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Association of Lipid, Inflammatory, and Metabolic Biomarkers With Age at Onset for Incident Coronary Heart Disease in Women

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IMPORTANCE Risk profiles for premature coronary heart disease (CHD) are unclear.

OBJECTIVE To examine baseline risk profiles for incident CHD in women by age at onset.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort of US female health professionals participating in the Women's Health Study was conducted; median follow-up was 21.4 years. Participants included 28 024 women aged 45 years or older without known cardiovascular disease. Baseline profiles were obtained from April 30, 1993, to January 24, 1996, and analyses were conducted from October 1, 2017, to October 1, 2020.

EXPOSURES More than 50 clinical, lipid, inflammatory, and metabolic risk factors and biomarkers.

MAIN OUTCOMES AND MEASURES Four age groups were examined (<55, 55 to <65, 65 to <75, and ≥75 years) for CHD onset, and adjusted hazard ratios (aHRs) were calculated using stratified Cox proportional hazard regression models with age as the time scale and adjusting for clinical factors. Women contributed to different age groups over time.

RESULTS Of the clinical factors in the women, diabetes had the highest aHR for CHD onset at any age, ranging from 10.71 (95% CI, 5.57-20.60) at CHD onset in those younger than 55 years to 3.47 (95% CI, 2.47-4.87) at CHD onset in those 75 years or older. Risks that were also noted for CHD onset in participants younger than 55 years included metabolic syndrome (aHR, 6.09; 95% CI, 3.60-10.29), hypertension (aHR, 4.58; 95% CI, 2.76-7.60), obesity (aHR, 4.33; 95% CI, 2.31-8.11), and smoking (aHR, 3.92; 95% CI, 2.32-6.63). Myocardial infarction in a parent before age 60 years was associated with 1.5- to 2-fold risk of CHD in participants up to age 75 years. From approximately 50 biomarkers, lipoprotein insulin resistance had the highest standardized aHR: 6.40 (95% CI, 3.14-13.06) for CHD onset in women younger than 55 years, attenuating with age. In comparison, weaker but significant associations with CHD in women younger than 55 years were noted (per SD increment) for low-density lipoprotein cholesterol (aHR, 1.38; 95% CI, 1.10-1.74), non–high-density lipoprotein cholesterol (aHR, 1.67; 95% CI, 1.36-2.04), apolipoprotein B (aHR, 1.89; 95% CI, 1.52-2.35), triglycerides (aHR, 2.14; 95% CI, 1.72-2.67), and inflammatory biomarkers (1.2- to 1.8-fold)—all attenuating with age. Some biomarkers had similar CHD age associations (eg, physical inactivity, lipoprotein[a], total high-density lipoprotein particles), while a few had no association with CHD onset at any age. Most risk factors and biomarkers had associations that attenuated with increasing age at onset.

CONCLUSIONS AND RELEVANCE In this cohort study, diabetes and insulin resistance, in addition to hypertension, obesity, and smoking, appeared to be the strongest risk factors for premature onset of CHD. Most risk factors had attenuated relative rates at older ages.

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Supplemental content

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Cardiovascular disease, which includes coronary heart disease (CHD), is a key factor in premature mortality.[1] Premature CHD generally refers to CHD occurring before age 65 years in women or before age 55 years in men,[2-4] to distinguish it from conventional CHD, which occurs at older ages. Therefore, identifying individuals at risk of premature CHD is essential to reducing the burden of premature morbidity and mortality.

Despite advances in CHD prevention and management, outcomes among younger adults have been suboptimal. Although CHD mortality of US adults younger than 55 years declined by 5.5% in men and 4.6% in women from 1979 to 1989, over the subsequent 20 years, mortality for women was virtually unchanged.[5] Analyses from 2010 to 2015 of 3098 counties in the US showed that CHD mortality declined in all age groups except for ages 55 to 64 years.[6] In western Australia, from 1996 to 2007, the annual incidence of myocardial infarction (MI) among women aged 35 to 54 years increased by 2.3%.[7] Between 2000 and 2009 in British Columbia, Canada, women aged 20 to 55 years had a 1.7% annual increase in the rates of acute MI, which was not observed among men.[8] Similarly, in the UK, younger adults showed minimal or no improvement in CHD mortality over a 20-year period from 1985 to 2005.[9] The reasons for suboptimal outcomes are multifactorial and may include temporal trends in age- or sex-based differences in risk factors, clinical presentation, acute management, or use of preventive therapies.[10-15]

There is also scarce information on determinants of premature CHD, particularly in women. Most biomarker studies of premature CHD have been cross-sectional and reported differences in the levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides for premature vs conventional CHD, as well as differences by sex for premature CHD.[11,12,16-18] Emerging evidence suggests that CHD risk may also be associated with novel biomarkers related to lipoprotein subfractions, inflammation, and metabolic pathways, and not merely with levels of standard risk factors.[19-27] However, characterization of biomarker profiles that identify premature CHD has been inadequate.[20-24] To our knowledge, there have been no large prospective studies on the association of an extensive panel of novel and traditional biomarkers according to age at the time of incident CHD, and none specifically in women.

To address these knowledge gaps, we investigated the relative risk of more than 50 clinical risk factors and lipid, lipoprotein, inflammatory, and metabolic biomarkers with incident CHD among 28 024 apparently healthy women in the Women's Health Study during a median follow-up of 21.4 years.

Key Points

Question Do risk profiles for coronary heart disease differ by age at onset?

Findings In this cohort study including 28 024 women, associations of most risk factors with coronary heart disease attenuated with increasing age at onset. Of more than 50 clinical and biomarker risk factors examined, diabetes and lipoprotein insulin resistance had the highest relative risk, particularly for premature coronary heart disease; some risk factors (eg, inactivity, lipoprotein[a]) had similar associations by age at onset, and others had no association with coronary heart disease onset at any age.

