Research Paper

Pathways explaining racial/ethnic and socio-economic disparities in dementia incidence: the UK Biobank study

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ABSTRACT

Background: Pathways explaining racial/ethnic disparities in dementia risk are under-evaluated.
Methods: We examine those disparities and their related pathways among UK Biobank study respondents (50–74 y, *N* = 323,483; 3.6% non-White minorities) using a series of Cox proportional hazards and generalized structural equations models (GSEM).
Results: After ≤15 years, 5,491 all-cause dementia cases were diagnosed. Racial minority status (RACE_ETHN, Non-White vs. White) increased dementia risk by 24% (HR = 1.24, 95% CI: 1.07–1.45, *P* = 0.005), an association attenuated by socio-economic status (SES), (HR = 1.12, 95% CI: 0.96–1.31). Total race-dementia effect was mediated through both SES and Life's Essential 8 lifestyle sub-score ($LE8_{LIFESTYLE}$), combining diet, smoking, physical activity, and sleep factors. SES was inversely related to dementia risk (HR = 0.69, 95% CI: 0.67, 0.72, *P* < 0.001). Pathways explaining excess dementia risk among racial minorities included 'RACE_ETHN(−) → SES(−) → DEMENTIA', 'RACE_ETHN(−) → SES(−) → Poor cognitive performance, COGN(+) → DEMENTIA' and 'RACE_ETHN(−) → SES(+) → $LE8_{LIFESTYLE}$(−) → DEMENTIA'.
Conclusions: Pending future interventions, lifestyle factors including diet, smoking, physical activity, and sleep are crucial for reducing racial and socio-economic disparities in dementia.

INTRODUCTION

Healthy cognitive functioning is required for performing activities of daily living, including attention, working or short-term memory, long-term memory, reasoning, movement coordination, and task-planning. The prevalence of brain disorders affecting cognition – such as stroke and dementia – increases with advancing age. Dementia is the loss of global abilities in multiple cognitive domains accompanied by the inability to perform usual activities of daily living dependence. The estimated prevalence of dementia is 4.7% among adults over 60 y [1], with 4.6–7.7 million cases added each year worldwide (3.5–10.5 per 1,000) [1–3]. Alzheimer's disease (AD), the most common form of dementia, accounts for 60–80% of cases [1]. A progressive neurodegenerative disorder known for its multi-factorial etiology, AD manifests with episodic memory deterioration followed by impairment in other cognitive domains [4]. AD is likely caused by age-dependent and

progressive Aβ-amyloid brain deposition, termed "the amyloid cascade hypothesis" [5]. AD is also characterized by neurofibrillary tangles (NFT), a second pathological hallmark that arises from hyper-phosphorylated tau protein [6]. AD is the leading cause of old age disability [7]. In developed countries, AD carries a greater health care burden.

With no current effective treatment, dementia prevention is crucial. Despite late-onset AD's partial genetic basis (e.g. ApoE *ε4*), the 2020 *Lancet commission* reported that 40% of dementia's risk can be attributed to early-life, mid-life and later life modifiable risk factors, including education, hearing loss, traumatic brain injury, hypertension, alcohol use obesity, smoking, depression, social isolation, physical inactivity, air pollution and diabetes [8]. Identification of novel mid-life risk factors and pathways between early and mid-life factors are thereby crucial in prevention efforts and for planning cost-effective interventions. Furthermore, cognitive decline and dementia have been positively associated with disadvantaged socioeconomic status (SES) [9, 10]. Socioeconomic status is commonly measured with education, occupation and income, with the former two being more relevant for dementia [11]. Neighborhood-level socioeconomic disadvantage including neighborhood structure, health outcomes within the area, personal housing and personal economics is also recognized as speeding cognitive decline in older adults [12]. Despite inconsistent evidence, long-term exposure to greenspace was associated with slower global cognition decline across the life span [13].

Among US adults, there are large racial disparities in numerous dementia risk factors, including obesity and related cardio-metabolic risk factors [14–16]. Moreover, wide racial, ethnic, and socio-economic disparities are found in AD and dementia incidence, with minority status and lower SES having adverse effects, often in combination. Related mediating pathways remain generally unexplored, particularly in the UK population [17–23].

The present study examines pathways that might explain racial, ethnic, and socio-economic disparities in AD or all-cause dementia in a large cohort study, the UK Biobank. Our study used several metho-dologies, including structural equation modeling coupled with survival analysis techniques to examine complex mediating effects between race, ethnicity, socioeconomic status, and dementia or AD risk in a sex-specific manner focusing on lifestyle, biological and cognitive pathways. It is also an attempt at replicating a previous study conducted among US older adults [24].

MATERIALS AND METHODS

Database

The UK Biobank is a prospective study of approximately 500,000 adults aged 37–73 y at baseline residing in the UK, and who were recruited between 2006 and 2010 [25]. Study rationale and design are detailed elsewhere [25]. Recruited participants attended one of 22 assessment centres (within 25 miles) in either England, Scotland, or Wales, completing a self-administered and touch-screen questionnaires as well as a face-to-face interview [25]. Phenotypic measurements and biological samples were collected [25]. After a careful review of former observational studies, clinical trials and population surveys and consulting with international experts, the UK Biobank questionnaire identified a wide array of quantifiable exposures in a wide range of interest areas [25].

Standard protocol approvals, registrations, and patient consents

The study was approved by the North West Multi-Centre Research Ethics Committee, while participants provided written informed consent for data collection, data analysis, and record linkage, provided that the data was de-identified [25]. This analysis was approved by the UK Biobank access management team, as part of application #77963 and the project was approved by the Institutional Review Board of the National Institutes of Health.

Incident AD and all-cause dementia

Focusing on the algorithmically derived dementia outcomes (fields 42018 and 42020), we excluded participants with onset of dementia occurring prior to baseline assessment [26]. The algorithm used included ICD-10 codes F00 or G30 for incident diagnosis for AD, whereas a number of codes were used for all-cause dementia, including vascular dementia (F01, I67.3), namely A81.0, F00, F01, F02, F03, F05, G30, G31.0, G31.1, G31.8, and I67.3. Date of the earliest occurrence of all-cause dementia was defined using the minimum of several date variables/fields that were available for each of the two outcomes [26].

Race/ethnicity

Participants' race/ethnicity was self-reported and was categorized in this study as White, Black, South Asian and Others as was done in a previous US study [24]. Moreover, the Non-White vs. White contrast was used in the main part of the pathway analyses. In our main analyses, RACE_ETHN referred to "racial minority

status", mainly contrasting Non-White to White (referent category).

Mediators

Socio-economic status

Socio-economic status was operationalized with 3 different measures: education, income and Townsend deprivation index. Baseline self-reported completed education was recoded as follows: 0 = Low, combining None, "CSEs/Equivalent", "NVQ/HND/HNC/Equivalent" and "Other professional qual"; 1 = Intermediate, combining "O Levels/GCSEs/Equivalent" and "A/AS Levels Equivalent; 2 = Higher level or "College/ University" [27]. Total household income before tax was measured on a 5-point scale with 1 denoting less than £18,000, 2 £18,000–£29,999, 3 £30,000–£51,999, 4 £52,000–£100,000, and 5 greater than £100,000. The Townsend deprivation index (TDI) scores were computed based on national census data that measures residential postcode-level car ownership, household overcrowding, owner occupation, and unemployment. Originally coded to reflect higher socioeconomic deprivation with higher TDI scores [28], it was multiplied by -1 in this study in order to reflect higher SES and be combined with z-scores of education and income into one SES summary score.

Study sample

Of the initial 502,399 UK Biobank participants, 384,627 were aged ≥50 y at baseline of whom 323,602 had available data on cognitive performance tests administered as well as all other key socio-demographic, SES, lifestyle and biological factors, including the $LE8_{LIFESTYLE}$ and the $LE_{BIOLOGICAL}$ scores. We additionally excluded 119 prevalent dementia cases at baseline assessment, which yielded a sample size of 323,483, of whom 2,314 had incident AD and 5,491 had incident all-cause dementia through the follow-up period of up to 15 years (Supplementary Figure 1). Participants who were excluded from analysis due to missing covariates differed from the remaining participants who were included, given an age at recruitment ≥50 y, by being younger, with lower likelihoods of being female or individuals from a racial minority group ($P < 0.001$), based on a multi-variable logistic regression model with selection (yes vs. no) as the outcome variable.

Life's essential 8

In 2010, the American Heart Association (AHA) defined a new measure of cardiovascular health (CVH) aiming at individual and population-level health promotion [29, 30]. CVH was initially operationalized with 7 potentially modifiable biological and lifestyle factors, that, when at optimal levels would result in greater cardiovascular disease (CVD)–free survival, longevity, and better quality of life. This measure was labelled "Life's Simple 7" (LS7), with its 7 components: better diet quality, greater physical activity, reduced cigarette smoking, lower body mass index (BMI), total cholesterol, fasting blood glucose, and optimal blood pressure levels. Using clinical thresholds, each metric was categorized as poor (0), intermediate (1), or ideal (2), with total score range from 0 to 14 [29, 30]. Upon re-evaluation, a new measure labeled "Life's Essential 8" (LE8) was formulated, retaining all 7 components of LS7 with major modifications to definitions and scales and by adding sleep health as an 8th component [30, 31] and one of four components of the LE8 lifestyle sub-scale. BMI, total cholesterol, glucose level, and blood pressure were included in the $LE8_{BIOLOGICAL}$ sub-scale. Both sub-scales of LE8 ($LE8_{LIFESTYLE}$ and $LE8_{BIOLOGICAL}$) were tested as potential mediators in our present study, reflecting better CVH with higher score. Proration was applied to all potential mediators following the guidelines of <50% missing per scale [32] (See Supplementary Tables 1–4 and Supplementary Methods 1 and 2) [32].

Lifestyle and health-related factors

In a supplementary analysis comparable to recent US studies [24, 33], lifestyle factors of interest included six concepts, namely "SMOKING", "ALCOHOL", "PHYSICAL ACTIVITY (PA)", "DIET QUALITY (DIET)", "NUTRITIONAL BIOMARKERS (NUTR)" and "SOCIAL SUPPORT (SS)". The poor general and cardio-metabolic health construct (HEALTH) combined body mass index (BMI), the allostatic load (AL), a co-morbidity index and self-rated health. All these measures are detailed in Supplementary Methods 1–3 and Supplementary Table 5.

Cognitive performance

Three cognitive test scores, available for most UK Biobank participants, included reaction time, pairs matching time to completion, and pairs matching number of errors. After being Log_e transformed, their z-scores were averaged to generate the COGN construct, reflecting poor cognitive performance in domains of visual memory and reaction time. The uni-dimensionality of COGN was tested using principal components analyses, from which the final COGN score was predicted (Supplementary Method 4).

Exogenous covariates

Exogenous variables included age at baseline assessment, sex and household size. Moreover, sex was

also considered as a key effect modifier in our analyses, while race/ethnicity was an exogenous variable in analyses with SES as the main exposure.

Statistical methods

All analyses used Stata 17.0 (StataCorp, College Station, TX, USA), and were mostly stratified by sex. Comparison with race/ethnicity groups and sex as key predictors, used OLS linear, logistic and multinomial logit models, comparing means and proportions of variables of interest. Specifically, race/ethnicity was categorized as Non-White vs. White and sex differences were examined in the overall sample. Moreover, racial/ethnic differences in main characteristics were examined within each sex group.

We defined time-to-event (in years) from age at entry ≥50 y (i.e., delayed entry) until age of exit when event of interest or censoring (death or end of follow-up) would have occurred. AD and DEMENTIA incidence rates (IR, with 95% CI) were estimated across race/ethnicity groups by sex. In the main analysis, we conducted nested and sex-stratified Cox proportional hazards (PH) models on imputed data whereby socio-demographic, SES, lifestyle, health, and cognitive performance factors were entered consecutively in five models for both outcomes, while testing heterogeneity of race/ethnicity by sex by adding interaction terms to unstratified models. LE8 sub-scales were entered into models where SES and COGN were adjusted for.

Mediation was further examined using parametric survival models (Weibull GSEM), optimal for causal mediation in survival analysis [34]. Within GSEM, time to dementia (TD) was modeled as the outcome. GSEM models tested mediating pathways between Non-White vs. White contrast and the outcome. The main pathways dictate that SES z-score predicts LE8's lifestyle component which predicts LE8's biological component. The latter was allowed to predict "COGN" (higher z-score → poorer performance), which was hypothesized to directly influence AD or DEMENTIA risk. Importantly, other pathways were also allowed, including between endogenous variables and between RACE_ETHN and each endogenous variable (Figure 1). The total effects of RACE_ETHN and SES were estimated using GSEM where only exogenous variables were included with outcome being time to dementia incidence (Weibull model, Eq. 1). RACE_ETHN was included among exogenous variables in the model whereby SES total effect is to be estimated.

