2015-04-24

Accumulation of metabolic cardiovascular risk factors in black and white young adults over 20 years

Nina P. Paynter
Harvard Medical School

Et al.

ORIGINAL RESEARCH

Accumulation of Metabolic Cardiovascular Risk Factors in Black and White Young Adults Over 20 Years

Nina P. Paynter, PhD, MHS; Catarina I. Kiefe, PhD, MD; Cora E. Lewis, MD, MSPH; Catherine M. Loria, PhD, MS; David C. Goff, Jr, MD, PhD; Donald M. Lloyd-Jones, MD, ScM

***Background*—**Cross-sectional clustering of metabolic risk factors for cardiovascular disease in middle-aged adults is well described, but less is known regarding the order in which risk factors develop through young adulthood and their relation to subclinical atherosclerosis.

***Method and Results*—**A total of 3178 black and white women and men in the Coronary Artery Risk Development in Young Adults study were assessed to identify the order in which cardiovascular disease risk factors including diabetes, hypertension, dyslipidemia (low high-density lipoprotein cholesterol or high triglyceride levels), hypercholesterolemia (high total or low-density lipoprotein cholesterol), and obesity develop. Observed patterns of risk factor development were compared with those expected if risk factors accumulated randomly, given their overall distribution in the population. Over the 20 years of follow-up, 80% of participants developed at least 1 risk factor. The first factor to occur was dyslipidemia in 39% of participants, obesity in 20%, hypercholesterolemia in 11%, hypertension in 7%, and diabetes in 1%. Dyslipidemia was the only risk factor both to occur first and to be followed by additional risk factors more often than expected ($P<0.001$ for both). Order of risk factor accrual did not affect subclinical atherosclerosis at year 20. Results were similar by sex, race, and smoking status.

***Conclusions*—**Multiple patterns of cardiovascular risk factor development were observed from young adulthood to middle age. Dyslipidemia, a potentially modifiable condition, often preceded the development of other risk factors and may be a useful target for intervention and monitoring. **(*J Am Heart Assoc*. 2015;4:e001548 doi: 10.1161/JAHA.114.001548)**

Key Words: atherosclerosis • epidemiology • lipids • obesity • primary prevention • risk factors • type 2 diabetes

Cardiovascular risk factors have been observed to cluster in youth,[1,2] young adulthood,[3] and middle age,[4] and the presence of additional risk factors has been shown to increase risk of subclinical atherosclerosis development in young and middle-aged adults[5,6] and risk of clinical cardiovascular disease in middle age.[4] It is not clear, however, which risk factors appear first and which are potentially early markers of subsequent additional risk, especially in the window between young adulthood and middle age.

Similarly, multiple studies have examined the subset of risk factors known as the metabolic syndrome; these risk factors have been observed to cluster together consistently over time,[7] but less is known about accrual order. Recent data have suggested that the order of accumulation in middle age is associated with clinical outcomes.[8] Interrelations between pairs of cardiovascular risk factors have also been studied extensively. Weight gain has been shown to be associated with changes in lipids, increases in fasting glucose, and increases in blood pressure in young adults.[9] Hypertension has been associated with incident diabetes,[10] and insulin resistance has been associated with incident hypertension.[11] Other studies have observed an increase in incident diabetes[12] and incident hypertension[13] following abnormal lipid levels.

This study aimed to identify patterns in the accrual of major metabolic cardiovascular risk factors in black and white women and men throughout young adulthood to middle age and to examine the relationship of these patterns with subclinical atherosclerosis. We used data from the Coronary

From the Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (N.P.P.); Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worchester, MA (C.I.K.); Division of Preventive Medicine, University of Alabama School of Medicine, Birmingham, AL (C.E.L.); Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD (C.M.L.); Department of Epidemiology & Prevention, Colorado School of Public Health, Aurora, CO (D.C.G.); Department of Preventive Medicine, and Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (D.M.L-J.).

Correspondence to: Nina P. Paynter, PhD, MHS, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA; E-mail: npaynter@partners.org

Received February 27, 2015; accepted March 28, 2015.

Artery Risk Development in Young Adults (CARDIA) study, which included 20 years of follow-up, to measure and examine patterns of cardiovascular risk factor accrual overall and by race, sex, and smoking status.

Methods

Study Population

The CARDIA study enrolled 5115 black and white women and men from 4 US sites.[14] Baseline (1985–1986) recruitment procedures were designed to balance age, sex, ethnicity, and education groups within each of 3 US communities studied (Birmingham, Alabama; Minneapolis, Minnesota; and Chicago, Illinois) and a health insurance company based in Oakland, California. Participants were aged 18 to 30 years at baseline and were followed up for 20 years, with examinations at baseline (year 0) and at years 2, 5, 7, 10, 15, and 20, with a retention rate of 72% of the surviving cohort at year 20. All participants provided informed consent at each examination, and all study protocols were approved by the institutional review board at each center. We excluded participants for whom complete risk factor information was not available at the year 20 examination (1935 participants) and excluded those who had all 5 metabolic risk factors at baseline (1 participant), leaving 3178 participants.

Risk Factors

We focused on 5 metabolic risk factors for cardiovascular disease: hypertension, hypercholesterolemia, dyslipidemia, diabetes, and obesity. Blood pressure was measured 3 times at each examination, according to previously published protocols.[14] The average systolic and diastolic pressures from the last 2 measurements were used. Participants were classified as having hypertension at the first visit at which they had elevated blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic) or reported use of antihypertensive medication.

Total cholesterol, low-density lipoprotein cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured at each visit from a fasting blood sample processed at a central laboratory.[14,15] Participants were classified as having hypercholesterolemia at the first visit at which total cholesterol was ≥240 mg/dL, low-density lipoprotein cholesterol was >160 mg/dL, or use of cholesterol-lowering medications was reported (for years 5 through 20).[16] Patients were classified as having dyslipidemia at the first visit at which HDL-C was <50 mg/dL in women or <40 mg/dL in men or triglyceride levels were >200 mg/dL in either sex.