Meaning Risk profiles appear to differ by age at coronary heart disease onset in women, with the greatest risk for premature events associated with diabetes and insulin resistance.

Methods

Study Design and Population

The study population has been previously described.[22,28-30] Briefly, from April 1993 to January 1996, the Women's Health Study randomized 39 876 women aged 45 years or older without cardiovascular disease or cancer to receive aspirin, vitamin E, β-carotene, or matching placebo to assess cardiovascular and cancer outcomes.[31] Participants provided written informed consent and reported on baseline demographic, risk factor, medication, and lifestyle information. The randomized intervention ended in 2004 with no significant reduction in the primary end points of the trial, and since then, participants have been followed up on an observational basis. This study includes women followed up for incident CHD through 2016 for a median of 21.4 years.

We divided study time into 4 age groups (<55, 55 to <65, 65 to <75, and ≥75 years) (**Table 1**) and women contributed to advancing age groups as they aged until the occurrence of incident CHD or censoring (death or last follow-up). The present study was approved by the institutional review board of Brigham and Women's Hospital, Boston, Massachusetts. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Incident CHD Ascertainment

Incident CHD was a composite of first MI, percutaneous coronary intervention, coronary artery bypass grafting, or CHD death. Coronary heart disease events were confirmed using medical records by a blinded end points committee of physicians, as previously described.[28]

Risk Factor Assessment

Baseline risk factors were determined.[22,25] Participants self-reported race/ethnicity, educational level, physical activity, smoking, alcohol intake, MI occurring in a parent before age 60 years, height, weight, blood pressure, menopausal status, and use of hormone therapy, antihypertensive medication, and medication for elevated cholesterol levels. Medical conditions, including diabetes and hypertension (based on diagnosis of hypertension, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication), were based on physician diagnoses reported by the participants. Body mass index (BMI) categories were overweight (BMI 25.0 to <30.0 [calculated as weight in kilograms divided by height in meters squared]) and obese (BM I≥30.0). Physical inactivity was defined as less than 7.5 metabolic equivalent task hours per week. Metabolic syndrome was defined as previously described.[32]

Table 1. Baseline Characteristics of Participants With and Without CHD[a]

Clinical risk factors[b]	No. (%)[c] Incident CHD At age <55 y (n = 63)	At 55 to <65 y (n = 384)	At 65 to <75 y (n = 654)	At age ≥75 y (n = 447)	Noncases (n = 26 476)[d]
Age, mean (SD), y	48.6 (2.2)	52.5 (4.3)	57.5 (6.3)	66.2 (6.0)	54.5 (7.0)
Self-reported race/ethnicity					
White	61 (98.4)	366 (96.6)	618 (95.8)	434 (97.8)	24996 (95.2)
Black	1 (1.6)	4 (1.1)	16 (2.5)	5 (1.1)	494 (1.9)
Hispanic	0	2 (0.5)	6 (0.9)	2 (0.5)	280 (1.1)
Asian	0	5 (1.3)	4 (0.6)	1 (0.2)	372 (1.4)
Other	0	2 (0.5)	1 (0.2)	1 (0.2)	115 (0.4)
Educational level					
<4 y Post high school	43 (69.4)	245 (64.5)	397 (62.5)	313 (71.0)	14383 (55.3)
Bachelor's degree	15 (24.2)	78 (20.5)	130 (20.5)	65 (14.7)	6207 (23.9)
Master's degree or doctorate	4 (6.5)	57 (15.0)	108 (17.0)	63 (14.3)	5427 (20.9)
BMI, mean (SD)	28.9 (5.6)	28.3 (5.8)	27.5 (5.1)	26.1 (4.9)	25.9 (4.9)
Current smoker	24 (38.1)	112 (29.2)	118 (18.1)	57 (12.8)	2955 (11.2)
Diabetes	11 (17.5)	76 (19.8)	69 (10.6)	39 (8.7)	575 (2.2)
Metabolic syndrome	39 (61.9)	221 (57.6)	312 (48.1)	179 (40.2)	6161 (23.3)
Hypertension	31 (49.2)	157 (40.9)	291 (44.5)	222 (49.7)	6665 (25.2)
Hypertension treatment	18 (28.6)	94 (24.5)	164 (25.1)	120 (26.9)	3358 (12.7)
Systolic blood pressure, median (IQR), mm Hg	135 (125-145)	125 (115-135)	135 (120-135)	135 (125-145)	125 (115-135)
Physical inactivity[e]	36 (57.1)	220 (57.3)	347 (53.1)	208 (46.5)	11 747 (44.4)
Parental myocardial infarction at age <60 y	19 (30.2)	99 (26.3)	123 (19.3)	53 (12.1)	3673 (14.1)
Postmenopausal	24 (38.7)	163 (42.5)	458 (70.3)	419 (94.0)	14 143 (53.5)
Postmenopausal hormone replacement therapy	17 (17.0)	83 (21.6)	236 (36.1)	159 (35.6)	8199 (31.0)
Cholesterol-lowering treatment	7 (11.1)	31 (8.1)	51 (7.8)	29 (6.5)	780 (3.0)

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; IQR, interquartile range.

[a] Baseline biomarkers are presented in eTable 5 in the Supplement.

[b] Risk factor data were missing for up to 2% of participants.

[c] Percentages may not total 100 owing to rounding.

[d] Noncases did not develop CHD during follow-up.

[e] Physical inactivity: less than 7.5 metabolic equivalent task hours per week.

