

## RESEARCH ARTICLE

# Midlife vascular risk factors and risk of incident dementia: Longitudinal cohort and Mendelian randomization analyses in the UK Biobank

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[Correction added on 11 February 2022, after first online publication: Rainer Malik has been designated as the corresponding author.]

## Abstract

**Introduction:** Midlife clustering of vascular risk factors has been associated with late-life dementia, but causal effects of individual biological and lifestyle factors remain largely unknown.

**Methods:** Among 229,976 individuals (mean follow-up 9 years), we explored whether midlife cardiovascular health measured by Life's Simple 7 (LS7) is associated with incident all-cause dementia and whether the individual components of the score are causally associated with dementia.

**Results:** Adherence to the biological metrics of LS7 (blood pressure, cholesterol, glycemic status) was associated with lower incident dementia risk (hazard ratio = 0.93 per 1-point increase, 95% confidence interval [CI; 0.89–0.96]). In contrast, there was no association between the composite LS7 score and the lifestyle subscore (smoking, body mass index, diet, physical activity) and incident dementia. In Mendelian randomization analyses, genetically elevated blood pressure was associated with higher risk of dementia (odds ratio = 1.31 per one-standard deviation increase, 95% CI [1.05–1.60]).

**Discussion:** These findings underscore the importance of blood pressure control in midlife to mitigate dementia risk.

## KEYWORDS

blood pressure, dementia, epidemiology, genetics, hypertension, Life's Simple 7, Mendelian randomization, risk factors

## 1 | INTRODUCTION

Dementia is a major public health concern posing substantial burden on patients, their proxies, and national health-care systems.<sup>1–3</sup> The patho-

physiological processes leading to dementia start many years before the manifestation of clinically identifiable cognitive deficits later in life. Consequently, preventive strategies should target risk factors that manifest during midlife, which is roughly defined as the period between

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## RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature on the association of the American Heart Association-defined Life's Simple 7 (LS7), a composite score composed of three biological (blood pressure, cholesterol levels, glycemic status) and four lifestyle (smoking, body mass index, diet, physical activity) cardiovascular health metrics with dementia. While adherence to the LS7 recommendations is associated with a lower risk of cardiometabolic disease, such as type 2 diabetes, myocardial infarction, and stroke, its value for dementia prevention is still debated.
2. Interpretation: In a longitudinal cohort study involving 229,976 dementia-free individuals of European ancestry aged 40 to 69 years, an increased midlife burden of classical biological risk factors (hypertension, hypercholesterolemia, diabetes) was associated with a higher risk for incident dementia over 9 years of follow-up. Mendelian randomization suggested genetically elevated blood pressure to be causally associated with a higher risk of incident dementia. Hence, midlife management of biological risk factors, specifically of high blood pressure, could reduce the risk of late-life dementia.
3. Future directions: These findings support the efficacy of blood-pressure-lowering strategies for reducing dementia burden and call for additional clinical trials.

40 and 65 years of age.<sup>1,3</sup> Indeed, previous studies support differential associations between midlife ( $\leq 65$  years) and late-life ( $> 65$  years) risk factors and dementia risk.<sup>4,5</sup> The American Heart Association (AHA) defined Life's Simple 7 (LS7), a composite score composed of three biological (blood pressure, cholesterol levels, glycemic status) and four lifestyle (smoking, body mass index [BMI], diet, physical activity) cardiovascular health (CVH) metrics for primordial or primary prevention of cardiovascular disease.<sup>6–8</sup> Adherence to the LS7 ideal CVH recommendations is associated with a lower risk of cardiometabolic disease, such as type 2 diabetes,<sup>9</sup> myocardial infarction,<sup>10</sup> and stroke. Whether adherence to these recommendations could also be of value for dementia prevention, is still debated.

Several cohort studies have explored the association between the LS7 score and risk of late-life dementia or cognitive decline, with inconsistent results.<sup>7,12–15</sup> Potential sources of the inconsistency between studies include differences with regard to sample characteristics and study design. For instance, a high age at baseline assessment and short duration of follow-up might introduce a bias by disregarding the long preclinical phase of dementia thus leading to reverse causation effects. This has been specifically demonstrated for blood pressure and BMI, two of the components of the LS7 score.<sup>4,5</sup> Furthermore, despite a rigorous adjustment for potential confounders, analyses of observational studies remain prone to residual unmeasured confounding. Hence, evi-

dence from observational data alone is insufficient to establish causal relationships between candidate risk factors and dementia risk and to support recommendations for preventive treatments.

Mendelian randomization (MR) uses genetic variants that are associated with an exposure of interest as instruments, and investigates their associations with disease outcomes, thus overcoming some of the key limitations of observational studies such as confounding and reverse causation.<sup>16</sup> As such, MR allows making inferences about causality.<sup>17,18</sup> Previous MR studies exploring associations of vascular risk factors with Alzheimer's disease (AD) failed to show significant causal associations<sup>19,20</sup> but the clinical diagnosis of AD dementia requires the exclusion of substantial concomitant cerebrovascular disease that could have a substantial effect on cognition.<sup>21</sup> Genetic signals representing vascular contribution to dementia are underrepresented in genome-wide association studies (GWAS) of AD, as shown before in a study of coronary artery disease and AD.<sup>22</sup> To inform broadly applicable strategies for dementia prevention, MR studies should, next to more focused MR studies on dementia subtypes, primarily focus on all-cause dementia as an outcome. To our knowledge, such studies currently do not exist.