Blood glucose was measured from fasting blood samples at baseline and at years 7, 10, 15, and 20.[14] Patients were asked at all visits about medication use and diagnosis of diabetes. Participants were classified as having diabetes at the first visit with fasting blood glucose ≥126 mg/dL (when available), reported use of diabetes medication, or reported physician diagnosis of diabetes.

Weight, height, and waist circumference were also measured at each study visit, with participants wearing light clothing, and body mass index was calculated as the weight in kilograms divided by height in square meters. Participants were classified as obese at the first visit at which body mass index was ≥30 or waist circumference was >88 cm in women or >102 cm in men.

Information on smoking, including whether the participant was currently smoking and the number of cigarettes smoked per day, was collected at each study visit. In addition, prior smoking information was collected at baseline. Using previously defined methods for this cohort, cumulative exposure to cigarettes in pack-years was calculated for each participant.[17]

Subclinical Cardiovascular Disease

Coronary artery calcium (CAC) was measured at year 20 using computed tomography scanning with 2 scans for each participant.[18] All scans were analyzed by cardiovascular radiologists blinded to participant characteristics, with high within- and between-reader reliability. Summary Agatston scores were calculated and dichotomized for this analysis into any calcification (score >0) or no calcification (score 0). Carotid intima-media thickness (CIMT) was measured at year 20 using the average of 4 ultrasound images measuring the maximum thickness of the common carotid artery.[19] A total of 2577 participants had information available on CAC and CIMT.

Statistical Methods

Risk factor accumulation was calculated by examining each participant's visit history. Visits were included if the status of all risk factors could be determined and if the participant did not report being pregnant at the time of the visit. Participants were classified into groups according to the order in which risk factors developed during follow-up. A participant who, for example, first developed obesity and then developed hypertension but no additional risk factors was placed in the obesity/hypertension group. There were 326 possible groups: 120 with 5 risk factors, 120 with 4 risk factors, 60 with 3 risk factors, 20 with 2 risk factors, 5 with 1 risk factor, and 1 with none. Weighted values corresponding to the probability of each combination were used when the order of risk factor development was unclear. A participant who had no risk factors at baseline, hypertension at year 2 and dyslipidemia at year 7 would contribute full weighted value to the hypertension/dyslipidemia group. A participant who had no risk factors at

Table 1. Rates for Component Criteria for Cardiovascular Risk Factors*

Indication	n	Risk Factor Identified by Criteria, %
Diabetes		
Nonfasting glucose >200 mg/dL	30	11
Fasting glucose ≥126 mg/dL	148	53
Diagnosis	54	19
Medication use	45	16
Dyslipidemia		
Both high triglycerides and low HDL	99	5
HDL <40 mg/dL in men or <50 mg/dL in women	1655	89
Triglycerides ≥200 mg/dL	103	6
Hypercholesterolemia		
LDL ≥160 mg/dL	584	71
Total cholesterol ≥240 mg/dL	103	13
Medication use	134	16
Hypertension		
Both high diastolic and systolic	150	17
Systolic blood pressure ≥140 mm Hg	87	10
Diastolic blood pressure ≥90 mm Hg	314	36
Medication use	331	38
Obesity		
Both high BMI and WC	654	44
BMI ≥30, kg/m^2	557	37
WC >102 cm in men or >88 cm in women	278	19

BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WC, waist circumference.
*Criteria are assessed hierarchically in the order displayed (ie, once assigned to a criterion, a participant is no longer evaluated for remaining criteria).

baseline and hypertension and dyslipidemia simultaneously at year 2 would contribute 0.5 of their weighted value to each of the hypertension/dyslipidemia and dyslipidemia/hypertension groups.

The overall (or marginal) probability of developing each risk factor over the 20-year follow-up period was calculated, and these probabilities were used to obtain the expected joint probabilities of each combination under the null hypothesis of risk factor independence. Similarly, the expected probabilities of combinations of risk factors and conditional probabilities were also obtained.

These expected probabilities were then compared with the observed rates for each question under examination. For example, to examine whether hypertension or dyslipidemia occurs first when they are both present, we restricted our analysis to the set of participants with hypertension and dyslipidemia. Although dyslipidemia occurs more frequently than hypertension in the population, within our restricted set, both were equally likely to occur (with probability of 100%). Under our null hypothesis, each factor has a uniform rate of occurrence throughout the follow-up period, meaning that hypertension or dyslipidemia could have occurred at any point in the follow-up, and each were equally likely to have occurred first. We then compared the observed rate of hypertension occurring first to the expected rate of 50%. All observed and expected probabilities were compared using a chi-square test of proportions.

For participants with CIMT measures at year 20, we generated expected CIMT values predicted by sex, race, age, and smoking status at year 15 and pack-years smoked using a linear model and subtracted these from the individual observed values to obtain the residual CIMT for each participant. These residuals were then combined using the weighting for each sequence to obtain the mean residual for each accumulation combination or conditional group. The mean residual for each group was compared with the expected mean residual CIMT of 0. A similar process was followed for those participants with measured CAC at year 20. We generated the expected probability of any CAC predicted by sex, race age, and smoking status and pack-years for each participant. Weighted average expected probabilities were obtained for each group and compared with the observed prevalence of CAC.

