Supplementary Online Content

Dugani SB, Moorthy MV, Li C, et al. Association of lipid, inflammatory, and metabolic biomarkers with age at onset for incident coronary heart disease in women. *JAMA Cardiol*. Published online January 20, 2021. doi:10.1001/jamacardio.2020.7073

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1: Development and measurement of selected biomarkers

1. Lipoprotein subfractions
Lipoprotein particle concentration and average size were determined using a deconvolution algorithm with nuclear magnetic resonance (NMR) spectroscopy, as described.[1] The following lipoprotein subfractions are described:

   A. Low-density lipoprotein (LDL) particles
   There are three LDL subclasses on the basis of estimated diameter:
   Large LDL particles: 21.5nm–23nm
   Medium LDL particles: 20.5nm–21.4nm
   Small LDL particles: 19nm–20.4nm

   B. Triglyceride-rich lipoprotein (TRL) particles
   Large lipoprotein subfractions previously named very-low density lipoprotein (VLDL) particles or chylomicrons now refer to specific TRL particle subfractions to acknowledge that NMR spectroscopy distinguishes particles based on size and not on protein composition or metabolic origin.
   There are five TRL subclasses on the basis of estimated diameter:
   Very large TRL particles: 90nm–240nm
   Large TRL particles: 50nm–89nm
   Medium TRL particles: 37nm–49nm
   Small TRL particles: 30nm–36nm
   Very small TRL particles: 24nm–29nm

   C. High-density lipoprotein (HDL) particles
   There are three HDL subclasses on the basis of estimated diameter:
   Large HDL particles: 10.3nm–13nm
   Medium HDL particles: 8.7nm–10.2nm
   Small HDL particles: 7.4nm–8.6nm

2. Total branched chain amino acids (BCAAs)
Isoleucine, leucine, and valine (BCAAs) were measured by proton NMR spectroscopy. NMR spectra were deconvoluted with software containing reference spectra for BCAAs, serum proteins, and lipoproteins, as described.[2] Since levels of these amino acids are highly correlated, their sum (total BCAAs) is used for analytic purposes.

3. GlycA
GlycA reflects the aggregated levels of glycosylated acute phase proteins. GlycA concentration is based on NMR signal amplitudes from N-acetyl methyl groups of N-acetylglucosamine moieties located on the bi-, tri-, and tetra-antennary branches of specific serum proteins (predominantly α1-acid glycoprotein, haptoglobin, α1-antitrypsin, α1-antichymotrypsin, and transferrin). GlycA levels are positively associated with risk of incident diabetes, cardiovascular disease, and mortality.[3–7]

4. Lipoprotein insulin resistance (LPIR) score
LPIR score is a correlate of insulin resistance and is derived as a weighted combination of six lipoprotein measures (average TRL particle size, concentration of large TRL particles, average HDL particle size, concentration of large HDL particles, concentration of small LDL particles, and average LDL particle size).[8,9] Briefly, the weighting scores are based on the strength and independence of each lipoprotein measure with insulin resistance; average TRL particle size (score 32) and concentration of large TRL particles (score 22), average HDL particle size (score 20), concentration of large HDL particles (score 12), concentration of small LDL particles (score 8) and average LDL particle size (score 6).[8,10] LPIR score ranges from 0–100, where higher scores predict increased risk of insulin resistance and incident diabetes[8,9].

eMethods 2: Study Strata and Time Contribution to Age Groups

Study Strata

We divided study time into four age groups (age<55, 55≤ age <65, 65≤ age <75, and age≥75 years) and two blood draw time categories (≤10 years, >10 years), and formed seven strata. Since the minimum age for enrollment in WHS was 45 years there were no participants in the stratum based on age <55 and blood draw time >10 years. We used stratified Cox proportional hazards regression models with the counting process method, stratified by the seven strata.

Women could contribute exposure time to more than one age group as they passed through time until the occurrence of incident CHD or censoring (death or last follow-up), as illustrated below.

Time Contribution to Age Groups

Example 1

The participant is 48 years old at time of enrollment, and experiences an incident CHD event at age 57 years.

She contributes 9 person-years to blood draw time category ≤10 years (and no time to blood draw time >10 years) as follows:

> age 48-55: 7 years to age <55 group
> age 55-57: 2 years to 55≤ age <65 group

Example 2

The participant is 58 years old at time of enrollment, and is censored at age 81 years.

She contributes 23 person-years as follows:

10 years to the ≤10 year blood draw time category:

> age 58-65: 7 years to 55≤ age <65 group
> age 65-68: 3 years to 65≤ age <75 group

13 years to the >10 year blood draw time category:

> age 68-75: 7 years to 65≤ age <75 group
> age 75-81: 6 years to age ≥75 group

eTable 1: Standard deviation of baseline levels from entire cohort (n = 28,024)

	Standard deviation
Body mass index, kg/m^2	5.0
Systolic blood pressure, mm Hg	13.7
Total cholesterol, mg/dL	41.8
LDL cholesterol, mg/dL	34.2
HDL cholesterol, mg/dL	15.0
Total/HDL cholesterol ratio	0.3
Triglycerides, mg/dL	0.5
Trig/HDL cholesterol ratio	0.7
Non-HDL cholesterol, mg/dL	41.2
Apolipoprotein B, mg/dL	27.9
Apolipoprotein A-I, mg/dL	25.6
Lipoprotein(a), mg/dL	1.3
Total LDL particles, nmol/L	397.1
Large LDL particles	222.5
Medium LDL particles	249.6
Small LDL particles	501.2
LDL particle average size, nm	0.5
Total TRL particles, nmol/L	61.4
Very large TRL particles	0.5
Large TRL particles	3.1
Medium TRL particles	1.4
Small TRL particles	1.2
Very small TRL particles	42.5
TRL particle average size, nm	7.5
TRL cholesterol, mg/dL	11.1
TRL triglycerides, mg/dL	0.5
Total HDL particles, µmol/L	3.8
Large HDL particles	0.7
Medium HDL particles	2.8
Small HDL particles	3.4
HDL particle average size, nm	0.4
CRP, mg/L	1.2
Fibrinogen, mg/dL	79.4
Intercellular adhesion molecule 1, ng/mL	83.0
Glycan biomarker of N-acetyl side chains of acute-phase proteins, µmol/L	68.5
Hemoglobin A1c, %	0.6
LPIR score (0–100)	1.2
Homocysteine, µmol/L	0.3
Citrate, µmol/L	28.3
Total branched chain amino acids, µmol/L	92.1
Valine, µmol/L	46.8
Leucine, µmol/L	35.8
Isoleucine, µmol/L	20.9
Alanine, µmol/L	108.7
Estimated glomerular filtration rate, mL/min per 1.73m^2	26.6
Creatinine, mg/dL	0.2

The following were log transformed: CRP, homocysteine, large HDL particles, lipoprotein (a), LPIR score, medium TRL particles, small TRL particles, total/HDL cholesterol ratio, triglycerides, trig/HDL cholesterol ratio, and TRL triglycerides.
Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPIR, lipoprotein insulin resistance; TRL, triglyceride-rich lipoprotein.

eTable 2: Association of risk factors with incident CHD by age of onset and blood draw time categories

