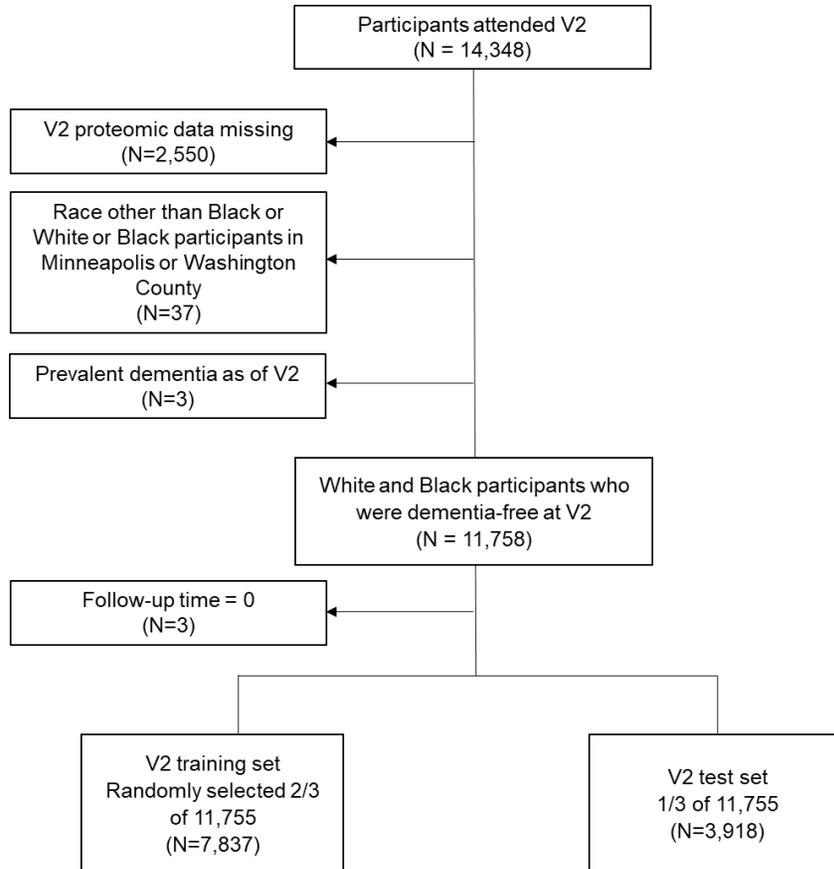


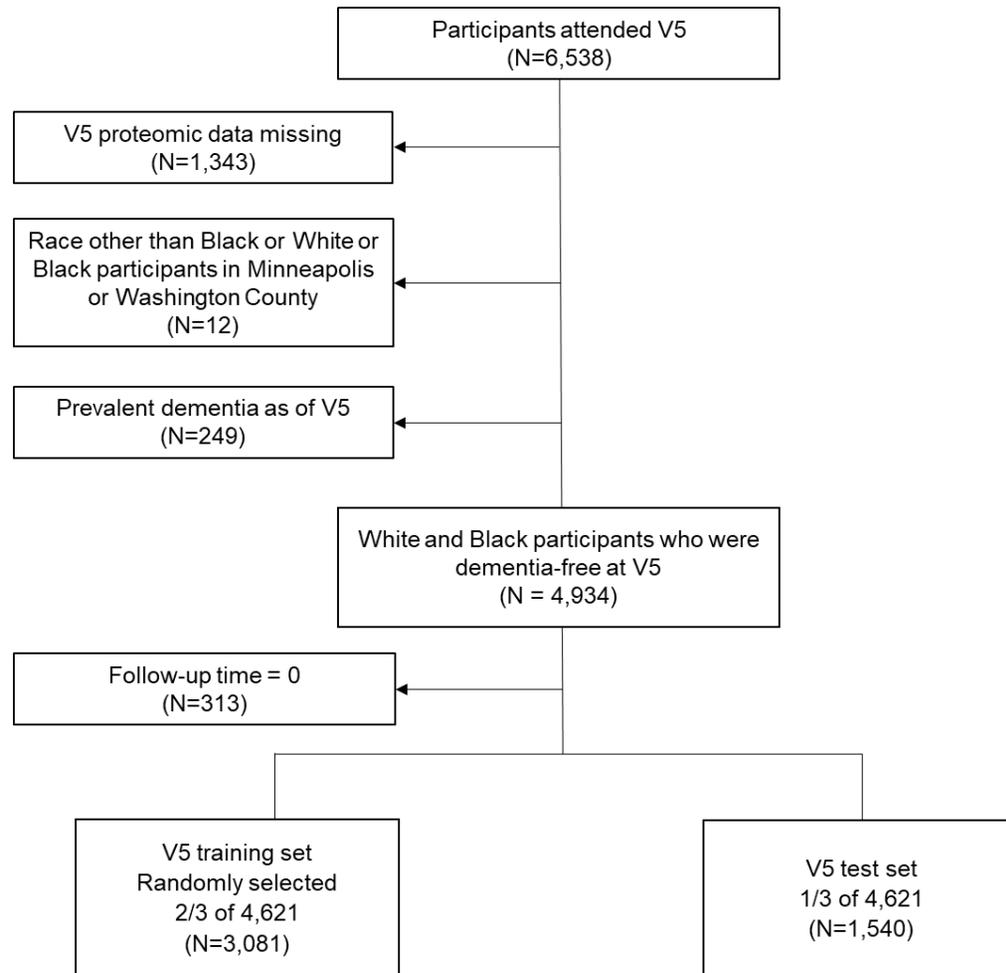
# Supplemental Documents

## Supplemental figures

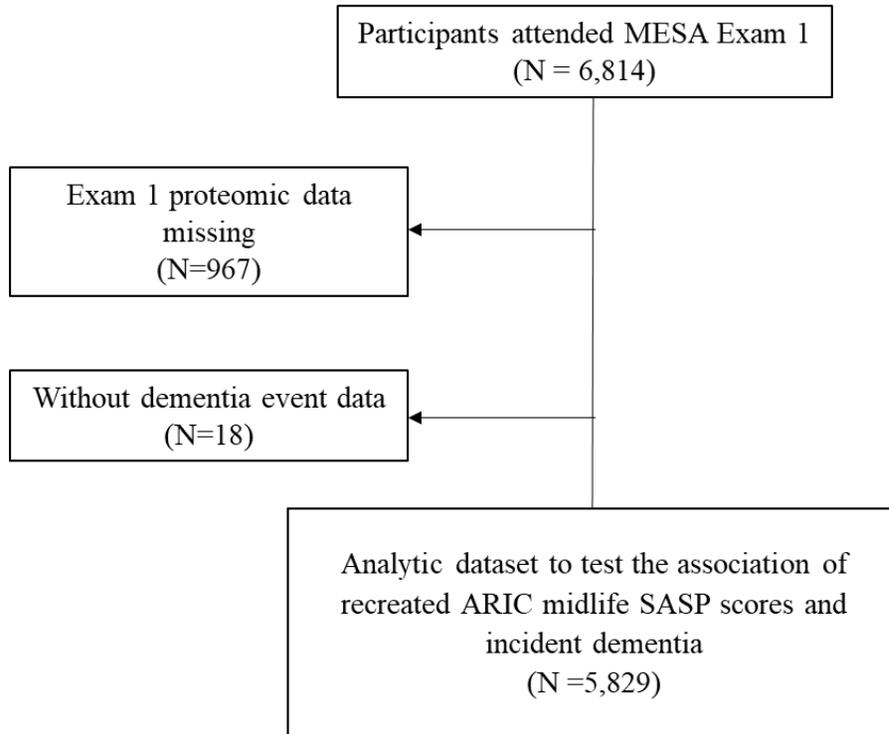
Figure S1A. Flowchart of the study population at ARIC midlife (Visit 2, 1990-1992).