To further describe the associations within subgroups, we performed the analyses stratified by race and sex categories

Table 2. Accumulation of Subsequent Metabolic Risk Factors When First Risk Factor Is Identified

First Risk Factor	Risk Factor Occurring First, n (% of Total)	Observed With Subsequent Risk Factor Accumulation, % (95% CI)	Expected With Subsequent Risk Factor Accumulation, %	Ratio of Observed to Expected	*P* Value for Accumulation
DIAB	44 (1)	59 (44 to 73)	73	0.8	0.045
DYSL	1243 (39)	63 (60 to 65)	55	1.1	<0.001
HCL	363 (11)	71 (66 to 75)	70	1.0	0.74
HTN	233 (7)	56 (50 to 63)	70	0.8	<0.001
OBST	650 (20)	67 (63 to 70)	62	1.1	0.020

DIAB indicates diabetes; DYSL, dyslipidemia; HCL, hypercholesterolemia; HTN, hypertension; OBST, obesity.

Table 3. Distribution of First Risk Factors in Sequences With at Least 2 Metabolic Risk Factors

Risk Factor	Observed With Risk Factor First, % (95% CI)	Expected With Risk Factor First, %	Ratio of Observed to Expected	*P* Value for Risk Factor First
DIAB	10 (6 to 14)	39	0.3	<0.001
DYSL	56 (53 to 59)	43	1.3	<0.001
HCL	36 (32 to 40)	40	0.9	0.020
HTN	17 (14 to 19)	40	0.4	<0.001
OBST	34 (31 to 37)	42	0.8	<0.001

DIAB indicates diabetes; DYSL, dyslipidemia; HCL, hypercholesterolemia; HTN, hypertension; OBST, obesity.

and by smoking status. We also performed an analysis using the ATP III metabolic syndrome criteria,[16] In this analysis, the cutoffs were changed to ≥110 mg/dL for fasting glucose, ≥150 mg/dL for triglycerides, and ≥130 mm Hg for systolic blood pressure.

All analyses were performed using R 2.10.0 (R Foundation). A 2-tailed *P* value of <0.05 was considered statistically significant for each comparison in this analysis because the results were meant to be hypothesis generating. The main results (Tables 2 through 4) include 30 comparisons in all, so a Bonferroni adjusted cutoff of 0.0017 could be used for those tables and would provide similar results.

Results

Of the 3178 participants, 57% were female and 46% were black. At baseline, the mean age was 25.1 years, with 25.6% current smokers and 14.4% former smokers. This group was more likely to be female, white, and nonsmokers than the CARDIA cohort members who were not included (mean age 24.5 years, 51% female, 62% black, 13% former smokers, and 40% current smokers). After 20 years, 26.1% of participants had hypertension, 25.8% had hypercholesterolemia, 55.4% had dyslipidemia, 8.7% had diabetes, and 46.0% were obese. More information on the definition of each risk factor is given in Table 1. Of note, 89% of dyslipidemia was identified by low HDL-C levels alone, and 5% had low HDL-C and elevated triglycerides.

Risk Factor Accumulation

Of the 326 potential sequences of accumulation for the 5 risk factors, 280 were observed in our data. The sequence in which no risk factors developed occurred 1.9 times as often as expected, suggesting that risk factors clustered rather than sorting independently. Among sequences with at least 1 risk factor, when the association between a risk factor occurring first and subsequent risk factor accumulation was examined (Table 2), we found that the probability of accumulating at least 1 additional risk factor was significantly greater than expected for dyslipidemia and obesity (1.1 times as much accumulation of other risk factors observed versus expected for both). In contrast, hypertension and diabetes occurring first were followed by an additional risk factor only 0.8 time as often as expected. Accumulation following hypercholesterolemia did not occur significantly more or less than expected.

Risk Factor Order

We next looked at the order within sequences that had at least 2 risk factors. The expected probability of a risk factor

Table 4. Frequency and Order of Pairs of Metabolic Risk Factors

Pair	Observed With Pair, n (95% CI)	Expected, n	Ratio of Observed to Expected	*P* Value	Risk Factor More Likely to be First	Observed as First,* n (95% CI)	*P* Value
DYSL and DIAB	213 (185 to 241)	514	0.4	<0.001	DYSL	86 (82 to 91)	<0.001
DYSL and HCL	582 (539 to 625)	867	0.7	<0.001	DYSL	60 (56 to 64)	<0.001
DYSL and HTN	610 (566 to 654)	153	4.0	<0.001	DYSL	80 (77 to 83)	<0.001
DYSL and OBST	1081 (1029 to 1133)	471	2.3	<0.001	DYSL	64 (61 to 67)	<0.001
HCL and DIAB	125 (104 to 146)	58	2.1	<0.001	HCL	60 (51 to 68)	0.040
HCL and HTN	327 (293 to 361)	223	1.5	<0.001	HCL	62 (57 to 67)	<0.001
HCL and OBST	459 (420 to 498)	380	1.2	<0.001	OBST	51 (56 to 46)	0.71
HTN and DIAB	171 (146 to 196)	72	2.4	<0.001	HTN	57 (50 to 64)	0.08
OBST and DIAB	220 (192 to 248)	125	1.8	<0.001	OBST	85 (81 to 90)	<0.001
OBST and HTN	601 (558 to 644)	412	1.5	<0.001	OBST	72 (69 to 76)	<0.001

DIAB indicates diabetes; DYSL, dyslipidemia; HCL, hypercholesterolemia; HTN, hypertension; OBST, obesity.
*The percentage of observations with both risk factors for which the risk factor in the previous column appears first.