Biomarker Measurements

At baseline, 28 345 participants provided a blood sample that was processed and stored at −170 °C until biomarker measurements. We excluded participants (n = 321) without biomarker measurements, yielding a cohort size of 28 024 participants. We measured levels of approximately 50 biomarkers: apolipoproteins, lipids, triglycerides, lipoprotein (HDL, LDL, triglyceride-rich lipoprotein [TRL] subfractions,[22,32] and lipoprotein[a]),[33] inflammatory markers (fibrinogen,[34] glycan biomarker of N-acetyl side chains of acute-phase proteins [GlycA],[26,35-38] and C-reactive protein),[34] intercellular adhesion molecule 1[34], and metabolic markers (creatinine, hemoglobin A_{1c}, homocysteine,[34] and branched-chain amino acids,[25] including leucine, isoleucine, and valine) (eMethods 1 in the Supplement). The lipoprotein insulin resistance (LPIR) score is derived as a weighted combination of 6 lipoprotein measures related to the concentration and size of HDL, LDL, and TRL particles (eMethods 1 in the Supplement).[32]

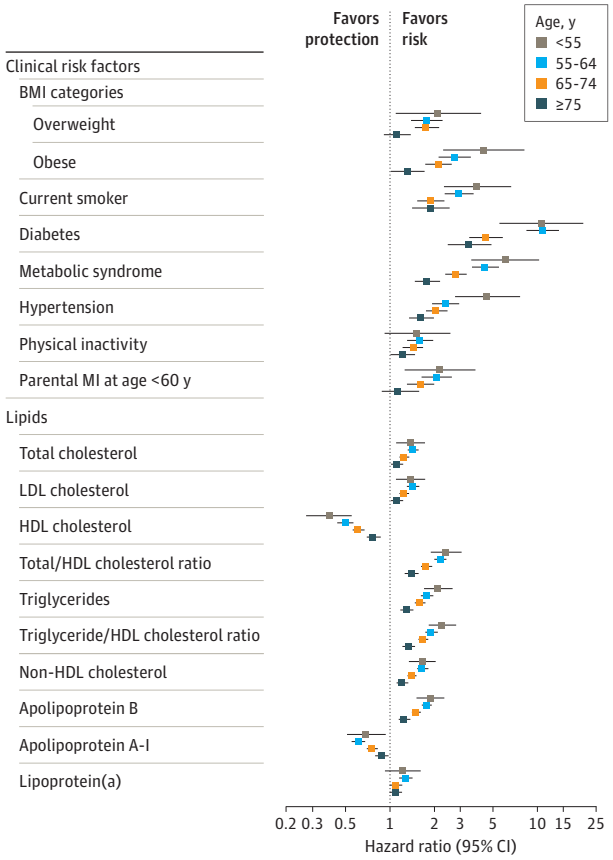
Blood Draw Time Categories

To evaluate whether the associations of clinical factors and biomarkers with incident CHD were modified by the time after the blood draw, we considered 2 blood draw time categories (≤10 and >10 years), denoting the time after blood samples were obtained at enrollment.

Statistical Analysis

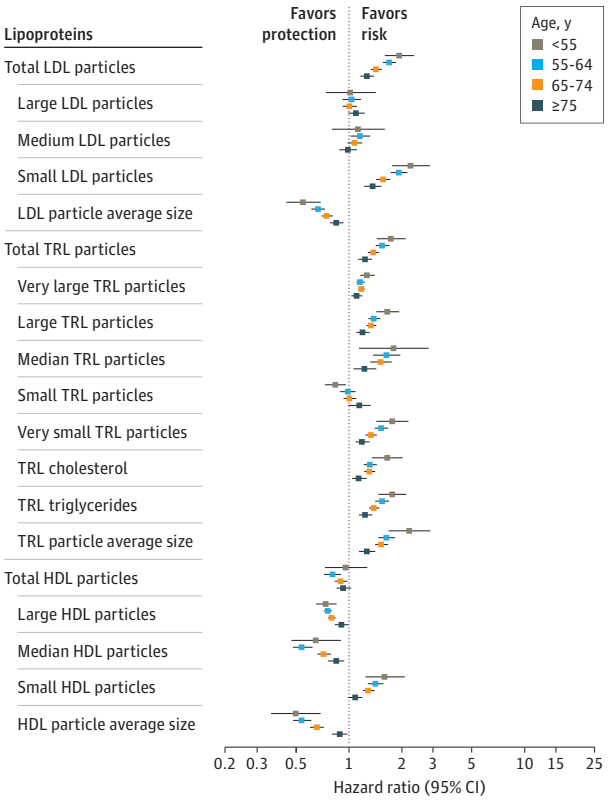
We divided the study time into 4 age groups (<55, 55 to <65, 65 to <75, and ≥75 years) and women contributed to advancing age groups over time until the occurrence of incident CHD or censoring (death or last follow-up), and calculated CHD incidence rates. Participants could contribute exposure time to more than 1 age group as they aged, as previously described.[39] We used stratified Cox proportional hazards regression models with the counting process method, stratified by the 4 age groups and blood draw time categories. We estimated adjusted hazard ratios (aHRs) with 95% CIs for incident CHD per SD increment of each biomarker and for clinical categories for risk factors with clinical cutoff points. Standard deviations were derived from the entire cohort (eTable 1 in the Supplement), and the following variables were log transformed: C-reactive protein, homocysteine, large HDL particles, lipoprotein(a), LPIR score, medium TRL particles, small TRL particles, total/HDL cholesterol ratio, triglyceride levels, triglyceride/HDL choles-

Figure 1. Associations of Clinical Risk Factors and Lipid Biomarkers per SD Increment With Incident Coronary Heart Disease (CHD) by Age at CHD Onset



Hazard ratios (95% CI) were obtained from stratified Cox proportional hazards regression models (stratified by age groups and blood draw time categories) adjusted for model 1 covariates (baseline race/ethnicity, educational level categories, menopause, postmenopausal hormone use, randomized treatment assignment, and interactions between the risk factor of interest and age groups). Hazard ratios were based on the presence vs absence of risk factors. Hazard ratios and 95% CIs are provided in Table 2, and SDs are provided in eTable 1 in the Supplement. BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and MI, myocardial infarction.

