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

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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, young adulthood, and middle age, and the presence of additional risk factors has been shown to increase risk of subclinical atherosclerosis development in young and middle-aged adults and risk of clinical cardiovascular disease in middle age. 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, but less is known about accrual order. Recent data have suggested that the order of accumulation in middle age is associated with clinical outcomes. 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. Hypertension has been associated with incident diabetes, and insulin resistance has been associated with incident hypertension. Other studies have observed an increase in incident diabetes and incident hypertension 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...
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 5,115 black and white women and men from 4 US sites. 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 (1,935 participants) and excluded those who had all 5 metabolic risk factors at baseline (1 participant), leaving 3,178 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. 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. 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). 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. 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.

Subclinical Cardiovascular Disease

Coronary artery calcium (CAC) was measured at year 20 using computed tomography scanning with 2 scans for each participant. 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. A total of 2,577 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
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.
and by smoking status. We also performed an analysis using the ATP III metabolic syndrome criteria. 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 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.

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)                | $<0.001$  |

*The percentage of observations with both risk factors for which the risk factor in the previous column appears first.
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 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.
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.

**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               |
|糖尿病未吸烟者         |                  |                                        |                                |                              |                      |
|                      | Ever Smokers     | 10 (4, 15)                             | 33                             | 0.3                          | <0.001               |
|糖尿病吸烟者           |                  |                                        |                                |                              |                      |
|                      | Black Women      | 10 (5, 16)                             | 34                             | 0.3                          | <0.001               |
|黑人女性              |                  |                                        |                                |                              |                      |
|                      | White Women      | 13 (2, 25)                             | 22                             | 0.6                          | 0.30                 |
|白人女性              |                  |                                        |                                |                              |                      |
|                      | Black Men        | 7 (0, 13)                              | 21                             | 0.3                          | 0.012                |
|黑人男性              |                  |                                        |                                |                              |                      |
|                      | White Men        | 10 (2, 18)                             | 26                             | 0.4                          | 0.012                |
|白人男性              |                  |                                        |                                |                              |                      |
| Dyslipidemia         | Never Smokers    | 55 (52, 59)                            | 44                             | 1.3                          | <0.001               |
|甘油三酯未吸烟者       |                  |                                        |                                |                              |                      |
|                      | Ever Smokers     | 57 (53, 61)                            | 44                             | 1.3                          | <0.001               |
|甘油三酯吸烟者         |                  |                                        |                                |                              |                      |
|                      | Black Women      | 52 (48, 56)                            | 41                             | 1.3                          | <0.001               |
|黑人女性              |                  |                                        |                                |                              |                      |
|                      | White Women      | 65 (60, 70)                            | 47                             | 1.4                          | <0.001               |
|白人女性              |                  |                                        |                                |                              |                      |
|                      | Black Men        | 47 (40, 54)                            | 44                             | 1.1                          | 0.45                 |
|黑人男性              |                  |                                        |                                |                              |                      |
|                      | White Men        | 58 (53, 63)                            | 45                             | 1.3                          | <0.001               |
|白人男性              |                  |                                        |                                |                              |                      |
| Hypercholesterolemia | Never Smokers    | 37 (32, 42)                            | 40                             | 0.9                          | 0.23                 |
|高胆固醇未吸烟者       |                  |                                        |                                |                              |                      |
|                      | Ever Smokers     | 34 (29, 40)                            | 41                             | 0.8                          | 0.032                |
|高胆固醇吸烟者         |                  |                                        |                                |                              |                      |
|                      | Black Women      | 31 (25, 38)                            | 37                             | 0.9                          | 0.15                 |
|黑人女性              |                  |                                        |                                |                              |                      |
|                      | White Women      | 31 (24, 38)                            | 43                             | 0.7                          | 0.004                |
|白人女性              |                  |                                        |                                |                              |                      |
|                      | Black Men        | 48 (39, 56)                            | 40                             | 1.2                          | 0.082                |
|黑人男性              |                  |                                        |                                |                              |                      |
|                      | White Men        | 36 (30, 42)                            | 42                             | 0.9                          | 0.060                |
|白人男性              |                  |                                        |                                |                              |                      |
| Hypertension         | Never Smokers    | 18 (14, 21)                            | 41                             | 0.4                          | <0.001               |
|高血压未吸烟者         |                  |                                        |                                |                              |                      |
|                      | Ever Smokers     | 16 (12, 20)                            | 40                             | 0.4                          | <0.001               |
|高血压吸烟者           |                  |                                        |                                |                              |                      |
|                      | Black Women      | 15 (11, 19)                            | 38                             | 0.4                          | <0.001               |
|黑人女性              |                  |                                        |                                |                              |                      |
|                      | White Women      | 12 (6, 18)                             | 43                             | 0.3                          | <0.001               |
|白人女性              |                  |                                        |                                |                              |                      |
|                      | Black Men        | 20 (14, 26)                            | 42                             | 0.5                          | <0.001               |
|黑人男性              |                  |                                        |                                |                              |                      |
|                      | White Men        | 20 (14, 26)                            | 41                             | 0.5                          | <0.001               |
|白人男性              |                  |                                        |                                |                              |                      |
| Obesity              | Never Smokers    | 35 (32, 38)                            | 42                             | 0.8                          | <0.001               |
|肥胖未吸烟者           |                  |                                        |                                |                              |                      |
|                      | Ever Smokers     | 32 (28, 36)                            | 43                             | 0.8                          | <0.001               |
|肥胖吸烟者             |                  |                                        |                                |                              |                      |
|                      | Black Women      | 40 (36, 44)                            | 41                             | 1.0                          | 0.73                 |
|黑人女性              |                  |                                        |                                |                              |                      |
|                      | White Women      | 30 (24, 35)                            | 45                             | 0.7                          | <0.001               |
|白人女性              |                  |                                        |                                |                              |                      |
|                      | Black Men        | 38 (32, 45)                            | 44                             | 0.9                          | 0.12                 |
|黑人男性              |                  |                                        |                                |                              |                      |
|                      | White Men        | 24 (19, 30)                            | 42                             | 0.6                          | <0.001               |
|白人男性              |                  |                                        |                                |                              |                      |

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
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 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 |
|                      | Observed N (95% CI) | P Value |
|                      | N | | | |
|                      | | | | |
| Black Women | 152 (130, 174) | 131 | 1.2 | 0.052 |
| White Women | 90 (72, 108) | 64 | 1.4 | <0.001 |
| Black Men | 88 (71, 105) | 65 | 1.3 | 0.003 |
| White Men | 129 (109, 149) | 97 | 1.3 | <0.001 |
| 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).
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/m²                            | 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).

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 to 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 \( (1/2)^9 \) (the number of participants with 2 risk factor combinations that include DYSL) + \( (1/3)^9 \) (the number of participants with 3 risk factor combinations that include DYSL) + \( (1/4)^9 \) (the number of participants with 4 risk factor combinations that include DYSL) + \( (1/5)^9 \) (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

| Pairwise Combination* | Number With Combination | Percentage Occurring in Listed Order |
|-----------------------|-------------------------|--------------------------------------|
|                       | Observed, n (95% CI)    | Expected, n                           | 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 56) | 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.

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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.

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*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

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