Table 5. Accumulation of Subsequent Metabolic Risk Factors by Subgroup When First Risk Factor is Identified

First Risk Factor	Subgroup	Risk Factor Occurring First N (%)*	Percent Observed With Accumulation (95% CI)	Percent Expected With Accumulation	Ratio of Observed to Expected	*P* Value for Accumulation
Diabetes	Never Smokers	26 (1)	57 (38, 76)	62	0.9	0.76
	Ever Smokers	18 (1)	61 (39, 84)	67	0.9	0.81
	Black Women	16 (<1)	74 (53, 96)	82	0.9	0.66
	White Women	15 (<1)	32 (8, 56)	26	1.2	0.83
	Black Men	7 (<1)	56 (19, 93)	38	1.5	0.58
	White Men	6 (<1)	84 (56, 112)	53	1.6	0.22
Dyslipidemia	Never Smokers	727 (23)	62 (58, 65)	55	1.1	<0.001
	Ever Smokers	507 (16)	64 (59, 68)	54	1.2	<0.001
	Black Women	334 (11)	77 (72, 81)	73	1.1	0.13
	White Women	407 (13)	51 (47, 56)	39	1.3	<0.001
	Black Men	156 (5)	64 (57, 72)	58	1.1	0.12
	White Men	345 (11)	61 (56, 67)	50	1.2	<0.001
Hypercholesterolemia	Never Smokers	221 (7)	69 (63, 75)	68	1.0	1.0
	Ever Smokers	140 (4)	74 (66, 81)	70	1.0	0.46
	Black Women	78 (2)	76 (66, 85)	84	0.9	0.054
	White Women	76 (2)	63 (52, 74)	58	1.1	0.48
	Black Men	86 (3)	75 (66, 85)	65	1.2	0.054
	White Men	124 (4)	69 (61, 77)	66	1.1	0.44
Hypertension	Never Smokers	140 (4)	60 (52, 68)	68	0.9	0.043
	Ever Smokers	92 (3)	50 (40, 60)	70	0.7	<0.001
	Black Women	74 (2)	66 (56, 77)	81	0.8	0.002
	White Women	33 (1)	40 (23, 57)	60	0.7	0.027
	Black Men	69 (2)	47 (35, 58)	63	0.7	0.006
	White Men	56 (2)	64 (51, 77)	69	0.9	0.55
Obesity	Never Smokers	415 (13)	65 (61, 70)	60	1.1	0.033
	Ever Smokers	228 (7)	69 (63, 75)	65	1.1	0.20
	Black Women	289 (9)	72 (67, 77)	70	1.0	0.47
	White Women	134 (4)	62 (54, 70)	52	1.2	0.028
	Black Men	130 (4)	60 (51, 68)	60	1.0	1.0
	White Men	97 (3)	66 (56, 75)	65	1.0	0.89

*Numbers include weighting when the exact order cannot be determined; see Methods section.

occurring first depended only on the number of risk factors in each sequence, for example, for all sequences of 3 risk factors that include hypertension, hypertension should be first in one-third of them. As shown in Table 3, when dyslipidemia was included in a sequence, it occurred first 1.3 times more often than expected. Conversely, diabetes occurred first in a sequence less often than expected (0.3 times as often as expected), as did hypertension (0.4), obesity (0.8) and hypercholesterolemia (0.9).

We also examined the occurrence of pairs of risk factors in a sequence, which included sequences with only the pair of risk factors and those with both the pair and additional risk factors (Table 4). Most pairs occurred more often than expected under random accrual, with the largest ratio of observed to expected in dyslipidemia/hypertension (4.0 times more often than expected); however, dyslipidemia/diabetes and dyslipidemia/hypercholesterolemia occurred significantly less often than expected. When we examined the order in which each pair occurred, dyslipidemia was more likely to occur before any other risk factor. Hypercholesterolemia was significantly more likely to occur before diabetes and hypertension; however, hypercholesterolemia and obesity

Table 6. Observed Versus Expected Percentage of Being First by Subgroup in Sequences in Participants With at Least Two Metabolic Risk Factors Accumulated Over 20 Years

Risk Factor	Subgroup	Percent Observed With RF First (95% CI)	Percent Expected With RF First	Ratio of Observed to Expected	*P* Value for RF First
Diabetes	Never Smokers	10 (5, 15)	31	0.3	<0.001
	Ever Smokers	10 (4, 15)	33	0.3	<0.001
	Black Women	10 (5, 16)	34	0.3	<0.001
	White Women	13 (2, 25)	22	0.6	0.30
	Black Men	7 (0, 13)	21	0.3	0.012
	White Men	10 (2, 18)	26	0.4	0.012
Dyslipidemia	Never Smokers	55 (52, 59)	44	1.3	<0.001
	Ever Smokers	57 (53, 61)	44	1.3	<0.001
	Black Women	52 (48, 56)	41	1.3	<0.001
	White Women	65 (60, 70)	47	1.4	<0.001
	Black Men	47 (40, 54)	44	1.1	0.45
	White Men	58 (53, 63)	45	1.3	<0.001
Hypercholesterolemia	Never Smokers	37 (32, 42)	40	0.9	0.23
	Ever Smokers	34 (29, 40)	41	0.8	0.032
	Black Women	31 (25, 38)	37	0.9	0.15
	White Women	31 (24, 38)	43	0.7	0.004
	Black Men	48 (39, 56)	40	1.2	0.082
	White Men	36 (30, 42)	42	0.9	0.060
Hypertension	Never Smokers	18 (14, 21)	41	0.4	<0.001
	Ever Smokers	16 (12, 20)	40	0.4	<0.001
	Black Women	15 (11, 19)	38	0.4	<0.001
	White Women	12 (6, 18)	43	0.3	<0.001
	Black Men	20 (14, 26)	42	0.5	<0.001
	White Men	20 (14, 26)	41	0.5	<0.001
Obesity	Never Smokers	35 (32, 38)	42	0.8	<0.001
	Ever Smokers	32 (28, 36)	43	0.8	<0.001
	Black Women	40 (36, 44)	41	1.0	0.73
	White Women	30 (24, 35)	45	0.7	<0.001
	Black Men	38 (32, 45)	44	0.9	0.12
	White Men	24 (19, 30)	42	0.6	<0.001

were not more likely to occur in either order, and neither were hypertension and diabetes. Obesity was more likely to occur prior to diabetes and hypertension.