Figure 2. Associations of Lipoprotein Particles per SD Increment With Incident Coronary Heart Disease (CHD) by Age at CHD Onset for Low-Density Lipoprotein (LDL) Particles, Triglyceride-Rich Lipoprotein (TRL) Particles, and High-Density Lipoprotein (HDL) Particles



Hazard ratios (95% CI) were obtained from stratified Cox proportional hazards regression models (stratified by age groups and blood draw time categories) adjusted for model 1 covariates (baseline race/ethnicity, educational level categories, menopause, postmenopausal hormone use, randomized treatment assignment, and interactions between the risk factor of interest and age groups). To further adjust for confounding among LDL subclasses, their models included model 1 covariates plus the other LDL subclasses (large, medium, or small LDL particles). To adjust for confounding between total LDL particles and LDL particle average size, their models included model 1 covariates plus the other LDL biomarkers (total LDL particles or LDL particle average size).

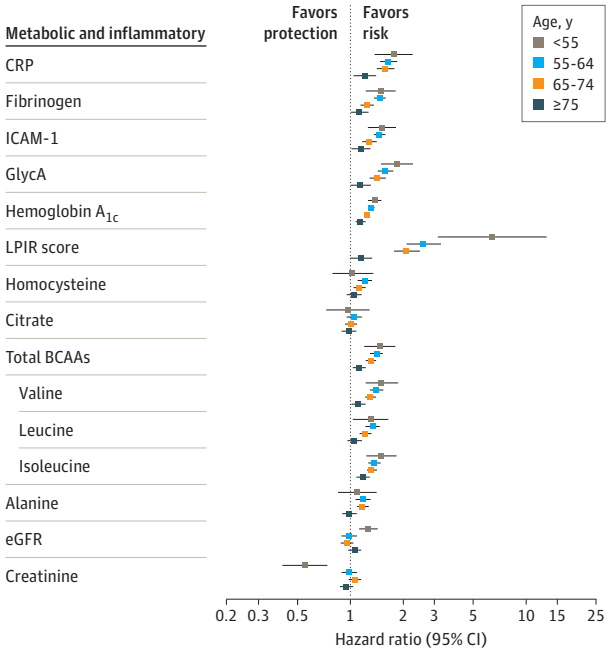
terol ratio, and TRL triglyceride levels. Model 1 included baseline race/ethnicity, educational level categories (3 categories: 1-4 years post high school, bachelor's degree, master's degree, or doctorate), menopause, postmenopausal hormone use, randomized treatment assignments, and 7 strata based on 4 age groups (<55, 55 to <65, 65 to <75, and ≥75 years) and blood draw time categories (≤10 years and >10 years) (**Figure 1**, **Figure 2**, and **Figure 3**, eTable 2 in the Supplement). The stratum based on age less than 55 years and blood draw time greater than 10 years had no CHD events and was dropped (eMethods 2 in the Supplement). In additional analyses, we examined the associations between risk factors and incident CHD in models that included the model 1 covariates plus the following additional covariates (physical activity [<7.5 and ≥7.5 metabolic equivalent task hours per week], current smoking, BMI, systolic blood pressure, diabetes, MI in a parent before age 60 years, and baseline treatment for hypertension or for high cholesterol levels) (eTable 3 in the Supplement). The population-attributable risk for clinical risk factors was calculated as previously described (eTable 4 in the Supplement).[40]

Likelihood ratio tests evaluated interactions between individual risk factors and age groups (3 *df*) (**Table 2**; eTable 3 in the Supplement) and between risk factors and blood draw time categories (3 *df*) (eTable 2 in the Supplement). Statistical significance for all analyses was established at 2-tailed $P < .01$. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Of the 28 024 participants included in the analysis, 26 476 participants (94.5%) did not develop CHD and incident CHD

Figure 3. Associations of Inflammatory and Metabolic Biomarkers per SD Increment With Incident Coronary Heart Disease (CHD) by Age at CHD Onset



Hazard ratios (95% CI) were obtained from stratified Cox proportional hazards regression models (stratified by age groups and blood draw time categories) adjusted for model 1 covariates (baseline race/ethnicity, educational level categories, menopause, postmenopausal hormone use, randomized treatment assignment, and interactions between the risk factor of interest and age groups). Hazard ratios were based on the presence vs absence of risk factors. BCAAs indicates branched chain amino acids; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GlycA, glycan biomarker of N-acetyl side chains of several acute-phase proteins; ICAM-1, intercellular adhesion molecule 1; and LPIR, lipoprotein insulin resistance.

occurred in 1548 participants (5.5%) during the study period. Most baseline characteristics differed between CHD cases and noncases (Table 1; eTable 5 in the Supplement) and in age groups (eTable 6 in the Supplement). The prevalence of most clinical risk factors (eg, diabetes, metabolic syndrome, and hypertension) and levels of biomarkers (eg, total cholesterol, C-reactive protein, and LPIR score) were higher in cases than noncases, particularly for cases in women younger than 55 years. During median follow-up of 21.4 years, CHD incidence rates per 100 person-years ranged from 0.07 (95% CI, 0.06-0.09) for CHD onset at less than 55 years to 0.62 (95% CI, 0.57-0.68) for CHD onset at 75 years or older (eTable 7 in the Supplement).