Risk factor	Incident CHD at age <55	Incident CHD at 55≤ age <65	Incident CHD at 65≤ age <75	Incident CHD at age ≥75	$P_{interaction}$[a] (risk factor) × (blood draw time category)
Clinical risk factors	Adjusted hazard ratio (95% CI)				
BMI, per SD increment					
Blood draw ≤10 years	1.47 (1.24 – 1.74)	1.39 (1.26 – 1.54)	1.35 (1.20 – 1.52)	1.06 (0.81 – 1.39)	.96
Blood draw >10 years	censored[b]	1.41 (1.25 – 1.59)	1.32 (1.22 – 1.43)	1.13 (1.01 – 1.26)	
BMI categories					
Overweight					
Blood draw ≤10 years	2.13 (1.10 – 4.14)	1.84 (1.36 – 2.50)	1.58 (1.17 – 2.13)	1.00 (0.61 – 1.67)	.71
Blood draw >10 years	censored	1.65 (1.08 – 2.52)	1.91 (1.52 – 2.40)	1.15 (0.91 – 1.45)	
Obese					
Blood draw ≤10 years	4.33 (2.31 – 8.11)	2.51 (1.82 – 3.46)	2.06 (1.46 – 2.90)	1.06 (0.51 – 2.18)	.69
Blood draw >10 years	censored	3.24 (2.16 – 4.86)	2.18 (1.69 – 2.81)	1.37 (1.03 – 1.81)	
Current smoker					
Blood draw ≤10 years	3.92 (2.32 – 6.63)	3.01 (2.28 – 3.98)	1.98 (1.41 – 2.76)	1.75 (0.84 – 3.67)	.98
Blood draw >10 years	censored	2.89 (1.98 – 4.22)	1.84 (1.42 – 2.38)	1.92 (1.41 – 2.61)	
Diabetes					
Blood draw ≤10 years	10.71 (5.57 – 20.60)	10.67 (7.84 – 14.53)	3.93 (2.70 – 5.72)	4.41 (2.18 – 8.91)	.65
Blood draw >10 years	censored	11.52 (7.23 – 18.37)	5.14 (3.60 – 7.35)	3.26 (2.21 – 4.79)	
Metabolic syndrome					
Blood draw ≤10 years	6.09 (3.60 – 10.29)	4.10 (3.17 – 5.31)	2.74 (2.11 – 3.56)	1.50 (0.93 – 2.41)	.62
Blood draw >10 years	censored	5.13 (3.64 – 7.22)	2.86 (2.35 – 3.49)	1.85 (1.50 – 2.29)	
Hypertension					
Blood draw ≤10 years	4.58 (2.76 – 7.60)	2.25 (1.74 – 2.91)	1.87 (1.44 – 2.43)	2.00 (1.24 – 3.21)	.51
Blood draw >10 years	censored	2.67 (1.87 – 3.81)	2.19 (1.79 – 2.69)	1.58 (1.28 – 1.94)	
Systolic BP, per SD increment					
Blood draw ≤10 years	2.24 (1.84 – 2.74)	1.61 (1.44 – 1.80)	1.48 (1.32 – 1.66)	1.38 (1.11 – 1.71)	.84
Blood draw >10 years	censored	1.62 (1.39 – 1.89)	1.48 (1.35 – 1.62)	1.23 (1.12 – 1.36)	
Physical inactivity					
Blood draw ≤10 years	1.53 (0.92 – 2.55)	1.64 (1.27 – 2.12)	1.65 (1.27 – 2.14)	1.54 (0.97 – 2.44)	.35
Blood draw >10 years	censored	1.51 (1.07 – 2.13)	1.31 (1.08 – 1.60)	1.15 (0.94 – 1.42)	
Parental MI <60 years					
Blood draw ≤10 years	2.19 (1.26 – 3.81)	2.29 (1.72 – 3.05)	1.41 (0.97 – 2.03)	0.65 (0.24 – 1.79)	.28
Blood draw >10 years	censored	1.73 (1.17 – 2.57)	1.70 (1.33 – 2.16)	1.27 (0.94 – 1.71)	
Lipids and lipoproteins	Adjusted hazard ratio (95% CI) per SD increment				
Total cholesterol					
Blood draw ≤10 years	1.39 (1.12 – 1.73)	1.35 (1.20 – 1.51)	1.18 (1.05 – 1.33)	1.18 (0.96 – 1.45)	.22
Blood draw >10 years	censored	1.58 (1.38 – 1.80)	1.28 (1.17 – 1.40)	1.10 (1.00 – 1.22)	
LDL cholesterol					
Blood draw ≤10 years	1.38 (1.10 – 1.74)	1.35 (1.20 – 1.51)	1.18 (1.05 – 1.34)	1.05 (0.84 – 1.31)	.19
Blood draw >10 years	censored	1.60 (1.39 – 1.84)	1.28 (1.17 – 1.41)	1.13 (1.03 – 1.25)	
HDL cholesterol					
Blood draw ≤10 years	0.39 (0.27 – 0.55)	0.51 (0.43 – 0.59)	0.56 (0.48 – 0.66)	0.97 (0.77 – 1.23)	.10
Blood draw >10 years	censored	0.47 (0.38 – 0.59)	0.64 (0.57 – 0.72)	0.74 (0.66 – 0.83)	
Total/HDL cholesterol ratio					