Relationship of Order With Presence of CAC or CIMT

No pairs of risk factors were associated with a significantly higher prevalence of CAC than expected from participant age, sex, race, smoking behavior at year 20, and pack-years at year 20. Similarly, no pairs of risk factors were associated with higher mean CIMTs than expected from participant age, sex, race, number of risk factors, smoking behavior at year 20, and pack-years at year 20.

Results for Additional Analysis

Separate analysis by sex, race, and smoking status at baseline resulted in similar patterns, with some relationships becoming nonsignificant because of smaller sample sizes (Tables 5 through 7). Results were also similar when the metabolic syndrome cut points were used (Tables 8 through 11).

Table 7. Observed and Expected Occurrence and Order of Pairs of Metabolic Risk Factor Combinations by Subgroup Accumulated Over 20 Years

Pairwise Combination	Subgroup	Number With Combination, Regardless of Temporal Sequence				Percent Occurring in Listed Sequence	
		Observed N (95% CI)	Expected N	Ratio of Observed to Expected	*P* Value	Observed (95% CI)	*P* Value*
Dyslipidemia and diabetes	Never Smokers	114 (94, 134)	303	0.4	<0.001	88 (82, 94)	<0.001
	Ever Smokers	95 (77, 113)	198	0.5	<0.001	84 (76, 91)	<0.001
	Black Women	93 (75, 111)	221	0.4	<0.001	84 (77, 92)	<0.001
	White Women	33 (22, 44)	69	0.5	<0.001	85 (73, 97)	<0.001
	Black Men	40 (28, 52)	87	0.5	<0.001	90 (81, 99)	<0.001
	White Men	47 (34, 60)	118	0.4	<0.001	88 (79, 97)	<0.001
Dyslipidemia and hypercholesterolemia	Never Smokers	317 (285, 349)	512	0.6	<0.001	59 (54, 65)	0.0011
	Ever Smokers	258 (230, 286)	334	0.8	<0.001	61 (55, 67)	<0.001
	Black Women	152 (130, 174)	380	0.4	<0.001	62 (54, 70)	0.005
	White Women	129 (108, 150)	185	0.7	<0.001	69 (61, 77)	<0.001
	Black Men	95 (78, 112)	115	0.8	0.040	46 (36, 56)	0.47
	White Men	206 (182, 230)	176	1.2	0.011	60 (54, 67)	0.003
Dyslipidemia and hypertension	Never Smokers	368 (334, 402)	63	5.8	<0.001	80 (76, 84)	<0.001
	Ever Smokers	236 (209, 263)	57	4.1	<0.001	82 (77, 87)	<0.001
	Black Women	260 (233, 287)	59	4.4	<0.001	84 (79, 88)	<0.001
	White Women	86 (69, 103)	13	6.7	<0.001	88 (82, 95)	<0.001
	Black Men	114 (95, 133)	10	11.9	<0.001	78 (70, 86)	<0.001
	White Men	150 (128, 172)	21	7.0	<0.001	72 (64, 79)	<0.001
Dyslipidemia and obesity	Never Smokers	638 (598, 678)	262	2.4	<0.001	63 (59, 67)	<0.001
	Ever Smokers	432 (399, 465)	198	2.2	<0.001	65 (61, 70)	<0.001
	Black Women	441 (412, 470)	124	3.6	<0.001	59 (54, 63)	<0.001
	White Women	252 (226, 278)	99	2.5	<0.001	72 (66, 78)	<0.001
	Black Men	155 (134, 176)	68	2.3	<0.001	55 (47, 63)	0.23
	White Men	233 (208, 258)	164	1.4	<0.001	71 (65, 77)	<0.001
Hypercholesterolemia and diabetes	Never Smokers	65 (49, 81)	22	3.0	<0.001	58 (46, 70)	0.21
	Ever Smokers	58 (43, 73)	18	3.1	<0.001	61 (49, 74)	0.12
	Black Women	46 (33, 59)	13	3.6	<0.001	50 (36, 64)	1.0000
	White Women	18 (10, 26)	3	5.8	<0.001	53 (30, 76)	1.0000
	Black Men	25 (15, 35)	4	6.9	<0.001	78 (62, 94)	0.009
	White Men	36 (25, 47)	11	3.2	<0.001	62 (47, 78)	0.18
Hypercholesterolemia and hypertension	Never Smokers	186 (161, 211)	130	1.4	<0.001	60 (53, 67)	0.008
	Ever Smokers	137 (115, 159)	87	1.6	<0.001	65 (57, 73)	<0.001
	Black Women	110 (91, 129)	77	1.4	<0.001	60 (50, 69)	0.057
	White Women	36 (24, 48)	23	1.6	0.007	61 (45, 77)	0.24
	Black Men	78 (62, 94)	51	1.5	<0.001	68 (58, 78)	0.002
	White Men	103 (84, 122)	64	1.6	<0.001	60 (50, 69)	0.061
Hypercholesterolemia and obesity	Never Smokers	268 (238, 298)	220	1.2	<0.001	49 (43, 55)	0.71
	Ever Smokers	185 (160, 210)	147	1.3	0.001	50 (43, 57)	1.0