Clinical Risk Factors

Diabetes had the highest relative risk for incident CHD onset at any age; for CHD onset in women younger than 55 years, the model 1 aHR was 10.71 (95% CI, 5.57-20.60) and attenuated with age, with a risk of 3.47 (95% CI, 2.47-4.87) at onset in those 75 years or older (Figure 1 and Table 2). Increased risks were also noted for CHD onset in women younger than 55 years for metabolic syndrome (aHR, 6.09; 95% CI, 3.60-10.29), hypertension (aHR, 4.58; 95% CI, 2.76-7.60), obesity (aHR, 4.33; 95% CI, 2.31-8.11), and smoking (aHR, 3.92; 95% CI, 2.32-6.63), which also attenuated with age. Myocardial infarction in a parent before age 60 years was associated with a 1.5- to 2-fold increased risk of CHD in participants up to age 75 years.

Lipids and Lipoproteins

Significant associations with CHD onset in women younger than 55 years were noted (per SD increment, model 1) for total cholesterol (aHR, 1.39; 95% CI, 1.12-1.73), LDL cholesterol (aHR, 1.38; 95% CI, 1.10-1.74), non-HDL cholesterol (aHR, 1.67; 95% CI, 1.36-2.04), apolipoprotein B (aHR, 1.89; 95% CI, 1.52-2.35), and triglyceride (aHR, 2.14; 95% CI, 1.72-2.67) levels (Figure 1 and Table 2) and attenuated with age. These biomarkers showed associations with incident CHD in all age groups.

A few of the lipid and lipoprotein biomarkers did not significantly attenuate in their CHD associations with increasing age at onset, including lipoprotein(a), several LDL and TRL subfractions, and total HDL particles (Figure 2 and Table 2). The LDL particle subfractions showed variable associations with CHD by age at onset (Figure 2 and Table 2). For CHD onset in women younger than 55 years, the strongest risk associations for LDL measures were seen for small LDL particles, total LDL particles, and smaller average LDL size (by approximately 2-fold per SD increment), which were all numerically greater than the association of LDL cholesterol with CHD onset at younger than 55 years. Further adjustment of total LDL particles with LDL particle average size and the converse did not materially alter the strength of their associations with CHD, indicating that both LDL particle number and particle size were associated with risk.

Similar to triglyceride levels, associations for TRL particle size, total TRL particles, and TRL triglyceride levels were associated with incident CHD in all age groups, with stronger associations in younger age groups (Figure 2 and Table 2). Variable associations were seen for TRL subfractions. Stronger associations with CHD at younger vs older (≥75 years) ages were seen for TRL size, large, medium, and very small TRL particles, but not for other sized TRL particles. Triglyceride-rich lipoprotein cholesterol was associated with an increased risk of CHD, but to a lesser magnitude than TRL particles or TRL triglyceride levels.

No significant difference was noted for total HDL particles with CHD by increasing age (Figure 2 and Table 2); however, for HDL particle subfractions, variable risk associations were noted that were more prominent for CHD onset at younger ages. Most HDL particles had an inverse association with CHD, except for small HDL particles, which had a positive association. Similar to HDL cholesterol, average HDL particle size was associated inversely with a risk of CHD, especially for women at younger ages—a risk that also attenuated with older age.

Inflammatory and Metabolic Biomarkers

Of all the approximately 50 lipid, inflammatory, and metabolic biomarkers examined, the LPIR score was associated with the highest standardized relative risk of incident CHD in most

Table 2. Associations of Risk Factors and Biomarkers With Incident CHD by Age at Onset