Blood draw ≤10 years	2.40 (1.90 – 3.05)	2.09 (1.85 – 2.36)	1.81 (1.59 – 2.06)	1.21 (0.95 – 1.53)	.25
Blood draw >10 years	censored	2.43 (2.07 – 2.85)	1.74 (1.58 – 1.92)	1.45 (1.30 – 1.61)	
Triglycerides					
Blood draw ≤10 years	2.14 (1.72 – 2.67)	1.70 (1.51 – 1.92)	1.69 (1.49 – 1.92)	1.37 (1.07 – 1.75)	.34
Blood draw >10 years	censored	1.96 (1.69 – 2.27)	1.57 (1.42 – 1.72)	1.28 (1.15 – 1.43)	
Trig/HDL cholesterol ratio					
Blood draw ≤10 years	2.27 (1.83 – 2.81)	1.84 (1.64 – 2.07)	1.78 (1.57 – 2.02)	1.28 (1.00 – 1.63)	.45
Blood draw >10 years	censored	2.05 (1.77 – 2.37)	1.64 (1.49 – 1.79)	1.36 (1.22 – 1.50)	
Non-HDL cholesterol					
Blood draw ≤10 years	1.67 (1.36 – 2.04)	1.57 (1.41 – 1.74)	1.36 (1.22 – 1.53)	1.19 (0.97 – 1.46)	.26
Blood draw >10 years	censored	1.83 (1.62 – 2.08)	1.44 (1.32 – 1.58)	1.21 (1.10 – 1.33)	
Apolipoprotein B					
Blood draw ≤10 years	1.89 (1.52 – 2.35)	1.67 (1.51 – 1.84)	1.51 (1.35 – 1.69)	1.16 (0.92 – 1.47)	.10
Blood draw >10 years	censored	2.04 (1.79 – 2.33)	1.52 (1.40 – 1.66)	1.28 (1.16 – 1.41)	
Apolipoprotein A-I					
Blood draw ≤10 years	0.69 (0.51 – 0.94)	0.60 (0.52 – 0.69)	0.72 (0.63 – 0.83)	1.05 (0.83 – 1.32)	.31
Blood draw >10 years	censored	0.63 (0.52 – 0.77)	0.78 (0.70 – 0.86)	0.85 (0.76 – 0.94)	
Lipoprotein (a)					
Blood draw ≤10 years	1.22 (0.92 – 1.62)	1.23 (1.08 – 1.41)	0.98 (0.86 – 1.12)	1.05 (0.83 – 1.33)	.09
Blood draw >10 years	censored	1.35 (1.13 – 1.62)	1.20 (1.08 – 1.33)	1.11 (1.00 – 1.23)	
Total LDL particles[c]					
Blood draw ≤10 years	1.75 (1.42 – 2.15)	1.52 (1.36 – 1.71)	1.36 (1.21 – 1.54)	1.34 (1.06 – 1.68)	.59
Blood draw >10 years	censored	1.70 (1.48 – 1.95)	1.37 (1.25 – 1.50)	1.22 (1.10 – 1.35)	
Large LDL particles[d]					
Blood draw ≤10 years	1.02 (0.74 – 1.42)	1.11 (0.95 – 1.28)	1.08 (0.93 – 1.25)	1.29 (1.00 – 1.66)	.12
Blood draw >10 years	censored	0.88 (0.69 – 1.11)	0.97 (0.86 – 1.09)	1.07 (0.95 – 1.20)	
Medium LDL particles[d]					
Blood draw ≤10 years	1.13 (0.80 – 1.60)	1.08 (0.91 – 1.27)	1.09 (0.93 – 1.27)	0.93 (0.69 – 1.26)	.49
Blood draw >10 years	censored	1.31 (1.08 – 1.59)	1.08 (0.95 – 1.22)	1.00 (0.88 – 1.13)	
Small LDL particles[d]					
Blood draw ≤10 years	2.25 (1.76 – 2.89)	1.80 (1.57 – 2.07)	1.57 (1.35 – 1.82)	1.48 (1.12 – 1.95)	.45
Blood draw >10 years	censored	2.14 (1.80 – 2.55)	1.57 (1.40 – 1.76)	1.35 (1.19 – 1.53)	
LDL particle average size[c]					
Blood draw ≤10 years	0.64 (0.50 – 0.80)	0.79 (0.70 – 0.89)	0.82 (0.72 – 0.92)	1.00 (0.79 – 1.26)	.23
Blood draw >10 years	censored	0.67 (0.57 – 0.78)	0.79 (0.72 – 0.87)	0.87 (0.78 – 0.96)	
Total TRL particles					
Blood draw ≤10 years	1.74 (1.44 – 2.10)	1.44 (1.28 – 1.61)	1.38 (1.23 – 1.55)	1.22 (0.98 – 1.53)	.14
Blood draw >10 years	censored	1.79 (1.55 – 2.06)	1.38 (1.26 – 1.51)	1.24 (1.13 – 1.37)	
Very large TRL particles					
Blood draw ≤10 years	1.27 (1.16 – 1.40)	1.14 (1.06 – 1.23)	1.21 (1.14 – 1.28)	1.10 (0.92 – 1.32)	.52
Blood draw >10 years	censored	1.20 (1.10 – 1.32)	1.15 (1.08 – 1.22)	1.11 (1.03 – 1.20)	
Large TRL particles					
Blood draw ≤10 years	1.66 (1.43 – 1.93)	1.30 (1.17 – 1.44)	1.34 (1.21 – 1.49)	1.32 (1.08 – 1.62)	.12
Blood draw >10 years	censored	1.55 (1.38 – 1.74)	1.34 (1.24 – 1.45)	1.18 (1.07 – 1.29)	
Medium TRL particles					
Blood draw ≤10 years	1.80 (1.14 – 2.84)	1.44 (1.15 – 1.79)	1.90 (1.47 – 2.46)	1.24 (0.85 – 1.80)	.05
Blood draw >10 years	censored	2.08 (1.51 – 2.85)	1.38 (1.17 – 1.62)	1.22 (1.04 – 1.44)	
Small TRL particles					
Blood draw ≤10 years	0.84 (0.73 – 0.96)	1.04 (0.90 – 1.20)	0.92 (0.83 – 1.02)	1.09 (0.76 – 1.55)	.12
Blood draw >10 years	censored	0.91 (0.80 – 1.05)	1.10 (0.96 – 1.25)	1.16 (0.99 – 1.36)	
Very small TRL particles					
Blood draw ≤10 years	1.77 (1.43 – 2.18)	1.40 (1.25 – 1.57)	1.37 (1.22 – 1.53)	1.21 (0.96 – 1.51)	.07
Blood draw >10 years	censored	1.78 (1.55 – 2.06)	1.32 (1.20 – 1.45)	1.19 (1.08 – 1.31)	
TRL cholesterol					
Blood draw ≤10 years	1.66 (1.35 – 2.02)	1.23 (1.10 – 1.38)	1.36 (1.21 – 1.52)	1.21 (0.96 – 1.53)	.22