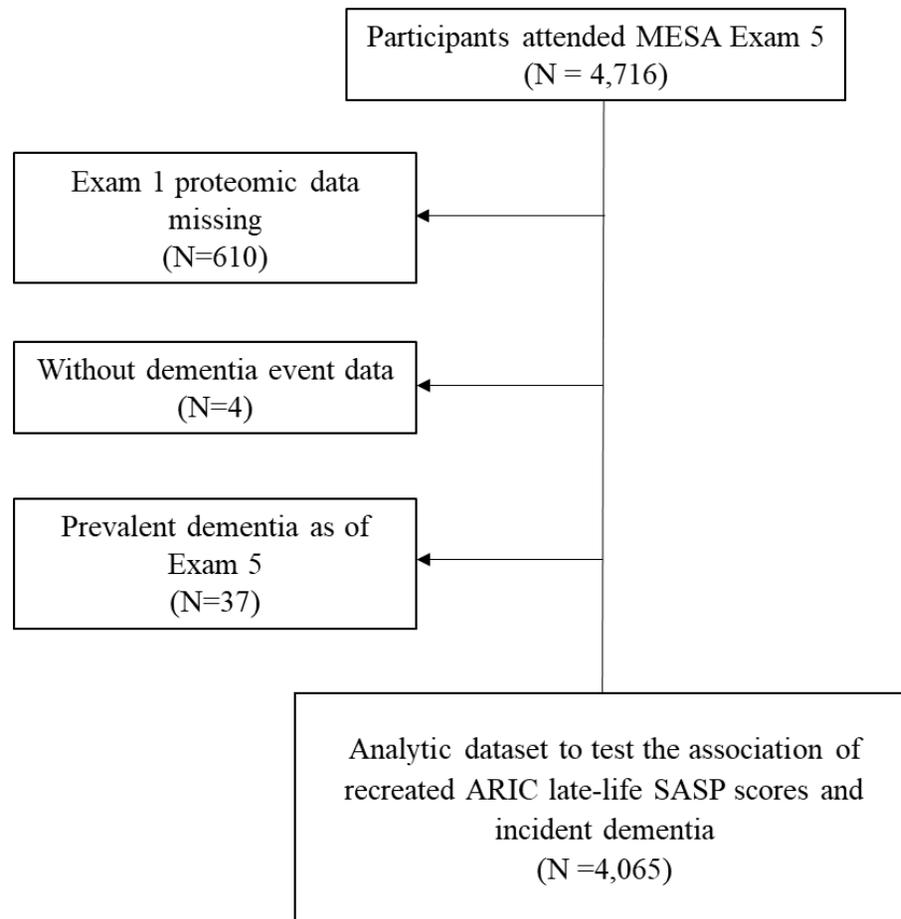
**Figure S1B. Flowchart of the study population at ARIC late life (Visit 5, 2011–2013).**



**Figure S2A. Flowchart of the study population at MESA Exam 1 (2000-2002).**



**Figure S2B. Flowchart of the study population at MESA Exam 5 (2010-2011).**



**Figure S3. Number of unique dementia-associated SASP proteins included in Scores 2 and 3 at ARIC midlife (Visit 2) and late-life (Visit 5).**

