, age at assessment, sex, smoking (binary [smoker/ever smoker]), and hypertension medication (binary [yes/no]). Red line indicates no effect. Red dots represent odds ratio (OR) per genetically predicted 10-mm Hg difference in BP, and bars represent 95% confidence intervals (CIs). bx (beta estimates$_{exposure(BP)}$) and by (beta estimates$_{outcome(AD)}$) were used in the MR analyses. *An MR-Egger test intercept different from zero was observed, indicating a source of pleiotropy. cov, covariates; Logistic Reg., logistic regression analysis.

On the contrary, the MR study published by Andrews *et al.* (30) included a larger number of instrument SNP variables compared with the two previously published MR studies and used the same exposure GWAS dataset associated with BP used in the present study (19). Owing to usage of different GWAS outcome datasets, we tested the instrument variables used in the analyses reported in this study [excluding the novel SNPs reported by Evangelou *et al.* (19) but included by Andrew *et al.* (30)] against the recent GWAS meta-analysis on AD diagnosis (31) used by Andrew *et al.* (30). Our analyses did not reach enough statistical power for either SBP (OR, 0.97 [95% CI, 0.89–1.05]; 13.3% power) or DBP (OR, 0.96 [95% CI, 0.84–1.10]; 8.4% power) to detect a true causal effect, whereas Andrew *et al.* (30) reported a power of 72% for SBP and 88% for DBP analyses. However, the authors (30) reported the presence of heterogeneity in both MR models, while we did not find any evidence that our analyses required further corrections when using only established SNPs associated with BP. These sensitivity analyses' results are reported in the Supplement (MR power analyses in Table S2 and MR analyses in Table S5) and have not been used in our main analyses owing to a lack of statistical power in the MR method.

Study Limitations

Self-reported parental family history of AD and dementia from UKBB participants was employed as a proxy phenotype for assignment of cases and controls in this study. We accept that this information could be affected by a self-reporting bias; however, along with variable accuracy, this was already evaluated through genetic correlation analysis in a global meta-analysis showing that self-reported information of parental AD can indeed reflect an accurate proxy for clinical diagnosis (21). It should be noted that all individuals included in these datasets were of European ancestry (19–21), which limits the applicability of our findings to more diverse ethnic populations.

There are several potential confounders that were considered when planning this study. First, to overcome the issue of population stratification, we corrected the UKBB genetic associations for population relationship by including genetic principal components (32). Second, antihypertensive medication use has a modifying effect on the exposure, and this confounding might have induced the inverse causal effect detected by our MR analysis between AD risk and high BP (17,28). Meta-analyses that published the effect of antihypertensive medications on AD show contradictory results (either a protective effect or no effect) (Table S4). Our observational results remained unaffected after adjusting for this (Figure 2), and a recent study that used an MR approach to determine the effect of antihypertensive drugs on AD risk did not detect any causal effect by alleviating high BP (33). Third, the risk of death associated with high BP could compete with the risk of dementia, and associations detected might be affected by survival bias (17,34). Specifically, the follow-up of individuals genetically predisposed to high BP (SBP/DBP) might be discontinued owing to the higher mortality rate (due to other clinical complications, such as stroke or heart attack) (35) of this group without reaching dementia diagnosis (17).

It is also important to note that the UKBB is a healthy volunteer cohort (36). Therefore, we tested whether the offspring of parents with an AD diagnosis had a healthier lifestyle by comparing the moderate-to-vigorous physical activity score (37) in individuals with either PFH or MFH history of AD against controls with no family history. The comparison of the moderate-to-vigorous physical activity score means in the offspring groups with family history of AD and no family history of AD showed no statistically significant differences (Table S6). Therefore, a change in the offspring lifestyle, hence physical activity, does not seem an attributable confounding factor influencing results interpretability.

The UKBB included individuals with AD family history with age at assessment close to AD average age at onset of 65 years (MFH: median age 61 years; PFH: median age 59 years) compared with subjects with no AD family history (median age 57.5 years) (Table S6). On the one hand, when comparing UKBB BP measurements in these two groups (Table S7A, B) by subgrouping them in age groups, hypertension was detected neither in the group $<$50 years of age nor in the group with age ranging from 50 to 59 years, nor was hypotension detected in the group $>$60 years of age, as we could expect considering recent findings of midlife hypertension and late-life hypotension in AD subjects (38). On the other hand, hypertension between 140 and 150 mm Hg was observed in the group $>$60 years of age, and the family history of AD groups showed a slightly lower overall BP compared with the group no family history of AD. This could still imply a healthier volunteer composition of the UKBB (36).