Blood draw >10 years	censored	1.48 (1.28 – 1.70)	1.29 (1.18 – 1.41)	1.13 (1.02 – 1.26)	
TRL triglycerides					
Blood draw ≤10 years	1.77 (1.47 – 2.12)	1.43 (1.27 – 1.60)	1.40 (1.25 – 1.56)	1.25 (1.00 – 1.56)	.14
Blood draw >10 years	censored	1.77 (1.54 – 2.02)	1.39 (1.27 – 1.52)	1.24 (1.13 – 1.37)	
TRL particle average size					
Blood draw ≤10 years	2.21 (1.68 – 2.90)	1.47 (1.28 – 1.68)	1.62 (1.40 – 1.88)	1.28 (0.99 – 1.66)	.05
Blood draw >10 years	censored	1.99 (1.66 – 2.38)	1.49 (1.34 – 1.65)	1.27 (1.13 – 1.42)	
Total HDL particles					
Blood draw ≤10 years	0.96 (0.73 – 1.27)	0.74 (0.65 – 0.85)	0.93 (0.81 – 1.06)	1.12 (0.89 – 1.42)	.06
Blood draw >10 years	censored	0.95 (0.79 – 1.14)	0.88 (0.80 – 0.98)	0.90 (0.81 – 1.00)	
Large HDL particles					
Blood draw ≤10 years	0.74 (0.65 – 0.85)	0.76 (0.71 – 0.81)	0.81 (0.75 – 0.87)	1.11 (0.85 – 1.44)	.37
Blood draw >10 years	censored	0.74 (0.68 – 0.81)	0.79 (0.74 – 0.85)	0.89 (0.81 – 0.96)	
Medium HDL particles					
Blood draw ≤10 years	0.65 (0.47 – 0.90)	0.58 (0.50 – 0.68)	0.74 (0.63 – 0.86)	0.93 (0.72 – 1.21)	.46
Blood draw >10 years	censored	0.47 (0.37 – 0.60)	0.71 (0.64 – 0.80)	0.84 (0.75 – 0.94)	
Small HDL particles					
Blood draw ≤10 years	1.60 (1.24 – 2.08)	1.25 (1.10 – 1.42)	1.32 (1.16 – 1.51)	1.16 (0.91 – 1.47)	.009
Blood draw >10 years	censored	1.80 (1.52 – 2.14)	1.28 (1.16 – 1.41)	1.07 (0.97 – 1.19)	
HDL particle average size					
Blood draw ≤10 years	0.50 (0.37 – 0.69)	0.57 (0.49 – 0.67)	0.64 (0.55 – 0.75)	1.03 (0.82 – 1.29)	.31
Blood draw >10 years	censored	0.48 (0.39 – 0.60)	0.66 (0.59 – 0.74)	0.86 (0.77 – 0.96)	
Inflammatory	Adjusted hazard ratio (95% CI) per SD increment				
CRP					
Blood draw ≤10 years	1.76 (1.37 – 2.27)	1.54 (1.34 – 1.76)	1.62 (1.40 – 1.88)	1.46 (1.12 – 1.90)	.14
Blood draw >10 years	censored	1.91 (1.61 – 2.27)	1.63 (1.46 – 1.80)	1.21 (1.08 – 1.36)	
Fibrinogen					
Blood draw ≤10 years	1.49 (1.22 – 1.81)	1.42 (1.29 – 1.56)	1.28 (1.15 – 1.41)	1.26 (1.03 – 1.54)	.21
Blood draw >10 years	censored	1.64 (1.48 – 1.82)	1.29 (1.19 – 1.41)	1.17 (1.06 – 1.28)	
ICAM-1					
Blood draw ≤10 years	1.52 (1.26 – 1.82)	1.42 (1.31 – 1.55)	1.38 (1.23 – 1.54)	1.03 (0.80 – 1.33)	.15
Blood draw >10 years	censored	1.62 (1.45 – 1.82)	1.31 (1.20 – 1.42)	1.23 (1.11 – 1.36)	
GlycA					
Blood draw ≤10 years	1.84 (1.49 – 2.27)	1.47 (1.30 – 1.66)	1.50 (1.32 – 1.70)	1.29 (1.02 – 1.62)	.09
Blood draw >10 years	censored	1.86 (1.61 – 2.15)	1.45 (1.32 – 1.59)	1.16 (1.04 – 1.30)	
Metabolic	Adjusted hazard ratio (95% CI) per SD increment				
Hemoglobin A1c					
Blood draw ≤10 years	1.38 (1.26 – 1.50)	1.30 (1.25 – 1.35)	1.21 (1.14 – 1.28)	1.14 (0.96 – 1.35)	.11
Blood draw >10 years	censored	1.41 (1.33 – 1.50)	1.26 (1.21 – 1.32)	1.14 (1.06 – 1.22)	
LPIR score					
Blood draw ≤10 years	6.40 (3.14 – 13.06)	2.25 (1.70 – 2.98)	2.76 (2.00 – 3.80)	0.90 (0.77 – 1.05)	.002
Blood draw >10 years	censored	3.37 (2.28 – 4.97)	1.86 (1.53 – 2.27)	1.32 (1.11 – 1.59)	
Homocysteine					
Blood draw ≤10 years	1.03 (0.79 – 1.35)	1.23 (1.09 – 1.38	1.07 (0.93 – 1.23)	0.86 (0.67 – 1.11)	.27
Blood draw >10 years	censored	1.19 (1.01 – 1.39)	1.15 (1.05 – 1.27)	1.09 (0.98 – 1.21)	
Citrate					
Blood draw ≤10 years	0.97 (0.73 – 1.29)	1.03 (0.91 – 1.16)	0.91 (0.79 – 1.05)	1.12 (0.92 – 1.35)	.16
Blood draw >10 years	censored	1.09 (0.93 – 1.27)	1.06 (0.97 – 1.16)	0.95 (0.86 – 1.06)	
Total BCAAs					
Blood draw ≤10 years	1.47 (1.20 – 1.80)	1.29 (1.15 – 1.44)	1.29 (1.15 – 1.45)	1.19 (0.95 – 1.49)	.06
Blood draw >10 years	censored	1.62 (1.43 – 1.84)	1.32 (1.21 – 1.43)	1.10 (0.99 – 1.23)	
Valine					
Blood draw ≤10 years	1.51 (1.22 – 1.87)	1.27 (1.13 – 1.42)	1.30 (1.15 – 1.47)	1.27 (1.01 – 1.59)	.01
Blood draw >10 years	censored	1.68 (1.46 – 1.92)	1.31 (1.19 – 1.43)	1.08 (0.97 – 1.20)	
Leucine					

Blood draw ≤10 years	1.30 (1.03 – 1.64)	1.23 (1.09 – 1.39)	1.16 (1.02 – 1.32)	1.07 (0.85 – 1.35)	.12
Blood draw >10 years	censored	1.53 (1.32 – 1.76)	1.25 (1.14 – 1.38)	1.05 (0.94 – 1.17)	
Isoleucine					
Blood draw ≤10 years	1.50 (1.23 – 1.83)	1.30 (1.16 – 1.45)	1.33 (1.19 – 1.49)	1.12 (0.89 – 1.42)	.37
Blood draw >10 years	censored	1.51 (1.32 – 1.72)	1.32 (1.21 – 1.43)	1.19 (1.08 – 1.32)	
Alanine					
Blood draw ≤10 years	1.10 (0.85 – 1.41)	1.14 (1.00 – 1.29)	1.27 (1.12 – 1.44)	0.96 (0.76 – 1.23)	.39
Blood draw >10 years	censored	1.25 (1.07 – 1.46)	1.13 (1.02 – 1.24)	1.00 (0.89 – 1.11)	
eGFR					
Blood draw ≤10 years	1.27 (1.12 – 1.43)	1.03 (0.91 – 1.16)	0.99 (0.87 – 1.13)	0.92 (0.70 – 1.20)	.40
Blood draw >10 years	censored	0.91 (0.75 – 1.10)	0.93 (0.84 – 1.04)	1.07 (0.99 – 1.17)	
Creatinine					
Blood draw ≤10 years	0.55 (0.41 – 0.74)	0.96 (0.85 – 1.10)	1.05 (0.93 – 1.18)	1.08 (0.89 – 1.31)	.44
Blood draw >10 years	censored	1.03 (0.86 – 1.22)	1.08 (0.98 – 1.19)	0.92 (0.83 – 1.01)	

HRs (95% CI) obtained from stratified Cox models (stratified on age groups and blood draw time categories) adjusted for model 1 covariates (baseline race, education categories, menopause, postmenopausal hormone use, randomized treatment assignment, and interactions between the risk factor of interest and the seven age group × blood draw time categories).

[a]Likelihood Ratio Test (LRT, 3 d.f.) of the null hypothesis that the risk factor has the same effect across blood draw time categories; i.e., the models in Table 2 fit adequately.

[b]Two participants with incident CHD at age <55 and blood draw >10 years were censored after 10 years of study entry. These participants contributed exposure time to the 'age<55 and blood draw ≤10 years' stratum.

[c]included model 1 covariates plus LDL particle concentration and LDL particle average size.

[d]included model 1 covariates plus other LDL subclasses (large, medium, or small LDL particles).

The following were log transformed: CRP, homocysteine, large HDL particles, lipoprotein (a), LPIR score, medium TRL particles, small TRL particles, total/HDL cholesterol ratio, triglycerides, trig/HDL cholesterol ratio, and TRL triglycerides.

BMI (kg/m^2) categories: 25.0 - <30 (overweight); ≥30.0 (obese).

Physical inactivity: <7.5 MET-hrs per week.

Blood draw time categories: ≤10 years and >10 years.

See eTable 1 for SDs.