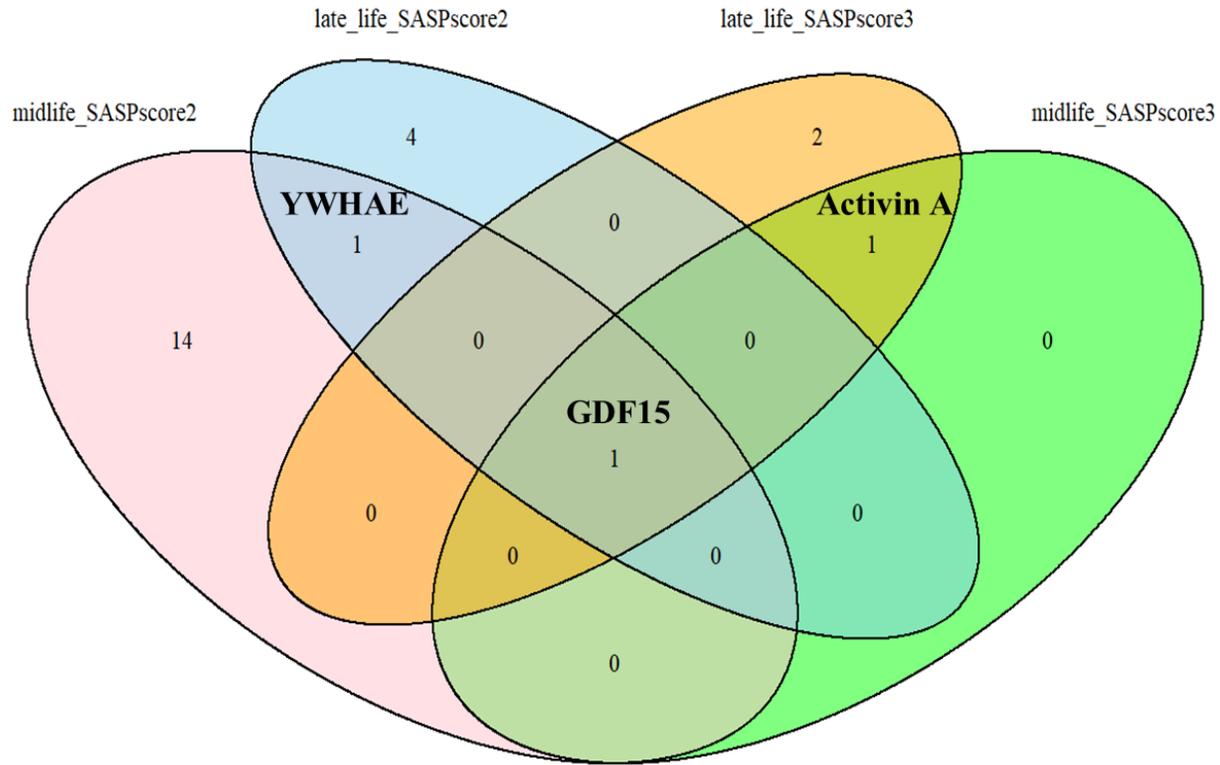
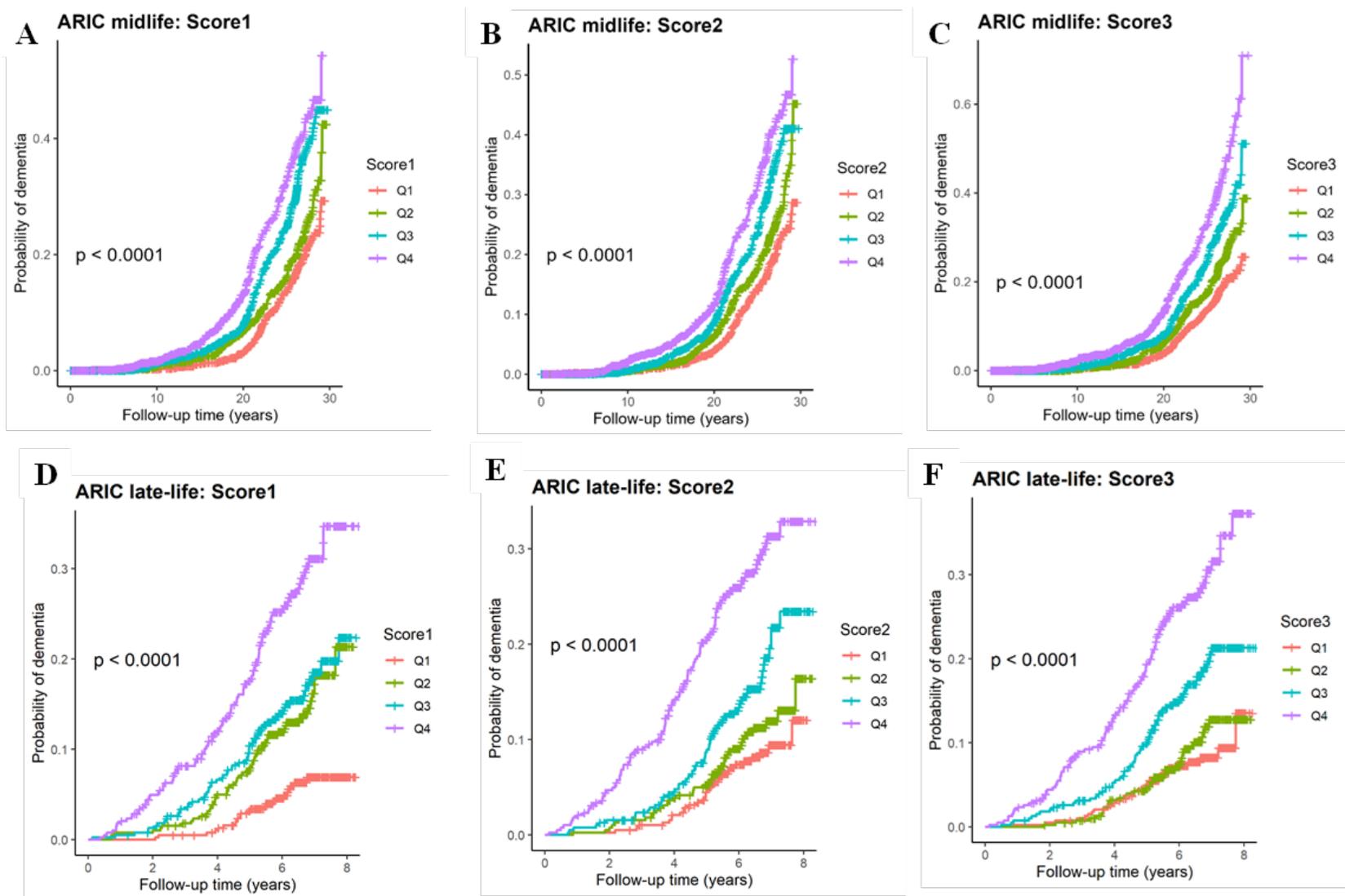
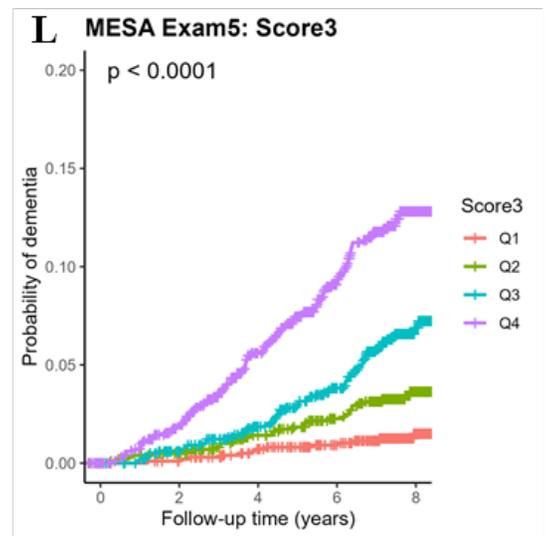
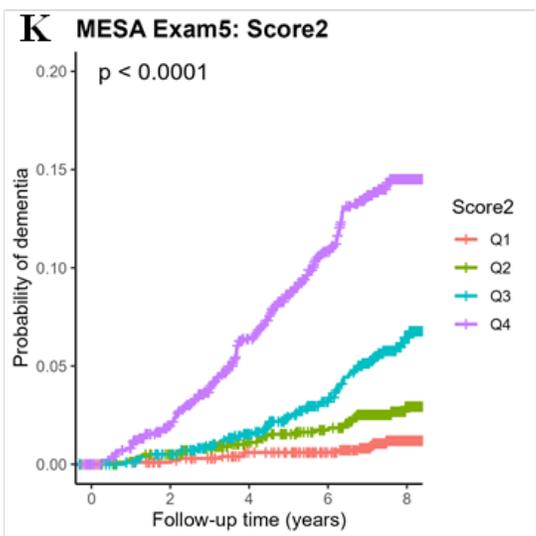
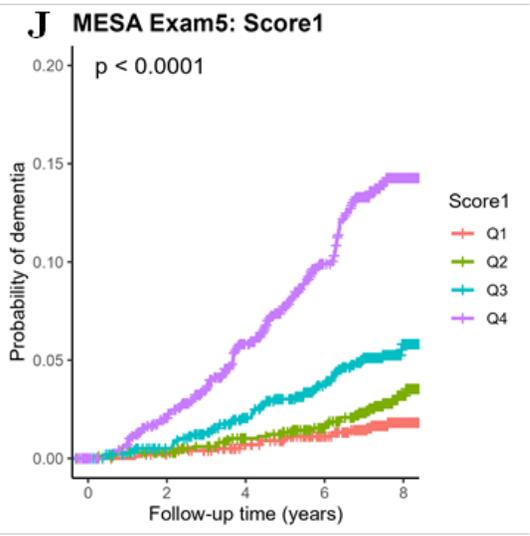
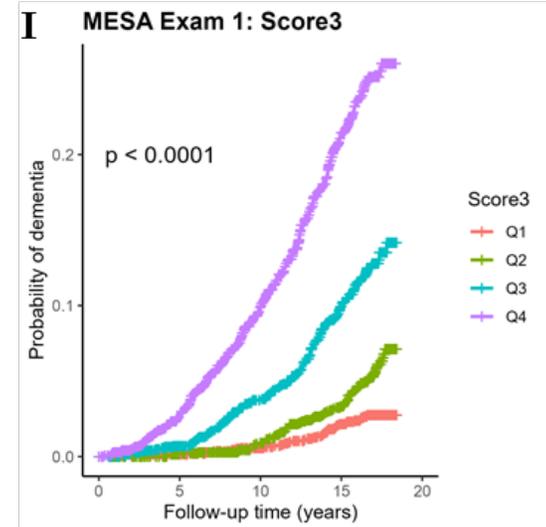
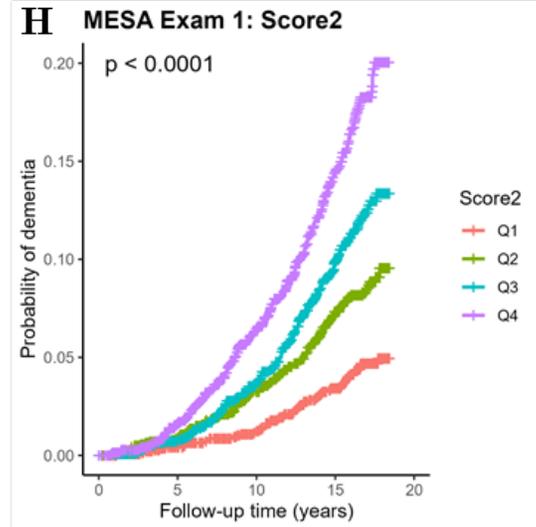
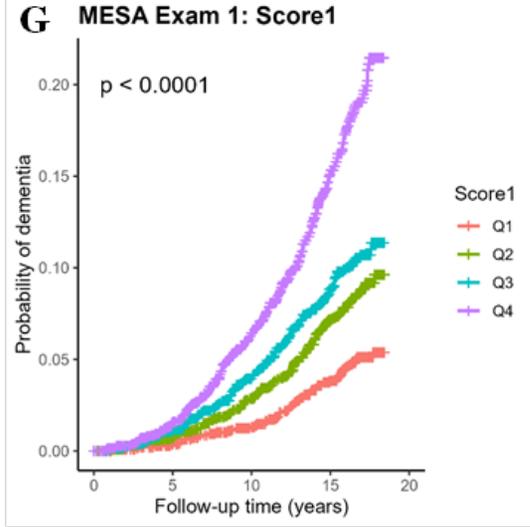