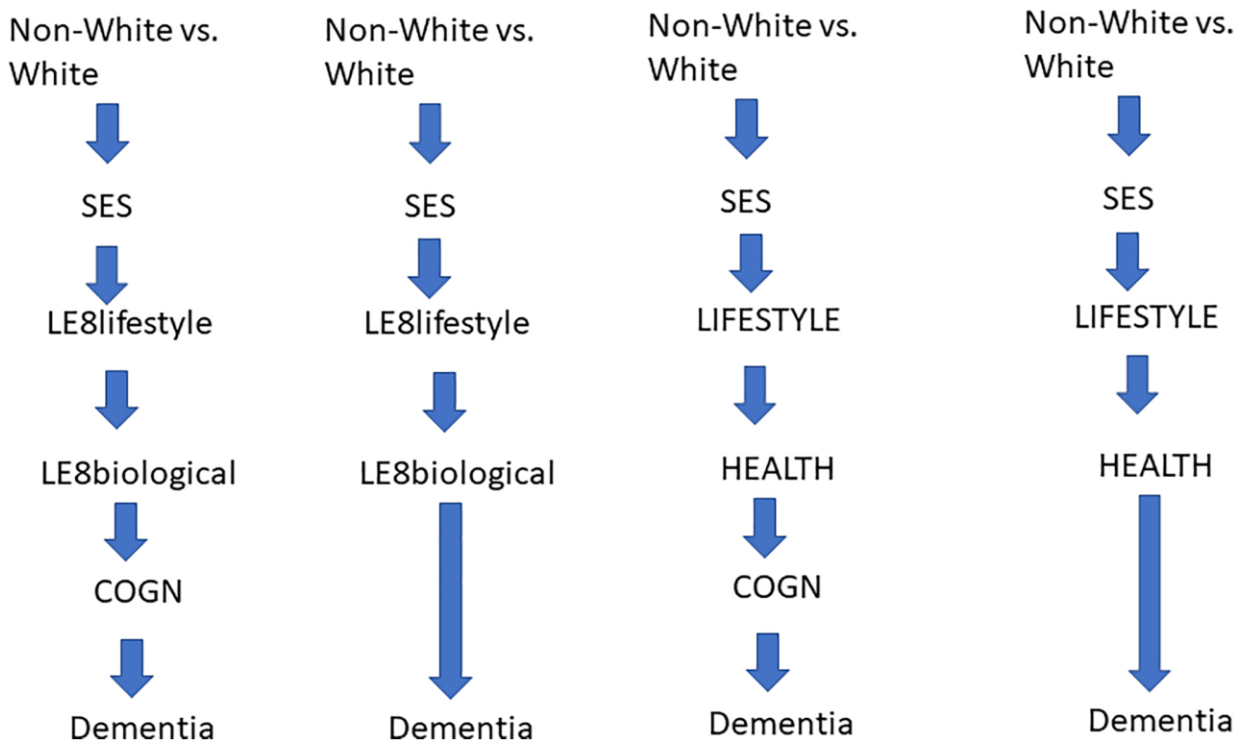

Figure 1. Conceptual framework. Abbreviations: ALCOHOL: Alcohol consumption *z*-score; COGN: Poor cognitive performance, *z*-score; DIET: Diet quality z-score; HEALTH: Poor cardio-metabolic and general health *z*-score; $LE8_{BIOLOGICAL}$: Biological sub-scale of Life's Essential 8; $LE8_{LIFESTYLE}$: Lifestyle sub-scale of Life's Essential 8; LIFESTYLE: Lifestyle factors including DIET, PA, SMOKING, ALCOHOL, NUTR and SS; NUTR: Nutritional biomarker *z*-score; PA: Physical Activity *z*-score; SES: Socio-economic status; SMOKING: Smoking *z*-score; SS: Social Support *z*-score.

Direct effects in a structured manner represent the main pathway: direct effects into final TD, relationships between endogenous variables outside the pathway, and direct effects of race contrast outside the pathway. Indirect effects were also estimated by multiplying and adding effects from race/ethnicity into the final outcome, and passing through each mediator [35], including pathways from race/ethnicity to TD, through SES → $LE8_{LIFESTYLE}$ → $LE8_{BIOLOGICAL}$ → POOR COGNITIVE PERFORMANCE (COGN) → DEMENTIA, which was hypothesized to be the main pathway. Those models (Models A) included COGN as most proximal mediator to dementia outcome. In another set of models (Models B), COGN was omitted and effects of SES and LE8 sub-scales, among others, directly predicted TD. Exogenous variables were added to all equations. Furthermore, total effect of SES on AD/DEMENTIA was studied through similar pathways, the main hypothesized pathway being SES → $LE8_{LIFESTYLE}$ → $LE8_{BIOLOGICAL}$ → COGN → DEMENTIA. Finally, a sensitivity analysis, DIET, PA, SMOKING, NUTR and SS were included in the GSEM model with COGN as alternative lifestyle factors, while HEALTH was entered instead of $LE8_{BIOLOGICAL}$. Direct and indirect effects are presented like the previous model with COGN. In all models, we adjusted for sample selectivity due to missing exposure and outcome data, relative to the initially recruited sample, using a two-stage Heckman selection strategy [36]. Initially, we predicted an indicator of selection with socio-demographic factors, namely, age, race/ethnicity and sex using probit regression, which yielded an inverse mills ratio (IMR) – a function of probability of being selected given those socio-demographic factors. Subsequently, we estimated our Cox proportional hazards regression and GSEM models adjusted for the IMR in addition to afore-mentioned covariates [36, 37], using 0.05 as Type-I error.

Eq 1. Weibull distribution

$$f(x;\lambda,k)=\frac{K}{\lambda}\left(\frac{x}{\lambda}\right)^{k-1} e-\left(\frac{x}{\lambda}\right)^{k}$$

Where λ is the scale parameter; k is the shape parameter; x is time to failure.
Y is f(x;λ,k) for $x \geq 0$ and Y is 0 for $x < 0$.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: UK Biobank is a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million United Kingdom participants. The database is regularly augmented with additional data and is globally accessible to approved researchers undertaking vital research into the most common and life-threatening diseases. Requests to access these datasets should be directed to https://www.ukbiobank.ac.uk/.

RESULTS

The selected sample consisted of 323,483 adults, of whom 5,491 had incident all-cause dementia (2,314 were AD) through 15 years of follow-up. Table 1 and Supplementary Table 6 show study sample characteristics across key socio-demographics (sex and race), with results summarized in Supplementary Results 1. Most notably, SES z-score was significantly lower among racial minority groups, as were LE8 total and sub-scale scores.

Table 2 presents Cox proportional hazards model findings, focusing on racial/ethnic disparities in incident all-cause and AD dementia. Adjusted for only exogenous variables (age, household size, and sex for non-stratified models), Model 1 shows that Black adults had on average 1.8 to 2.2-fold risk of all-cause dementia compared to their White counterparts in both sexes. This ethnic and racial disparity was markedly attenuated when SES was entered into the model (Model 2), particularly among women. Among men, the HR was non-significant upon further adjustment for lifestyle factors (Model 3). A similar gap was found for AD dementia outcome. In contrast, no disparity was detected between South Asian and White adults, and this contrast was inversely related to all-cause dementia incidence upon adjustment for baseline cognitive performance in both sexes (Model 5: women HR = 0.56, 95% CI: 0.34–0.9; men HR = 0.76, 95% CI: 0.62–0.94). Overall, non-White adults, particularly men, were at 24% greater risk for all-cause dementia compared to their White counterparts in Model 1. This association was attenuated after entering SES into the model (HR = 1.12, 95%CI: 0.96–1.31) and inverted when all lifestyle, health-related and cognitive performance scores were included (Model 5: HR = 0.75, 95% CI: 0.64–0.87). For AD, there was no disparity detected in Model 1, which then became an inverse relationship of Non-White vs. White with AD incidence in fully adjusted model 5. Nevertheless, in Model 6, which included cognitive performance, SES, LE8 sub-scores and exogenous variables, no relationship between race/ethnicity (Non-White vs. White) and dementia outcomes was detected.

Table 3 focuses on potential socio-economic disparities in all-cause and AD dementia after adjusting for race and ethnicity (Non-White vs. White) and other exogenous variables. SES was a statistically significant

Table 1. Study sample characteristics by race/ethnicity: The UK Biobank 2006–2021[a].

Study sample characteristics	All participants	vBoth sexes combined, *n* = 323,483		*P*
		White	Non-white	
Socio-demographic				
Baseline age, y	60.4 ± 5.4	60.5 ± 5.4	58.6 ± 5.6	<0.001
Sex, % female	53.6	53.6	53.8	0.81
Race/ethnicity				—
White	96.4	100.0	0.0	—
Black	0.9	0.0	25.2	—
South Asian	1.2	0.0	33.6	—
Other	1.5	0.0	41.1	—
Household size	2.2 ± 1.2	2.2 ± 1.1	2.7 ± 1.6	<0.001
Socio-economic status				
Education				
Low	21.8	21.7	23.4	—
Intermediate	39.6	40.0	29.8	<0.001
High	38.6	38.3	46.8	<0.001
Income				<0.001
Less than £18,000	25.3	25.2	30.3	—
£18,000–£29,999	28.0	28.0	27.8	—
£30,000–£51,999	24.9	24.9	22.5	—
£52,000–£100,000	17.4	17.5	15.1	—
greater than £100,000	4.4	4.4	4.3	—
TDI	−1.56 ± 2.95	−1.63 ± 2.90	0.47 ± 3.48	<0.001
SES z-score	−0.03 ± 0.70	−0.02 ± 0.70	−0.28 ± 0.79	<0.001
Lifestyle factors				
Smoking				
Smoking status				
Never	81.3	81.2	86.0	—
Former	9.5	9.7	4.2	<0.001
Current	9.2	9.2	9.9	0.61
Environmental tobacco smoke	0.88 ± 5.2	0.88 ± 5.26	1.03 ± 4.72	0.002
Pack-years of tobacco smoke	0.08 ± 0.26	0.08 ± 0.26	0.05 ± 0.19	<0.001
SMOKING z-score	−0.005 ± 0.442	−0.004 ± 0.442	−0.025 ± 0.418	<0.001
Alcohol consumption				
Alcohol consumption frequency				
0 “never”	7.3	6.6	24.5	—
1 “special occasions only”	11.1	10.6	23.7	<0.001
2 “1–3 times per month”	10.4	10.4	10.9	<0.001
3 “1–3 times per week”	24.7	25.0	18.2	<0.001
4 “3–4 times per week”	23.7	24.2	12.0	<0.001
5 “daily or almost daily”	22.8	23.2	10.7	<0.001
ALCOHOL z-score	0.00 ± 1.00	+0.03 ± 0.98	−0.743 ± 1.11	<0.001
Physical activity, PA				
PA, Met.min.wk^{-1}	1,963 ± 2,812	1,971 ± 2,817	1,772 ± 2,796	<0.001
PA z-score	0.00 ± 1.00	+0.00 ± 1.00	−0.068 ± 0.992	<0.001
Diet quality				
HDI total score	5.11 ± 1.50	5.10 ± 1.50	5.36 ± 1.43	<0.001
DIET z-score	0.00 ± 1.00	−0.01 ± 1.00	0.17 ± 0.96	<0.001
Nutritional Biomarkers				
25-hydroxyvitamin D	49.6 ± 20.9	50.2 ± 20.8	35.4 ± 18.1	<0.001
Red cell distribution width	13.5 ± 0.9	13.5 ± 0.9	13.8 ± 1.2	<0.001
NUTR z-score	−0.001 ± 0.757	+0.017 ± 0.746	−0.496 ± 0.871	<0.001
Social Support				
“How often do you visit friends or family or have them visit you?”	5.27 ± 1.13	5.28 ± 1.13	4.84 ± 1.21	<0.001

"How often are you able to confide in someone close to you?"	1.04 ± 0.87	1.04 ± 0.87	0.95 ± 0.83	<0.001
"Which of the following do you attend once a week or more often?"	3.55 ± 1.89	3.56 ± 1.88	3.03 ± 1.98	<0.001
SS z-score	−0.001 ± 0.630	+0.008 ± 0.631	−0.254 ± 0.669	<0.001
Cardio-metabolic and general health-related factors				
Body mass index, kg.m^{-1}	27.5 ± 4.7	27.5 ± 4.7	27.8 ± 5.0	<0.001
Allostatic load	2.10 ± 1.39	2.10 ± 1.38	2.23 ± 1.41	<0.001
Co-morbidity index	2.11 ± 1.94	2.11 ± 1.94	2.12 ± 1.92	<0.001
Self-rated health				<0.001
Excellent	16.5	16.7	11.2	
Good	59.0	59.2	53.2	
Fair	20.4	20.1	28.8	
Poor	4.1	4.0	6.7	
HEALTH z-score	0.0004 ± 0.687	−0.004 ± 0.687	0.110 ± 0.701	<0.001
Cognitive performance				
Reaction Time	6.33 ± 0.19	6.32 ± 0.18	6.41 ± 0.22	<0.001
Pairs matching, errors	0.72 ± 0.70	0.70 ± 0.70	0.99 ± 0.73	<0.001
Pairs matching, time to complete	5.35 ± 0.37	5.34 ± 0.4	5.57 ± 0.46	<0.001
COGN z-score	0.000 ± 0.756	−0.018 ± 0.743	0.481 ± 0.917	<0.001
LE8				
Total score	502.3 ± 95.6	502.8 ± 95.6	488.8 ± 95.2	<0.001
Biological score	246.4 ± 65.9	246.8 ± 65.7	236.0 ± 63.1	<0.001
Lifestyle score	255.9 ± 63.3	256.0 ± 63.3	251.9 ± 63.1	<0.001
Incidence proportion				
All-cause dementia	1.70 (*n* = 5,491)	1.71 (*n* = 5,321)	1.45 (*n* = 170)	0.035
AD dementia	0.72 (*n* = 2,314)	0.72 (*n* = 2,245)	0.59 (*n* = 69)	0.098

Abbreviations: AD: Alzheimer's Disease; ALCOHOL: Alcohol consumption z-score; COGN: Poor cognitive performance z-score; DIET: diet quality z-score; HDI: Healthy Diet Index; HEALTH: Poor cardio-metabolic and general health z-score; LE8: Life's Essential 8; PA: Physical Activity z-score; NUTR: Nutritional biomarker z-score; SES: Socio-economic status z-score; SMOKING: Smoking z-score; SS: Social Support z-score; TDI: Townsend Deprivation Index. [a]Values are percentages or means +/− standard deviations. *P* for null hypothesis of no difference by race.

Table 2. Racial/ethnic disparities in incident all-cause and Alzheimer's disease dementia among middle-aged males and females (*N* = 323,483): Cox proportional hazards models; The UK Biobank 2006–2021[a].