Abbreviations: BCAAs, branched chain amino acids; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GlycA, glycan biomarker of N-acetyl side chains of acute-phase proteins; HDL, high-density lipoprotein; ICAM-1, Intercellular adhesion molecule 1; LDL, low-density lipoprotein; LPIR, lipoprotein insulin resistance; MI, myocardial infarction; TRL, triglyceride-rich lipoprotein.

eTable 3: Association of risk factors and biomarkers with incident CHD after additional adjustment for covariates*

Risk factor	Incident CHD at age <55	Incident CHD at 55≤ age <65	Incident CHD at 65≤ age <75	Incident CHD at age ≥75	$P_{interaction}$[a] (risk factor) × (age group)
Clinical risk factors	Adjusted hazard ratio (95% CI)				
BMI, per SD increment	1.24 (1.04 – 1.48)	1.19 (1.09 – 1.29)	1.12 (1.04 – 1.21)	0.97 (0.88 – 1.08)	.01
BMI categories					
Overweight	1.68 (0.86 – 3.30)	1.52 (1.18 – 1.95)	1.53 (1.27 – 1.84)	1.01 (0.81 – 1.25)	.02
Obese	2.63 (1.40 – 4.93)	1.76 (1.36 – 2.29)	1.37 (1.10 – 1.70)	0.94 (0.72 – 1.24)	.001
Current smoker	3.69 (2.16 – 6.29)	3.03 (2.41 – 3.81)	2.04 (1.66 – 2.52)	2.03 (1.51 – 2.72)	.02
Diabetes	6.58 (3.41 – 12.72)	7.18 (5.49 – 9.38)	3.29 (2.51 – 4.31)	2.89 (2.05 – 4.08)	<.001
Diabetes[b]	4.64 (2.21 – 9.73)	6.59 (4.94 – 8.78)	3.25 (2.46 – 4.30)	2.95 (2.06 – 4.23)	.001
Metabolic syndrome	4.01 (2.34 – 6.87)	3.17 (2.51 – 3.99)	2.05 (1.70 – 2.47)	1.38 (1.12 – 1.70)	<.001
Hypertension	3.74 (2.25 – 6.21)	2.01 (1.62 – 2.49)	1.71 (1.45 – 2.03)	1.42 (1.17 – 1.72)	.002
Systolic BP, per SD increment	2.00 (1.62 – 2.48)	1.41 (1.28 – 1.55)	1.30 (1.20 – 1.40)	1.14 (1.04 – 1.25)	<.001
Physical inactivity	1.24 (0.74 – 2.07)	1.26 (1.02 – 1.56)	1.17 (0.99 – 1.38)	1.03 (0.85 – 1.25)	.52
Parental MI <60 years	1.79 (1.02 – 3.15)	1.94 (1.54 – 2.45)	1.54 (1.26 – 1.89)	1.16 (0.87 – 1.56)	.05
Lipids and lipoproteins	Adjusted hazard ratio (95% CI) per SD increment				
Total cholesterol	1.26 (1.01 – 1.57)	1.33 (1.22 – 1.45)	1.20 (1.11 – 1.29)	1.11 (1.02 – 1.22)	.05
LDL cholesterol	1.25 (0.99 – 1.58)	1.35 (1.23 – 1.48)	1.21 (1.12 – 1.30)	1.12 (1.02 – 1.23)	.04
HDL cholesterol	0.50 (0.36 – 0.70)	0.60 (0.53 – 0.69)	0.72 (0.65 – 0.79)	0.83 (0.75 – 0.92)	<.001
Total/HDL cholesterol ratio	1.92 (1.52 – 2.42)	1.83 (1.65 – 2.01)	1.54 (1.42 – 1.67)	1.32 (1.20 – 1.46)	<.001
Triglycerides	1.71 (1.38 – 2.12)	1.48 (1.35 – 1.63)	1.39 (1.28 – 1.50)	1.19 (1.08 – 1.32)	.002
Trig/HDL cholesterol ratio	1.82 (1.47 – 2.25)	1.58 (1.44 – 1.74)	1.45 (1.34 – 1.57)	1.24 (1.13 – 1.37)	<.001
Non-HDL cholesterol	1.43 (1.16 – 1.76)	1.47 (1.35 – 1.60)	1.30 (1.21 – 1.39)	1.18 (1.07 – 1.29)	.004
Apolipoprotein B	1.56 (1.25 – 1.95)	1.55 (1.42 – 1.68)	1.37 (1.27 – 1.47)	1.19 (1.08 – 1.31)	.001
Apolipoprotein A-I	0.80 (0.59 – 1.08)	0.70 (0.62 – 0.78)	0.84 (0.77 – 0.92)	0.92 (0.83 – 1.02)	.002
Lipoprotein (a)	1.22 (0.92 – 1.60)	1.29 (1.16 – 1.43)	1.13 (1.04 – 1.23)	1.09 (0.99 – 1.20)	.12
Total LDL particles[c]	1.60 (1.29 – 1.99)	1.45 (1.32 – 1.59)	1.27 (1.18 – 1.37)	1.18 (1.07 – 1.30)	.005
Large LDL particles[d]	1.10 (0.80 – 1.52)	1.07 (0.95 – 1.21)	1.04 (0.94 – 1.14)	1.13 (1.02 – 1.26)	.68
Medium LDL particles[d]	1.11 (0.80 – 1.56)	1.12 (0.98 – 1.27)	1.07 (0.97 – 1.18)	0.99 (0.88 – 1.12)	.59
Small LDL particles[d]	1.97 (1.51 – 2.56)	1.67 (1.49 – 1.87)	1.40 (1.28 – 1.54)	1.27 (1.12 – 1.43)	<.001
LDL particle average size[c]	0.74 (0.59 – 0.94)	0.83 (0.76 – 0.92)	0.88 (0.82 – 0.96)	0.96 (0.88 – 1.06)	.08
Total TRL particles	1.55 (1.24 – 1.93)	1.38 (1.26 – 1.52)	1.26 (1.17 – 1.35)	1.18 (1.08 – 1.29)	.03
Very large TRL particles	1.19 (1.06 – 1.33)	1.07 (1.00 – 1.14)	1.09 (1.04 – 1.14)	1.02 (0.94 – 1.12)	.23
Large TRL particles	1.41 (1.21 – 1.63)	1.20 (1.11 – 1.31)	1.18 (1.10 – 1.26)	1.09 (1.00 – 1.20)	.05
Medium TRL particles	1.40 (0.92 – 2.12)	1.35 (1.14 – 1.61)	1.31 (1.14 – 1.49)	1.16 (1.00 – 1.35)	.52
Small TRL particles	0.84 (0.73 – 0.97)	1.01 (0.91 – 1.12)	1.03 (0.95 – 1.13)	1.20 (1.03 – 1.40)	.03
Very small TRL particles	1.52 (1.22 – 1.89)	1.36 (1.24 – 1.49)	1.22 (1.13 – 1.31)	1.11 (1.01 – 1.22)	.006
TRL cholesterol	1.41 (1.14 – 1.74)	1.15 (1.04 – 1.26)	1.16 (1.08 – 1.25)	1.02 (0.93 – 1.13)	.03
TRL triglycerides	1.55 (1.26 – 1.91)	1.36 (1.24 – 1.49)	1.26 (1.17 – 1.36)	1.18 (1.08 – 1.29)	.04
TRL particle average size	1.77 (1.36 – 2.30)	1.38 (1.24 – 1.54)	1.33 (1.22 – 1.45)	1.17 (1.05 – 1.29)	.01
Total HDL particles	1.01 (0.77 – 1.33)	0.85 (0.76 – 0.95)	0.93 (0.86 – 1.01)	0.93 (0.84 – 1.03)	.49
Large HDL particles	0.78 (0.66 – 0.93)	0.82 (0.77 – 0.87)	0.87 (0.82 – 0.92)	0.96 (0.87 – 1.06)	.03
Medium HDL particles	0.76 (0.56 – 1.04)	0.65 (0.57 – 0.74)	0.81 (0.74 – 0.88)	0.91 (0.82 – 1.01)	<.001
Small HDL particles	1.43 (1.09 – 1.86)	1.27 (1.14 – 1.41)	1.17 (1.08 – 1.27)	1.00 (0.90 – 1.10)	.002
HDL particle average size	0.61 (0.44 – 0.84)	0.63 (0.56 – 0.72)	0.76 (0.69 – 0.83)	0.96 (0.87 – 1.06)	<.001
Inflammatory	Adjusted hazard ratio (95% CI) per SD increment				
CRP	1.46 (1.13 – 1.87)	1.43 (1.28 – 1.60)	1.38 (1.26 – 1.52)	1.14 (1.02 – 1.27)	.01
Fibrinogen	1.22 (0.98 – 1.52)	1.32 (1.22 – 1.43)	1.16 (1.08 – 1.24)	1.07 (0.98 – 1.17)	.003
ICAM-1	1.24 (1.01 – 1.51)	1.28 (1.18 – 1.38)	1.13 (1.05 – 1.22)	1.04 (0.95 – 1.15)	.009