Figure S4. Kaplan–Meier curves of incident dementia by SASP score quartiles in ARIC and MESA.





**Table S1. Baseline participants' characteristics at midlife (ARIC Visit 2: 1990–92; MESA Exam 1: 2000–02) and late-life (ARIC Visit 5: 2011–13; MESA Exam 5: 2010–11).**

Characteristics	ARIC <sup>1</sup>		MESA <sup>2</sup>	
	Midlife	Late-life	Midlife	Late-life
	N=3,918	N=1,540	N=5,829	N=4,065
<i>Demographics</i>				
<b>Mean age, years (SD)</b>	57.0 (5.7)	75.3 (5.2)	62.1 (10.3)	69.6 (9.4)
<b>Sex, N (Female %)</b>	2,147 (54.8%)	898.0 (58.3%)	3,033 (52.0%)	1,907 (46.9%)
<b>Race, N (Black %)</b>				
Black	920 (23.5%)	282.0 (18.3%)	1,525 (26.2%)	1,046 (25.7%)
White	2,998 (76.5%)	1,258.0 (81.7%)	2,301 (39.5%)	1,258.0 (81.7%)
Hispanic/Latino	-	-	1,305 (22.4%)	870 (21.4%)
Chinese	-	-	698 (12.0%)	446 (11.0%)
<b>Education, N (%)</b>				
Less than High School	821 (21.0%)	184.0 (12.0%)	1,045 (17.9%)	571 (14.0%)
High School Equivalent	1,630 (41.7%)	647.0 (42.1%)	1,068 (18.3%)	715 (17.6%)
Greater than High School	1,461 (37.3%)	706.0 (45.9%)	3,716 (63.8%)	2,779 (68.4%)
<i>Lifestyle/Comorbidity Factors</i>				
<b>Mean BMI, kg/m<sup>2</sup> (SD)</b>	28.0 (5.3)	28.6 (5.6)	28.4 (5.5)	28.6 (5.7)
<b>Smoking Status, N (%)</b>				
Current Smoker	866 (22.2%)	84.0 (6.0%)	762 (13.1%)	329 (8.2%)
Former Smoker	1,496 (38.3%)	720.0 (51.5%)	2,154 (37.1%)	1,906 (47.3%)
Never Smoked	1,546 (39.6%)	594.0 (42.5%)	2,896 (49.8%)	1,794 (44.5%)
<b>Hypertension, N (%)</b>	1,402 (35.9%)	1,119.0 (73.2%)	2,590 (44.4%)	2,428 (59.8%)
<b>Diabetes, N (%)</b>	573 (14.7%)	488.0 (32.4%)	1,579 (27.1%)	1,655 (40.7%)
<b>Mean eGFR, ml/min/1.73 m<sup>2</sup> (SD)</b>	98.4 (16.3)	69.8 (19.0)	74.4 (16.6)	67.0 (15.0)
<b>Mean Cholesterol, mg/dL (SD)</b>	210.5 (39.3)	180.6 (41.2)	194.3 (35.9)	183.1 (37.6)

Abbreviations: ARIC = Atherosclerosis Risk in Communities, MESA = Multi-Ethnic Study of Atherosclerosis, SD = standard deviation, BMI = body mass index, eGFR = estimated glomerular filtration rate

**Table S2. List of proteins significantly associated with dementia risk in ARIC midlife or late-life<sup>1</sup>.**

<b>Gene name</b>	<b>Protein name</b>	<b>Biological function</b>
TBCA	Tubulin-specific chaperone A	Tubulin bindings, protein folding, tubulin complex assembly
GDF15	Growth/differentiation factor 15	Inflammation-associated hormone; it is produced in response to stresses; triggers neurons activation, induces expression of genes involved in metabolism, related to age-related diseases.
HSPA1A	Heat shock 70 kDa protein 1A	Molecular chaperones, participate in many cellular processes: protection of the proteome from stress, folding and transport of newly synthesized polypeptides, chaperone-mediated autophagy, activation of proteolysis of misfolded proteins, formation and dissociation of protein complexes, and antigen presentation. Play pivotal role in the protein quality control system, ensuring the correct folding of proteins, the re-folding of misfolded proteins and controlling the targeting of proteins for subsequent degradation.
HSPA1B	Heat shock 70 kDa protein 1B	
HSPA8	Heat shock cognate 71 kDa protein	
COTL1	Coactosin-like protein	Actin-binding protein, regulates the actin cytoskeleton. Stabilizes 5-lipoxygenase, enzyme involved in the metabolism of arachidonic acid and leukotrienes (pro-inflammatory lipid mediators) and platelet formation.
YWHAE	14-3-3 protein epsilon	Implicated in the regulation of diverse signaling processes, e.g., cell division regulation of insulin sensitivity. It binds to phosphoserine-containing proteins.
INHBA	Inhibin beta A chain (activin A)	Homodimer of INHBA. It is involved in embryonic development, stem cell maintenance and differentiation, haematopoiesis, cell proliferation and tissue fibrosis, insulin and other hormone secretion, nerve cell survival.
CST3	Cystatin-C	Inhibitor of cysteine proteinases. Local regulator of this enzyme activity.
TAGLN	Transgelin	Actin cross-linking protein. Involved in calcium interactions and contractile properties of the cell that may contribute to replicative senescence
HSPG2	Basement membrane-specific heparan sulfate proteoglycan core protein	Component of basement membranes, serves as an attachment substrate for cells. Critical for normal heart development and for regulating the vascular response to injury. Also required for a vascular cartilage development.
IGF2	Insulin-like growth factor-binding protein 2	Growth-promoting activity. Involved in regulating fetoplacental development and tissue differentiation. In adults, involved in glucose metabolism in adipose tissue, skeletal muscle and liver. Acts as a ligand for integrin which is required for IGF2 signaling, controlling muscle terminal differentiation.