Here, using large-scale data from  $\approx 230,000$  individuals aged 40 to 69 years from the UK Biobank (UKB), who were followed for a period of up to 12 years, we aimed to (1) determine associations of the baseline LS7 score, as well as its biological and lifestyle subscores with incident all-cause dementia; (2) identify linear and non-linear relationships between individual vascular risk factors and incident all-cause dementia; and (3) exploit MR analyses to establish causal associations between individual vascular risk factors and all-cause dementia.

## 2 | METHODS

This study is based on data from the UKB study that received approval from the National Information Governance Board for Health and Social Care and the National Health Service NorthWestMulticenter Research Ethics Committee. All participants provided informed consent through electronic signature at baseline assessment. Data were accessed via the UKB project proposals 2532 and 33018.

## 2.1 | Study population

The UKB is a population-based cohort of more than 500,000 participants who attended 1 of 22 assessment centers across the United Kingdom between 2006 and 2010.<sup>23</sup> Clinical, genetic, and risk factor data were obtained at baseline. Clinical outcomes including dementia diagnoses are available over a follow-up period extending up to 2017 via self-report; hospital in-patient records; death certificates; and, for a subset of 229,976 participants, also primary care records. Here, we restricted our analyses to only those individuals with available primary care records to minimize the risk of misclassification of dementia cases and to better reflect the spectrum of dementia cases in the general population than would be the case with hospital codes alone. Furthermore, the current analyses are restricted to participants without self-reported or prevalent dementia at baseline (Figure S1 in supporting

information). Censoring was performed at the last available date in the primary care records dataset (December 29, 2018).

## 2.2 | Life's Simple 7 score

The LS7 score was constructed based on AHA recommendations categorizing each metric into three levels (coded as poor = 0, intermediate = 1, and optimal = 2),<sup>6</sup> as detail in Table S1 in supporting information. The variables used from the UKB dataset to construct each metric are detailed in Table S2 in supporting information.

Missing raw values were imputed by multiple imputations using chained equations with 40 imputations and all remaining variables as predictors, as implemented in the "mice" package in R. We used the sum of each metric to calculate the LS7 score (range 0–14) with higher scores corresponding to more optimal CVH. We calculated two subscores: a biological subscore defined by the sum of the biological metrics (blood pressure, cholesterol, glycemic status) ranging from 0 (worst) to 6 (best), and a lifestyle subscore defined by the sum of the behavioral metrics (smoking status, BMI, physical activity, diet) ranging from 0 (worst) to 8 (best), as recommended by the AHA.<sup>6</sup>

## 2.3 | Dementia diagnosis

All-cause dementia was ascertained using hospital in-patient records containing data on admissions and diagnoses obtained from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales. Additional cases were detected through linkage to death register data provided by the National Health Service Digital for England and Wales and the Information Services Division for Scotland. Diagnoses were recorded using the International Classification of Diseases (ICD9 and ICD10) coding system. For the current analyses, the algorithmically defined all-cause dementia outcomes (Fields 42018 and 42019) were used.<sup>24</sup> In addition, dementia diagnoses were retrieved from primary care data using read codes (version 2 [Read v2] and version 3 [CTV3 or Read v3]). Both non-administrative and administrative codings were used, as suggested by a recent study showing that dementia diagnoses can be reliably identified from these sources with a positive predictive value (PPV) of 82.5% combining all data sources.<sup>25</sup> Events based solely on self-report (N = 24) were discarded from the analysis.

## 2.4 | Covariates

All main models were adjusted for age at baseline (Field 21022); sex (Field 31); education, categorized as higher (college/university degree or other professional qualification) or lower (Field 6138); and socioeconomic status, categorized as quintiles 1, 2 to 4, and 5 (Field 189: Townsend deprivation index [combining information on social class, employment, car availability and housing]). For the extended model, we also considered the following additional variables: apolipoprotein E (APOE)  $\epsilon$ 4 carrier status (carrier/non-carrier status as defined by genetic information); baseline depression defined as a combined score of > 3 (Field 2050 and 2060); history of depression (Field 2090); prevalent or incident cardiovascular disease (Fields 42006–42013,

ICD10, and OPCS4 codes) and self-reported ethnicity (White/non-White; Field 21000).

Genetic models were additionally corrected for genotyping chip, assessment center visited, and the first 20 principal components of ancestry to correct for population stratification.