GlycA	1.51 (1.20 – 1.89)	1.34 (1.21 – 1.48)	1.24 (1.14 – 1.34)	1.02 (0.92 – 1.12)	<.001
Metabolic	Adjusted hazard ratio (95% CI) per SD increment				
Hemoglobin A1c	1.16 (1.04 – 1.28)	1.14 (1.09 – 1.19)	1.05 (1.00 – 1.11)	0.97 (0.89 – 1.05)	<.001
LPIR score	3.85 (1.97 – 7.53)	1.91 (1.52 – 2.40)	1.56 (1.32 – 1.84)	1.04 (0.93 – 1.17)	<.001
Homocysteine	0.96 (0.74 – 1.26)	1.15 (1.04 – 1.26)	1.08 (0.99 – 1.16)	1.02 (0.93 – 1.13)	.33
Citrate	0.93 (0.69 – 1.25)	1.03 (0.93 – 1.14)	0.99 (0.91 – 1.08)	0.97 (0.88 – 1.08)	.85
Total BCAAs	1.26 (1.02 – 1.57)	1.19 (1.09 – 1.30)	1.12 (1.04 – 1.20)	0.99 (0.90 – 1.09)	.02
Valine	1.25 (1.01 – 1.55)	1.18 (1.07 – 1.29)	1.11 (1.03 – 1.19)	0.97 (0.88 – 1.07)	.01
Leucine	1.15 (0.91 – 1.47)	1.15 (1.04 – 1.26)	1.07 (0.99 – 1.15)	0.96 (0.87 – 1.06)	.06
Isoleucine	1.34 (1.09 – 1.66)	1.20 (1.09 – 1.31)	1.16 (1.08 – 1.25)	1.07 (0.98 – 1.18)	.16
Alanine	1.02 (0.79 – 1.33)	1.10 (0.99 – 1.22)	1.11 (1.02 – 1.20)	0.92 (0.83 – 1.02)	.03
eGFR	1.26 (1.10 – 1.43)	0.93 (0.83 – 1.04)	0.91 (0.83 – 0.99)	1.04 (0.96 – 1.14)	.003
Creatinine	0.59 (0.44 – 0.80)	1.03 (0.93 – 1.14)	1.10 (1.02 – 1.18)	0.96 (0.87 – 1.05)	<.001

*HRs (95% CI) obtained from stratified Cox models (stratified on age groups and blood draw time categories) adjusted for model 1 covariates (baseline race, education categories, menopause, postmenopausal hormone use, randomized treatment assignment, and interactions between the risk factor of interest and age groups) plus additional covariates (physical activity, smoking, BMI, systolic blood pressure, diabetes, parental MI<60 years, and baseline treatment for hypertension or for high cholesterol).

[a]Likelihood Ratio Test (LRT, 3 d.f.) of the null hypothesis that the risk factor has the same effect across age groups.

An individual risk factor used as an exposure variable was not included as a covariate in that model.

[b] included model 1 covariates plus additional covariates plus LPIR score.

[c]included model 1 covariates plus additional covariates plus LDL particle concentration and LDL particle average size.

[d] included model 1 covariates plus additional covariates plus the other LDL subclasses (large, medium, or small LDL particles).

The following were log transformed: CRP, homocysteine, large HDL particles, lipoprotein (a), LPIR score, medium TRL particles, small TRL particles, total/HDL cholesterol ratio, triglycerides, trig/HDL cholesterol ratio, and TRL triglycerides.

BMI (kg/m^2) categories: 25.0 - <30 (overweight); ≥30.0 (obese).

Physical inactivity: <7.5 MET-hours per week.

See eTable 1 for SDs.

Abbreviations: BCAAs, branched chain amino acids; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GlycA, glycan biomarker of N-acetyl side chains of acute-phase proteins; HDL, high-density lipoprotein; ICAM-1, Intercellular adhesion molecule 1; LDL, low-density lipoprotein; LPIR, lipoprotein insulin resistance; MI, myocardial infarction; TRL, triglyceride-rich lipoprotein.

eTable 4: Population-attributable risk analysis by age of CHD onset

Biomarker	Incident CHD at age <55	Incident CHD at 55≤ age <65	Incident CHD at 65≤ age <75	Incident CHD at age ≥75
Overweight				
Prevalence	29.3%	29.9%	31.1%	32.5%
PAR	24.9%	18.9%	19.5%	3.7%
Obese				
Prevalence	18.5%	18.1%	17.2%	15.7%
PAR	38.1%	24.2%	16.4%	4.8%
Current smoker				
Prevalence	12.4%	11.9%	10.5%	8.7%
PAR	26.6%	18.9%	8.5%	7.1%
Diabetes				
Prevalence	2.1%	2.2%	2.5%	2.8%
PAR	17.1%	18.1%	8.0%	6.5%
Metabolic syndrome				
Prevalence	22.3%	23.0%	24.3%	26.5%
PAR	53.1%	44.2%	30.6%	17.3%
Hypertension				
Prevalence	19.1%	21.2%	26.0%	33.6%
PAR	40.6%	22.7%	21.6%	17.7%
Parental MI <60 years				
Prevalence	15.8%	15.2%	13.8%	11.9%
PAR	15.9%	14.0%	7.6%	2.1%
Physical inactivity				
Prevalence	45.4%	45.1%	44.2%	42.0%
PAR	19.4%	21.0%	16.0%	8.1%

Population attributable risk was calculated using HRs (95% CI) from stratified Cox models (stratified on age groups and blood draw time categories). adjusted for model 1 covariates (baseline race, education categories, menopause, postmenopausal hormone use, randomized treatment assignment, and interactions between the risk factor of interest and age groups).

BMI (kg/m^2) categories: 25.0 - <30 (overweight); ≥30.0 (obese).

Physical inactivity: <7.5 MET-hrs per week.