BGN	Biglycan	Involved in collagen assembly, cytokine binding, extracellular matrix structure, blood vessel and bone remodeling
TXNDR1	Thioredoxin reductase 1, cytoplasmic	Important in cellular redox homeostasis, Depending on the isoform, may induce actin and tubulin polymerization, enhance the transcriptional activity of estrogen receptors, or may mediate cell death.
AKR1A1	Aldo-keto reductase family 1 member A1	Catalyzes the NADPH-dependent reduction of a wide variety of carbonyl-containing compounds to their corresponding alcohols. Functions as a detoxifying enzyme by reducing a range of toxic aldehydes.
PRCP	Lysosomal Pro-X carboxypeptidase	Lysosomal Pro-X carboxypeptidase; Cleaves C-terminal amino acids linked to proline in peptides such as angiotensin II, III and des-Arg9-bradykinin.
PRDX1	Peroxiredoxin-1	Peroxidase. Plays a role in cell protection against oxidative, may participate in the signaling cascades of growth factors and tumor necrosis factor-alpha, may inhibit postmitotic motor neuron differentiation
OSTP	Osteopontin	Major non-collagenous bone protein, forms an integral part of the mineralized matrix, may be important to cell-matrix interaction. Acts as a cytokine enhances production of INF- $\gamma$ and IL-12 and reduces production of IL-10; it is essential in the pathway that leads to type I immunity
GPI	Glucose-6-phosphate isomerase	Glycolytic enzyme, also acts as a secreted cytokine: acts as an angiogenic factor that stimulates endothelial cell motility acts as a neurotrophic factor, for spinal and sensory neurons. It is secreted by lectin-stimulated T-cells and induces immunoglobulin secretion
S100A11	Protein S100-A11	Facilitates the differentiation and the cornification of keratinocytes
TNFRSF1A	Tumor necrosis factor receptor superfamily member 1A	Acts as a receptor for TNFSF2/TNF-alpha to trigger caspase-8 proteolytic activation which initiates the subsequent cascade of caspases mediating apoptosis and contributing to inflammation
PLOD3	Multifunctional procollagen lysine hydroxylase and glycosyltransferase LH3	Multifunctional enzyme that catalyzes a series of essential post-translational modifications on Lys residues in procollagen. Essential for normal biosynthesis and secretion of type IV collagens for normal formation of basement membranes
CTSD	Cathepsin D	Lysosomal enzyme participates in intracellular protein breakdown, cell growth regulation, and apoptosis

<sup>1</sup> Information derived from <https://www.uniprot.org/> and <https://string-db.org/>

**Table S3. Pearson correlation between SASP scores at ARIC Visit 2 (midlife, N=3,918) and Visit 5 (late-life, N=1,540)<sup>1</sup>.**

<i>Midlife SASP scores; Visit 2</i>	Score-1	Score-2	Score-3
Score-1	1.00		
Score-2	0.81	1.00	
Score-3	0.46	0.55	1.00
<i>Late life SASP scores; Visit 5</i>	Score-1	Score-2	Score-3
Score-1	1.00		
Score-2	0.58	1.00	
Score-3	0.40	0.69	1.00

<sup>1</sup>All P-values for each pair of correlations were <0.001.

**Table S4. Pearson correlation between SASP scores at MESA Exam 1 (midlife, N= 5,829) and Exam 5 (late-life N=4,065)<sup>1</sup>.**

<i>Midlife SASP scores; Exam 1</i>	Score-1	Score-2	Score-3
Score-1	1.00		
Score-2	0.80	1.00	
Score-3	0.41		0.52
			1.00
<i>Late life SASP scores; Exam 5</i>	Score-1	Score-2	Score-3
Score-1	1.00		
Score-2	0.65	1.00	
Score-3	0.45	0.74	1.00

<sup>1</sup>All P-values for each pair of correlations were <0.001.

**Table S5.** Late-life participants' characteristics across Score-1 quartiles: ARIC Visit 5 (2011–13) and MESA Exam 5 (2010–11).

Late-life Score-1 (quartiles, range)	Late-life Score-1 in ARIC (67-90 years, N = 1,540)					Late-life Score-1 in MESA (53-94 years, N = 4,065)				
	<i>Increasing senescence</i> →					<i>Increasing senescence</i> →				
	Q1 (N = 385)	Q2 (N = 385)	Q3 (N = 385)	Q4 (N = 385)	P-value <sup>1</sup>	Q1 (N = 1,017)	Q2 (N = 1,016)	Q3 (N=1,016)	Q4 (N=1,016)	P-value <sup>1</sup>
	15.10 – 15.88	>15.88 –16.07	>16.07 –16.27	>16.27 –17.28		15.68 –16.35	>16.35 –16.53	>16.53 –16.74	>16.74 –18.04	
Mean chronological age, (SD) years	73.5 (4.4)	74.7 (4.7)	75.7 (5.3)	77.5 (5.3)	3.47e- 28	64.7 (7.6)	67.6 (8.5)	70.9 (8.8)	75.4 (9.2)	3.33e-173
Female, %	59.7	58.2	60.3	55.1	0.46	50.7	52.4	54.1	55.1	0.20
Race, %					0.02					0.001
White	84.7	82.1	83.4	76.6		42.3	41.2	41.6	42.4	
Black	15.3	17.9	16.6	23.4		11.5	13.6	9.3	9.5	
Chinese	-	-	-	-		22.0	24.4	28.3	28.1	
Hispanic/Latino	-	-	-	-		24.2	20.8	20.8	19.9	
Education, %					0.01					2.37e-05
< high school	8.1	13.8	11.2	14.8		12.6	13.0	13.2	17.4	
High school	39.2	44.7	44.2	40.4		15.9	14.9	19.7	19.9	
>high school	52.7	41.6	44.7	44.8		71.5	72.1	67.1	62.7	
BMI, kg/m <sup>2</sup> (SD)	29.0 (4.9)	29.0 (5.8)	28.5 (5.5)	28.1 (6.0)	0.08	29.5 (5.4)	28.7 (5.3)	28.6 (5.9)	27.5 (6.1)	1.04e-13
Smoking status, %					1.95e- 25					0.07
Current smoker	4.3	6.3	6.3	7.2		9.7	7.5	7.9	7.5	
Former smoker	53.6	52.8	49.4	50.1		47.0	44.8	47.1	50.4	
Never smoker	42.2	40.9	44.3	42.6		43.3	47.7	45.0	42.1	