Continued

Table 7. Continued

Pairwise Combination	Subgroup	Number With Combination, Regardless of Temporal Sequence				Percent Occurring in Listed Sequence	
		Observed N (95% CI)	Expected N	Ratio of Observed to Expected	*P* Value	Observed (95% CI)	*P* Value*
	Black Women	152 (130, 174)	131	1.2	0.052	46 (38, 54)	0.33
	White Women	90 (72, 108)	64	1.4	<0.001	46 (35, 56)	0.46
	Black Men	88 (71, 105)	65	1.3	0.003	53 (43, 64)	0.59
	White Men	129 (109, 149)	97	1.3	<0.001	52 (44, 61)	0.66
Hypertension and diabetes	Never Smokers	101 (82, 120)	36	2.8	<0.001	60 (50, 69)	0.059
	Ever Smokers	68 (52, 84)	20	3.3	<0.001	51 (40, 63)	0.90
	Black Women	83 (66, 100)	32	2.6	<0.001	54 (43, 64)	0.58
	White Women	17 (9, 25)	1	21.4	<0.001	32 (10, 55)	0.23
	Black Men	35 (24, 46)	10	3.5	<0.001	63 (47, 79)	0.18
	White Men	36 (25, 47)	8	4.4	<0.001	71 (56, 86)	0.020
Obesity and diabetes	Never Smokers	123 (102, 144)	62	2.0	<0.001	85 (78, 91)	<0.001
	Ever Smokers	94 (76, 112)	44	2.1	<0.001	86 (79, 93)	<0.001
	Black Women	102 (83, 121)	64	1.6	<0.001	82 (74, 89)	<0.001
	White Women	28 (18, 38)	6	4.9	<0.001	84 (70, 98)	<0.001
	Black Men	49 (36, 62)	14	3.6	<0.001	91 (83, 99)	<0.001
	White Men	41 (29, 53)	13	3.1	<0.001	88 (78, 98)	<0.001
Obesity and hypertension	Never Smokers	381 (347, 415)	254	1.5	<0.001	72 (67, 76)	<0.001
	Ever Smokers	212 (186, 238)	148	1.4	<0.001	73 (67, 79)	<0.001
	Black Women	293 (266, 320)	235	1.2	<0.001	75 (70, 80)	<0.001
	White Women	86 (69, 103)	45	1.9	<0.001	79 (70, 88)	<0.001
	Black Men	114 (95, 133)	86	1.3	0.002	67 (58, 76)	<0.001
	White Men	108 (89, 127)	69	1.6	<0.001	64 (55, 73)	0.005

*Compared with a null of 50% (equally likely to be either order).

Discussion

In this cohort study of 3178 young black and white women and men, we found that dyslipidemia—primarily low HDL-C but also including high triglyceride levels—was more likely to occur first in a sequence or in a pair with any other risk factor, and accumulation of other risk factors was more likely when dyslipidemia occurred first. Hypertension, hypercholesterolemia, obesity, and diabetes were less likely than expected to occur first in a sequence, although obesity and hypercholesterolemia occurred first more often in pairs with hypertension and diabetes. Hypertension and diabetes were also less likely to be followed by additional risk factors. These results were similar when stratified by sex, race, and smoking status at baseline and suggest that dyslipidemia screening in early adulthood may be a good target for early prevention of cardiovascular risk factor accumulation.

Our results complement previous findings that dyslipidemia, specifically low HDL-C, precedes development of other metabolic risk factors including insulin resistance, hypertension, and abdominal adiposity.[8] Our results are also consistent with other studies showing lipid abnormalities prior to hypertension and diabetes. In the Women's Health Study cohort, the lowest quintile of HDL-C levels was associated with a 4-fold increase in incident diabetes compared with the highest quintile, even after adjustment for other risk factors, whereas the highest quintile of triglyceride levels was associated with a 3.7-fold increase in risk compared with the lowest quintile.[20] In the same cohort, low HDL-C was also associated with an increased risk of incident hypertension after adjustment for other risk factors (hazard ratio 1.23 for lowest quintile compared with highest), as were high triglyceride levels (hazard ratio 1.53 for highest quintile compared with lowest).[13] Both studies also suggest that there may be additional information in the lipoprotein

Table 8. Rates for ATP III–Based Metabolic Syndrome Criteria for Cardiovascular Risk Factors (N=3178)*

Indication	n	Risk Factor Identified by Criteria, %
Diabetes		
Nonfasting glucose >200 mg/dL	22	4
Fasting glucose ≥110 mg/dL	393	79
Diagnosis	53	11
Medication use	28	6
Dyslipidemia		
Both high triglycerides and low HDL	226	11
HDL <40 mg/dL in men or <50 mg/dL in women	1476	74
Triglycerides ≥150 mg/dL	291	11
Hypercholesterolemia		
LDL ≥160 mg/dL	584	71
Total cholesterol ≥240 mg/dL	103	13
Medication use	134	16
Hypertension		
Both high diastolic and systolic	287	23
Systolic blood pressure ≥130 mm Hg	278	22
Diastolic blood pressure ≥85 mm Hg	485	39
Medication use	199	16
Obesity		
Both high BMI and WC	655	44
BMI ≥25, kg/m^2	559	37
WC >102 cm in men or >88 cm in women	278	19

BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WC, waist circumference.
*Criteria are assessed hierarchically in the order displayed (ie, once assigned to a criterion, a participant is no longer evaluated for remaining criteria).

particle sizes, with stronger associations in small HDL-C particles and larger triglyceride-rich particles. Our results examining all risk factors simultaneously, suggest that HDL-C and triglycerides are early markers of underlying metabolic dysfunction leading to additional cardiovascular disease risk factor accumulation and increased cardiovascular disease risk.

Strengths of our study include the ability to assess cardiovascular risk factor development in early adulthood, which is a critical period of risk development. We also had multiple visits with high-quality repeated measures over 20 years to obtain risk factor information. Risk factors were directly measured using standardized methods, which reduce the risk of ascertainment bias. We were not able to calculate the exact timing of risk factor accrual, leaving residual ambiguity in our calculations, nor was enough follow-up time available to assess hard cardiovascular outcomes. We limited this analysis to dichotomous measures of risk factors and did not examine reduction in risk factors at subsequent visits, and we did not examine the effects of risk factor treatment. The analysis was also limited to those who had complete risk factor information at the 20-year visit, potentially limiting the generalizability of the results. In addition, there was no information on other ethnic groups, such as Asian populations, which may have different patterns of risk factors accumulation; however, the study population included black and white women and men, and stratified analyses were similar to the overall results.