## 2.5 | Statistical analysis

### 2.5.1 | Observational analysis

Cox proportional hazard regression models were used to examine the association of the overall LS7 score and the biological and lifestyle subscores with time to incident all-cause dementia in the primary care dataset (N = 229,976). Participants were considered at risk for dementia from baseline (2006–2010) and were followed up until the date of first diagnosis, death, loss to follow-up, or the last date with available information from hospital admission. Proportional hazards were tested using scaled Schoenfeld's residuals without indication for violation of the assumption (all global Schoenfeld tests  $P > 0.05$ ). As shown before,<sup>7</sup> prevalent or incident cardiovascular disease can modify the association between the LS7 score and incident dementia. Hence, we performed a sensitivity analysis excluding both prevalent and incident cardiovascular disease. For competing risk analysis, a Fine–Gray proportional subhazard model was used.<sup>26</sup> Seven thousand six hundred seventy-seven participants (3.3%) without an incident dementia event died within the follow-up period and were thus considered in multivariable competing mortality risks analyses. As an additional competing risks analysis, we also performed cause-specific Cox proportional hazard regression (CSC) with incident dementia and death as the two competing causes. To explore non-linear effects of individual components of the LS7 score on incident dementia cubic spline terms were introduced in the models using continuous measures of the individual components: systolic blood pressure (SBP), low-density lipoprotein (LDL) cholesterol, and glycated hemoglobin A1c (HbA1c) levels as well as a previously described lifetime smoking index,<sup>27</sup> BMI, metabolic equivalent task (MET) minutes per week, and a healthy diet score.<sup>28,29</sup>

### 2.5.2 | Mendelian randomization

Two-sample MR analyses were conducted to explore associations between the above-mentioned continuous variables and risk of dementia. Exposures were chosen as continuous variables, as MR analyses of binary exposures can be biased due to violation of the exclusion restriction assumption.<sup>30</sup> Genetic variants to be used as instruments for MR were derived from previous GWAS studies or GWAS analyses that we performed for this purpose in the UKB, as detailed in the supporting information. The sets of the used genetic instruments are available in Tables S3–S9 in supporting information.

A GWAS on all-cause dementia was performed using logistic regression with PLINK2 on unrelated White British UKB participants in the primary care dataset (N = 190,154; 1868 dementia cases and 188,286 dementia-free controls). GWAS summary statistics were used as the outcome variable in MR. MR estimates for each instrument

**TABLE 1** Baseline characteristics of study participants by incident dementia status

Variables	Incident dementia (N = 2143)	No incident dementia (N = 227,833)	P
Age at baseline, mean (SD), y	63.2 (5.7)	56.4 (8.1)	< 0.001
Sex, N (%)			
Male	1126 (52.5)	103,120 (45.3)	< 0.001
Female	1017 (47.5)	124,713 (54.7)	
Education, N (%) <sup>a</sup>			
Low	1708 (79.7)	155,072 (68.1)	< 0.001
High	435 (20.3)	72,761 (31.9)	
Socioeconomic status, N (%) <sup>b</sup>			
Quintile 1	405 (18.9)	45,115 (19.8)	< 0.001
Quintile 2–4	1194 (55.7)	138,382 (60.7)	
Quintile 5	544 (25.4)	43,997 (19.3)	
Smoking status			
Never smoked	1068 (49.8)	125,220 (55.0)	< 0.001
Former smoker	845 (39.4)	78,502 (34.5)	
Current smoker	230 (10.7)	24,111 (10.6)	
BMI, mean (SD), kg/m <sup>2</sup>	27.6 (4.8)	27.5 (4.8)	0.28
Physical activity, median (IQR), h/week	5 (5)	5 (6)	0.025
Diet score, mean (SD) <sup>c</sup>	4.4 (1.5)	4.2 (1.5)	< 0.001
SBP, mean (SD), mmHg	143.4 (20.3)	138.2 (18.7)	< 0.001
DBP, mean (SD), mmHg	81.9 (10.3)	82.4 (10.2)	0.025
Antihypertensive medications, N (%)	777 (36.3)	47,456 (20.8)	< 0.001
HbA1c, median (IQR), %	5.5 (5.2–5.8)	5.4 (5.1–5.6)	< 0.001
Glucose-lowering medications, N (%)	88 (4.1)	2,527 (1.1)	< 0.001
LDL-C, mean (SD), mg/dL	134.0 (37.1)	137.8 (33.8)	< 0.001
Lipid-modifying medications, N (%)	728 (33.9)	39,845 (17.5)	< 0.001

Note: P-values are derived using either Student's t-test, Wilcoxon rank sum test, or Chi-square test.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation.

<sup>a</sup>Education categorized as higher (college/university degree or other professional qualification) or lower.

<sup>b</sup>Socioeconomic status quintiles according to Townsend deprivation index combining information on social class, employment, car availability, and housing.