Mean eGFR, (SD) mL/min/1.73 m <sup>2</sup>	76.5 (16.8)	71.8 (17.0)	68.6 (18.9)	62.2 (20.4)	0.02	71.0 (13.5)	68.2 (12.8)	67.1 (15.0)	61.7 (17.0)	7.36e-45
Hypertension, %	67.7	72.8	77.1	75.3	0.02	49.5	56.7	61.2	71.6	1.78e-23
Diabetes, %	32.7	32.7	29.0	35.2	0.34	41.6	38.3	41.3	41.6	0.34
Mean cholesterol, (SD), mg/dL	189.7 (42.7)	181.9 (40.1)	180.5 (40.8)	170.2 (39.2)	1.32e- 09	191.2 (36.6)	185.1 (36.7)	180.0 (37.6)	176.1 (37.7)	3.30e-20

Abbreviations: eGFR – Estimated Glomerular Filtration Rate; Q– Quartiles.

<sup>1</sup>P-values were calculated using chi-square tests for categorical variables and ANOVA tests for continuous variables.

**Table S6. Associations between SASP scores at midlife and late-life and dementia risk in ARIC and MESA<sup>1,2</sup>.**

<b>ARIC Visit 2 (N = 3,918)</b>		<b>MESA Exam 1 (N = 5,829)</b>	
No. of dementia cases	758	No. of dementia cases	508
Total person-years	81,572	Total person-years	83,386
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score	SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score
Score-1	1.33 (1.23, 1.45)	Score-1	1.38 (1.26, 1.51)
Score-2	1.20 (1.11, 1.31)	Score-2	1.26 (1.14, 1.39)
Score-3	1.20 (1.08, 1.32)	Score-3	1.28 (1.14, 1.43)
<b>ARIC Visit 2 (N=1,540)</b>		<b>MESA Exam 1 (N = 4,065)</b>	
No. of dementia cases	241	No. of dementia cases	215
Total person-years	9,365	Total person-years	28,584
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score	SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score
Score-1	1.50 (1.28, 1.75)	Score-1	1.62 (1.39, 1.87)
Score-2	1.47 (1.20, 1.79)	Score-2	1.70 (1.40, 2.07)
Score-3	1.39 (1.20, 1.62)	Score-3	1.40 (1.18, 1.66)

Abbreviations: ARIC – Atherosclerosis Risk in Communities; MESA – Multi-Ethnic Study of Atherosclerosis; CI – confidence interval; HR – Hazard ratio; SD – standard deviation.

<sup>1</sup>In ARIC, follow-up was through the end of 2019 (Visit 7); in MESA, follow-up was through the end of 2018.

<sup>2</sup>Model 2 (fully adjusted): adjusted for chronological age, sex, joint race–center terms in ARIC (Black participants from Mississippi; Black participants from other centers; White participants from Maryland, North Carolina, and Minnesota), and separate terms for race and study site in MESA, education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit.

<sup>3</sup>All SASP scores were standardized to mean=0 and SD=1.

**Table S7.** C-index for predicting dementia risk at midlife and late-life in ARIC and MESA.<sup>1</sup>

ARIC	C-index	
	Midlife	Late-life
<b>No scores</b>	0.749	0.760
<b>Score-1 only</b>	0.622	0.670
All-covariates <sup>1</sup> + Score-1	0.759	0.769
<b>Score-2 only</b>	0.610	0.670
All-covariates + Score-2	0.753	0.765
<b>Score-3 only</b>	0.617	0.667
All-covariates + Score-3	0.752	0.771
MESA	C-index	
	Midlife	Late-life
<b>No scores</b>	0.847	0.802
<b>Score-1 only</b>	0.647	0.744
All-covariates + Score-1	0.854	0.819
<b>Score-2 only</b>	0.644	0.768
All-covariates + Score-2	0.850	0.813
<b>Score-3 only</b>	0.661	0.722
All-covariates + Score-3	0.850	0.810

Abbreviations: ARIC – Atherosclerosis Risk in Communities; MESA – Multi-Ethnic Study of Atherosclerosis; C-index – concordance index.

<sup>1</sup>Covariates included age, sex, joint term of race and center in ARIC (race and center in MESA), education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit as predictors.

**Table S8. Associations of midlife and late-life SASP Score-2 (with and without GDF-15) with incident dementia in midlife (ARIC Visit 2, MESA Exam 1) and late-life (ARIC Visit 5, MESA Exam 5)<sup>1,2</sup>.**

<b>ARIC Visit 2 (N = 3,918)</b>		<b>MESA Exam 1 (N = 5,829)</b>	
No. of dementia cases	758	No. of dementia cases	508
Total person-years	81,572	Total person-years	83,386
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score	SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score
Score-2	1.20 (1.11, 1.31)	Score-2	1.24 (1.13, 1.37)
Score-2 wo GDF15	1.18 (1.09, 1.28)	Score-2 wo GDF15	1.20 (1.09, 1.32)
<b>ARIC Visit 5 (N=1,540)</b>		<b>MESA Exam 5 (N = 4,065)</b>	
No. of dementia cases	241	No. of dementia case	215
Total person-years	9,365	Total person-years	28,584
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score	SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score
Score-2	1.47 (1.20, 1.79)	Score-2	1.70 (1.40, 2.07)
Score-2 wo GDF15	1.37 (1.12, 1.68)	Score-2 wo GDF15	1.62 (1.34, 1.96)

Abbreviations: ARIC – Atherosclerosis Risk in Communities; MESA – Multi-Ethnic Study of Atherosclerosis; CI – confidence interval; HR – Hazard ratio; SD – standard deviation.

<sup>1</sup>In ARIC, follow-up was through the end of 2019 (visit 7); in MESA, follow-up was through the end of 2018.

<sup>2</sup>Models were adjusted for chronological age, sex, joint race–center terms in ARIC (Black participants from Mississippi; Black participants from other centers; White participants from Maryland, North Carolina, and Minnesota), and separate terms for race and study site in MESA, education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit.

<sup>3</sup>All SASP scores were standardized to mean=0 and SD=1.