Conclusions

Our results suggest that dyslipidemia, primarily due to low HDL-C but also including elevated triglyceride levels, may precede development of other established cardiovascular risk factors. Screening for dyslipidemia and continuing follow-up of for those young adults who develop dyslipidemia may provide an opportunity for lifestyle interventions.

Table 9. Accumulation of Subsequent Metabolic Risk Factors When First Risk Factor Is Identified: ATP III–Based Metabolic Syndrome Criteria

First Risk Factor	Risk Factor Occurring First, n (% of Total)*	Observed With Subsequent Risk Factor Accumulation, % (95% CI)	Expected With Subsequent Risk Factor Accumulation, %	Ratio of Observed to Expected	*P* Value for Accumulation
DIAB	73 (2)	61 (50 to 73)	78	0.8	<0.001
DYSL	1264 (40)	65 (62 to 68)	62	1.0	0.028
HCL	314 (10)	79 (74 to 83)	77	1.0	0.49
HTN	428 (13)	65 (60 to 69)	73	0.9	<0.001
OBST	580 (18)	75 (72 to 79)	71	1.1	0.020

DIAB indicates diabetes; DYSL, dyslipidemia; HCL, hypercholesterolemia; HTN, hypertension; OBST, obesity.
*Numbers include weighting when the exact order cannot be determined (described in the "Methods" section).

Table 10. Observed Versus Expected Percentage of Being First in Sequences in Participants With at Least 2 Metabolic Risk Factors Accumulated Over 20 Years: ATP III–Based Metabolic Syndrome Criteria

Risk Factor	Observed With Risk Factor First, % (95% CI)	Expected With Risk Factor First,* %	Ratio of Observed t o Expected	*P* Value for Risk Factor First
DIAB	10 (7 to 12)	37	0.3	<0.001
DYSL	53 (50 to 55)	41	1.3	<0.001
HCL	33 (29 to 36)	38	0.9	0.003
HTN	25 (23 to 28)	39	0.6	<0.001
OBST	32 (30 to 35)	40	0.8	<0.001

DIAB indicates diabetes; DYSL, dyslipidemia; HCL, hypercholesterolemia; HTN, hypertension; OBST, obesity.
*The expected value is generated as follows: For the risk factor DYSL, the expected probability of DYSL occurring first would be (1/2)×(the number of participants with 2 risk factor combinations that include DYSL)+(1/3)×(the number of participants with 3 risk factor combinations that include DYSL)+(1/4)×(the number of participants with 4 risk factor combinations that include DYSL)+(1/5)×(the number of participants with 5 risk factor combinations that include DYSL).

Table 11. Observed and Expected Occurrence and Order of Pairs of Metabolic Risk Factor Combinations Accumulated Over 20 Years: ATP III–Based Metabolic Syndrome Criteria

	Number With Combination				Percentage Occurring in Listed Order	
Pairwise Combination*	Observed, n (95% CI)	Expected, n	Ratio of Observed to Expected	*P* Value	Observed, % (95% CI)	*P* Value†
DYSL and DIAB	377 (341 to 413)	780	0.5	<0.001	87 (84 to 91)	<0.001
DYSL and HCL	630 (586 to 674)	929	0.7	<0.001	61 (57 to 65)	<0.001
DYSL and HTN	870 (821 to 919)	301	2.9	<0.001	70 (67 to 73)	<0.001
DYSL and OBST	1137 (1084 to 1190)	505	2.3	<0.001	63 (61 to 66)	<0.001
HCL and DIAB	204 (177 to 231)	118	1.7	<0.001	60 (54 to 67)	0.004
HCL and HTN	425 (387 to 463)	320	1.3	<0.001	53 (49 to 58)	0.19
HCL and OBST	459 (420 to 498)	380	1.2	<0.001	49 (44 to 54)	0.71
HTN and DIAB	328 (294 to 362)	192	1.7	<0.001	68 (63 to 73)	<0.001
OBST and DIAB	368 (333 to 403)	227	1.6	<0.001	81 (77 to 85)	<0.001
OBST and HTN	805 (757 to 853)	583	1.4	<0.001	64 (60 to 67)	<0.001

DIAB indicates diabetes; DYSL, dyslipidemia; HCL, hypercholesterolemia; HTN, hypertension; OBST, obesity.
*Risk factors do not have to be directly contiguous in time, for example, a sequence of diabetes followed by hypercholesterolemia and then hypertension would contribute to the HTN and DIAB row as a combination but not to the percentage in the listed order, to the HCL and DIAB row as a combination but not to the percentage in the listed order, and to the HCL and HTN row as both a combination and as part of the percentage in the listed order.
†Compared with a null of 50% (equally likely to be either order).

Acknowledgments

This manuscript has been reviewed by CARDIA for scientific content and consistency of data interpretation with previous CARDIA publications. Dr Paynter conducted all analysis, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and agree to the manuscript as written and the manuscript was approved by the CARDIA Publications Committee.

Sources of Funding

The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (N01-HC95095 & N01-HC48047), University of Minnesota (N01-HC48048), Northwestern University (N01-HC48049), and Kaiser Foundation Research Institute (N01-HC48050).

Disclosures

None.