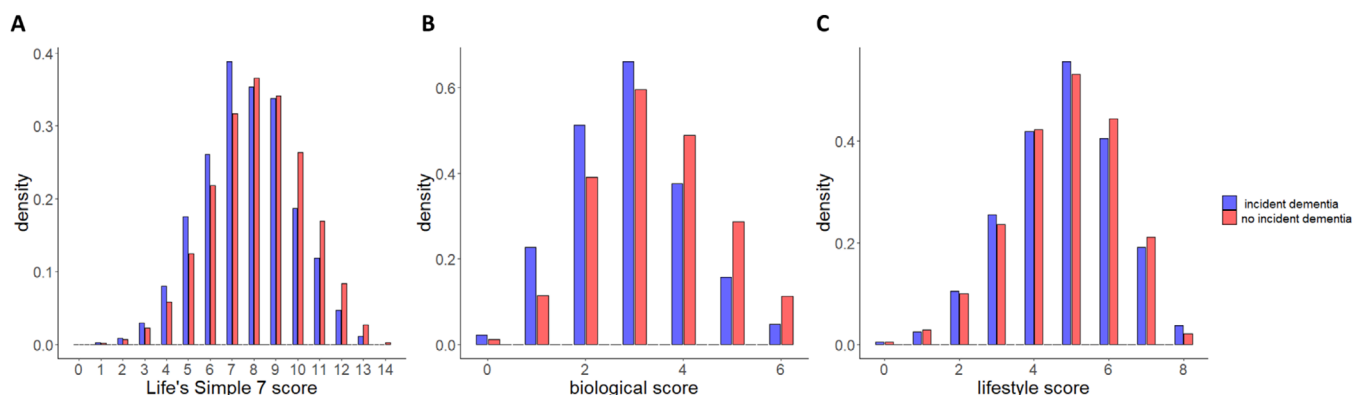
<sup>c</sup>Healthy diet score according to Mozaffarian et al.<sup>28</sup> and Said et al;<sup>29</sup> higher scores indicate adherence to a healthier diet for prevention of cardiovascular disease.

were computed with the Wald statistics and standard errors were calculated with the Delta method. As the primary method of analysis, individual MR estimates were pooled using random-effects inverse-variance weighted (IVW) meta-analyses.<sup>31</sup> Statistical significance was set at a *P*-value < 0.05. MR estimates derived from the IVW approach might be biased if the variants are pleiotropic. As a measure of overall pleiotropy, heterogeneity in the IVW MR analyses was assessed with the Cochran's Q statistic (statistical significance set at a *P* < 0.05).<sup>32</sup> Further, alternative MR methods were applied, which are more robust to pleiotropic variants. These were the weighted median estimator,<sup>33</sup> the contamination-mixture method,<sup>34</sup> and the MR-PRESSO.<sup>35</sup> Details about these approaches and their underlying assumptions are provided in the supporting information. All analyses were performed in R (v3.5.0; The R Foundation for Statistical Computing) using the MendelianRandomization, TwoSampleMR, and the MRPRESSO packages.

### 3 | RESULTS

At baseline, 229,976 participants from the primary care dataset were included in the observational analysis (Figure S1). Their mean age was 56.5 (standard deviation [SD] 8.1) years; 125,730 participants (54.6%) were women. During a median follow-up of 8.98 years (interquartile range [IQR] 8.34–9.74), 2143 incident dementia events were recorded, with 375 derived from hospital in-patient records alone, 1075 from primary care records alone, 32 from death records alone, and 661 from multiple sources. Baseline characteristics of participants by incident dementia status are shown in Table 1.

The LS7 score was normally distributed with a mean of 8.2 (SD 2.1). At baseline, 4.4% of individuals scored 0 to 4 points, 68.3% scored 5 to 9 points, and 27.3% scored 10 points or higher. The biological and lifestyle subscores were normally distributed with means of 3.4 (SD



**FIGURE 1** Distributions of (A) the Life's Simple 7 score, (B) the biological score, and (C) the lifestyle score at baseline, by incident dementia status. The y-axis represents the probability density function for the kernel density estimation

1.3) and 4.8 (SD 1.5), respectively. The total LS7 score at inclusion was significantly lower among individuals who developed incident dementia compared to individuals without incident dementia (mean 7.67 vs. 8.17,  $P < 2 \times 10^{-16}$ ). Focusing on the subscores, the biological subscore was significantly lower in individuals who developed incident dementia compared to individuals who did not develop incident dementia (mean 2.90 vs. 3.37,  $P < 2 \times 10^{-16}$ ), while there was no significant difference in the lifestyle subscores between individuals with and without incident dementia (mean 4.77 vs. 4.80,  $P = 0.354$ ; Figure 1A-C).

### 3.1 | Cardiovascular health at baseline and incident dementia

In the observational longitudinal analyses, there was a significant association between a higher biological subscore and a decreased risk of incident dementia (hazard ratio [HR] = 0.93 per 1-point increase, 95% confidence interval [CI]: 0.89–0.96,  $P = 8.5E-5$ ). This association followed a dose-response pattern with individuals scoring 2 to 3 and 4 or higher in the biological subscale showing gradually lower risks for incident dementia, compared to individuals scoring 0 or 1 (HR = 0.73 for 2–3, 95% CI [0.63–0.83],  $P = 1.2E-6$ ; HR = 0.67 for 4–6, 95% CI [0.58–0.76],  $P = 1.0E-7$ ). There was neither an association of the lifestyle subscore (HR = 1.01 per 1-point increase, 95% CI [0.98–1.04],  $P = 0.53$ ) nor of the composite LS7 score (HR = 0.98 per 1-point increment, 95% CI [0.96–1.00],  $P = 0.08$ ) with risk of incident dementia (Table 2). In an extended analysis, further correcting for APOE  $\epsilon 4$  carrier status, baseline depression, history of depression, incident or prevalent cardiovascular disease, and ethnicity, we still observed a significant association between a higher biological subscore and a decreased risk of incident dementia (HR = 0.96 per 1-point increase, 95% CI [0.83–0.99],  $P = 9.2E-3$ ), while the LS7 score and the lifestyle subscore remained non-significant (HR = 0.99 per 1-point increase, 95% CI [0.97–1.01],  $P = 0.405$  and HR = 1.02 per 1-point increase, 95% CI [0.98–1.05],  $P = 0.223$ , respectively).