However, the IGAP study, by including AD-diagnosed patients with a minimum age at onset of 68 years and older, presented similar MR results, included either as an MR outcome by itself or in combination with the UKBB in an overall meta-analysis (MA-AD) (21). It still needs to be addressed whether possible hypotension could explain the results obtained using the IGAP summary statistics, considering that no BP measurement was provided by the IGAP consortium.

In conclusion, this study leverages support for a causal association between high SBP and/or high DBP BP profiles and a reduced late-life risk of AD. Our findings were obtained by analysis of the estimates associated with genetic instruments, previously identified by GWASs within participants of European ancestry. This was followed by the application of multiple MR methods to minimize the extent of confounding factors and allow exclusion of genetic instrument outliers. Nevertheless, further research is required to confirm the impact of the use of antihypertensive drugs on dementia outcomes and address potential survival bias, in order to determine whether the protective causal effect detected in the present and previous MR studies (26) can describe the true nature of the relationship between BP and AD.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by Janssen Research and Development, LLC (of Johnson & Johnson). The authors who received direct salary support were WS, LW, DN, and MF.

WS and LW had full access to the UK Biobank data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. WS, AJN-H, LW, and DN were involved in concept and design. All authors were involved in acquisition, analysis, or interpretation of data. WS and LW were involved in drafting of the manuscript. WS, LW, DN, MF, LS, SMG, AP-U, DPA, and AJN-H were involved in critical revision of the manuscript for important intellectual content. WS and LW were involved in statistical analysis. DN and AJN-H obtained funding. LW, DN, AJN-H, and NB were involved in administrative, technical, or material support. LW, AJN-H, and NB supervised.

We thank Prof. Simon Lovestone, Prof. John Isaac, Dr. Vaibhav A. Narayan, and Dr. Dai Wang for the helpful discussion on the project.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry (WS, LW, DN, MF, LS, SMG, NJB, AJN-H) and the Centre for Statistics in Medicine (AP-U, DPA), Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, United Kingdom; and 4YouandMe (SMG), Seattle, Washington.

Address correspondence to William Sproviero, Ph.D., at william.sproviero@psych.ox.ac.uk.

Received Jan 7, 2020; revised Dec 11, 2020; accepted Dec 14, 2020.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2020.12.015.

REFERENCES

1. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pèrez JM, Evans AC, Alzheimer's Disease Neuroimaging Initiative (2016): Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun 7:11934.
2. Emdin CA, Rothwell PM, Salimi-Khorshidi G, Kiran A, Conrad N, Callender T, *et al.* (2016): Blood pressure and risk of vascular dementia: Evidence from a primary care registry and a cohort study of transient ischemic attack and stroke. Stroke 47:1429–1435.
3. Prince M, Albanese E, Maelenn G, Prina AM (2014): World Alzheimer Report 2014. London, UK: Alzheimer's Disease International.
4. Peila R, White LR, Petrovich H, Masaki K, Ross GW, Havlik RJ, *et al.* (2001): Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment. Stroke 32:2882–2889.
5. Skoog I, Nilsson L, Persson L, Lernfelt B, Landahl S, Palmertz B, *et al.* (1996): 15-Year longitudinal study of blood pressure and dementia. Lancet 347:1141–1145.
6. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, *et al.* (2002): Apolipoprotein Epsilon 4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med 137:149–155.
7. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ (2000): Midlife blood pressure and dementia: The Honolulu-Asia aging study. Neurobiol Aging 21:49–55.
8. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K (2005): Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 64:277–281.
9. Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G (2003): Association between dementia and midlife risk factors: The Radiation Effects Research Foundation Adult Health Study. J Am Geriatr Soc 51:410–414.
10. Barnes DE, Yaffe K (2011): The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 10:819–828.
11. Meng XF, Yu JT, Wang HF, Tan MS, Wang C, Tan CC, Tan L (2014): Midlife vascular risk factors and the risk of Alzheimer's disease: A systematic review and meta-analysis. Journal of Alzheimer's Disease 42:1295–1310.
12. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D (2011): The association between blood pressure and incident Alzheimer disease: A systematic review and meta-analysis. Epidemiology 22:646–659.

13. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014): Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. Lancet Neurol 13:788–794.
14. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, *et al.* (2017): Dementia prevention, intervention, and care. Lancet 390:2673–2734.
15. SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, *et al.* (2019): Effect of intensive vs standard blood pressure control on probable dementia: A randomized clinical trial. JAMA 321:553–561.
16. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, *et al.* (2008): Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): A double-blind, placebo controlled trial. Lancet Neurol 7:683–689.
17. Gregson J, Qizilbash N, Iwagami M, Douglas I, Johnson M, Pearce N, Pocock S (2019): Blood pressure and risk of dementia and its subtypes: A historical cohort study with long-term follow-up in 2.6 million people. Eur J Neurol 26:1479–1486.
18. Hemani G, Bowden J, Davey Smith G (2018): Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum Mol Genet 27:R195–R208.
19. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, *et al.* (2018): Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet 50:1412–1415.
20. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, *et al.* (2013): Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 45:1452–1458.
21. Marioni RE, Harris SE, Zhang Q, McRae AF, Hagenaars SP, Hill WD, *et al.* (2018): GWAS on family history of Alzheimer's disease [published correction appears in Transl Psychiatry 2019; 9:161]. Transl Psychiatry 8:99.
22. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, *et al.* (2017): Genome-wide genetic data on ~500,000 UK Biobank participants. bioRxiv. https://doi.org/10.1101/166298.
23. Staley JR, Blackshaw J, Kamat MA, Ellis S, Surendran P, Sun BB, *et al.* (2016): PhenoScanner: A database of human genotype-phenotype associations. Bioinformatics 32:3207–3209.
24. Zhu Z, Zheng Z, Zhang F, Wu Y, Trzaskowski M, Maier R, *et al.* (2018): Causal associations between risk factors and common diseases inferred from GWAS summary data. Nat Commun 9:224.
25. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, *et al.* (2018): The MR-Base platform supports systematic causal inference across the human phenome. Elife 7:e34408.
26. Bowden J, Davey Smith G, Burgess S (2015): Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. Int J Epidemiol 44:512–525.
27. Burgess S (2014): Sample size and power calculations in Mendelian randomization with a single instrumental variable and a binary outcome. Int J Epidemiol 43:922–929.
28. Østergaard SD, Mukherjee S, Sharp SJ, Proitsi P, Lotta LA, Day F, *et al.* (2015): Associations between potentially modifiable risk factors and Alzheimer disease: A Mendelian randomization study. PLoS Med 12:e1001841; discussion e1001841
29. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS (2017): Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. BMJ 359:j5375.
30. Andrews SJ, Marcora E, Goatea A (2020): Causal associations between potentially modifiable risk factors and the Alzheimer's disease phenome: A Mendelian randomization study. bioRxiv. https://doi.org/10.1101/689752.
31. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, *et al.* (2019): Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet 51:414–430.
32. Ma J, Amos CI (2012): Principal components analysis of population admixture. PLoS One 7:e40115.
33. Walker VM, Kehoe PG, Martin RM, Davies NK (2020): Repurposing antihypertensive drugs for the prevention of Alzheimer's disease: A Mendelian randomization study. Int J Epidemiol 49:1132–1140.
34. Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiébaut R, *et al.* (2015): Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. Alzheimers Dement 11:1098–1109.
35. Ghazi L, Oparil S (2018): Impact of the SPRINT trial on hypertension management. Annu Rev Med 69:81–95.
36. Chudasama YV, Khunti KK, Zaccardi F, Rowlands AV, Yates T, Gillies CL, *et al.* (2019): Physical activity, multimorbidity, and life expectancy: A UK Biobank longitudinal study. BMC Med 17:108.
37. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, *et al.* (2017): Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 186:1026–1034.
38. Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, *et al.* (2019): Association of midlife to late-life blood pressure patterns with incident dementia. JAMA 322:535–545.