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; PAR, population-attributable risk.

eTable 5: Baseline biomarker levels for CHD cases (by age of onset) and noncases

	Incident CHD at age <55 years N=63	Incident CHD at 55≤ age <65 N=384	Incident CHD at 65≤ age <75 N=654	Incident CHD at age ≥75 N=447	Noncases N=26476
Lipid/lipoprotein biomarkers					
Total cholesterol, mg/dL	220.0 (192.0 – 251.0)	224.0 (199.0 – 252.0)	223.0 (196.0 – 250.0)	222.0 (198.0 – 250.0)	208.0 (183.0 – 235.0)
LDL cholesterol, mg/dL	133.6 (108.0 – 150.4)	133.3 (111.5 – 158.1)	132.4 (110.0 – 156.6)	132.1 (110.0 – 157.6)	120.9 (100.0 – 143.6)
HDL cholesterol, mg/dL	41.0 (34.8 – 50.1)	43.3 (35.7 – 52.5)	45.9 (37.9 – 56.1)	48.2 (39.7 – 60.0)	52.2 (43.5 – 62.6)
Total/HDL cholesterol ratio	5.3 (4.4 – 6.6)	5.2 (4.0 – 6.5)	4.7 (3.9 – 5.9)	4.4 (3.7 – 5.6)	3.9 (3.2 – 4.9)
Triglycerides, mg/dL	177.0 (125.0 – 299.0)	163.0 (113.0 – 258.0)	162.0 (111.0 – 238.0)	147.0 (104.0 – 207.0)	117.0 (83.0 – 173.0)
Trig/HDL cholesterol ratio	4.4 (2.6 – 8.4)	3.8 (2.2 – 6.5)	3.4 (2.2 – 5.8)	2.9 (1.8 – 5.0)	2.2 (1.4 – 3.7)
Non-HDL cholesterol, mg/dL	174.3 (156.1 – 204.9)	178.0 (148.9 – 207.9)	176.0 (147.5 – 200.8)	172.4 (144.4 – 197.2)	153.4 (128.4 – 180.8)
Apolipoprotein B, mg/dL	1.2 (1.0 – 1.4)	1.20 (1.0 – 1.4)	1.2 (1.0 – 1.4)	1.2 (1.0 – 1.4)	1.0 (0.8 – 1.2)
Apolipoprotein A-I, mg/dL	137.7 (121.7 – 155.7)	135.3 (121.1 – 154.9)	143.7 (128.5 – 163.3)	148.9 (131.2 – 170.0)	149.2 (132.7 – 168.1)
Lipoprotein (a), mg/dL	18.1 (4.5 – 67.8)	14.7 (5.2 – 52.4)	12.5 (4.7 – 51.6)	12.2 (5.1 – 48.3)	10.5 (4.4 – 31.6)
Total LDL particles, nmol/L	1851.9 (1559.2 – 2241.9)	1774.6 (1540.9 – 2091.5)	1760.2 (1470.0 – 2071.2)	1767.9 (1528.8 – 2022.3)	1557.6 (1321.8 – 1824.0)
Large LDL particles	189.5 (2.5 – 343.4)	192.5 (64.3 – 409.4)	256.9 (84.8 – 433.6)	294.2 (122.5 – 491.3)	308.5 (163.7 – 468.4)
Medium LDL particles	0.0 (0.0 – 245.4)	80.4 (0.0 – 268.4)	73.0 (0.0 – 287.1)	83.9 (0.0 – 289.0)	160.4 (0.4 – 350.0)
Small LDL particles	1592.0 (1050.1 – 1830.9)	1367.2 (898.7 – 1788.2)	1260.9 (851.1 – 1742.5)	1221.6 (846.5 – 1689.2)	940.2 (680.3 – 1313.4)
LDL particle average size, nm	20.6 (20.2 – 21.0)	20.7 (20.3 – 21.1)	20.8 (20.4 – 21.1)	20.9 (20.5 – 21.2)	20.9 (20.6 – 21.2)
Total TRL particles, nmol/L	189.5 (159.8 – 241.3)	189.9 (156.9 – 234.7)	190.7 (152.1 – 235.7)	193.1 (154.4 – 234.8)	165.2 (129.4 – 206.8)
Very large TRL particles	0.2 (0.1– 0.6)	0.2 (0.1 – 0.4)	0.2 (0.1 – 0.4)	0.1 (0.1 – 0.3)	0.1 (0.1 – 0.2)
Large TRL particles	3.8 (1.4 – 7.6)	3.2 (0.9 – 6.1)	3.0 (0.9 – 6.1)	2.7 (0.6 – 5.2)	1.5 (0.3 – 4.2)
Medium TRL particles	22.9 (14.1 – 36.1)	20.6 (13.2 – 33.0)	20.1 (12.4 – 31.3)	19.5 (10.7 – 29.0)	15.6 (8.4 – 25.2)
Small TRL particles	54.7 (34.1 – 92.0)	59.0 (33.6 – 83.9)	58.9 (36.3 – 87.2)	59.9 (39.7 – 88.8)	55.2 (33.8 – 81.6)
Very small TRL particles	100.8 (81.8 – 141.1)	98.8 (75.5 – 134.5)	98.4 (70.7 – 132.2)	99.8 (71.9 – 134.2)	83.6 (58.2 – 113.8)
TRL cholesterol, mg/dL	34.9 (27.9 – 43.3)	33.1 (26.9 – 41.0)	33.5 (26.3 – 41.1)	32.9 (26.7 – 40.6)	28.6 (22.0 – 36.1)
TRL triglycerides, mg/dL	123.0 (75.0 – 154.4)	99.4 (72.7 – 146.4)	103.2 (73.6 – 145.6)	97.3 (68.7 – 137.7)	81.2 (55.3 – 116.6)
TRL particle average size, nm	47.2 (40.7 – 55.2)	45.1 (39.7 – 51.7)	44.6 (40.4 – 51.4)	43.5 (39.6 – 49.0)	42.4 (38.5 – 47.8)
Total HDL particles, µmol/L	23.4 (21.3 – 26.3)	23.3 (20.9 – 26.3)	24.3 (22.0 – 26.8)	24.6 (22.2 – 27.2)	24.4 (22.0 – 27.0)
Large HDL particles	1.4 (0.8 – 1.9)	1.5 (1.0 – 2.3)	1.6 (1.0 – 2.5)	2.0 (1.3 – 3.1)	2.1 (1.3 – 3.3)
Medium HDL particles	4.4 (2.8 – 6.0)	4.1 (2.4 – 6.2)	4.5 (2.8 – 6.7)	4.7 (2.9 – 6.6)	5.4 (3.7 – 7.3)
Small HDL particles	17.5 (16.2 – 19.1)	17.1 (15.3 – 19.5)	17.5 (15.2 – 19.8)	17.2 (14.8 – 19.5)	16.3 (14.1 – 18.6)
HDL particle average size, nm	8.7 (8.5 – 8.9)	8.7 (8.5 – 8.9)	8.8 (8.6 – 9.0)	8.8 (8.6 – 9.1)	8.9 (8.7 – 9.2)
Inflammatory biomarkers					
CRP, mg/L	3.1 (1.7 – 5.8)	3.5 (1.5 – 7.4)	3.5 (1.6 – 6.5)	2.9 (1.2 – 5.3)	2.0 (0.8 – 4.3)
Fibrinogen, mg/dL	375.6 (322.7 – 428.8)	387.4 (330.3 – 453.7)	376.8 (323.4 – 432.4)	381.4 (331.9 – 433.1)	349.5 (306.7 – 400.8)