In sensitivity analyses, the association between the biological subscore and incident dementia remained significant and of similar magnitude when diagnoses were derived either from hospital-based records

alone (HR 0.93 per 1-point increase, 95% CI [0.88–0.98],  $P = 0.0051$ ) or from primary care records alone (HR 0.93 per 1-point increase, 95% CI [0.90–0.97],  $P = 0.0013$ ). The results further remained stable when excluding individuals with a history of myocardial infarction or stroke at baseline ( $N = 6847$  individuals; HR 0.94 per 1-point increase, 95% CI [0.90–0.97],  $P = 0.0034$ ) and when additionally excluding participants with incident myocardial infarction or stroke during follow-up ( $N = 12,305$  individuals; HR 0.94 per 1-point increase, 95% CI [0.90–0.98],  $P = 0.0065$ ), and when restricting the analysis to participants with a follow-up period  $> 8$  years ( $N = 190,064$  individuals, number of events = 204; HR 0.89 per 1-point increase, 95% CI [0.79–0.99],  $P = 0.039$ ). In addition, we observed significant associations between the biological score and both early-onset ( $< 65$  years: HR 0.93 per 1-point increase, 95% CI [0.86–0.99],  $P = 0.037$ ) and late-onset incident dementia ( $\geq 65$  years: HR 0.91 per 1-point increase, 95% CI [0.87–0.95],  $P = 1.65E-5$ ). We further stratified participants into four age groups at baseline (40–49 years, 50–59 years, 60–69 years, and  $> 69$  years). Results of these analyses are available in Table S10 in supporting information. While significance is lost in the youngest and oldest age groups due to reduced number of events, the effect is directionally consistent within all age groups. We did not observe differences when stratifying by sex (Table S11 in supporting information) or by antihypertensive medication use (Table S12 in supporting information). Also, competing risk analyses using Fine–Gray proportional subhazards and cause-specific CSC showed identical point estimates and confidence intervals for the biological subscore when considering death as a competing risk. Finally, we performed a sensitivity analysis using age as the time variable in the Cox proportional hazards model. Importantly, the results remained unchanged (HR 0.93 per 1-point increase, 95% CI [0.89–0.96],  $P = 1.31E-4$ ), further supporting the robustness of our model.

### 3.2 | Individual vascular risk factors and incident dementia

To gain additional insights into the relationship between LS7 and risk of incident dementia, associations with individual components of the



**TABLE 2** Risk for incident dementia according to the Life's Simple 7 score and its lifestyle and biological subscales

Predictor	Number of incident dementia events/Number of participants	Hazard ratio for incident dementia	95% confidence intervals	P
<b>unadjusted</b>				
Life's Simple 7 score (0–14; 1-point increment)		0.89	0.88–0.91	<b>&lt;2e-16</b>
0–4	130/10,018	1.00	(reference)	
5–9	1624/155,677	0.80	0.68–0.96	<b>0.019</b>
10–14	389/62,138	0.49	0.40–0.59	<b>1.2 × 10<sup>-12</sup></b>
Biological score (0–6; 1-point increment)		0.74	0.72–0.77	<b>&lt;2e-16</b>
0–1	266/14,391	1.00	(reference)	
2–3	1257/112,285	0.61	0.53–0.69	<b>1.5 × 10<sup>-13</sup></b>
4–6	620/101,157	0.33	0.29–0.38	<b>&lt;2e-16</b>
Lifestyle score (0–8; 1-point increment)		0.99	0.96–1.02	0.406
0–2	144/15,187	1.00	(reference)	
3–5	1319/135,669	1.03	0.87–1.22	0.741
6–8	680/76,977	0.94	0.78–1.12	0.490
<b>Adjusted for sex, age at baseline, education, deprivation index, and the lifestyle score (for biological) and biological score (for lifestyle)</b>				
Life's simple 7 score (0–14; 1-point increment)		0.98	0.96–1.00	0.081
0–4	130/10,018	1.00	(reference)	
5–9	1624/155,677	0.90	0.76–1.08	0.270
10–14	389/62,138	0.86	0.71–1.06	0.155
Biological score (0–6; 1-point increment)		0.93	0.89–0.96	<b>8.5 × 10<sup>-5</sup></b>
0–1	266/14,391	1.00	(reference)	
2–3	1,257/112,285	0.73	0.63–0.83	<b>1.2 × 10<sup>-6</sup></b>
4–6	620/101,157	0.67	0.58–0.76	<b>1.0 × 10<sup>-7</sup></b>
Lifestyle score (0–8; 1-point increment)		1.01	0.98–1.04	0.525
0–2	144/15,187	1.00	(reference)	
3–5	1,319/135,669	1.01	0.85–1.20	0.872
6–8	680/76,977	0.98	0.81–1.18	0.807