	All-cause Dementia			AD Dementia		
	HR	**(95% CI)**	***P***	**HR**	**95% CI**	***P***
Males, Black vs. White						
Model 1	**2.18**	**(1.53, 3.11)**	**<0.001**	**1.87**	**(1.00, 3.48)**	**0.049**
Model 2	**1.63**	**(1.14, 2.33)**	**0.007**	1.45	(0.78, 2.72)	0.24
Model 3	1.32	(0.92, 1.88)	0.13	1.28	(0.68, 2.40)	0.44
Model 4	1.41	(0.99, 2.02)	0.058	1.31	(0.70, 2.46)	0.40
Model 5	0.96	(0.67, 1.37)	0.82	0.89	(0.47, 1.68)	0.72
Model 6	1.06	(0.74, 1.52)	0.75	0.96	(0.51, 1.81)	0.90
Females, Black vs. White						
Model 1	**1.83**	**(1.25, 2.67)**	**0.002**	**1.92**	**(1.11, 3.32)**	**0.019**
Model 2	1.41	(0.96, 2.07)	0.079	1.46	(0.84, 2.54)	0.18
Model 3	1.17	(0.80, 1.73)	0.41	1.23	(0.71, 2.15)	0.46
Model 4	1.12	(0.76, 1.65)	0.55	1.19	(0.68, 2.07)	0.54
Model 5	0.77	(0.53, 1.14)	0.20	0.80	(0.46, 1.39)	0.43
Model 6	0.95	(0.66, 1.40)	0.80	0.93	(0.53, 1.63)	0.81
Males, South Asian vs. White						
Model 1	1.06	(0.75, 1.48)	0.76	1.18	(0.71, 1.97)	0.53
Model 2	1.00	(0.71, 1.40)	0.98	1.13	(0.68, 1.89)	0.63
Model 3	0.77	(0.54, 1.08)	0.13	0.97	(0.58, 1.64)	0.92
Model 4	0.79	(0.56, 1.11)	0.17	0.98	(0.59, 1.65)	0.95

Model 5	**0.60**	**(0.42, 0.85)**	**0.004**	0.76	(0.45, 1.27)	0.29
Model 6	0.75	(0.53, 1.05)	0.093	0.85	(0.51, 1.42)	0.54
Females, South Asian vs. White						
Model 1	0.95	(0.58, 1.56)	0.85	1.13	(0.59, 2.18)	0.71
Model 2	0.91	(0.56, 1.49)	0.71	1.09	(0.57, 2.11)	0.79
Model 3	0.72	(0.44, 1.18)	0.20	0.90	(0.46, 1.74)	0.75
Model 4	0.73	(0.44, 1.19)	0.21	0.90	(0.47, 1.75)	0.76
Model 5	**0.56**	**(0.34, 0.92)**	**0.022**	0.68	(0.35, 1.33)	0.26
Model 6	0.70	(0.43, 1.15)	0.16	0.81	(0.42, 1.56)	0.52
Males, Non-White vs. White						
Model 1	**1.26**	**(1.03, 1.54)**	**0.025**	1.20	(0.86, 1.68)	0.28
Model 2	1.14	(0.93, 1.40)	0.20	1.11	(0.79, 1.55)	0.54
Model 3	0.93	(0.76, 1.15)	0.52	0.99	(0.70, 1.38)	0.94
Model 4	0.96	(0.78, 1.18)	0.73	1.00	(0.71, 1.40)	0.98
Model 5	**0.76**	**(0.62, 0.94)**	**0.010**	0.80	(0.57, 1.12)	0.19
Model 6	0.88	(0.72, 1.08)	0.24	0.87	(0.62, 1.22)	0.42
Females, Non-White vs. White						
Model 1	1.23	(0.97, 1.56)	0.084	1.22	(0.86, 1.72)	0.27
Model 2	1.11	(0.87, 1.40)	0.40	1.09	(0.77, 1.55)	0.61
Model 3	0.93	(0.73, 1.18)	0.55	0.94	(0.66, 1.34)	0.74
Model 4	0.93	(0.73, 1.18)	0.55	0.94	(0.66, 1.34)	0.73
Model 5	**0.73**	**(0.57, 0.93)**	**0.010**	0.72	(0.51, 1.03)	0.076
Model 6	0.86	(0.68, 1.09)	0.22	0.82	(0.58, 1.17)	0.28
Overall, Non-White vs. White						
Model 1	**1.24**	**(1.07, 1.45)**	**0.005**	1.20	(0.95, 1.53)	0.13
Model 2	1.12	(0.96, 1.31)	0.14	1.10	(0.86, 1.40)	0.44
Model 3	0.93	(0.80, 1.09)	0.38	0.96	(0.75, 1.23)	0.75
Model 4	0.95	(0.81, 1.11)	0.51	0.97	(0.76, 1.24)	0.79
Model 5	**0.75**	**(0.64, 0.87)**	**<0.001**	**0.76**	**(0.59, 0.97)**	**0.030**
Model 6	0.88	(0.76, 1.03)	0.12	0.85	(0.69, 1.09)	0.20

Abbreviations: AD: Alzheimer's Disease; ALCOHOL: Alcohol consumption z-score; COGN: Poor cognitive performance z-score; DIET: diet quality z-score; HEALTH: Poor cardio-metabolic and general health z-score; NUTR: Nutritional biomarker z-score; PA: Physical Activity z-score; RACE_ETHN: Race/ethnicity; SES: Socio-economic status z-score; SMOKING: Smoking z-score; SS: Social Support z-score. [a]Values are β ± SE (Log_e(HR)). Model 1: adjusted for age (or age and sex); Model 2: adjusted for demographic factors other than age and sex, and SES score; Model 3: Model 2 further adjusted for lifestyle-related factors (average of z-scores of measured variables for SMOKING, ALCOHOL, DIET, NUTR, SS and PA); Model 4: Model 3 + health-related factors (HEALTH score); Model 5: Full model with cognitive test PCA score; Model 6: is Model 2+LE8 lifestyle and biological sub-scales+ cognitive test PCA score. *P* for null hypothesis that Loge(HR) = 0.

Table 3. Socio-economic disparities in incident all-cause and Alzheimer's disease dementia among middle-aged adults (*N* = 323,483): Cox proportional hazards models; The UK Biobank 2006–2021[a,b].

	All-cause dementia			AD dementia		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Model 1						
Non-White vs. White	1.12	(0.96, 1.31)	0.14	1.10	(0.86, 1.40)	0.44
SES	**0.69**	**(0.67, 0.72)**	**<0.001**	**0.71**	**(0.66, 0.75)**	**<0.001**
Model 2						
Non-White vs. White	0.93	(0.80, 1.09)	0.38	0.96	(0.75, 1.23)	0.75
SES	**0.74**	**(0.71, 0.77)**	**<0.001**	**0.72**	**(0.68, 0.77)**	**<0.001**
SMOKING	0.98	(0.96, 1.02)	0.38	**0.89**	**(0.83, 0.95)**	**0.001**
DIET	1.01	(0.98, 1.03)	0.66	1.04	(1.00, 1.08)	0.070
PA	0.99	(0.96, 1.02)	0.68	**1.04**	**(1.01, 1.08)**	**0.024**
ALCOHOL	**0.90**	**(0.88, 0.93)**	**<0.001**	**0.92**	**(0.88, 0.97)**	**0.001**
NUTR	**0.85**	**(0.83, 0.88)**	**<0.001**	**0.91**	**(0.87, 0.96)**	**<0.001**
SS	**0.83**	**(0.80, 0.87)**	**<0.001**	**0.90**	**(0.84, 0.96)**	**0.001**

Model 3						
Non-White vs. White	0.95	(0.82, 1.11)	0.51	0.97	(0.76, 1.24)	0.79
SES	**0.78**	**(0.75, 0.82)**	**<0.001**	**0.75**	**(0.70, 0.80)**	**<0.001**
SMOKING	0.98	(0.94, 1.02)	0.26	**0.88**	**(0.83, 0.95)**	**<0.001**
DIET	**1.03**	**(1.00, 1.06)**	**0.026**	**1.05**	**(1.01, 1.10)**	**0.013**
PA	1.03	(1.04, 1.06)	0.054	**1.06**	**(1.02, 1.10)**	**0.002**
ALCOHOL	**0.93**	**(0.91, 0.96)**	**<0.001**	**0.94**	**(0.90, 0.98)**	**0.004**
NUTR	**0.90**	**(0.87, 0.93)**	**<0.001**	**0.94**	**(0.89, 1.00)**	**0.037**
SS	**0.84**	**(0.81, 0.88)**	**<0.001**	**0.90**	**(0.84, 0.96)**	**0.002**
HEALTH	**1.44**	**(1.38, 1.50)**	**<0.001**	**1.24**	**(1.16, 1.32)**	**<0.001**
Model 4						
Non-White vs. White	**0.75**	**(0.64, 0.87)**	**<0.001**	**0.76**	**(0.59, 0.97)**	**0.030**
SES	**0.83**	**(0.80, 0.87)**	**<0.001**	**0.79**	**(0.75, 0.85)**	**<0.001**
SMOKING	0.99	(0.95, 1.03)	0.60	**0.90**	**(0.84, 0.96)**	**0.002**
DIET	1.03	(1.00, 1.05)	0.06	**1.05**	**(1.01, 1.09)**	**0.025**
PA	1.02	(0.99, 1.04)	0.16	**1.05**	**(1.01, 1.09)**	**0.006**
ALCOHOL	**0.94**	**(0.92, 0.97)**	**<0.001**	**0.95**	**(0.91, 0.99)**	**0.023**
NUTR	**0.90**	**(0.87, 0.93)**	**<0.001**	0.95	(0.90, 1.00)	0.054
SS	**0.86**	**(0.82, 0.90)**	**<0.001**	**0.92**	**(0.86, 0.98)**	**0.010**
HEALTH	**1.44**	**(1.39, 1.50)**	**<0.001**	**1.25**	**(1.17, 1.32)**	**<0.001**
COGN	**1.50**	**(1.45, 1.55)**	**<0.001**	**1.50**	**(1.43, 1.58)**	**<0.001**
Model 5						
Non-White vs. White	0.88	(0.76, 1.03)	0.12	0.85	(0.67, 1.09)	0.20
SES	**0.77**	**(0.74, 0.80)**	**<0.001**	**0.76**	**(0.96, 1.04)**	**<0.001**
$LE8_{LIFESTYLE}$	**0.88**	**(0.86, 0.90)**	**<0.001**	0.99	(0.95, 1.03)	0.77
$LE8_{BIOLOGICAL}$	0.98	(0.96, 1.01)	0.21	0.99	(0.95, 1.02)	0.53
COGN	**1.50**	**(1.45, 1.55)**	**<0.001**	**1.51**	**(1.44, 1.60)**	**<0.001**

Abbreviations: AD: Alzheimer's Disease; ALCOHOL: Alcohol consumption z-score; COGN: Poor cognitive performance z-score; DIET: diet quality z-score; HEALTH: Poor cardio-metabolic and general health z-score; LE8: Life's Essential 8; NUTR: Nutritional biomarker z-score; PA: Physical Activity z-score; SES: Socio-economic status z-score; SMOKING: Smoking z-score; SS: Social Support z-score. [a]Values are β ± SE (Log_e(HR)). Model 1: adjusted for age, sex and race/ethnicity; Model 2: adjusted for demographic factors other than age, sex and race/ethnicity; Model 3: Model 2 further adjusted for lifestyle-related factors (average of z-scores of measured variables for SMOKING, ALCOHOL, DIET, NUTR, SS and PA); Model 4: Model 3 + health-related factors (HEALTH score); Model 5: Full model with cognitive test PCA score; Model 6: is Model 2+LE8 lifestyle and biological sub-scales+ cognitive test PCA score. [b]*P* < 0.05 for sex × SES interaction in unstratified model. *P* for null hypothesis of Log_e(HR) = 0.

predictor for dementia risk, even upon adjustment for lifestyle, health-related and cognitive performance factors. $LE8_{LIFESTYLE}$ was an independent predictor for reduced all-cause dementia risk, independently from $LE8_{BIOLOGICAL}$, SES, race and ethnicity, and baseline cognitive performance. However, neither $LE8_{LIFESTYLE}$ nor $LE8_{BIOLOGICAL}$ were associated with AD; only lower SES and poor cognitive performance were important predictors. In Model 4, the HEALTH construct, reflecting poor cardiometabolic and general health, directly predicted both AD and all-cause dementia, while greater social support, alcohol consumption and higher levels of nutritional biomarkers were among lifestyle factors that were inversely related to dementia and AD risk, independently of SES and baseline cognitive performance.

Table 4 tests mediating effects in a more structured manner with LE8 sub-scores used among mediators by applying the GSEM approach. The results indicate that there was no direct association between Non-White vs. White contrast and dementia risk. However, several mediating pathways were uncovered, including SES as the key paths, particularly 'RACE_ETHN(−) → SES(−) → DEMENTIA' and 'RACE_ETHN(−) → SES(−) → COGN(+) → DEMENTIA'. These paths accounted for approximately half of the total effect of race/ethnicity on dementia risk. In contrast, only 5% of the total effect was accounted for by 'RACE_ETHN(−) → SES(+) → $LE8_{LIFESTYLE}$(−) → DEMENTIA'.

Table 5 examined the mediating roles of LE8 sub-scores and COGN in dementia risk's socio-economic disparities using a similar GSEM approach and adjusting for exogenous variables in all equations. While the total effect of SES was an inverse one (TE = −0.370, *P* < 0.001), around 8% of this effect was explained by $LE8_{LIFESTYLE}$ in comparison to 16% being explained by greater baseline cognitive performance. Thus, a large

Table 4. Total, direct, and indirect effects of race/ethnicity (Non-White vs. White) vs. time to all-cause dementia through SES, lifestyle, health-related and cognitive performance factors among middle-aged adults (Age_{base}: 50–74 y); The UK Biobank 2006–2021[a].

	MODEL A		MODEL B	
	β	(SE), *p*	β	(SE), *p*
Main pathway				
RACE_ETHN → SES (β_{12})	**−0.350**	**(0.006), <0.001**	**−0.351**	**(0.006), <0.001**
SES → $LE8_{LIFESTYLE}$ (β_{23})	**+0.270**	**(0.003), <0.001**	**+0.270**	**(0.003), <0.001**
$LE8_{LIFESTYLE}$ → $LE8_{BIOLOGICAL}$ (β_{34})	**+0.098**	**(0.002), <0.001**	**+0.098**	**(0.002), <0.001**
$LE8_{BIOLOGICAL}$ → COGN(β_{45})	**+0.025**	**(0.001), <0.001**	—	—
COGN → DEMENTIA (β_{56})	**+0.417**	**(0.018), <0.001**	—	—
Selected direct effects on final outcomes				
RACE_ETHN → DEMENTIA(β_{16})	−0.123	(0.079), 0.12	+0.133	(0.078), 0.089
SES → DEMENTIA(β_{26})	**−0.271**	**(0.020), <0.001**	**−0.338**	**(0.020), <0.001**
$LE8_{LIFESTYLE}$ → DEMENTIA(β_{36})	**−0.113**	**(0.014), <0.001**	**−0.110**	**(0.014), <0.001**
$LE8_{BIOLOGICAL}$ → DEMENTIA(β_{46})	−0.027	(0.014), 0.054	−0.017	(0.014), 0.24
Other effects between endogenous variables				
SES → $LE8_{BIOLOGICAL}$ (β_{24})	**+0.122**	**(0.003), <0.001**	**+0.122**	**(0.003), <0.001**
SES → COGN (β_{25})	**−0.138**	**(0.002), <0.001**	—	—
$LE8_{LIFESTYLE}$ → COGN (β_{35})	**+0.008**	**(0.001), <0.001**	—	—
Other direct effects of race				
RACE_ETHN → $LE8_{LIFESTYLE}$ (β_{13})	**+0.040**	**(0.009), <0.001**	**+0.040**	**(0.009), <0.001**
RACE_ETHN → $LE8_{BIOLOGICAL}$(β_{14})	**−0.162**	**(0.009), <0.001**	**−0.163**	**(0.009), <0.001**
RACE_ETHN → COGN(β_{15})	**+0.530**	**(0.006), <0.001**	—	—
Selected Indirect effects				
RACE_ETHN → SES → DEMENTIA(β_A)	**+0.095**	**(0.007), <0.001**	**+0.119**	**(0.007), <0.001**
RACE_ETHN → SES → $LE8_{LIFESTYLE}$ → DEMENTIA(β_B)	**+0.011**	**(0.001), <0.001**	**+0.0104**	**(0.0013), <0.001**
RACE_ETHN → SES → $LE8_{LIFESTYLE}$ → $LE8_{BIOLOGICAL}$ → DEMENTIA(β_C)	+0.0002	(0.0001), 0.054	+0.00015	(0.0001), 0.24
RACE_ETHN → SES → $LE8_{LIFESTYLE}$ → $LE8_{BIOLOGICAL}$ → COGN → DEMENTIA(β_D)	**−0.00010**	**(0.0000), 0.001**	—	—
RACE_ETHN → SES → $LE8_{LIFESTYLE}$ → COGN → DEMENTIA(β_E)	**−0.00032**	**(0.00005), <0.001**	—	—
RACE_ETHN → SES → COGN → DEMENTIA(β_F)	**+0.0202**	**(0.010), <0.001**	—	—
TOTAL EFFECT OF RACE_ETHN	**+0.232**	**(0.078), 0.003**	**+0.232**	**(0.078), 0.003**

Abbreviations: COGN: Poor cognitive performance z-score; DEMENTIA: Dementia; LE8: Life's essential 8'; RACE_ETHN: Racial minority status (Non-White vs. White); SES: Socio-economic status z-score. [a]Values are path coefficients β ± SE or non-linear combinations of path coefficients to compute selected indirect effects. → DEMENTIA associations are interpreted as Log_e(HR) of these incident outcomes per unit exposure, as are total effects of RACE_ETHN. *P* for null hypothesis of β = 0.