**Table S9. Association between standardized SASP scores at midlife and late-life and dementia risk stratified by sex in ARIC and MESA <sup>1,2</sup>.**

	ARIC Visit 2	MESA Exam 1
	No. of events/No. of participants	No. of events/No. of participants
Female	462/2147	256/3033
Male	296/1475	252/2796
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in SASP score	HR (95% CI) per 1 SD increase in SASP score
<b>Score-1</b>		
Female	1.28 (1.15, 1.42)	1.59 (1.38, 1.82)
Male	1.46 (1.27, 1.67)	1.25 (1.10, 1.43)
<i>P</i> -interaction	0.04	0.02
<b>Score-2</b>		
Female	1.18 (1.06, 1.31)	1.45 (1.26, 1.68)
Male	1.25 (1.09, 1.44)	1.12 (0.98, 1.29)
<i>P</i> -interaction	0.24	0.01
<b>Score-3</b>		
Female	1.06 (0.93, 1.21)	1.29 (1.09, 1.53)
Male	1.41 (1.21, 1.64)	1.27 (1.08, 1.49)
<i>P</i> -interaction	0.01	0.63
	ARIC Visit 5	MESA Exam 5
	No. of events/No. of participants	No. of events/No. of participants
Female	151/898	115/2158
Male	90/642	100/1907
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in SASP score	HR (95% CI) per 1 SD increase in SASP score
<b>Score-1</b>		
Female	1.60 (1.31, 1.93)	1.71 (1.40, 2.08)
Male	1.35 (1.03, 1.76)	1.47 (1.16, 1.87)
<i>P</i> -interaction	0.09	0.26
<b>Score-2</b>		
Female	1.70 (1.33, 2.18)	1.86 (1.43, 2.3)
Male	1.17 (0.82, 1.68)	1.65 (1.22, 2.23)
<i>P</i> -interaction	0.02	0.60
<b>Score-3</b>		
Female	1.61 (1.32, 1.97)	1.50 (1.20, 1.88)
Male	1.23 (0.89, 1.71)	1.38 (1.05, 1.82)
<i>P</i> -interaction	0.06	0.86

Abbreviations: ARIC – Atherosclerosis Risk in Communities; MESA – Multi-Ethnic Study of Atherosclerosis; CI – confidence interval; HR – Hazard ratio; SD – standard deviation.

<sup>1</sup>In ARIC, follow-up was through the end of 2019 (visit 7); in MESA, follow-up was through the end of 2018.

<sup>2</sup>Models were adjusted for chronological age, sex, joint race–center terms in ARIC (Black participants from Mississippi; Black participants from other centers; White participants from Maryland, North Carolina, and Minnesota), and separate terms for race and study site in MESA, education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit.

<sup>3</sup>All SASP scores were standardized to mean=0 and SD=1.

**Table S10. Association between standardized SASP scores at midlife and late-life and dementia risk stratified by race in ARIC and MESA<sup>1,2</sup>.**

	<b>ARIC Visit 2</b>	<b>MESA Exam 1</b>
	No. of events/No. of participants	No. of events/No. of participants
White	535/2998	235/2301
Black	223/920	129/1525
Chinese		36/698
Hispanic		108/1305
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in SASP score	HR (95% CI) per 1 SD increase in SASP score
<b>Score-1</b>		
White	1.38 (1.25, 1.52)	1.47 (1.27, 1.70)
Black	1.27 (1.09, 1.47)	1.30 (1.09, 1.57)
Chinese		1.28 (0.85, 1.95)
Hispanic		1.43 (1.17, 1.76)
<i>P</i> -interaction	0.24	0.55
<b>Score-2</b>		
White	1.23 (1.12, 1.35)	1.22 (1.04, 1.42)
Black	1.13 (0.95, 1.33)	1.38 (1.14, 1.67)
Chinese		1.05 (0.67, 1.66)
Hispanic		1.33 (1.09, 1.63)
<i>P</i> -interaction	0.27	0.87
<b>Score-3</b>		
White	1.27 (1.13, 1.42)	1.18 (0.97, 1.43)
Black	1.06 (0.87, 1.28)	1.30 (1.05, 1.61)
Chinese		0.93 (0.58, 1.47)
Hispanic		1.66 (1.30, 2.11)
<i>P</i> -interaction	0.06	0.62
	<b>ARIC Visit 5</b>	<b>MESA Exam 5</b>
	No. of events/No. of participants	No. of events/No. of participants
White	179/1256	102/1703
Black	62/281	52/1046
Chinese		12/446
Hispanic		49/870
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in SASP score	HR (95% CI) per 1 SD increase in SASP score
<b>Score-1</b>		
White	1.57 (1.30, 1.90)	1.46 (1.17, 1.81)
Black	1.39 (1.04, 1.84)	1.67 (1.19, 2.34)
Chinese		2.07 (0.96, 4.48)
Hispanic		1.77 (1.34, 2.35)
<i>P</i> -interaction	0.47	0.91
<b>Score-2</b>		
White	1.36 (1.06, 1.74)	1.58 (1.19, 2.11)
Black	1.54 (1.10, 2.17)	1.68 (1.11, 2.54)
Chinese		1.31 (0.60, 2.87)
Hispanic		2.25 (1.58, 3.19)
<i>P</i> -interaction	0.36	0.83
<b>Score-3</b>		
White	1.24 (1.03, 1.49)	1.38 (1.06, 1.79)
Black	1.54 (1.13, 2.11)	1.32 (0.93, 1.87)
Chinese		2.05 (1.05, 3.99)

Hispanic		1.62 (1.16, 2.28)
<i>P</i> -interaction	0.22	0.49

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Abbreviations: ARIC – Atherosclerosis Risk in Communities; MESA – Multi-Ethnic Study of Atherosclerosis; CI – confidence interval; HR – Hazard ratio; SD – standard deviation.

<sup>1</sup>In ARIC, follow-up was through the end of 2019 (visit 7).

<sup>2</sup>Models were adjusted for chronological age, sex, joint race–center terms, education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit.

<sup>3</sup>All SASP scores were standardized to mean=0 and SD=1.

**Table S11. Association between standardized SASP scores at midlife and late-life and dementia risk stratified by APOE ε4 in ARIC and MESA<sup>1,2</sup>.**

	<b>ARIC Visit 2</b>	<b>MESA Exam 1</b>
	No. of events/No. of participants	No. of events/No. of participants
APOE ε4 non-carrier	462/2147	323/4098
APOE ε4 carrier	296/1475	169/1479
SASP Score <sup>3</sup>	HR (95% CI) per 1 SD increase in SASP score	HR (95% CI) per 1 SD increase in SASP score
<b>Score-1</b>		
APOE ε4 non-carrier	1.17 (1.04, 1.31)	1.30 (1.14, 1.48)
APOE ε4 carrier	1.23 (1.07, 1.43)	1.27 (1.06, 1.51)
<i>P</i> -interaction	0.67	0.77
<b>Score-2</b>		
APOE ε4 non-carrier	1.13 (1.00, 1.26)	1.19 (1.04, 1.35)
APOE ε4 carrier	1.08 (0.93, 1.25)	1.19 (0.98, 1.44)
<i>P</i> -interaction	0.49	0.73
<b>Score-3</b>		
APOE ε4 non-carrier	1.15 (1.01, 1.31)	1.34 (1.16, 1.56)
APOE ε4 carrier	1.24 (1.06, 1.46)	1.16 (0.94, 1.42)
<i>P</i> -interaction	0.44	0.10
	<b>ARIC Visit 5</b>	<b>MESA Exam 5</b>
	No. of events/No. of participants	No. of events/No. of participants
APOE ε4 non-carrier	151/898	130/2840
APOE ε4 carrier	90/642	75/1026
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in SASP score	HR (95% CI) per 1 SD increase in SASP score
<b>Score-1</b>		
APOE ε4 non-carrier	1.43 (1.17, 1.75)	1.43 (1.09, 1.86)
APOE ε4 carrier	1.38 (1.03, 1.85)	1.55 (1.27, 1.89)
<i>P</i> -interaction	0.66	0.85
<b>Score-2</b>		
APOE ε4 non-carrier	1.43 (1.10, 1.86)	1.82 (1.28, 2.60)
APOE ε4 carrier	1.64 (1.13, 2.38)	1.58 (1.22, 2.05)
<i>P</i> -interaction	0.85	0.53
<b>Score-3</b>		
APOE ε4 non-carrier	1.24 (1.02, 1.50)	1.48 (1.11, 1.98)
APOE ε4 carrier	1.62 (1.23, 2.12)	1.37 (1.09, 1.73)
<i>P</i> -interaction	0.40	0.74