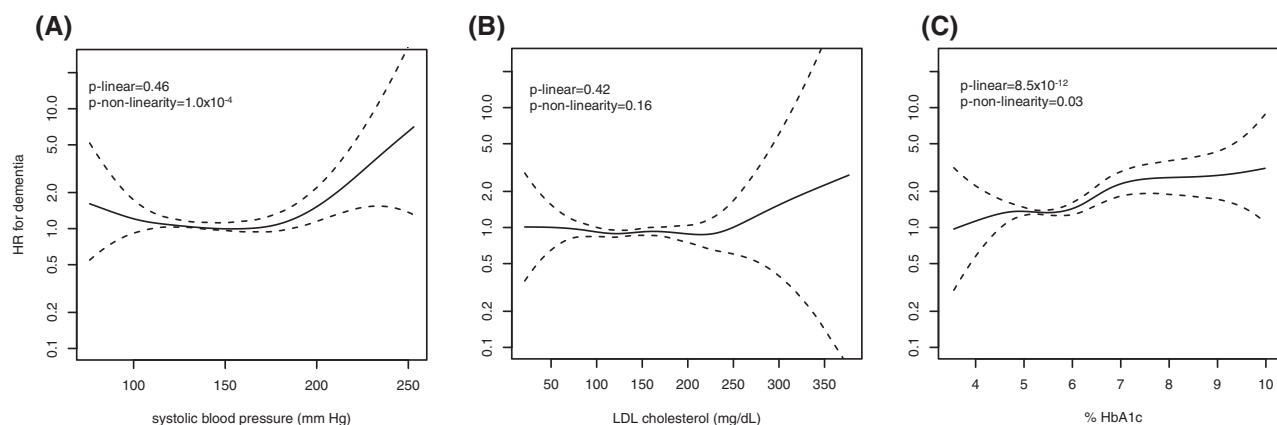
Notes: The results are derived from Cox proportional hazard regression models either unadjusted or adjusted for sex, age at baseline, education, deprivation index, and the lifestyle score (for biological), and biological score (for lifestyle) as covariates.

**Bold** indicates statistical significance ( $P$ -value < 0.05).

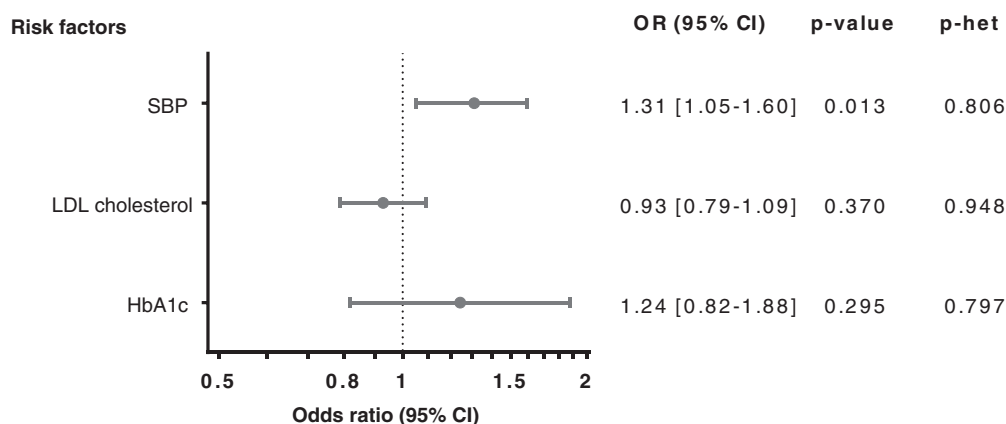
LS7 score were explored in cubic spline models. In analyses focusing on biological components of LS7, there was a significant ( $p$ -value for non-linearity =  $1E-4$ ) non-linear U-shape association between baseline SBP and incident dementia, a significant linear association between higher baseline HbA1c levels and increased risk of incident dementia, and no evidence for an association between baseline LDL cholesterol levels and incident dementia (Figure 2A–C). While the composite lifestyle score was not related to dementia risk, there was a significant association between lower BMI and increased risk of incident dementia (HR = 0.83 per 5 kg/m<sup>2</sup> increase, 95% CI [0.78–0.89],  $P = 0.0022$ ). Physical activity, smoking, and diet showed non-linear associations (Figure S2 in supporting information).