Clinical risk factors[a]	Incident CHD, adjusted HR (95% CI)				*P* value for interaction[b]
	At age <55 y	At 55 to <65 y	At 65 to <75 y	At age ≥75 y	
BMI, per SD increment	1.47 (1.24-1.74)	1.40 (1.29-1.51)	1.33 (1.24-1.42)	1.12 (1.01-1.24)	.002
BMI categories					
Overweight (25.0 to <30.0)	2.13 (1.10-4.14)	1.78 (1.39-2.28)	1.78 (1.48-2.14)	1.12 (0.91-1.39)	.004
Obese (≥30.0)	4.33 (2.31-8.11)	2.76 (2.15-3.55)	2.14 (1.74-2.62)	1.32 (1.02-1.71)	<.001
Current smoker	3.92 (2.32-6.63)	2.97 (2.37-3.71)	1.89 (1.54-2.32)	1.89 (1.42 - 2.52)	.003
Diabetes	10.71 (5.57-20.60)	10.92 (8.44-14.13)	4.49 (3.46-5.83)	3.47 (2.47-4.87)	<.001
Metabolic syndrome	6.09 (3.60-10.29)	4.45 (3.62-5.47)	2.82 (2.40-3.30)	1.79 (1.48-2.17)	<.001
Hypertension	4.58 (2.76-7.60)	2.38 (1.93-2.94)	2.06 (1.76-2.43)	1.64 (1.36-1.98)	<.001
Systolic BP, per SD increment, mm Hg	2.24 (1.84-2.74)	1.61 (1.48-1.76)	1.48 (1.38-1.59)	1.26 (1.15-1.37)	<.001
Physical inactivity[c]	1.53 (0.92-2.55)	1.59 (1.30-1.96)	1.43 (1.22-1.67)	1.21 (1.00-1.46)	.25
Parental MI at age <60 y	2.19 (1.26-3.81)	2.07 (1.64-2.61)	1.60 (1.31-1.96)	1.18 (0.88-1.57)	.02
Lipids and lipoproteins, per SD increment					
Cholesterol					
Total	1.39 (1.12-1.73)	1.43 (1.32-1.56)	1.24 (1.16-1.34)	1.12 (1.02-1.22)	<.001
LDL	1.38 (1.10-1.74)	1.44 (1.31-1.57)	1.24 (1.16-1.34)	1.12 (1.02-1.22)	.001
HDL	0.39 (0.27-0.55)	0.50 (0.44-0.56)	0.61 (0.56-0.67)	0.77 (0.70-0.86)	<.001
Total/HDL cholesterol ratio	2.40 (1.90-3.05)	2.21 (2.01-2.43)	1.76 (1.63-1.91)	1.40 (1.27-1.55)	<.001
Triglycerides	2.14 (1.72-2.67)	1.80 (1.64-1.97)	1.61 (1.49-1.74)	1.30 (1.18-1.43)	<.001
Triglyceride/HDL cholesterol ratio	2.27 (1.83-2.81)	1.92 (1.75-2.10)	1.69 (1.57-1.82)	1.34 (1.22-1.48)	<.001
Non-HDL cholesterol	1.67 (1.36-2.04)	1.67 (1.54-1.81)	1.41 (1.32-1.51)	1.21 (1.11-1.32)	<.001
Apolipoprotein B	1.89 (1.52-2.35)	1.78 (1.65-1.93)	1.52 (1.42-1.62)	1.26 (1.15-1.38)	<.001
Apolipoprotein A-I	0.69 (0.51-0.94)	0.61 (0.55-0.68)	0.76 (0.70-0.82)	0.88 (0.80-0.97)	<.001
Lipoprotein(a)	1.22 (0.92-1.62)	1.27 (1.15-1.42)	1.11 (1.03-1.21)	1.10 (1.00-1.21)	.15
LDL particles					
Total[d]	1.75 (1.42-2.15)	1.59 (1.45-1.74)	1.36 (1.27-1.47)	1.24 (1.13-1.36)	<.001
Large[e]	1.02 (0.74-1.42)	1.04 (0.92-1.17)	1.01 (0.92-1.11)	1.10 (0.99-1.23)	.67
Medium[e]	1.13 (0.80-1.60)	1.16 (1.02-1.32)	1.08 (0.98-1.19)	0.99 (0.88-1.10)	.32
Small[e]	2.25 (1.76-2.89)	1.93 (1.73-2.15)	1.57 (1.43-1.72)	1.37 (1.22-1.53)	<.001
LDL particle average size[d]	0.64 (0.50-0.80)	0.74 (0.67-0.82)	0.80 (0.74-0.86)	0.89 (0.81-0.97)	.01
TRL particles					
Total	1.74 (1.44-2.10)	1.55 (1.42-1.70)	1.38 (1.28-1.48)	1.24 (1.13-1.35)	<.001
Very large	1.27 (1.16-1.40)	1.16 (1.10-1.23)	1.18 (1.13-1.23)	1.11 (1.03-1.19)	.20
Large	1.66 (1.43-1.93)	1.39 (1.29-1.51)	1.34 (1.26-1.43)	1.20 (1.10-1.31)	.002
Medium	1.80 (1.14-2.84)	1.64 (1.37-1.96)	1.52 (1.32-1.75)	1.23 (1.06-1.43)	.05
Small	0.84 (0.73-0.96)	0.99 (0.89-1.09)	1.01 (0.93-1.10)	1.15 (0.99-1.33)	.04
Very small	1.77 (1.43-2.18)	1.53 (1.40-1.67)	1.34 (1.24-1.44)	1.19 (1.09-1.31)	<.001
TRL cholesterol	1.66 (1.35-2.02)	1.32 (1.21-1.44)	1.31 (1.22-1.41)	1.14 (1.04-1.26)	.006
TRL triglycerides	1.77 (1.47-2.12)	1.55 (1.41-1.69)	1.39 (1.30-1.49)	1.24 (1.14-1.36)	<.001
TRL particle average size	2.21 (1.68-2.90)	1.64 (1.47-1.83)	1.53 (1.41-1.67)	1.27 (1.14-1.41)	<.001
HDL particles					
Total	0.96 (0.73-1.27)	0.81 (0.72-0.90)	0.90 (0.83-0.98)	0.93 (0.85-1.03)	.21
Large	0.74 (0.65-0.85)	0.76 (0.72-0.80)	0.80 (0.76-0.84)	0.91 (0.83-0.99)	.001
Medium	0.65 (0.47-0.90)	0.54 (0.48-0.62)	0.72 (0.66-0.79)	0.85 (0.76-0.94)	<.001
Small	1.60 (1.24-2.08)	1.42 (1.28-1.57)	1.29 (1.20-1.40)	1.09 (0.99-1.19)	<.001
HDL particle average size	0.50 (0.36-0.69)	0.54 (0.48-0.61)	0.66 (0.60-0.72)	0.89 (0.80-0.98)	<.001
Inflammatory, per SD increment					
CRP	1.76 (1.37-2.27)	1.67 (1.50-1.86)	1.62 (1.49-1.77)	1.25 (1.12-1.39)	<.001
Fibrinogen	1.49 (1.22-1.81)	1.50 (1.40-1.61)	1.29 (1.20-1.37)	1.18 (1.09-1.28)	<.001
ICAM-1	1.52 (1.26-1.82)	1.49 (1.39-1.59)	1.33 (1.25-1.42)	1.20 (1.09-1.32)	.002
GlycA	1.84 (1.49-2.27)	1.61 (1.47-1.77)	1.47 (1.36-1.58)	1.18 (1.07-1.31)	<.001

(continued)

Table 2. Associations of Risk Factors and Biomarkers With Incident CHD by Age at Onset (continued)