Table 5. Total and selected indirect effects of socio-economic status vs. all-cause dementia through $LE8_{LIFESTYLE}$, $LE8_{BIOLOGICAL}$ and cognitive performance factors among middle-aged adults (Age_{base}: 50–74 y); The UK Biobank 2006–2021[a].

	MODEL A		MODEL B	
	β	(SE), *p*	β	(SE), *p*
Selected Indirect effects				
SES → $LE8_{LIFESTYLE}$ → DEMENTIA($\beta_{A'}$)	**−0.030**	**(0.004), <0.001**	**−0.030**	**(0.004), <0.001**
SES → $LE8_{LIFESTYLE}$ → $LE8_{BIOLOGICAL}$ →	−0.0007	(0.0004), 0.054	−0.0004	(0.0004), 0.24

DEMENTIA($\beta_{B'}$)				
SES → $LE8_{LIFESTYLE}$ → $LE8_{BIOLOGICAL}$ → COGN → DEMENTIA($\beta_{C'}$)	**+0.00027**	**(0.00002), <0.001**	—	—
SES → $LE8_{LIFESTYLE}$ → COGN → DEMENTIA($\beta_{D'}$)	**+0.00092**	**(0.0002), <0.001**	—	—
SES → COGN → DEMENTIA($\beta_{E'}$)	**−0.0576**	**(0.0025), <0.001**	—	—
TOTAL EFFECT OF SES	**−0.370**	**(0.020), <0.001**	**−0.370**	**(0.020), <0.001**

Abbreviations: COGN: Poor cognitive performance z-score; DEMENTIA: Dementia; LE8: Life's Essential 8; SES: Socio-economic status z-score. [a]Values are path coefficients β ± SE or non-linear combinations of path coefficients to compute selected indirect effects → DEMENTIA associations are interpreted as Log_e(HR) of these incident outcomes per unit exposure, as are total effect of SES. *P* for null hypothesis of β = 0.

portion of the total effect SES on dementia risk was a direct effect, unexplained by the pathways under consideration. Findings from Tables 4 and 5 are illustrated further in a qualitative manner in Figure 2. Supplementary analyses using different potential mediators as shown in Figure 1, are presented in Supplementary Tables 7 and 8 and illustrated in Supplementary Figure 2 for Models A and B. Supplementary Results 1 summarizes the key findings. Most notably, social support and nutritional biomarkers were among mediators explaining a large portion of racial/ethnic disparities in dementia (17–25% of the total effect), without necessarily going through SES as an antecedent mediator. Nevertheless, in these models, SES mediated about half of the total race-dementia effect. It is also worth noting that in Model A, pathways going through COGN indicated possible reverse causation, with poor cognitive performance positively predicting dementia risk while being concurrently associated with improved dietary and other lifestyle habits. This pattern was also observed in Model A, Figure 2.

DISCUSSION

The present study is among few to examine racial/ethnic disparities in dementia risk and their related pathways among UK Biobank study respondents (50–74 y, *N* = 323,483; 3.6% non-White minorities) using a series of Cox proportional hazards and generalized structural equations models (GSEM). It is the first to do so in a UK population. Among key findings, and after ≤15 years, 5,491 all-cause dementia cases were diagnosed. Racial minority status increased dementia risk by 24% (HR = 1.24, 95% CI: 1.07–1.45, *P* = 0.005), an association attenuated by socio-economic status (SES), (HR = 1.12, 95% CI: 0.96–1.31). Total race-dementia effect was mediated through both SES and lifestyle factors (e.g., $LE8_{LIFESTYLE}$). SES was inversely related to dementia risk (HR = 0.69, 95% CI: 0.67, 0.72, *P* < 0.001). Pathways

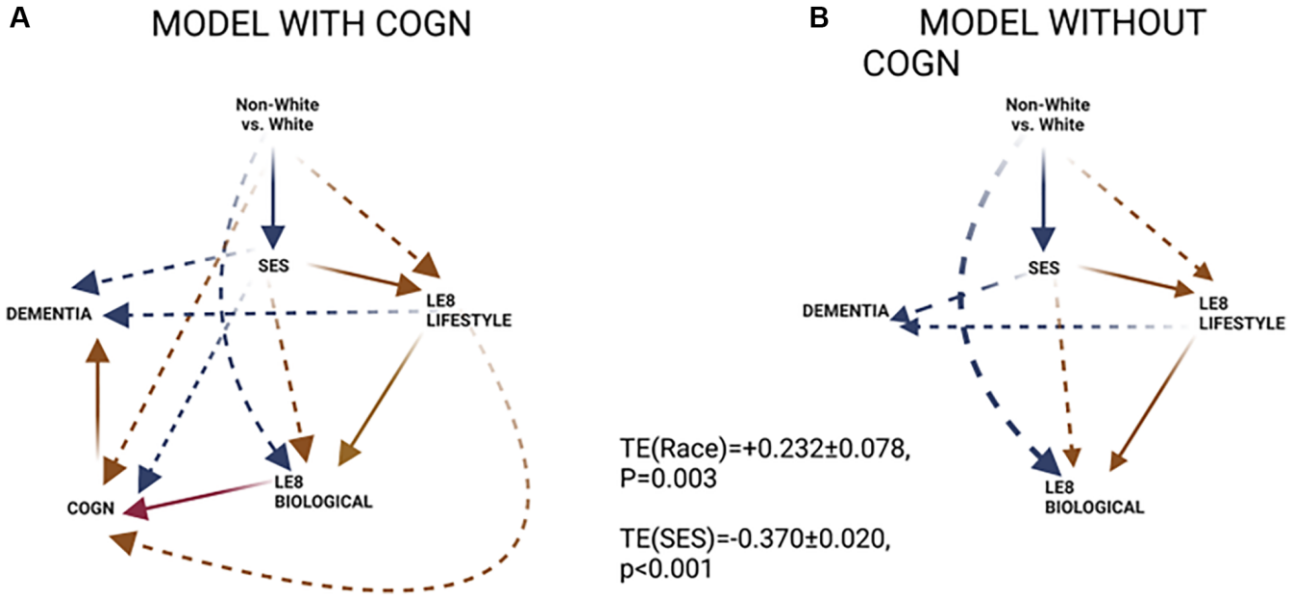

Figure 2. GSEM findings. (**A**) Model with COGN as a proximal mediator; (**B**) Model without COGN as a proximal mediator. Abbreviations: COGN: Poor cognitive performance, *z*-score; $LE8_{BIOLOGICAL}$: Biological sub-scale of Life's Essential 8; $LE8_{LIFESTYLE}$: Lifestyle sub-scale of Life's Essential 8; SES: Socio-economic status; Red lines: positive associations; Blue lines: inverse associations; Solid line: within hypothesized pathway; Dashed line: outside hypothesized pathway.

explaining excess dementia risk among racial minorities included 'RACE_ETHN(−) → SES(−) → DEMENTIA', 'RACE_ETH(−) → SES(−) → COGN(+) → DEMENTIA' and 'RACE_ETHN(−) → SES(+) → $LE8_{LIFESTYLE}$(−) → DEMENTIA'.

Previous studies report lower SES to be associated with higher health risk behavior levels and generally reduced access to quality resources [38]. The latter is among key structural determinant that can link low SES to dementia occurrence, particularly among racial minority groups that have been historically marginalized [39]. Additive chronic stress triggered by low SES coupled with lack of social support can lead to an accumulation of allostatic load, a mechanism thought to explain the relationship between chronic stress and cognitive dysfunction [40]. Thus, lack of social support is an antecedent factor to cardiometabolic health, as is the case for socio-economic status, and can indirectly lead to adverse cognitive outcomes through factors such as allostatic load [39]. Additionally, a combination of low SES and chronic stress may trigger maladaptive responses leading to neuroendocrine, autonomic, and behavioral modifications, which are thought to directly related with poor cognitive function. For instance, the prefrontal cortex was shown to be negatively affected by chronic stress resulting from lower SES [41]. Thus, low SES is linked to a complex interplay of biological, physiological, and environmental factors which, in turn, results in cognitive dysfunction.

We found that SES is a key mediator between race and dementia incidence, and that it was sufficient in its mediating effect even though lifestyle and health-related factors as well as cognitive performance at baseline assessment had an important role to play in the race-dementia relationship. Previous studies suggest that there are marked racial disparities in occurrence of AD and related dementias [17, 18, 24]. In a multi-ethnic cohort, for instance, the age standardized diagnostic incidence rate of dementia from all causes was increased in African American (22.9 in women, 21.5 in men) and Native Hawaiian (19.3, 19.4) older adults compared to their White counterparts (16.4, 15.5), while being comparable in the Latino group (16.8, 14.7) and significantly reduced among Japanese American (14.8, 13.8), and Filipino (12.5, 9.7) older adults [18]. In another more recent study, incident all-cause dementia among older adults in the US was significantly greater among NHB women compared to NHW women, whereas Mexican-American women were at reduced AD risk compared with their NHW counterparts, especially upon further adjustment for SES and upstream factors [24]. SES mediated a large portion of the NHB-NHW women disparity in dementia, in addition to several other lifestyle factors, most notably diet and physical activity [24]. Income-level differences in pathways between race/ethnicity and dementia risk were observed in another comparable study, highlighting the importance of social support in reducing dementia risk within the lowest income category [33]. The socio-economic gradient in dementia incidence playing a major role in racial/ethnic disparities in this health outcome was also suggested in other studies [20–23]. More recently, beneficial effects ascribed to education included reduced cognitive adverse effects of tau accumulation, one of two hallmarks of AD, as imaged with *in vivo* positron emission tomography, with higher education [23].

Other upstream factors including poor diet, reduced physical activity, smoking status and patterns, alcohol consumption and abuse, nutritional biomarkers including measures of anemia and vitamin D deficiency, social support and cardio-metabolic risk including elevated mid-life body mass index, blood pressure and blood glucose (or HbA1c), as well as elevated total cholesterol and measures of inflammation, have been confirmed in recent meta-analyses to be important predictors of cognitive performance, decline and incidence of dementia [16, 42–47]. Moreover, poor cognitive performance at a point in time during mid-adulthood was generally predictive of later onset dementia [48]. We found minority race status to be associated with lower SES which then predicted improved lifestyle factors in general, the latter predicting better general and cardio-metabolic health, and poorer health was associated with greater dementia risk. This pattern of associations was particularly supported in models with LE8 sub-scales with two dominant pathways ('RACE(−) → SES(−) → DEMENTIA' and 'RACE(−) → SES(+) → $LE8_{LIFESYLE}$(−) → DEMENTIA') explaining the net excess dementia risk among Non-White adults vs. White adults. Despite poor cognitive performance predicting future dementia risk, there may be indication of reverse causality between cognitive performance and $LE8_{LIFESTYLE}$ in particular, whereby perceived poor cognition is leading individuals to improve their diet, physical activity, and smoking habits among others. This potential reverse causation is also observed in models with individual lifestyle factors, rendering models without cognitive performance as a mediator more interpretable.

Our study has several strengths. First, our analyses were well-powered to evaluate and detect mediating effects across different racial/ethnic subgroups, overall and among males and females separately. Second, we were able to use the exact diagnosis dates for respondents due to the record linkage processes maintained by the UK Biobank investigators. Third, whereas prior work

utilizing electronic health record data tends to rely on a limited set of demographic measures collected during patient encounters [49]. We were able to incorporate a broad range of characteristics across multiple domains in conjunction with electronic health record linkage, minimizing potential bias due to unmeasured confounding. Potential study limitations included residual confounding, measurement error, and potential selection bias due to missing data on cognitive performance. Furthermore, there were some limitations related to studying each racial/ethnic minority group separately, particularly African Caribbean and South Asian as contrasted with the larger group of European ancestry, for sub-types of dementia including AD and VaD, and examining in more detail those pathways through socioeconomic status and cardiovascular health as measured by LE8. Nevertheless, as follow-up continues in the UK Biobank study, more incident cases of AD and VaD will allow for more granular analyses by race/ethnicity and sex. It is worth noting that we included several covariates to estimate each construct of interest among mediators and adjusted our models for potential confounding exogenous variables. Our findings are further supported by a parallel study conducted among older adults in the US [24] which revealed pathways similar to those uncovered in the current study. For example, in both studies, SES and several lifestyle factors—including diet and physical activity—were identified in explaining racial/ethnic disparities in dementia incidence. Moreover, other recent work further corroborates some of the other pathways observed in the current study, including mechanisms related to diet and social support across different income groups [33]. It is worth noting that given the contemporaneous measurement of cognitive performance and lifestyle factors among others, reverse causality whereby behavior change is driven by perceived poor cognition is observed in some of the models that included cognitive performance as a potential mediator.