Abbreviations: ARIC – Atherosclerosis Risk in Communities; MESA – Multi-Ethnic Study of Atherosclerosis; CI – confidence interval; HR – Hazard ratio; SD – standard deviation.

<sup>1</sup>In ARIC, follow-up was through the end of 2019 (visit 7); in MESA, follow-up was through the end of 2018.

<sup>2</sup>Models were adjusted for chronological age, sex, joint race–center terms in ARIC (Black participants from Mississippi; Black participants from other centers; White participants from Maryland, North Carolina, and Minnesota), and separate terms for race and study site in MESA, education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit.

<sup>3</sup>All SASP scores were standardized to mean=0 and SD=1.

**Table S12. Characteristics of ARIC participants at baseline (Visit 2) by Visit 5 attendance status.**

<b>Characteristic</b>	<b>Midlife participants who missed V5 (N = 2,560)<sup>1</sup></b>	<b>Midlife participants who attend V5 (N = 1,358)<sup>1</sup></b>	<b>P-value<sup>2</sup></b>
<b>SASP score 1</b>	5.23 (0.32)	5.09 (0.29)	1.22e-36
<b>SASP score 2</b>	39.46 (0.90)	39.11 (0.80)	3.07e-33
<b>SASP score 3</b>	18.96 (0.54)	18.71 (0.45)	2.53e-44
<b>Age, years (SD)</b>	58.25 (5.67)	54.74 (4.94)	4.00e-75
<b>Female, N (%)</b>	1,374 (53.7%)	773 (56.9%)	0.05
<b>Black, N (%)</b>	677 (26.4%)	243 (17.9%)	1.86e-09
<b>Education, N (%)</b>			2.81e-30
Less than high school	663 (25.9%)	158 (11.6%)	
High school equivalent	1,066 (41.7%)	564 (41.6%)	
Greater than high school	826 (32.3%)	635 (46.8%)	
<b>Mean BMI, kg/m<sup>2</sup> (SD)</b>	28.29 (5.56)	27.46 (4.82)	9.53e-06
<b>Smoking status, N (%)</b>			4.23e-09
Current smoker	642 (25.2%)	224 (16.5%)	
Former smoker	946 (37.1%)	550 (40.6%)	
Never smoker	964 (37.8%)	582 (42.9%)	
<b>Hypertension, N (%)</b>	1,067 (41.8%)	335 (24.7%)	2.16e-26
<b>Diabetes, N (%)</b>	473 (18.6%)	100 (7.4%)	5.49e-21
<b>Mean eGFR, ml/min/1.73 m<sup>2</sup> (SD)</b>	96.38 (17.13)	102.05 (13.83)	2.05e-21
<b>Mean cholesterol level, mg/dL (SD)</b>	211.77 (39.87)	208.00 (38.19)	1.31e-03

<sup>1</sup>Mean (SD); n (%)<sup>2</sup> Wilcoxon rank-sum tests were used for continuous variables, and Pearson's chi-squared tests were used for categorical variables.

**Table S13. Associations between late-life scores and incident dementia in ARIC (Visit 5, N = 1,540, number of dementia cases =241) with and without applying inverse probability weights (IPW).<sup>1,2</sup>**

Without applying IPWs		Applying IPWs	
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score	SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score
Score-1	1.50 (1.28, 1.75)	Score-1	1.60 (1.36, 1.89)
Score-2	1.47 (1.20, 1.79)	Score-2	1.58 (1.28, 1.95)
Score-3	1.39 (1.20, 1.62)	Score-3	1.40 (1.20, 1.63)

<sup>1</sup>Follow-up was through the end of 2019 (visit 7).

<sup>2</sup>Models were adjusted for chronological age, sex, joint race–center terms in ARIC (Black participants from Mississippi; Black participants from other centers; White participants from Maryland, North Carolina, and Minnesota), and separate terms for race and study site in MESA, education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit.

<sup>3</sup>All SASP scores were standardized to mean=0 and SD=1.

**Table S14. Associations of midlife (MESA Exam 1) and late-life (MESA Exam 5) SASP scores with incident dementia in all MESA participants and in the participants with age ranges restricted to the ARIC age ranges.<sup>1,2</sup>**

<b>All participants (ages 44-84) at MESA Exam 1 (N = 5,829)</b>		<b>Participants restricted to ages (46-69) at MESA Exam 1 (N = 4102)</b>	
No. of dementia cases	508	No. of dementia cases	157
Total person-years	83,386	Total person-years	62,335
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score	SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score
Score-1	1.38 (1.26, 1.51)	Score-1	1.54 (1.30, 1.82)
Score-2	1.26 (1.14, 1.39)	Score-2	1.29 (1.10, 1.53)
Score-3	1.28 (1.14, 1.43)	Score-3	1.27 (1.05, 1.54)
<b>All participants (ages 53-94) at MESA Exam 5 (N=4,065)</b>		<b>Participants restricted to ages (67-90) at MESA Exam 5 (N=2,335)</b>	
No. of dementia cases	215	No. of dementia cases	186/2,335
Total person-years	28,584	Total person-years	15,703
SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score	SASP score <sup>3</sup>	HR (95% CI) per 1 SD increase in score
Score-1	1.62 (1.39, 1.87)	Score-1	1.66 (1.42, 1.94)
Score-2	1.70 (1.40, 2.07)	Score-2	1.74 (1.44, 2.09)
Score-3	1.40 (1.18, 1.66)	Score-3	1.44 (1.21, 1.72)

Abbreviations: ARIC – Atherosclerosis Risk in Communities; MESA – Multi-Ethnic Study of Atherosclerosis; CI – confidence interval; HR – Hazard ratio; SD – standard deviation.

<sup>1</sup>In ARIC, follow-up was through the end of 2019 (visit 7); in MESA, follow-up was through the end of 2018.

<sup>2</sup>Models were adjusted for chronological age, sex, joint race–center terms in ARIC (Black participants from Mississippi; Black participants from other centers; White participants from Maryland, North Carolina, and Minnesota), and separate terms for race and study site in MESA, education, BMI, smoking status, diabetes, total cholesterol level, hypertension, and eGFR at the corresponding visit.

<sup>3</sup>All SASP scores were standardized to mean=0 and SD=1.