Clinical risk factors[a]	Incident CHD, adjusted HR (95% CI)				*P* value for interaction[b]
	At age <55 y	At 55 to <65 y	At 65 to <75 y	At age ≥75 y	
Metabolic, per SD increment					
Hemoglobin A_{1c}	1.38 (1.26-1.50)	1.32 (1.28-1.37)	1.24 (1.20-1.28)	1.14 (1.07-1.22)	<.001
LPIR score	6.40 (3.14-13.06)	2.61 (2.08-3.28)	2.09 (1.77-2.48)	1.15 (1.00-1.33)	<.001
Homocysteine	1.03 (0.79-1.35)	1.21 (1.10-1.33)	1.12 (1.04-1.22)	1.05 (0.95-1.16)	.18
Citrate	0.97 (0.73-1.29)	1.05 (0.95-1.16)	1.01 (0.93-1.09)	0.98 (0.89-1.08)	.80
Branched-chain amino acids	1.47 (1.20-1.80)	1.41 (1.29-1.53)	1.31 (1.22-1.40)	1.12 (1.02-1.23)	.002
Valine	1.51 (1.22-1.87)	1.41 (1.29-1.54)	1.30 (1.21-1.40)	1.11 (1.01-1.22)	.001
Leucine	1.30 (1.03-1.64)	1.34 (1.22-1.47)	1.22 (1.13-1.32)	1.05 (0.96-1.16)	.005
Isoleucine	1.50 (1.23-1.83)	1.37 (1.26-1.49)	1.32 (1.24-1.42)	1.18 (1.08-1.29)	.04
Alanine	1.10 (0.85-1.41)	1.18 (1.07-1.30)	1.17 (1.09-1.27)	0.99 (0.90-1.09)	.03
eGFR	1.27 (1.12-1.43)	0.99 (0.89-1.09)	0.96 (0.88-1.04)	1.06 (0.97-1.15)	.01
Creatinine	0.55 (0.41-0.74)	0.99 (0.89-1.09)	1.07 (0.99-1.15)	0.95 (0.87-1.04)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GlycA, glycan biomarker of *N*-acetyl side chains of several acute-phase proteins; HDL, high-density lipoprotein; HR, hazard ratio; ICAM-1, Intercellular adhesion molecule 1; LDL, low-density lipoprotein; LPIR, lipoprotein insulin resistance; MI, myocardial infarction; TRL, triglyceride-rich lipoprotein.

[a] Hazard ratios (95% CI) were obtained from stratified Cox proportional hazards regression models (stratified on age groups and blood draw time categories) adjusted for model 1 covariates (baseline race/ethnicity, educational level, menopause, postmenopausal hormone use, randomized treatment assignment, and interactions between the risk factor of interest and age groups). 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, triglyceride/HDL cholesterol ratio, and TRL triglycerides. eTable 1 in the Supplement provides the SDs.

[b] Likelihood ratio test (3 *df*) of the null hypothesis that the risk factor or biomarker has the same effect across age groups. *P* value for interaction determined as risk factor × age group.

[c] Physical inactivity: less than 7.5 metabolic equivalent task hours per week.

[d] Included model 1 covariates plus LDL particle concentration and LDL particle average size.

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

age groups in model 1 (aHR, 6.40; 95% CI, 3.14-13.06 for CHD onset at <55 years, attenuating with age) (Figure 3 and Table 2). Compared with the LPIR score, the hemoglobin A_{1c} level was weakly associated with incident CHD, and some of the other metabolic biomarkers (eg, citrate) showed no association with incident CHD across age groups. The total branched chain amino acid biomarkers implicated in the pathway of insulin resistance, in particular isoleucine and valine, showed positive associations with incident CHD at all age groups. All the inflammatory biomarkers examined showed positive associations (by approximately 1.2- to 1.8-fold per SD) with incident CHD, which attenuated with age (Figure 3 and Table 2).

Blood Draw Time Categories

Within age groups, the associations of clinical risk factors, biomarkers, and incident CHD did not differ significantly by blood draw time categories (eTable 2 in the Supplement).

Additional Analyses

We examined the associations with incident CHD using models adjusted for model 1 covariates plus additional covariates (physical activity, current smoking, BMI, systolic blood pressure, diabetes, MI in a parent at age <60 years, and baseline treatment for hypertension or for high cholesterol levels) and evaluated the associations using separate models for each clinical risk factor or biomarker at a time. The associations of biomarkers with incident CHD observed in model 1 (Table 2) were generally preserved in this model (eTable 3 in the Supplement). The association of LPIR with incident CHD was minimally attenuated, despite adjustment for prevalent diabetes.

Population-Attributable Risk

The population-attributable risk for the clinical risk factors attenuated with age (eTable 4 in the Supplement). Of the 7 clinical risk factors analyzed (model 1), metabolic syndrome had the highest population-attributable risk in all age groups, which ranged from 53.1% (<55 years) to 17.3% (≥75 years), while parental MI before age 60 years had the lowest population-attributable risk in all age groups.

Discussion

In this large prospective study of apparently healthy women, we identified risk profiles associated with the risk of CHD occurring at younger ages. Of the clinical factors, diabetes was associated with the highest relative risk for incident CHD in women younger than 55 years (>10-fold higher adjusted relative risk), in addition to hypertension, obesity, and smoking, which were also strong risk factors for premature CHD. Of the approximately 50 measured biomarkers examined in women with CHD younger than 55 years, the LPIR score reflecting insulin resistance had the highest magnitude of relative risk (>6-fold higher adjusted standardized relative risk), which was greater than the association of LDL cholesterol levels, standard lipid levels, or inflammatory biomarkers. Most clinical factors and biomarkers of cardiovascular risk showed age-attenuated associations with incident CHD. The study findings underscore the importance of diabetes and insulin resistance as major determinants of premature CHD, as well as other modifiable major risk factors that can be addressed with lifestyle or preventive interventions.