ICAM-1, ng/mL	383.7 (315.5 – 466.4)	377.8 (328.1 – 450.3)	371.6 (323.3 – 429.8)	366.1 (330.3 – 420.9)	341.3 (300.0 – 392.48)
GlycA, µmol/L	423.0 (387.0 – 485.0)	418.0 (363.5 – 467.5)	410.0 (369.0 – 462.0)	396.0 (360.0 – 440.0)	381.0 (338.0 – 428.0)
Metabolic biomarkers					
Hemoglobin A1c, %	5.1 (4.9 – 5.4)	5.1 (4.9 – 5.6)	5.1 (4.9 – 5.3)	5.1 (4.9 – 5.3)	5.0 (4.8 – 5.2)
LPIR score (0–100)	65 (43 – 79)	58 (35 – 74)	55 (35 – 72)	49 (28 – 68)	39 (20 – 60)
Homocysteine, µmol/L	10.3 (9.3 – 12.7)	11.2 (8.9 – 14.1)	11.0 (9.0 – 13.5)	11.2 (9.2 – 14.0)	10.4 (8.7 – 12.8)
Citrate, µmol/L	91.1 (72.1 – 105.9)	95.1 (81.1 – 110.6)	96.6 (79.6 – 113.3)	98.5 (82.0 – 115.2)	93.7 (78.3 – 110.5)
Total BCAAs, µmol/L	442.3 (370.9 – 529.7)	430.6 (375.6 – 509.4)	426.5 (368.0 – 490.6)	413.0 (352.6 – 478.9)	399.9 (349.3 – 459.2)
Valine, µmol/L	246.2 (203.9 – 283.8)	235.1 (205.6 – 270.9)	230.0 (204.3 – 264.0)	225.5 (193.8 – 259.8)	219.4 (192.5 – 249.8)
Leucine, µmol/L	132.8 (118.4 – 176.2)	140.5 (115.6 – 175.7)	136.2 (115.3 – 165.5)	134.5 (110.2 – 158.4)	131.2 (110.0 – 154.4)
Isoleucine, µmol/L	61.8 (44.2 – 76.6)	58.4 (42.2 – 77.0)	55.5 (43.0 – 70.1)	51.6 (42.0 – 68.4)	50.2 (38.6 – 63.7)
Alanine, µmol/L	414.2 (337.5 – 477.6)	420.4 (359.1 – 505.9)	420.8 (357.3 – 499.0)	407.5 (335.6 – 476.0)	402.1 (334.1 – 477.3)
eGFR, mL/min per 1.73m^2	101.3 (89.4 – 131.6)	92.8 (81.0 – 105.2)	89.3 (76.6 – 104.1)	87.2 (73.5 – 103.5)	91.9 (79.7 – 105.5)
Creatinine, mg/dL	0.7 (0.5 – 0.7)	0.7 (0.6 – 0.8)	0.7 (0.6 – 0.8)	0.7 (0.6 – 0.8)	0.7 (0.6 – 0.8)

Data presented as median (interquartile range).

Non-cases were defined as participants free of CHD during follow-up.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; CRP to nanomoles per liter, multiply by 9.524; and creatinine to micromoles per liter, multiply by 88.42.

See eMethods 1 for biomarker measurement.

Abbreviations: BCAA, branched chain amino acids; CHD, coronary heart disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GlycA, glycan biomarker of N-acetyl side chains of acute-phase proteins; HDL, high-density lipoprotein; ICAM-1, Intercellular adhesion molecule 1; LDL, low-density lipoprotein; LPIR, lipoprotein insulin resistance; TRL, triglyceride-rich lipoprotein.

eTable 6: Characteristics of participants in each age group

	Age <55	55≤ Age <65	65≤ Age <75	Age ≥75
Age at time of entry into age group, years	50.0 ± 2.6	56.4 ± 2.6	65.4 ± 1.4	75.1 ± 0.6
Baseline characteristics				
Age, years	50.0 ± 2.6	53.0 ± 5.2	55.0 ± 6.9	60.9 ± 6.0
Self-reported race/ethnicity				
White	15769 (95.0)	23457 (95.1)	23892 (95.5)	10797 (96.1)
Black	316 (1.9)	479 (1.9)	438 (1.8)	179 (1.6)
Hispanic	182 (1.1)	270 (1.1)	253 (1.0)	104 (0.9)
Asian	260 (1.6)	360 (1.5)	325 (1.3)	120 (1.1)
Other	81 (0.5)	111 (0.5)	100 (0.4)	36 (0.3)
Education				
<4 years education	8579 (52.2)	13356 (54.6)	13609 (54.9)	6612 (59.1)
Bachelor's degree	4222 (25.7)	5971 (24.4)	5945 (24.0)	2437 (21.8)
Master's degree or Doctorate	3630 (22.1)	5117 (20.9)	5227 (21.1)	2137 (19.1)
Body mass index, kg/m^2	26.0 ± 5.2	26.0 ± 5.0	25.9 ± 4.9	25.8 ± 4.6
Current smoker	2081 (12.4)	2948 (11.9)	2667 (10.6)	1015 (9.0)
Diabetes	355 (2.1)	622 (2.5)	602 (2.4)	302 (2.7)
Metabolic syndrome	3722 (22.3)	5931 (23.9)	5963 (23.7)	2924 (25.8)
Hypertension	3343 (20.0)	5965 (24.0)	6543 (25.9)	3782 (33.3)
Hypertension treatment	1600 (9.6)	2992 (12.0)	3320 (13.2)	1984 (17.5)
Systolic blood pressure, mm Hg	115 (115 – 125)	125 (115 – 135)	125 (115 – 135)	125 (115 – 135)
Physical inactivity	7593 (45.4)	11232 (45.1)	11147 (44.2)	4816 (42.5)
Parental MI<60 years	2615 (15.8)	3638 (14.9)	3480 (14.0)	1373 (12.3)
Postmenopausal	5389 (32.3)	12171 (49.0)	14062 (55.9)	9420 (83.1)
Postmenopausal HRT use	3935 (23.5)	7652 (30.8)	8064 (32.0)	4747 (41.9)
Cholesterol lowering treatment	295 (1.8)	671 (2.7)	800 (3.2)	537 (4.7)

Data presented as frequency (percentage) for categorical variables, mean ± standard deviation (for age, body mass index), and median (systolic blood pressure).

Baseline characteristics were determined at time of enrollment in WHS.

Percentages may not total 100 due to rounding. Participants could contribute to more than one age group as they passed through time until the occurrence of incident CHD or censoring (death or last follow-up).

Physical inactivity: <7.5 MET-hrs per week.

Abbreviations: HRT, hormone replacement therapy; MI, myocardial infarction.

eTable 7: Types of incident CHD events by age of onset

Age group	Outcome				
	Myocardial infarction	Percutaneous coronary intervention	Coronary artery bypass grafting	Coronary heart disease death	Total
age <55	27	20	16	0	63
55≤ age <65	135	159	76	14	384
65≤ age <75	245	266	118	25	654
age ≥75	143	122	73	109	447

Outcomes may overlap within categories.
Abbreviation: CHD, coronary heart disease.

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