To explore the causal effects of individual components of LS7 on risk of dementia, two-sample MR analyses were conducted starting with the biological components of the score. The number of independent genetic variants that were used as instruments for SBP, LDL chole-

sterol levels, and HbA1C levels was 460, 189, and 176, respectively. In the primary IVW MR analyses, genetically elevated SBP was associated with higher risk of incident dementia (OR for 1 SD increase = 1.31, 95% CI [1.05–1.65],  $P = 0.013$ ; Figure 3), whereas there were no significant associations between genetically elevated levels of LDL cholesterol and HbA1c levels, respectively, and incident dementia risk. The effect estimates were consistent using alternative MR methods (weighted median, contamination mixture, MR-PRESSO; Table S13 in supporting information). In a sensitivity analysis, excluding individuals on antihypertensive medication from our outcome GWAS analysis, the results were directionally consistent, but non-significant (OR for 1 SD increase = 1.18, 95% CI [0.82–1.54],  $P = 0.12$ ). The number of independent genetic variants as instruments for smoking, BMI, physical activity, and diet was 126, 941, 3, and 12, respectively. There were no significant associations between smoking, BMI, physical activity, or diet in IVW or alternative MR methods (Table S13). Scatter plots for



**FIGURE 2** Risk for incident dementia according to individual items of the biological score (systolic blood pressure [A], LDL cholesterol [B], HbA1c levels [C]) of Life's Simple 7 using restricted cubic spline functions in Cox proportional hazard regression models. Median scores were used as a reference. The model is adjusted for sex, age at baseline, education, deprivation index, and the lifestyle scale score as covariates. Four knots were used in the calculation. p-linear refers to the linear association between the variable and the risk of dementia; p-non-linearity refers to the comparisons of the associations observed across the different splines in the non-linear cubic spline models. Dotted lines represent the 95% confidence intervals. Abbreviations. HbA1c, glycated hemoglobin A1c; HR, hazard ratio; LDL, low-density lipoprotein



**FIGURE 3** Mendelian randomization associations between genetic predisposition to individual items of the biological score (SBP, LDL cholesterol, HbA1c) of Life's Simple 7 and risk of incident dementia. Results are derived from random-effects inverse-variance weighted analyses and refer to 1 SD increment of the reported variables. Bars represent the 95% confidence intervals. The numbers of genetics variants included in the analyses were 460 for SBP, 189 for LDL cholesterol, and 176 for HbA1c. Variants in the apolipoprotein E region were excluded from the analysis for LDL cholesterol. Variants related to erythrocyte traits were excluded from the analysis for HbA1c. P-het refers to the p-value from the Cochran's Q statistic for heterogeneity. HbA1c, glycated hemoglobin A1c; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation

the MR results are presented in Figure S3 in supporting information. Due to partial overlap in the SBP exposure and the dementia outcome samples, we conducted a sensitivity analysis using effect sizes for the genetic instruments derived from the subsample of the UKB without primary care data available, making the two datasets independent. The results remained significant in this sensitivity analysis (IVW method: OR for 1-SD increment 1.35, 95% CI [1.03–1.78],  $P = 0.028$ ).

## 4 | DISCUSSION

Leveraging data from 230,000 individuals from the UKB and from large-scale genetic consortia, this study aimed to investigate the rela-

tionship between midlife CVH as measured with the LS7 score and risk of incident dementia over a 9-year follow-up period. Adherence to the biological component of the LS7 score (blood pressure, blood cholesterol, glycemic status) was associated with a lower risk of dementia during follow-up. Moreover, life-long genetically elevated SBP was associated with a higher risk of incident all-cause dementia, thus supporting a causal effect of elevated BP levels on dementia risk.

The current results support the candidacy of blood-pressure lowering in midlife as a key strategy for preventing late-life dementia. These results contrast with previous MR studies that found no or even beneficial effects of genetically elevated blood pressure on the risk of AD.<sup>19,20</sup> One recent study found no effect of blood pressure on AD via the protein targets of antihypertensive drugs.<sup>36</sup> However, these

studies focused on AD and not on all-cause dementia as the outcome and used a limited set of genetic instruments (25 and 93, respectively). Hence, these studies do not provide results comparable to those from the current study. Our results support a causal effect of genetically elevated SBP on dementia risk and broadly agree with results from the SPRINT-MIND trial, which found intensive blood-pressure lowering to < 120 mmHg to be associated with a reduction in the combined risk of mild cognitive impairment and probable dementia.<sup>37</sup> Moreover, in a recent meta-analysis of 12 clinical trials,<sup>38</sup> blood-pressure lowering was significantly associated with reduced risk of dementia or cognitive impairment. Previous observational studies support these effects of blood pressure to be age-dependent and midlife-specific. In the Whitehall II cohort systolic blood pressure at the age of 50, but not at age 60 or 70, was associated with the incidence of dementia.<sup>5</sup> Similarly, analyses of the Framingham Offspring study suggest that elevated blood pressure at the age of 40 to 64 years, but not from 65 years onward, associates with risk of incident dementia.<sup>39</sup> It is still debated through which mechanisms blood-pressure lowering might influence dementia risk. Two large meta-analyses did not reveal a specific antihypertensive drug class as optimal for preventing cognitive decline,<sup>40,41</sup> while one study showed that overall antihypertensive drug use is beneficial.<sup>42</sup> Our results were confirmed after excluding individuals on antihypertensive medication in our outcome dataset to be directionally consistent, but did not show statistical significance, most likely due to reduced power. On this basis, future large-scale clinical trials should continue exploring the effects of blood-pressure lowering in midlife on the risk of incident dementia later in life.