Most previous studies on dyslipidemia and premature CHD measured biomarkers at the time of the acute CHD event and reported on the prevalence of dyslipidemia or risk of CHD based on unadjusted models, reaching disparate conclusions. These studies showed mixed results with a higher[18,41,42] or lower[43,44] prevalence of dyslipidemia in younger vs older adults with acute coronary syndromes, MI in individuals younger than 40 years vs controls,[45,46] or similar levels of HDL cholesterol and triglycerides among women younger than 65 years vs older women with acute syndromes.[47] INTERHEART examined adults by age deciles (from <40 to >70 years) and observed that younger vs older adults had a higher risk of MI associated with apolipoprotein B levels measured at the time of presentation of MI,[48] consistent with our findings regarding apolipoprotein B measured several years before the onset of CHD. In the present study, the association of lipoprotein subfractions with premature CHD was consistent with atherogenic properties reported in non-age-stratified analyses[21-24,49,50] and in individuals aged 40 years or younger with MI vs controls.[45,46] A previous study reported on non-age-stratified associations of lipoproteins with incident cardiovascular disease[22] showed that small LDL particles confound the association of atherogenic large LDL particles with both carotid intima-media thickness[51] and cardiovascular disease.[22] Our present results are consistent with these previous observations and provide further evidence for the atherogenicity of different LDL particles at different ages. In particular, for premature CHD risk, both the size and number matter for LDL, with somewhat stronger associations than found for LDL cholesterol.

The positive association of inflammatory biomarkers with CHD, which was more pronounced for premature CHD, supports the growing evidence on the role of inflammation in initial and recurrent cardiovascular events.[52-55] A previous study reported that GlycA, a glycosylation biomarker of certain acute phase reactants, was associated with an increased risk of type 2 diabetes.[37] GlycA, as well as intercellular adhesion molecule 1 and fibrinogen, were more strongly associated with premature CHD, suggesting that the inflammation that accompanies excess adiposity states, such as diabetes and insulin resistance, could be even more relevant for CHD occurring at younger ages.

In the present study, insulin resistance as measured by the LPIR score had the strongest association with premature CHD out of approximately 50 novel and standard biomarkers examined. Previous studies reported that LPIR was associated with incident diabetes both in the presence and absence of statin therapy.[32,56] Lipoprotein insulin resistance is a nuclear magnetic resonance–measured score that was developed from lipoprotein subfraction profiles as a correlate of insulin resistance as measured by the homeostasis model assessment of insulin resistance and provides an estimate of the probability of incident diabetes.[57] In the present study, the LPIR score had a greater association with CHD occurring in women at younger ages and up to age 75 years than all the other biomarker measures, including hemoglobin A_{1c}, LDL cholesterol, non-HDL cholesterol. The LPIR score potentially links insulin resistance and its concomitant atherogenic dyslipoproteinemia with future risk of both diabetes and premature CHD; this role requires further investigation, especially because the risk of LPIR was minimally attenuated after further adjustment for prevalent diabetes. In addition to the observation that a history of diabetes was associated with a 10-fold increase in the risk of premature CHD, we found that metabolic syndrome was positively associated with CHD, albeit at a lower magnitude. Metabolic syndrome has been studied extensively, involves the measurement of widely available biomarkers (triglyceride, HDL cholesterol, and glucose levels) and is easier to quantify. On the other hand, the LPIR score is a newer biomarker composite and involves measurement of lipoproteins through specialized laboratory testing.

Similarly, obesity and overweight were associated with incident CHD and could be targeted to reduce the risk of CHD, in particular for younger women. Behavioral modification could also target smoking, as smoking was associated with a higher risk of incident CHD and other studies have related smoking cessation to a lower risk of CHD mortality.[58] Smoking remains a major public health problem across all ages but in particular for younger individuals, and smoking cessation initiatives should remain part of efforts to reduce cardiovascular risk across all ages.[59]

In this study, the incidence rates of CHD increased with age and were approximately 10-fold higher for CHD onset at age 75 years or older vs younger than 55 years, consistent with age being a substantial risk factor. Analysis of the relative rates of risk factors for incident CHD should not, however, imply that risk factors are more important at younger vs older ages. Thus, the importance of primary cardiovascular disease prevention among older women is not diminished by the observed attenuation of relative rates of risk factors with incident CHD in older individuals. Rather, these results suggest the stronger relative associations of risk factors at younger vs older ages and emphasize the need for improved primary prevention among younger women. Furthermore, the age-related attenuation of relative risk has implications for cardiovascular risk modeling depending on the age group in which CHD occurs. In this context, a modeling analysis of participants pooled from 4 observational studies showed that age, race/ethnicity, and sex can apparently estimate the probability of cardiovascular risk.[60] Improving modifiable clinical risk factors (eg, smoking and diabetes) could substantially reduce CHD events.[60]

Strengths and Limitations

Our study has strengths and limitations. The generalizability of our findings to women younger than 45 years, men, or non-White racial/ethnic groups needs further evaluation. Participants self-reported lifestyle and medical history, which is subject to recall bias. We had limited data on pregnancy complications or vasomotor symptoms, which are emerging as important risk factors for CHD. Measurement of other biomarker pathways may also contribute to CHD risk. Our study has strengths, including that it was large, had a prospective design with robust follow-up of prespecified end points (incident CHD), and included information on various lifestyle factors and biomarkers. In addition, there are challenges to comparing the risks associated with clinical categorical vari-

ables vs continuous biomarkers. Similar issues affect the population-attributable risks, which depend on the magnitude of risk association and the prevalence of the risk factors in the population.

Conclusions

In this cohort study, we have identified biomarkers that may be associated with the risk of CHD occurring in women at younger vs older ages, finding the most substantial risk of premature CHD associated with diabetes and insulin resistance biomarkers, as well as hypertension, obesity, and smoking. Although LDL and non-HDL cholesterol levels were associated with premature CHD risk, their relative magnitude was less than that of LPIR, an indicator of atherogenic dyslipoproteinemia. Future work should examine the role of these biomarkers in improving determination of the estimated probability and classification of premature CHD beyond traditional biomarkers to guide preventive efforts. Cardiometabolic risk factor prevention and management remain important at all ages. This intervention is particularly relevant given that most countries are encumbered by a substantial burden of premature cardiovascular mortality and would benefit from strategies to improve identification of risk, screening, stratification, and early treatment.[61]

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