References

1. Andersen LB, Wedderkopp N, Hansen HS, Cooper AR, Froberg K. Biological cardiovascular risk factors cluster in Danish children and adolescents: the European Youth Heart Study. *Prev Med*. 2003;37:363–367.
2. Smoak CG, Burke GL, Webber LS, Harsha DW, Srinivasan SR, Berenson GS. Relation of obesity to clustering of cardiovascular disease risk factors in children and young adults. *Am J Epidemiol*. 1987;125:364–372.

3. Manolio T, Savage P, Burke G, Liu K, Wagenknecht L, Sidney S, Jacobs D, Roseman J, Donahue R, Oberman A. Association of fasting insulin with blood pressure and lipids in young adults. The CARDIA study. *Arterioscler Thromb Vasc Biol*. 1990;10:430–436.
4. Wilson PWF, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med*. 1999;159: 1104–1109.
5. Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, Williams OD, Bild DE, Detrano R. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA study. *J Am Coll Cardiol*. 2007;49:2013–2020.
6. Berry JD, Liu K, Folsom AR, Lewis CE, Carr JJ, Polak JF, Shea S, Sidney S, O'Leary DH, Chan C, Lloyd-Jones DM. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease. *Circulation*. 2009;119:382–389.
7. Bao W, Srinivasan SR, Wattigney WA, Berenson GS. Persistence of multiple cardiovascular risk clustering related to syndrome X from childhood to young adulthood: the Bogalusa Heart Study. *Arch Intern Med*. 1994;154: 1842–1847.
8. Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino RB. Trajectories of entering the metabolic syndrome. *Circulation*. 2009;120:1943–1950.
9. Lloyd-Jones DM, Liu K, Colangelo LA, Yan LL, Klein L, Loria CM, Lewis CE, Savage P. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components: the Coronary Artery Risk Development in Young Adults Study. *Circulation*. 2007;115:1004–1011.
10. Wilson PWF, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med*. 2007;167:1068–1074.
11. Goff DC, Zaccaro DJ, Haffner SM, Saad MF. Insulin sensitivity and the risk of incident hypertension. *Diabetes Care*. 2003;26:805–809.
12. Mora S, Otvos JD, Rosenson RS, Pradhan A, Buring JE, Ridker PM. Lipoprotein particle size and concentration by nuclear magnetic resonance and incident type 2 diabetes in women. *Diabetes*. 2010;59:1153–1160.
13. Paynter NP, Sesso HD, Conen D, Otvos JD, Mora S. Lipoprotein subclass abnormalities and incident hypertension in initially healthy women. *Clin Chem*. 2011;57:1178–1187.
14. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41:1105–1116.
15. Warnick GR, Mayfield C, Benderson J, Chen JS, Albers JJ. HDL cholesterol quantitation by phosphotungstate-Mg2+ and by dextran sulfate-Mn2+-polyethylene glycol precipitation, both with enzymic cholesterol assay compared with the lipid research method. *Am J Clin Pathol*. 1982;78:718–723.
16. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation*. 2002;106:3143.
17. Pletcher MJ, Hulley BJ, Houston T, Kiefe CI, Benowitz N, Sidney S. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary function: the coronary artery risk development in young adults (CARDIA) study. *Arch Intern Med*. 2006;166:1915.
18. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR, Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of multiethnic study of atherosclerosis (MESA) and coronary artery risk development in young adults (CARDIA) study. *Radiology*. 2005;234:35–43.
19. Polak JF, Person SD, Wei GS, Godreau A, Jacobs DR Jr, Harrington A, Sidney S, O'Leary DH. Segment-specific associations of carotid intima-media thickness with cardiovascular risk factors: the coronary artery risk development in young adults (CARDIA) study. *Stroke*. 2010;41:9–15.
20. Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of type 2 diabetes. *Clin Chem*. 2010;56:1252–1260.

American Heart Association | American Stroke Association

Accumulation of Metabolic Cardiovascular Risk Factors in Black and White Young Adults Over 20 Years

In the article by Paynter et al, "Accumulation of Metabolic Cardiovascular Risk Factors in Black and White Young Adults Over 20 Years," which published online April 24, 2015, and appeared in the April 2015 issue of the journal (*J Am Heart Assoc.* 2015;4:e001548 doi: 10.1161/JAHA.114.001548), the eLocator number was incorrectly listed as e00940 in the article's metadata. This affected the article's citation on several Web pages, as well as the URL for the article. The eLocator number has been corrected to e001548.

The publisher regrets these errors.

The online version of the article has been updated and is available at http://jaha.ahajournals.org/content/4/4/e001548.

J Am Heart Assoc. 2015;4:e000666 doi: 10.1161/JAHA.115.000666.

Accumulation of Metabolic Cardiovascular Risk Factors in Black and White Young Adults Over 20 Years

Nina P. Paynter, Catarina I. Kiefe, Cora E. Lewis, Catherine M. Loria, David C. Goff and Donald M. Lloyd-Jones

J Am Heart Assoc. 2015;4:e001548; originally published April 24, 2015;
doi: 10.1161/JAHA.114.001548
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

American Heart Association | American Stroke Association

Accumulation of Metabolic Cardiovascular Risk Factors in Black and White Young Adults Over 20 Years

In the article by Paynter et al, "Accumulation of Metabolic Cardiovascular Risk Factors in Black and White Young Adults Over 20 Years," which published online April 24, 2015, and appeared in the April 2015 issue of the journal (*J Am Heart Assoc.* 2015;4:e001548 doi: 10.1161/JAHA.114.001548), the eLocator number was incorrectly listed as e00940 in the article's metadata. This affected the article's citation on several Web pages, as well as the URL for the article. The eLocator number has been corrected to e001548.

The publisher regrets these errors.

The online version of the article has been updated and is available at http://jaha.ahajournals.org/content/4/4/e001548.

J Am Heart Assoc. 2015;4:e000666 doi: 10.1161/JAHA.115.000666.