Our study provides evidence for modifiable risk factors that can delay dementia onset and explain a significant portion of the SES-dementia as well as the race-dementia relationships. Our findings underscore the importance of lifestyle factors such as diet, smoking, physical activity, sleep and social support for future interventions aimed at reducing racial and socioeconomic disparities in dementia.

Abbreviations

AD: Alzheimer's Disease; AL: Allostatic Load; ALCOHOL: alcohol consumption, z-score; BMI: Body Mass Index; CI: Confidence Interval; COGN: Poor cognitive performance principal component variable (3 measured variables); DIET/NUTR: diet and nutritional biomarkers z-score variable (3 dietary quality measures and 4 nutritional biomarkers); DX: Diagnosis; GSEM: Generalized Structural Equations Modeling; HEALTH: Poor health-related factors as mean of z-scores for allostatic load, self-rated health, co-morbidity index and body mass index; HR: Hazard Ratio; IR: Incidence Rate; ICD-9: International Classification of Diseases, 9th revision; ICD-10: International Classification of Disease, 10th revision; LCL: Lower Confidence Limit; LIFESTYLE: Lifestyle-related factors composed of social support, physical activity, diet, nutritional biomarkers, smoking and alcohol consumption using means of z-scores for related measured variables; LOAD: Late-Onset Alzheimer's Disease; N: number of participants; N': number of observations; PA: Physical activity z-score variable (3 measured variables); RACE_ETHN: racial/ethnic contrast; SES: Socioeconomic status mean of z-scores composed of income, education and Townsend deprivation index; SMOKING: smoking z-score variable; UCL: Upper Confidence Limit; UKB: UK Biobank.

AUTHOR CONTRIBUTIONS

M. A. B.: Study concept, plan of analysis, data management, statistical analysis, literature search and review, write-up of the manuscript, revision of the manuscript; H. A. B.: Plan of analysis, literature search and review, write-up of parts of the manuscript, revision of the manuscript; M. T. F-K.: Literature search and review, write-up of parts of the manuscript, revision of the manuscript; J. W.: Plan of analysis, assistance with statistical analysis; literature search and review, write-up of parts of the manuscript, revision of the manuscript; M. F. G.: Literature search and review, write-up of parts of the manuscript, revision of the manuscript; M. K. E.: Data acquisition, write-up of parts of the manuscript, revision of the manuscript; OM: Plan of analysis, write-up of parts of the manuscript, revision of the manuscript; DL: Plan of analysis, literature search and review, revision of the manuscript; A. B. Z.: Data acquisition, plan of analysis, write-up of parts of the manuscript, revision of the manuscript.

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CONFLICTS OF INTEREST

All authors declare no conflict of interest. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or U.S. Government. Reference to any commercial products within this publication does not create or imply any endorsement by Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or U.S. Government.

ETHICAL STATEMENT

The protocol of this study involving human participants was reviewed and approved by the UK Biobank. The approval was received from the Institutional Review Boards, namely, the North West Multi-Centre Research Ethics Committee for the United Kingdom, from the National Information Governance Board for Health and Social Care for England and Wales, and from the Community Health Index Advisory Group for Scotland. All participants gave informed consent for the study via a touch-screen interface that required agreement for all individual statements on the consent form as well as the participant's signature on an electronic pad. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements.

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SUPPLEMENTARY MATERIALS

Supplementary Methods and Results

Supplementary Method 1: Dietary intake and other lifestyle factors

The touchscreen questionnaire of the UKB main study included twenty-nine questions regarding diet and eighteen questions related to alcohol. The touchscreen questionnaire inquired about food consumption frequency and nature, over the past year of the following food groups: cooked vegetables, salad/raw vegetables, fresh fruit, dried fruit, oily fish, other fish, processed meats, poultry, beef, lamb, pork, cheese, salt added to food, tea, water, as well as questions on the type of milk most commonly consumed, type of spread most commonly consumed, number of slices and type of bread most commonly consumed, number of bowls and type of breakfast cereal most commonly consumed, cups of coffee and type most commonly consumed, as well as questions on the avoidance of specific foods and food groups (eggs, dairy products, wheat, sugar), age last ate meat (for participants who reported never consuming processed meats, poultry, beef, lamb or pork), temperature preference of hot drinks, changes in diet in the past 5 years, and variation in diet. Four of the dietary questions originally utilized in the pilot trial were slightly altered for the main assessment phase: these were the items related to avoiding specific foods and food groups; spread type; bread type; and variation in diet.

The Healthy Diet Index (HDI) score combined several food groups in terms of quantity and frequency of consumption per week, when available to reflect the guidelines listed in Supplementary Table 2. However, those criteria were modified to fit the availability of data in the UK Biobank. Supplementary Table 3 represents the food groups that were selected, their respective coding scheme and the scoring system to reflect better diet quality, approximating the criteria in Supplementary Table 2. The touchscreen questionnaire was later validated against the 24-hr recall that was administered over time to UK Biobank participants and has shown adequate agreement in terms of ranking for each food group of interest [1].

Smoking

We utilized several fields of data to generate three tobacco exposure variables, based on the touchscreen questionnaire at the assessment centre visit, namely smoking status, environmental tobacco smoke and pack-years of smoking. Those three constructs were transformed into standardized z-scores which were then averaged into the latent construct SMOKING.

Alcohol

The touchscreen questionnaire also provided several questions related to alcohol consumption, which were quantity-frequency in nature. One question asked "About how often do you drink alcohol?" with 6 possible responses that were reverse coded to the following: 0 "never" 1 "special occasions only" 2 "1–3 times per month" 3 "1–3 times per week" 4 "3–4 times per week" 5 "daily or almost daily". The construct ALCOHOL was the standardized z-score for this item.

Physical activity

Physical activity (PA) was operationalized using a set of self-reported responses that can be used to assess mild (i.e., walking), moderate and vigorous activities based on the short form of the International Physical Activity Questions [2] in terms of frequency (# of days) per week and number of minutes per day. Those were then combined to generate MET.min/week for each category of physical activity intensity. Finally, the MET.min/week values were added together. Given that missing data does exist, addition was made on the imputed data, whereby MET.min/week per intensity were imputed where missing using chained equations. This single measured variable reflecting total MET.min/week was transformed into a standardized z-score, labelled PA and used in our pathway analyses.

Diet quality

We utilized the dietary questionnaire data category, based on a set of questions administered at the assessment visit. A measure of diet quality was constructed to approximate dietary recommendations listed in Supplementary Table 2. The criteria applied to each food or nutrient item derived the food frequency questionnaire (FFQ) to obtain an overall measure of diet quality is described in Supplementary Table 3. The resulting z-score was used to obtain the DIET construct.

Nutritional biomarkers

Vitamin D was additionally selected from the list as a nutritional biomarker that was previously shown to be inversely associated with cognitive aging [3–6]. Of the long list of hematological factors, we selected red cell distribution width (RDW) as an additional nutritional biomarker, reflecting iron metabolism, as it was previously shown to be directly associated with cognitive aging [7–9]. Thus, the z-score of RDW was multiplied by -1. The average of the two z-scores was used reflect nutritional biomarkers, or NUTR.

Social support

Three social support variables were used to operationalize SS standardized z-score. The first variable pertained to the question: "How often do you visit friends or family or have them visit you?", with potential responses reverse coded to range from 1 = "No friends/family" to 7 = "Almost daily". Intermediate responses were "Never or almost never", "Once every few months", "About once a month", "About once a week" and "2–4 times a week". Similarly, another question asked: "How often are you able to confide in someone close to you?" With no reverse coding necessary, the responses ranged from 0 = "Never or almost never" to 5 = "almost daily" and intermediate responses being "Once every few months", "About once a month", "About once a week" and "2–4 times a week". Finally, a third question asked "Which of the following do you attend once a week or more often?" and was used to count leisure and social activities among "sports and club or gym", "pub or social club", "religious group", "adult education class" and "other group activity". These three measures were then transformed into a standardized z-score and averaged into the SS measure.

Supplementary Method 2: Life's Essential 8

Life's Essential 8 was computed using guidelines from Supplementary Table 4 and all available data fields that correspond to these guidelines, while ensuring maximal sample preservation. The HDI was used for the dietary quality component, while other criteria were used that fit the guidelines well. In order to further preserve the sample and increase statistical power, two methods were available. The first one was multiple imputations using chained equations. Given the large sample to be used, this method was deemed infeasible as a main tool for the analysis. Another method that is widely used in the social science is proration [10, 11], with general guidelines for large sample to allow for up to 50% of the items to be missing per observation, as shown in Supplementary Table 1. Beyond this threshold, the entire observation was dropped from analysis. For scales that relied on totals (e.g., LE8), the row means were multiplied by the total number of items (4 for the LE8 sub-scales and 8 for the total score). This method was also applied to SES, DIET, SMOKING, ALCOHOL, NUTR, SS and HEALTH. COGN score was obtained using principal components analysis with complete cases and thus proration was not needed. In the final sample, 99.9% of participants had 2 items or less missing on the LE8 total score.

Supplementary Method 3: Health-related factors

Blood biochemistry was conducted at baseline assessment the full list of markers, included markers for liver and kidney function, systemic inflammation, lipid metabolism, glucose homeostasis and calcium metabolism among others. Some of these markers were included into the measure of allostatic load, including albumin, C-reactive protein, total cholesterol, HDL-cholesterol, and glycated hemoglobin (HbA1c). Clinical criteria summarized in Supplementary Table 5 were used to obtain risk indicators. Glycosylated hemoglobin was measured in mmol/mol and converted to %, with a cutoff of 6.4% corresponding to 41.8 mmol/mol, using high performance liquid chromatography, Bio-Rad Variant II. Nurses and phlebotomists collected blood and urine samples from participants at the assessment center after an overnight fast, which was determined largely compliant based on the pilot testing phase [14]. Among blood measures, we used total cholesterol (mg/dl), HDL-cholesterol (mg/dl), CRP (mg/dl), albumin (g/dl) and glycosylated hemoglobin (%) which were analyzed by contract laboratories [14]. Specifically, blood lipids were measured using direct enzymatic methods (Konelab, Thermo Fisher Scientific, Waltham, MA, USA). Using standard protocols, waist-to-hip ratio, radial pulse (beats/min), and systolic and diastolic blood pressure (mmHg) were measured by trained examiners. Specifically, both blood pressure and pulse rate were measured using the Omron HEM-7015IT digital blood pressure monitor [14].

BMI

The body mass index was computed at baseline assessment measured weight in kilograms divided by measured height-squared in squared-meters.

Allostatic load (AL)

Using a method described previously, [15] AL total score is an index that adds up with equal weighting (range: 0–9), cardiovascular (systolic and diastolic blood pressure, pulse rate), metabolic (total cholesterol, HDL-cholesterol, glycosylated Hb, sex-specific waist-to-hip ratio) and inflammatory (albumin and C-reactive protein (CRP)) risk indicators.

Co-morbidity index

Two data fields (134 and 135) were used to construct a variable for cancer and non-cancer co-morbidity index at the baseline assessment. These are based on self-reported data on pre-existing co-morbidities.

Self-rated health

Self-rated health (or overall health rating) was obtained as part of the touchscreen questionnaire at baseline assessment the UK Biobank. Possible responses were: 1. Excellent, 2. Good, 3. Fair, 4. Poor. The coding was left as is to reflect poorer health with higher score.

Supplementary Method 4: Cognitive test performance: assessment and scoring

The UK Biobank performed touchscreen computer assessment of cognitive performance on all participants in the case of the pairs memory test and the reaction time test. A sub-sample also completed the numeric memory test, a prospective memory task and a numeric and verbal reasoning test [24, 25]. Those tests were shown to correlate with general cognitive ability (R^2: 0.3–0.6), though generally had a lower test-retest reliability compared to reference cognitive tasks (R^2 varied from 0.4 to 0.6) [24, 25]. For our purpose, we used a total of three cognitive test scores from the pairs memory test (two scores) the reaction time test (one score), to preserve the final sample size.

Visual memory

The visual memory task involved memorizing positions of pairs of cards, followed by successfully matching them after the cards have been turned face down on the screen. In the first round, participants had 3 pairs to remember, while in the second round, they were asked to remember 6 pairs. The number of incorrect matches were of interest and Cronbach α reliability = 0.62 [26]. We have focused on the 6 pair version due to its greater difficulty. In addition, the time to complete the visual memory test was also of interest in this study.

Reaction time

Participants completed a touch screen version of the game snap and the time to match each symbol was recorded. They completed twelve rounds with the reaction time averaged across rounds. Cronbach α reliability = 0.85 [26].

Supplementary Results 1

The estimated incidence rate of all-cause dementia among men was 164 per 100,000 person-years (P-Y); among women it was 117 per 100,000 per year. For AD, incidence estimates were 63 per 100,000 P-Y among men and 54 per 100,000 P-Y among women. Dementia incidence rates for both sexes were greater among Black adults compared to White adults, which was the reverse for rates among SA and other ethnic groups. Racial/ethnic composition differed significantly across sexes, with greater percentage of Black adults among women compared to men (1.0% (F) vs. 0.8% (M)), coupled with a greater percentage SA among men vs. women (1.4% (M) vs. 1.0% (F)). Moreover, minority groups overall were younger than White adults in this sample (58.6 (NW) vs. 60.5 y (W), mean age). Household size was larger in the minority group compared to White adults (2.7 (NW) vs. 2.2 (W)) in both sexes. Importantly, non-White adults had lower SES compared to White adults (z-score: −0.28 (NW), −0.02 (W)). There were both sex and racial differences in the smoking construct. The SMOKING z-score was lower among minority groups compared to White adults (−0.025 (NW) vs. −0.004 (W)), and higher among men (−0.002) compared to women (−0.008). In contrast, men tended to consume alcohol more frequently than women, and non-White adults were less heavy consumers compared to their White counterparts. Physical activity measured in Met.min.wk^{-1} was lower among non-White adults vs. White adults, and among women compared to men. There were notable racial and ethnic differences in the NUTR z-score, owing mainly to reduced vitamin D level among non-White compared to White adults. Minority groups had poorer general and cardiometabolic health compared to White adults as did men compared with women. Minority groups combined and women performed worse on a set of cognitive test scores compared to their White and male counterparts. LE8 total, lifestyle and biological scores were markedly higher among White adults compared to non-White adults, and were also higher among women than men, suggesting a more optimal cardiovascular health among White adults and women.