Our observational analyses further provide evidence for an association between glycemic status in midlife and risk of dementia. Specifically, there was a linear association between elevated HbA1c levels and incident dementia. The MR analyses did not confirm a causal relationship possibly because of insufficient statistical power. While not significant, the effect in the MR analyses was toward the same direction and of similar magnitude as in the observational analysis. The results further agree with previous cohort studies suggesting strong effects of glucose-related traits on dementia risk.<sup>43</sup> At any rate, the current findings highlight the need for further research on the potential causal role of glycemic traits on incident dementia risk.

In contradiction to the negative result of the total lifestyle subscore, we find linear and non-linear associations with individual items of the lifestyle subscore. However, none of these associations could be confirmed in MR analyses, thus suggesting presence of bias due to reverse causation, unmeasured confounding, or weak instruments. For example, the strong association of higher BMI with a decreased dementia risk observed here has been previously reported<sup>4</sup> and is believed to result from reverse causation. Specifically, the association is confounded by weight loss during the preclinical dementia phase causing a harmful exposure to appear protective.<sup>4</sup> Furthermore, the other items of the lifestyle subscore are prone to measurement or recall bias as they are typically ascertained by questionnaires. As opposed to these lifestyle metrics, the individual items of the biological subscore were directly measured in the UKB population and therefore do not suffer from those types of bias. Altogether, our findings raise concerns

regarding the use of the composite lifestyle scores in observational studies, given the inconsistent associations of its individual components with the risk of dementia.

This study has several strengths. In contrast to a recent study of CVH and incident dementia in the UKB,<sup>44</sup> this study incorporated the recently released UKB primary care dataset and data on biomarkers including LDL and HbA1c levels. Both offer distinct advantages over previous analyses in the UKB: The inclusion of primary care data added 1075 dementia events to the analysis (> 50% of total dementia cases) that would remain undetected by hospital in-patient records or death records. Dementia diagnoses derived from hospital in-patient and death records represent a different case mix. Indeed, in a subset of the UKB the proportion of dementia cases diagnosed as AD was 31% of hospital admission codes compared to 43% of primary care codes, which is closer to published figures for the general population.<sup>25,45</sup> Thus, the combined sample should be more representative of all-cause dementia in the UK general population. Direct measurements of circulating LDL cholesterol and HbA1c levels in the UKB enabled us to derive the LS7 and biological scores in the same cohort, whereas previous studies<sup>44</sup> suffered from incomplete assessment of individual items of the LS7. The use of observational analyses and MR both have advantages: The observational analyses enabled us to integrate individual components into composite scores (LS7 and subscores) and to investigate non-linear relationships between individual components of the LS7 score, while the use of MR enabled inferences on causal relationships between individual components of the LS7 score and dementia risk. Indeed, relationships of items included in the LS7 with dementia are in some instances not linear or even go in opposite directions.

This study also has limitations. First, because of the short follow-up period the number of incident dementia events is relatively small, leading to imprecise effect estimates in MR analyses because of reduced power in the GWAS analysis. Second, primary care data in the UKB have so far only been released for roughly half of the participants. This confined the analyses to half the dataset, thus limiting power. Third, participants in the UKB are primarily of White British origin. Consequently, findings might not be generalizable to other ethnicities or populations. Moreover, UK Biobank participants are not representative of the general population and hence cannot be used to provide representative disease prevalence and incidence rates. However, valid assessment of exposure-disease relationships is nonetheless widely generalizable and does not require participants to be representative of the population at large. Fourth, dementia diagnoses were obtained from registry-based data and not through detailed neuropsychological assessments. While the overall accuracy of obtaining dementia diagnoses via registries is good,<sup>25</sup> misclassification of some study participants remains a possibility. While there is evidence for a relatively low false-positive rate, the rate of false-negatives still is largely unknown.<sup>25</sup> Finally, although MR analyses for most of the vascular risk factors were based on a sufficient number of genetic variants, the number of genetic instruments associated with physical activity and diet was relatively small, thus limiting statistical power in these analyses. In conclusion, midlife adherence to the AHA LS7 recommendations regarding biological risk factors (hypertension, hypercholesterolemia, diabetes) was



associated with a lower risk of incident dementia. Genetically elevated blood pressure was further associated with a lower risk of dementia. These findings support the efficacy of blood-pressure lowering strategies for reducing dementia burden and call for additional clinical trials.

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## AUTHOR CONTRIBUTIONS

Drs Malik and Georgakis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Malik and Georgakis contributed equally. R.M., M.K.G., and M.D. designed the study. All authors acquired data, analyzed data, or contributed to interpretation of data. R.M., M.K.G., and M.D. drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. R.M., M.K.G., and J.N. performed statistical analysis.

## CONFLICTS OF INTEREST

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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## SUPPORTING INFORMATION

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

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