Supplementary Figure 2 illustrates the results of Supplementary Tables 7 and 8, which examined similar GSEM models by substituting $LE8_{LIFESTYLE}$ with other alternative LIFESTYLE factors (DIET, PA, SMOKING, ALCOHOL, NUTR and SS), and $LE8_{BIOLOGICAL}$ with the HEALTH score. The results were comparable to the LE8 findings. Focusing on Model B, NUTR and SS were among the key antecedent mediators to HEALTH explaining racial/ethnic and SES disparities in all-cause dementia risk, both of which by being associated with reduced risk. More specifically, 'RACE_ETHN(−) → SES(+) → NUTR(−) → DEMENTIA' and 'RACE_ETHN(−) → SES(+) → SS(−) → DEMENTIA' are pathways that explained 0.9% and 0.3% of the total effect RACE_ETHN → DEMENTIA, respectively. This is in contrast with 'RACE_ETHN(−) → NUTR(−) → DEMENTIA' and 'RACE_ETHN(−) → SS(−) → DEMENTIA', which explained about 25% and 17% of the total effect, respectively. Nevertheless, the residual pathway 'RACE_ETHN → SES → DEMENTIA' in these models explained around half of the RACE_ETHN → DEMENTIA total effect. Other notable pathways by which RACE_ETHN could adversely impact dementia risk included 'RACE_ETHN(−) → SES(+)→ DIET(−) → HEALTH(+) → DEMENTIA'; 'RACE_ETHN(−) → PA(−) → HEALTH(+) → DEMENTIA'; 'RACE_ETHN(−) → SES(−) →SMOKING(+) → HEALTH(+) → DEMENTIA'; and 'RACE_ETHN(−) → SES(−) → HEALTH(+) → DEMENTIA'.

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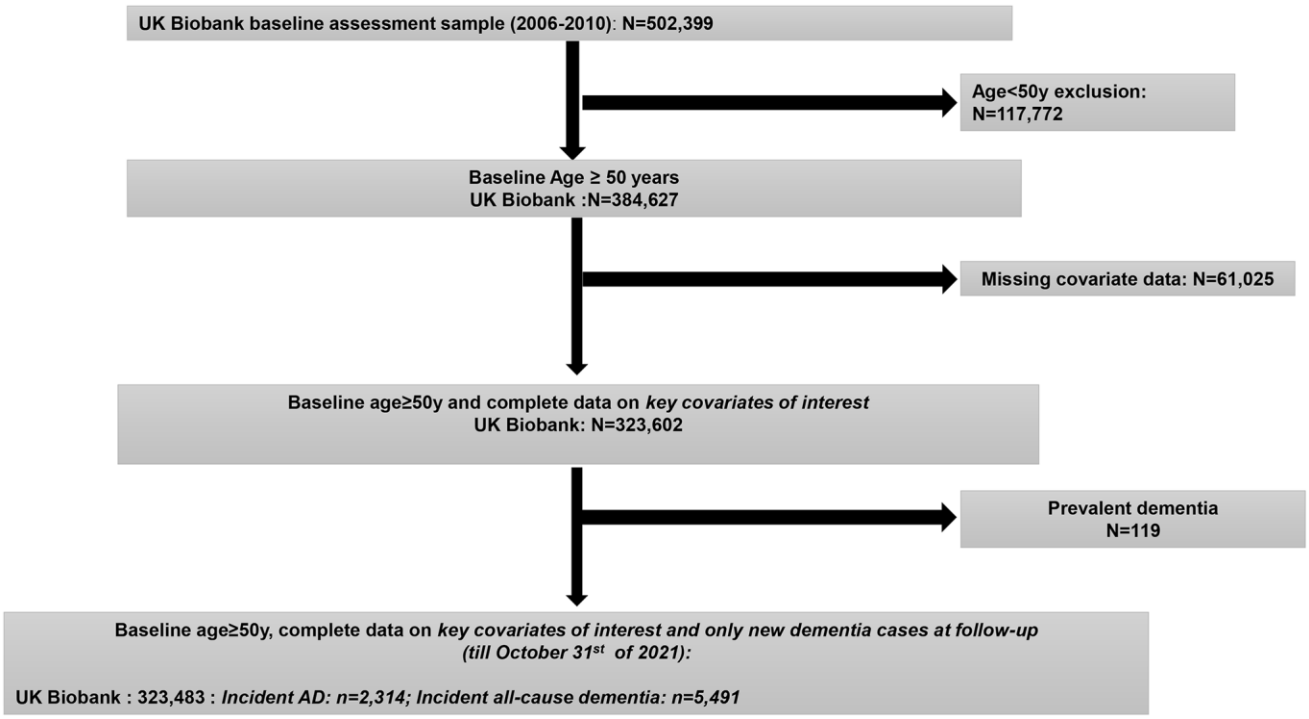
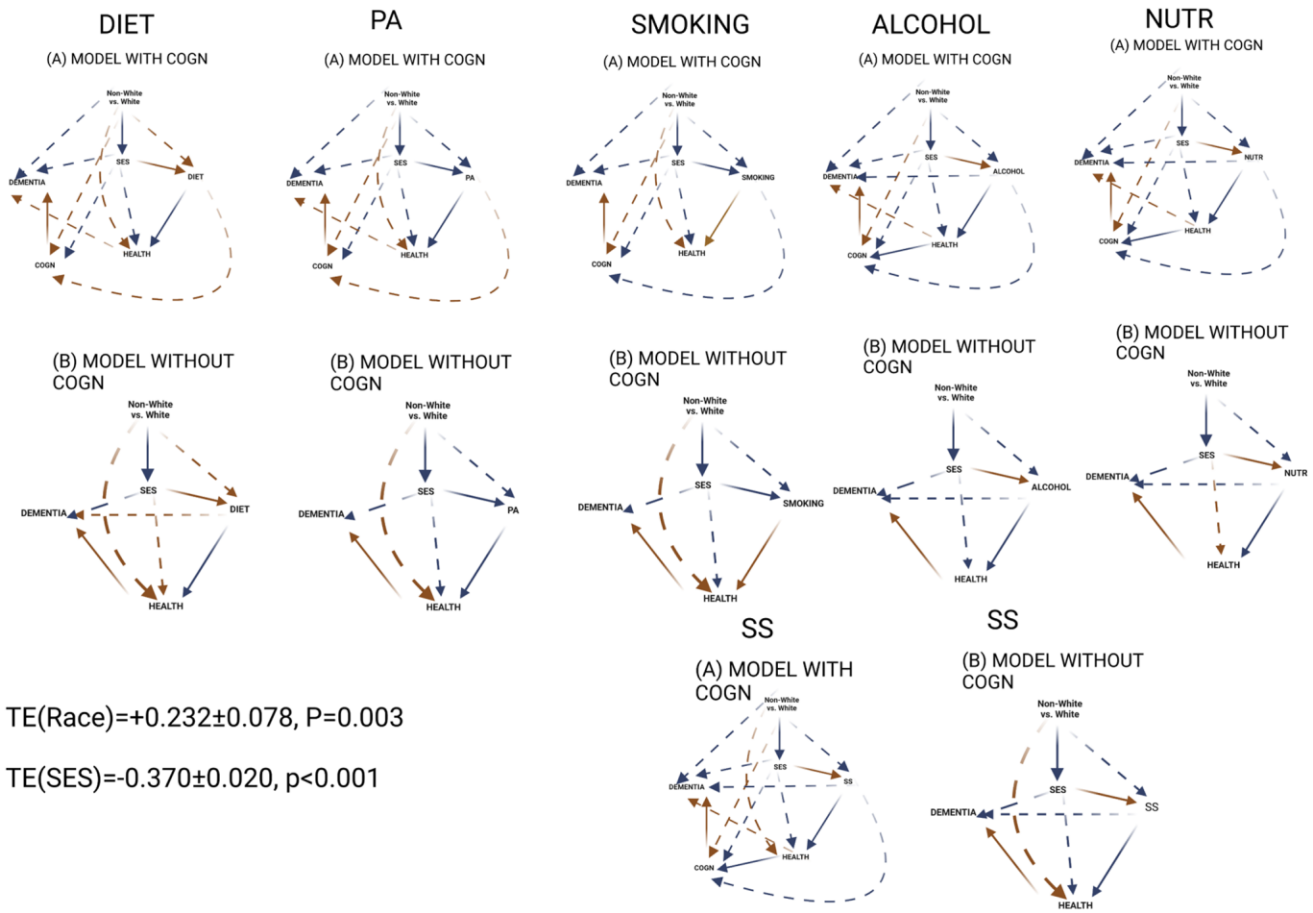
Supplementary Figures



Supplementary Figure 1. Participant flowchart: The UK biobank 2006–2021. Abbreviations: AD: Alzheimer's disease; N: Sample size; UK: United Kingdom.



Supplementary Figure 2. GSEM findings from models with alternative mediators, HEALTH and COGN. Abbreviations: AD: Alzheimer's Disease; ALCOHOL: Alcohol consumption z-score; COGN: Poor cognitive performance z-score; DIET: diet quality z-score; HEALTH: Poor cardio-metabolic and general health z-score; PA: Physical Activity z-score; NUTR: Nutritional biomarker z-score; SES: Socio-economic status z-score; SMOKING: Smoking z-score; SS: Social Support z-score; TE: Total Effect. Red lines: Positive associations; Blue lines: Inverse associations; Solid lines: Within hypothesized pathway; Dashed lines: Outside hypothesized pathway.

Supplementary Tables

Supplementary Table 1. Proration of mediators including LE8 sub-scales.

Items	Number of missing items/participant allowed for prorating
1	0
2	1
3	1
4	2
5	2
6	3
7	3
8	4
9	4
10	5
11	5
12	6

Supplementary Table 2. Goals and guidelines used to construct the healthy diet score.

Consume more	Goal*	One serving equals…
Fruits	3 servings/d	1 medium-sized fruit; ½ cup of fresh, frozen, or unsweetened canned fruit; ½ cup of dried fruit; ½ cup of 100% juice
Nuts, seeds	4 servings/wk	1 ounce
Vegetables, including legumes (excluding russet or white potatoes)	3 servings/d	1 cup of raw leafy vegetables; ½ cup of cut-up raw vegetables, cooked vegetables, or 100% vegetable juice
Whole grains†	3 servings/d, in place of refined grains	1 slice of whole-grain bread; 1 cup of high-fiber, whole-grain cereal; ½ cup of cooked whole-grain rice, pasta, or cereal
Fish, shellfish	≥2 servings/wk	3.5 ounces (100 g)
Dairy products, especially yogurt and cheese‡	2–3 servings/d	1 cup of milk or yogurt; 1 ounce of cheese
Vegetable oils	2–6 servings/d	1 teaspoon oil, 1 tablespoon vegetable spread
Consume less		
Refined grains, starches, added sugars†	No more than 1–2 servings/d	
Processed meats	No more than 1 serving/wk	1.75 ounces (50 g)
Unprocessed red meats	No more than 1–2 servings/wk	3.5 ounces (100 g)
Industrial trans fat§	Don't eat	Any food containing or made with partially hydrogenated vegetable oil
Sugar-sweetened beverages	Don't drink	8 ounces of beverage; 1 small sweet, pastry, or dessert
Sodium	No more than 2000 mg/d	n/a

Source: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.115.018585#d3e341. *Based on a 2000 kcal/d diet. Servings should be adjusted accordingly for higher or lower energy consumption. †As a practical rule-of-thumb for selecting healthful whole grains and avoiding carbohydrate-rich products high in starches and added sugars, the ratio of total carbohydrate to dietary fiber (g/serving of each) appears useful. Foods with ratios <10:1 are preferable; i.e., food containing

at least 1 g of fiber for every 10 g of total carbohydrate. In addition, minimally processed whole grains (e.g., steel-cut oats, stone-ground bread) are generally preferable to finely milled whole grains (e.g., many commercial whole-grain breads and breakfast cereals) because of the larger glycemic responses of the latter. [‡]Current evidence does not permit clear differentiation of whether low-fat or whole-fat products are superior for cardiometabolic health. Other characteristics, such as probiotic content or fermentation, may be far more relevant than fat content. [§]The US Food and Drug Administration recently ruled that the use of partially hydrogenated vegetable oils is no longer "generally regarded as safe," which should effectively eliminate the majority of industrial trans fats from the US food supply. Several countries including Denmark, Argentina, Austria, Iceland, and Switzerland have effectively eliminated the use of partially hydrogenated vegetable oils through direct legislation on the amounts of allowable trans fats in foods. Small amounts of certain trans fatty acids may be formed through other industrial processes, including oil deodorization and high-temperature cooking; the health effects of these trace industrial trans fats require careful investigation.

Supplementary Table 3. Healthy Diet Index, HDI, using touchscreen questionnaire in the UK Biobank study[†,§].

Food group/ nutrient item	UKB fields used	Definition of meeting criterion	Criteria and scoring
Consume more			
Fruits, fresh or dried	1309 and 1319	≥3 servings per day including fresh and dried fruits 1 piece of dried fruit (e.g., apricot) ~=2.5 TBSP, 1 TBSP: 0.063 cups; ½ cup of dried fruit (1 serving) is 3 pieces of dried fruit. 1 medium sized fruit is one serving.	1: meets criterion, 0: does not meet criterion
Vegetables, salad/cooked	1289 and 1299	≥3 servings per day Including salad, raw and cooked 1 cup of raw leafy vegetables is 16 TBSP. ½ cup of cooked or non-leafy raw vegetables is 8 TBSP. 1 serving of raw leafy or non-leafy vegetables is on average ~=12 TBSP; 1 serving of cooked vegetables is ~=8 TBSP	1: meets criterion, 0: does not meet criterion
Whole grains		≥3 servings per day	1: meets criterion, 0: does not meet criterion
Slices of bread	1438 and 1448	Daily slices of wholemeal or wholegrain bread (servings per day), convert from weekly slices.	
Cereal	1458 and 1448	Daily bowls of whole wheat cereal as servings/day (bran cereal, biscuit cereal, oat cereal and muesli), convert from weekly bowls.	
Fish shellfish	1329 and 1339	Sum weekly frequencies to obtain total servings/week. ≥2 servings/wk	1: meets criterion, 0: does not meet criterion
Oily fish	…	…	
Non-oily fish	…	…	
Dairy products	6114, 1408 and 1418	Reporting consumption of two milk items and eating cheese once a day to meet the 2–3 servings/day criterion.	1: meets criterion, 0: does not meet criterion
Milk	…		
Cheese	…		
Vegetable oil	2654	Reporting use of olive oil or polyunsaturated/sunflower oil (yes: 1, 0: no)	1: meets criterion, 0: does not meet criterion
Consume less			
Refined grains, starches, added sugars[†]	1438 and 1448	Follow a similar coding scheme as for whole grains but select non-whole grains; <1.5 servings per day	1: meets criterion, 0: does not meet criterion
Processed meats	1349	Once a week or less would meet the criterion.	1: meets criterion,

			0: does not meet criterion
Unprocessed red meats	1369, 1379, and 1389	Summation of frequency of consumption across three types of red meats (lamb/mutton, beef or pork). <3 on the summation corresponds to the criterion of <1–2 servings per week.	1: meets criterion, 0: does not meet criterion
Industrial trans fat[§]	1428	Never use spread, e.g., butter or margarine etc. would meet the criterion	1: meets criterion, 0: does not meet criterion
Sugar-sweetened beverages	6144	Never eat sugar or food/drink containing sugar would meet the criterion	1: meets criterion, 0: does not meet criterion
Sodium	1478	Salt added to food, never or rarely would meet the criterion	1: meets criterion, 0: does not meet criterion

Source: https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100052. Stata code can be made available upon request.

Supplementary Table 4. Definition and scoring approach for quantifying cardiovascular health, as per the American Heart Association's Life's Essential 8 score [12, 13], and as applied in the National Health and Nutrition Examination Surveys, 2013–2018.

Domain	CVH metric	Method of measurement	Quantification of CVH metric - adults (≥20 years)
Health Behaviors	**Diet**	**Measurement: Self-reported daily intake of a DASH-style eating pattern** **Example tools for measurement: DASH diet score (populations)**	Quantiles of DASH-style diet adherence **Scoring (Population):** Points Quantile 100 ≥95th %ile (top/ideal diet) 80 75th – 94th %ile 50 50th – 74th %ile 25 25th – 49th %ile 0 1st – 24th %ile (bottom/least ideal quartile)
	Physical activity	**Measurement: Self-reported minutes of moderate or vigorous physical activity per week** **Example tools for measurement:** NHANES PAQ-K questionnaire	**Metric: Minutes of moderate (or greater) intensity activity per week** **Scoring:** Points Minutes 100≥150 90 120 – 149 80 90 – 119 60 60 – 89 40 30 – 59 20 1 – 29 0 0
	Nicotine exposure	**Measurement:** Self-reported use of cigarettes or inhaled nicotine- delivery system **Example tools for measurement:** NHANES SMQ	**Metric: Combustible tobacco use and/or inhaled NDS use; or secondhand smoke exposure** **Scoring:** Points Status 100 Never smoker 75Former smoker, quit≥5 yrs 50 Former smoker, quit 1 - <5 yrs 25 Former smoker, quit <1 year, or currently using inhaled NDS 0 Current smoker Subtract 20 points (unless score is 0) for living with active indoor smoker in home
	Sleep health	**Measurement:** Self-reported average hours of sleep per night **Example tools for measurement:** "On average, how many hours of sleep do you get per night?" Consider objective sleep/actigraphy data from wearable technology, if available	**Metric:** Average hours of sleep per night **Scoring:** Points Level 100 7 – <9 90 9 – <10 70 6 – <7 40 5 – <6 or ≥10 20 4 – <5 0 <4

Health Factors	**Body mass index**	**Measurement:** Body weight (kg) divided by height squared (m2) **Example tools for measurement:** Objective measurement of height and weight	**Metric: Body mass index (kg/m^2)** **Scoring:** Points Level 100 <25 70 25.0 – 29.9 30 30.0 – 34.9 15 35.0 – 39.9 0 ≥ 40.0
	Blood lipids	**Measurement:** Plasma total and HDL-cholesterol with calculation of non-HDL-cholesterol **Example tools for measurement:** Fasting or non-fasting blood sample	**Metric: Non-HDL-cholesterol (mg/dL)** **Scoring:** Points Level 100 <130 60 130 – 159 40 160 – 189 20 190 – 219 0 ≥220 If drug-treated level, subtract 20 points
	Blood glucose	**Measurement: Fasting blood glucose or casual hemoglobin A1c Example tools for measurement: Fasting (FBG, HbA1c) or non- fasting (HbA1c) blood sample**	**Metric: Fasting blood glucose (mg/dL) or Hemoglobin A1c (%)** **Scoring:** Points Level 100 No history of diabetes and FBG <100 (or HbA1c < 5.7) 60 No diabetes and FBG 100 – 125 (or HbA1c 5.7–6.4) (Pre-diabetes) 40 Diabetes with HbA1c <7.0 30 Diabetes with HbA1c 7.0 – 7.9 20 Diabetes with HbA1c 8.0 – 8.9 10 Diabetes with Hb A1c 9.0 – 9.9 0 Diabetes with HbA1c ≥10.0
	Blood pressure	**Measurement:** Appropriately measured systolic and diastolic blood pressure **Example tools for measurement:** Appropriately sized blood pressure cuff	**Metric:** Systolic and diastolic blood pressure (mm Hg) **Scoring:** Points Level 100 <120/<80 (Optimal) 75 120−129/<80 (Elevated) 50 130−139 or 80–89 (Stage I HTN) 25 140−159 or 90–99 0 ≥ 160 or ≥100

Supplementary Table 5. Allostatic load indicator criteria [15].

	High-risk clinical
Albumin (g/dL)	<3.8 [16]
C-reactive protein (mg/dL)	≥0.3 [17]
Waist: Hip Ratio	>0.9 for males; >0.85 for females [18]
Total cholesterol (mg/dL)	≥240 [19]
HDL-C (mg/dL)	<40 [19]
Glycated hemoglobin (%)	≥6.4 [20, 21]
Resting heart rate (beat/min)	≥90 [22]
Systolic BP	≥140 [23]
Diastolic BP	≥90 [23]

Abbreviations: BP: Blood Pressure; HDL: High Density Lipoprotein-Cholesterol.

Supplementary Table 6. Study sample characteristics by sex: The UK Biobank 2006–2021[a].

	Males, *n* = 148,958				Females, *n* = 173,525				P_{sex}
Study sample characteristics	**All males**	**White**	**Non-White**	***P***	**All females**	**White**	**Non-White**	***P***	
Socio-demographic									
Baseline age, y	60.7 ± 5.4	60.8 ± 5.4	59.1 ± 5.7	<0.001	60.1 ± 5.4	60.2 ± 5.4	58.1 ± 5.5	<0.001	**<0.001**
Sex, % female	0.0	0.0	0.0	—	100.0	100.0	100.0	—	—
Race/ethnicity				—				—	
White	96.4	100.0	0.0	—	96.4	100.0	0.0	—	<0.001
Black	0.8	0.0	22.6	—	1.0	0.0	27.5	—	—
South Asian	1.4	0.0_	39.8	—	1.0	0.0	28.3	—	<0.001
Other	1.4	0.0	37.6	—	1.6	0.0	44.2		0.45
Household size	2.3 ± 1.2	2.3 ± 1.1	2.9 ± 1.5	<0.001	2.2 ± 1.2	2.1 ± 1.1	2.6 ± 1.7	<0.001	<0.001
Socio-economic status									
Education									
Low	24.1	24.2	21.6	—	19.8	19.6	24.9	—	—
Intermediate	34.8	35.1	27.9	0.001	43.7	44.2	32.1	<0.001	<0.001
High	41.1	40.7	51.4	<0.001	36.5	36.2	43.0	<0.001	<0.001
Income				<0.001				<0.001	<0.001
Less than £18,000	22.6	22.4	28.1	—	27.8	27.7	32.3	—	—
£18,000–£29,999	26.9	26.9	27.3	—	29.0	29.0	28.3	—	—
£30,000–£51,999	25.8	25.9	22.8	—	24.0	24.0	22.2	—	—
£52,000–£100,000	19.5	19.6	16.7	—	15.5	15.5	13.6	—	—
greater than £100,000	5.2	5.2	5.1	—	3.7	3.7	3.6		
TDI	−1.54 ± 2.99	−1.62 ± 2.9	0.41 ± 3.53	<0.001	−1.57 ± 2.91	−1.65 ± 2.85	0.53 ± 3.43	<0.001	0.013
SES z-score	−0.01 ± 0.73	0.00 ± 0.72	−0.23 ± 0.80	<0.001	−0.05 ± 0.68	−0.03 ± 0.68	−0.33 ± 0.78	<0.001	<0.001
Lifestyle factors									
Smoking									
Smoking status									
Never	78.5	78.4	81.4	—	83.8	83.6	89.9	—	—
Former	10.6	10.8	5.4	<0.001	8.5	8.7	3.1	<0.001	<0.001
Current	10.9	10.8	13.2	<0.001	7.7	7.8	7.1	0.001	<0.001
Environmental tobacco smoke	0.97 ± 5.4	0.97 ± 5.4	1.02 ± 4.72	0.48	0.81 ± 5.1	0.80 ± 5.1	1.04 ± 4.73	<0.001	<0.001
Pack-years of tobacco smoke	0.10 ± 0.30	0.10 ± 0.30	0.07 ± 0.22	<0.001	0.07 ± 0.22	0.07 ± 0.22	0.04 ± 0.16	<0.001	<0.001
SMOKING z-score	−0.002 ± 0.481	−0.000 ± 0.482	−0.050 ± 0.454	<0.001	−0.008 ± 0.405	−0.008 ± 0.406	−0.004 ± 0.383	0.51	<0.001
Alcohol consumption									
Alcohol consumption frequency									
0 "never"	5.5	4.9	21.2	—	8.8	8.1	27.4	—	—
1 "special occasions only"	6.8	6.5	16.5	<0.001	14.8	14.2	30.0	<0.001	<0.001
2 "1–3 times per month"	8.0	8.0	10.1	<0.001	12.5	12.5	11.6	<0.001	0.020
3 "1–3 times per week"	24.5	24.6	21.4	<0.001	25.0	25.3	15.4	<0.001	<0.001
4 "3–4 times per week"	26.8	27.2	15.6	<0.001	21.6	21.5	8.9	<0.001	<0.001
5 "daily or almost daily"	28.4	28.9	15.2	<0.001	17.9	18.4	6.8	<0.001	<0.001
ALCOHOL z-score	+0.20 ± 0.94	0.23 ± 0.92	−0.49 ± 1.15	<0.001	−0.17 ± 1.00	−0.14 ± 1.00	−0.96 ± 1.02	<0.001	<0.001
Physical activity, PA									
PA, Met.min.wk^{-1}	2,169 ± 3.189	2,180 ± 3,194	1,853 ± 3,023	<0.001	1,787 ± 2,437	1,790 ± 2,431	1,703 ± 2,580	0.005	
PA z-score	0.07 ± 1.13	0.08 ± 1.13	−0.039 ± 1.07	<0.001	−0.06 ± 0.86	−0.06 ± 0.86	−0.09 ± 0.92	0.005	<0.001
Diet quality									
HDI total score	4.81 ± 1.56	4.79 ± 1.57	5.13 ± 1.49	<0.001	5.37 ± 1.39	5.36 ± 1.39	5.57 ± 1.35	<0.001	<0.001
DIET z-score	−0.20 ± 1.04	−0.21 ± 1.04	+0.01 ± 0.99	<0.001	+0.17 ± 0.93	0.17 ± 0.93	0.31 ± 0.90	<0.001	<0.001
Nutritional Biomarkers									
25-hydroxyvitamin D	49.7 ± 21.1	50.3 ± 20.9	33.8 ± 17.9	<0.001	49.6 ± 20.7	50.0 ± 20.6	36.9 ± 18.1	<0.001	0.016
Red cell distribution width	13.5 ± 0.9	13.5 ± 0.9	13.7 ± 1.1	<0.001	13.5 ± 1.0	13.5 ± 0.9	13.9 ± 1.3	<0.001	0.002
NUTR z-score	0.004 ± 0.733	+0.023 ± 0.723	−0.500 ± 0.823	<0.001	−0.005 ± 0.777	0.013 ± 0.766	−0.49 ± 0.91	<0.001	0.001
Social Support									
"How often do you visit friends or family or have them visit you?"	5.09 ± 1.16	5.10 ± 1.16	4.81 ± 1.20	<0.001	5.42 ± 1.09	5.44 ± 1.08	4.86 ± 1.21	<0.001	<0.001
"How often are you able to confide in someone close to you?"	1.00 ± 0.83	1.00 ± 0.83	0.91 ± 0.80	<0.001	1.08 ± 0.90	1.08 ± 0.90	0.98 ± 0.85	<0.001	<0.001
"Which of the following do you attend once a week or more often?"	3.43 ± 2.02	3.44 ± 2.02	2.93 ± 2.04	<0.001	3.65 ± 1.76	3.67 ± 1.75	3.12 ± 1.92	<0.001	<0.001
SS z-score	−0.089 ± 0.645	−0.082 ± 0.642	−0.293 ± 0.671	<0.001	0.075 ± 0.614	0.086 ± 0.609	−0.221 ± 0.664	<0.001	<0.001
Cardio-metabolic and general health-related factors									
Body mass index, kg.m^{-1}	27.9 ± 4.2	27.9 ± 4.2	27.5 ± 4.1	<0.001	27.2 ± 5.1	27.1 ± 5.0	28.1 ± 5.6	<0.001	<0.001
Allostatic load	2.42 ± 1.35	2.41 ± 1.35	2.46 ± 1.38	0.019	1.83 ± 1.35	1.82 ± 1.34	2.02 ± 1.40	<0.001	<0.001
Co-morbidity index	2.07 ± 1.86	2.07 ± 1.86	2.08 ± 1.84	0.91	2.15 ± 2.00	2.15 ± 2.01	2.16 ± 1.98	0.50	<0.001

Self-rated health				<0.001				<0.001	<0.001
Excellent	15.8	16.0	11.9		17.1	17.4	10.7		
Good	56.9	57.0	52.4		60.8	61.1	53.9		
Fair	22.5	22.2	28.8		18.7	18.3	28.8		
Poor	4.9	4.8	6.9		3.4	3.3	6.6		
HEALTH z-score	0.077 ± 0.660	0.076 ± 0.661	0.117 ± 0.650	<0.001	−0.066 ± 0.704	−0.072 ± 0.702	0.104 ± 0.743	<0.001	<0.001
Cognitive performance									
Reaction Time	6.31 ± 0.19	6.31 ± 0.18	6.40 ± 0.22	<0.001	6.34 ± 0.18	6.34 ± 0.18	6.42 ± 0.22	<0.001	<0.001
Pairs matching, errors	0.71 ± 0.71	0.70 ± 0.70	1.00 ± 0.75	<0.001	0.72 ± 0.69	0.71 ± 0.69	0.99 ± 0.71	<0.001	<0.001
Pairs matching, time to complete	5.34 ± 0.37	5.33 ± 0.37	5.57 ± 0.47	<0.001	5.36 ± 0.37	5.35 ± 0.36	5.58 ± 0.46	<0.001	<0.001
COGN z-score	−0.043 ± 0.764	−0.062 ± 0.750	+0.456 ± 0.940	<0.001	0.037 ± 0.746	0.019 ± 0.73	0.504 ± 0.896	<0.001	<0.001
LE8									
Total score	493.3 ± 93.0	493.7 ± 93.0	483.7 ± 94.0	<0.001	510.1 ± 97.1	510.8 ± 97.1	493.2 ± 96.1	<0.001	<0.001
Biological score	243.7 ± 62.0	243.8 ± 61.9	239.5 ± 64.3	<0.001	248.7 ± 69.0	249.3 ± 68.3	233.1 ± 73.7	<0.001	<0.001
Lifestyle score	249.6 ± 63.8	249.8 ± 63.7	243.9 ± 64.9	<0.001	261.2 ± 62.3	261.3 ± 62.3	258.7 ± 60.8	0.001	<0.001
Incidence proportion									
All-cause dementia	1.99 (*n* = 2,980)	1.99 (*n* = 2,882)	1.81 (*n* = 98)	0.34	1.45 (*n* = 2,511)	1.46 (*n* = 2,439)	1.14 (*n* = 72)	0.040	<0.001
AD dementia	0.76 (*n* = 1,147)	0.77 (*n* = 1,111)	0.66 (*n* = 36)	0.39	0.67 (*n* = 1,167)	0.68 (*n* = 1,134)	0.53 (*n* = 33)	0.14	0.002
Incident rates, per 100,000 P-Y									
All-cause dementia	164	164	214 (Black) 132 (SA) 134 (Others)		117	117	130 (Black) 74 (SA) 85 (Others)	—	—
AD dementia	63	63	69 (Black) 58 (SA) 45 (Others)		54	54	63 (Black) 41 (SA) 32 (Others)	—	—

Abbreviations: AD: Alzheimer's Disease; ALCOHOL: Alcohol consumption z-score; COGN: Poor cognitive performance z-score; DIET: diet quality z-score; HEALTH: Poor cardio-metabolic and general health z-score; PA: Physical Activity z-score; NUTR: Nutritional biomarker z-score; SES: Socio-economic status z-score; SMOKING: Smoking z-score; SS: Social Support z-score. [a]Values are means +/− SD or percentages.

Supplementary Table 7. Generalized Structural Equations models (GSEM) for racial/ethnic disparities in all-cause dementia: mediation through SES, alternative lifestyle factors (LIFESTYLE), health-related factors (HEALTH) and cognitive performance (COGN): The UK Biobank 2006–2021[a].

	LIFESYLTE					
	DIET	**PA**	**SMOKING**	**ALCOHOL**	**NUTR**	**SS**
Main pathway						
RACE_ETHN→SES (β_{12})	**−0.351 ± 0.006*****	**−0.351 ± 0.006*****	**−0.351 ± 0.006*****	**−0.351 ± 0.006*****	**−0.351 ± 0.006*****	**−0.351 ± 0.006*****
SES→LIFESTYLE (β_{23})	**+0.192 ± 0.003*****	**−0.059 ± 0.003*****	**−0.152 ± 0.002*****	**+0.305 ± 0.002*****	**+0.102 ± 0.002*****	**+0.086 ± 0.002*****
LIFESTYLE → HEALTH (β_{34})	**−0.081 ± 0.001*****	**−0.091 ± 0.001*****	**+0.046 ± 0.002*****	**−0.094 ± 0.001*****	**−0.168 ± 0.002*****	**−0.063 ± 0.002*****
HEALTH→COGN(β_{45})	−0.002 ± 0.002	−0.001 ± 0.002	−0.003 ± 0.002	**−0.010 ± 0.002*****	**−0.007 ± 0.002*****	**−0.006 ± 0.002*****
COGN → DEMENTIA (β_{56})	**+0.416 ± 0.017*****	**+0.416 ± 0.017*****	**+0.416 ± 0.017*****	**+0.412 ± 0.017*****	**+0.414 ± 0.017*****	**+0.410 ± 0.017*****
Selected direct effects on final outcomes						
RACE_ETHN→DEMENTIA(β_{16})	**−0.167 ± 0.080***	**−0.156 ± 0.079***	**−0.157 ± 0.079***	**−0.202 ± 0.080***	**−0.209 ± 0.080****	**−0.184 ± 0.079***
SES → DEMENTIA(β_{26})	**−0.220 ± 0.020*****	**−0.215 ± 0.020*****	**−0.216 ± 0.020*****	**−0.196 ± 0.020*****	**−0.209 ± 0.020*****	**−0.203 ± 0.020***
LIFESTYLE → DEMENTIA(β_{36})	+0.026 ± 0.014	+0.011 ± 0.013	−0.004 ± 0.019	**−0.075 ± 0.014*****	**−0.111 ± 0.017*****	**−0.163 ± 0.021*****
HEALTH → DEMENTIA(β_{46})	**+0.408 ± 0.019*****	**+0.407 ± 0.019*****	**+0.404 ± 0.019*****	**+0.388 ± 0.019*****	**+0.378 ± 0.020*****	**+0.395 ± 0.019*****
Other effects between endogenous variables						
SES→HEALTH (β_{24})	**−0.211 ± 0.002*****	**−0.232 ± 0.002*****	**−0.219 ± 0.002*****	**−0.198 ± 0.002*****	**−0.209 ± 0.002*****	**−0.221 ± 0.002*****
SES→COGN (β_{25})	**−0.135 ± 0.002*****	**−0.131 ± 0.002*****	**−0.136 ± 0.002*****	**−0.125 ± 0.002*****	**−0.132 ± 0.002*****	**−0.131 ± 0.002*****
LIFESTYLE→COGN (β_{35})	**+0.015 ± 0.001*****	**+0.016 ± 0.001*****	**−0.023 ± 0.002*****	**−0.029 ± 0.001*****	**−0.014 ± 0.0017*****	**−0.131 ± 0.002*****
Other direct effects of race						
RACE_ETHN→LIFESTYLE (β_{13})	**+0.257 ± 0.009*****	**−0.076 ± 0.009*****	**−0.103 ± 0.007*****	**−0.675 ± 0.009*****	**−0.482 ± 0.007*****	**−0.217 ± 0.006*****
RACE_ETHN→HEALTH(β_{14})	**+0.093 ± 0.006*****	**+0.065 ± 0.006*****	**+0.077 ± 0.006*****	+0.009 ± 0.006	−0.009 ± 0.006	**+0.059 ± 0.006*****
RACE_ETHN→COGN(β_{15})	**+0.523 ± 0.007*****	**+0.528 ± 0.007*****	**+0.524 ± 0.007*****	**+0.507 ± 0.007*****	**+0.521 ± 0.007*****	**+0.520 ± 0.007*****
Selected Indirect effects						
RACE_ETHN → SES → DEMENTIA(β_A)	**+0.077 ± 0.007*****	**+0.075 ± 0.007*****	**+0.076 ± 0.007*****	**+0.068 ± 0.007*****	**+0.073 ± 0.007*****	**+0.071 ± 0.007*****
RACE_ETHN → SES → LIFESTYLE → DEMENTIA(β_B)	−0.002 ± 0.001	+0.0002 ± 0.0003	−0.0002 ± 0.0010	**+0.0081 ± 0.0015*****	**+0.0040 ± 0.0006*****	**+0.0050 ± 0.0006*****
RACE_ETHN → SES → LIFESTYLE → HEALTH → DEMENTIA(β_C)	**+0.0022 ± 0.0001*****	**−0.00076 ± 0.00005*****	**+0.00099 ± 0.00006*****	**+0.0039 ± 0.0002*****	**+0.0023 ± 0.0001*****	**+0.00075 ± 0.0000*****

RACE_ETHN → SES → LIFESTYLE → HEALTH → COGN → DEMENTIA(β_D)	0.0000 ± 0.0000	0.00000 ± 0.00000	+0.0000 ± 0.0000	**−0.00004 ± 0.0000*****	**−0.00002 ± 0.00000*****	**+0.0000 ± +0.0000****
RACE_ETHN → SES → LIFESTYLE→ COGN → DEMENTIA(β_E)	**−0.00043 ± 0.00004*****	**0.000136 ± 0.000014*****	**−0.00051 ± 0.00005*****	**+0.00129 ± 0.00008*****	**+0.00021 ± 0.0000*****	**+0.00039 ± 0.00003*****
RACE_ETHN → SES → COGN → DEMENTIA(β_F)	**+0.0197 ± 0.0009*****	**0.0191 ± 0.0009*****	**+0.0198 ± 0.0009*****	**+0.0181 ± 0.0009*****	**+0.0192 ± 0.0009*****	**+0.0188 ± 0.0009*****
TOTAL EFFECT OF RACE_ETHN	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****

Abbreviations: AD: Alzheimer's Disease; ALCOHOL: Alcohol consumption z-score; COGN: Poor cognitive performance z-score; DIET: diet quality z-score; HEALTH: Poor cardio-metabolic and general health z-score; NUTR: Nutritional biomarker z-score; PA: Physical Activity z-score; RACE_ETHN: Racial minority status (Non-White vs. White); SES: Socio-economic status z-score; SMOKING: Smoking z-score; SS: Social Support z-score. [a]Values are path coefficients β ± SE or non-linear combinations of path coefficients to compute selected indirect effects. → DEMENTIA associations are interpreted as Log_e(HR) of these incident outcomes per unit exposure, as are total effects of RACE_ETHN. $^{*}P < 0.05$ $^{**}P < 0.01$ $^{***}P < 0.001$ for null hypothesis of β = 0.

Supplementary Table 8. Generalized Structural Equations models (GSEM) models for racial/ethnic disparities in all-cause dementia: mediation through SES, alternative lifestyle factors (LIFESTYLE) and health-related factors (HEALTH): The UK Biobank 2006–2021[a].

	LIFESYLTE					
	DIET	**PA**	**SMOKING**	**ALCOHOL**	**NUTR**	**SS**
Main pathway						
RACE_ETHN→SES (β_{12})	**−0.351 ± 0.006*****	**−0.350 ± 0.006*****	**−0.350 ± 0.006*****	**−0.351 ± 0.006*****	**−0.351 ± 0.006*****	**−0.351 ± 0.006*****
SES→LIFESTYLE (β_{23})	**+0.192 ± 0.003*****	**−0.059 ± 0.003*****	**−0.152 ± 0.002*****	**+0.305 ± 0.002*****	**+0.102 ± 0.002*****	**+0.086 ± 0.002*****
LIFESTYLE → HEALTH (β_{34})	**−0.081 ± 0.001*****	**−0.091 ± 0.001*****	**+0.046 ± 0.002*****	**−0.094 ± 0.001*****	**−0.168 ± 0.002*****	**−0.063 ± 0.002*****
HEALTH → DEMENTIA(β_{46})	**+0.408 ± 0.019*****	**+0.408 ± 0.019*****	**+0.404 ± 0.019*****	**+0.384 ± 0.019*****	**+0.376 ± 0.020*****	**+0.394 ± 0.020*****
Selected direct effects on final outcomes						
RACE_ETHN→DEMENTIA(β_{16})	+0.092 ± 0.079	+0.104 ± 0.078	+0.101 ± 0.078	+0.048 ± 0.079	+0.050 ± 0.079	+0.067 ± 0.079
SES → DEMENTIA(β_{26})	**−0.284 ± 0.020*****	**−0.278 ± 0.020*****	**−0.281 ± 0.020*****	**−0.255 ± 0.020*****	**−0.272 ± 0.020*****	**−0.265 ± 0.020*****
LIFESTYLE → DEMENTIA(β_{36})	**0.032 ± 0.014***	+0.018 ± 0.013	−0.017 ± 0.020	**−0.091 ± 0.014*****	**−0.117 ± 0.017*****	**−0.184 ± 0.021*****
Other effects between endogenous variables						
SES→HEALTH (β_{24})	**−0.211 ± 0.002*****	**−0.232 ± 0.002*****	**−0.219 ± 0.002*****	**−0.198 ± 0.002*****	**+0.102 ± 0.002*****	**−0.221 ± 0.002*****
Other direct effects of race						
RACE_ETHN→LIFESTYLE (β_{13})	**+0.257 ± 0.009*****	**−0.076 ± 0.009*****	**−0.104 ± 0.007*****	**−0.675 ± 0.009*****	**−0.482 ± 0.007*****	**−0.217 ± 0.006*****
RACE_ETHN→HEALTH(β_{14})	**+0.093 ± 0.006*****	**+0.065 ± 0.006*****	**+0.077 ± 0.006*****	+0.009 ± 0.006	−0.009 ± 0.006	**+0.059 ± 0.006*****
Selected Indirect effects						
RACE_ETHN → SES → DEMENTIA(β_A)	**+0.0998 ± 0.0073*****	**+0.0977 ± 0.0070*****	**+0.0987 ± 0.0073*****	**+0.0896 ± 0.0073*****	**+0.096 ± 0.007*****	**+0.093 ± 0.007*****
RACE_ETHN → SES → LIFESTYLE → DEMENTIA(β_B)	**−0.0022 ± 0.0009***	+0.0004 ± 0.0003	−0.0009 ± 0.0010	**+0.0097 ± 0.0014*****	**+0.0042 ± 0.0006*****	**+0.0055 ± 0.0007*****
RACE_ETHN → SES → LIFESTYLE → HEALTH → DEMENTIA(β_C)	**+0.0022 ± 0.0001*****	**−0.00076 ± 0.00005*****	**+0.000991 ± 0.00006*****	**+0.0039 ± 0.0002*****	**+0.0023 ± 0.0001*****	**+0.00075 ± 0.0000*****
TOTAL EFFECT OF RACE_ETHN	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****	**+0.232 ± 0.078****

Abbreviations: AD: Alzheimer's Disease; ALCOHOL: Alcohol consumption z-score; COGN: Poor cognitive performance z-score; DIET: diet quality z-score; HEALTH: Poor cardio-metabolic and general health z-score; NUTR: Nutritional biomarker z-score; PA: Physical Activity z-score; RACE_ETHN: Racial minority status (Non-White vs. White); SES: Socio-economic status z-score; SMOKING: Smoking z-score; SS: Social Support z-score. [a]Values are path coefficients β ± SE or non-linear combinations of path coefficients to compute selected indirect effects. →DEMENTIA associations are interpreted as Log_e(HR) of these incident outcomes per unit exposure, as are total effects of RACE_ETHN. $^{*}P < 0.05$ $^{**}P < 0.01$ $^{***}P < 0.001$ for null hypothesis of β = 0.