Risk Factor Groupings Related to Insulin Resistance and Their Synergistic Effects on Subclinical Atherosclerosis

The Atherosclerosis Risk in Communities Study

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The extent to which groupings of insulin resistance–related cardiovascular risk factors synergize to produce atherosclerosis beyond what is expected from their additive effects is uncertain. The objective of this study was to measure interactions among groupings of the features of the insulin resistance syndrome (IRS) on carotid intimal-medial thickness (IMT). This cross-sectional study used baseline data from the Atherosclerosis Risk in Communities Study on 11,790 adults aged 45–64 years without diagnosed diabetes, treated dyslipidemia, or coronary heart disease. The main outcome was carotid IMT, assessed using B-mode ultrasound. The excess carotid IMT attributable to each IRS grouping was determined using multiple linear regression models. There were 57 possible combinations of six IRS components (hypertension, hyperinsulinemia, obesity, hypertriglyceridemia, low HDL cholesterol, and hyperglycemia). In multivariate analysis, 29 of the 57 groupings were associated with excess carotid IMT. Individuals with all six IRS components had the greatest excess IMT compared with those without this grouping (71 μm; 95% CI 40–102 μm). The groupings most strongly associated with excess carotid IMT included hypertension and hypertriglyceridemia. Interventions aimed at ameliorating the IRS may produce reductions in atherosclerotic risk beyond that predicted by treatment of individual IRS-related risk factors. *Diabetes* 51: 3069–3076, 2002

Type 2 diabetes and atherosclerotic cardiovascular disease share common metabolic antecedents, including impaired glucose tolerance, hypertension, dyslipidemia, and abdominal obesity (1–3). These physiologic risk factors tend to cluster with one another in large part because they are thought to be manifestations of an underlying insulin resistance syndrome (IRS), also referred to as the metabolic syndrome or syndrome X (2,4–7). Although there is still some debate about the nature of this syndrome, various clusters of IRS-related components have been found to predict cardiovascular disease (8–12).

In theory, one might apply such knowledge to identify individuals at high risk for IRS-related atherosclerosis with an eye toward intensified treatment. In fact, such application has been difficult because of limited data relating atherosclerosis to specific groupings of IRS components that are routinely measured in clinical practice. This obstacle might be overcome by demonstrating synergy in atherosclerosis risk for particular IRS groupings (i.e., excess atherosclerosis beyond that predicted by the additive effect of the individual components for a particular grouping). Such synergy would be especially compelling if it exceeded the synergy associated with traditional cardiovascular risk factors that are not related to the IRS (e.g., smoking). Prior studies have not formally assessed all possible combinations of IRS components, owing to lack of power (7,13–16) or incomplete physiologic characterization (17), to determine which components are most strongly associated with atherosclerosis.

We therefore undertook a cross-sectional study using baseline data from the Atherosclerosis Risk in Communities Study, a community-based cohort study of ~16,000 middle-aged adults, which is large enough to evaluate the association between various IRS groupings and subclinical atherosclerosis, assessed by carotid intimal-medial thickness (IMT). We hypothesized that the components of IRS—specifically hyperinsulinemia, hyperglycemia, hypertriglyceridemia, low HDL cholesterol, hypertension, and obesity—would be associated with excess carotid IMT beyond merely additive effects, and that this synergy would be stronger than that found for non-IRS risk factors.

RESEARCH DESIGN AND METHODS

Study population. The Atherosclerosis Risk in Communities (ARIC) cohort is a sample of 15,972 men and women aged 45–64 years from four U.S. communities; the study is designed to assess the etiology and natural history of atherosclerosis (18). These communities include Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and several suburbs of Minneapolis, Minnesota. The Minneapolis and Washington County cohorts were virtually all white, and the Forsyth County cohort was ~15%

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ADA, American Diabetes Association; ARIC, Atherosclerosis Risk in Communities; AUC, area under the curve; CHD, coronary heart disease; IMT, intimal-medial thickness; IRS, insulin resistance syndrome.

African-American. The Jackson study participants were chosen from African-Americans only.

Participants were excluded if they were missing data for carotid IMT (n = 1,129) or other variables used in analysis (weight, height, hip circumference, prevalent hypertension, fasting time, total cholesterol, prevalent diabetes, HDL cholesterol, LDL cholesterol, plasma triglycerides, fasting serum insulin, or fasting serum glucose) (n = 750) or if they reported race other than white or black (n = 48). Prevalent hypertension was defined as physician diagnosis, use of antihypertensive medications, or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Prevalent diabetes was defined as physician diagnosis, use of antidiabetic medications, or fasting blood glucose ≥7.7 mmol/l (based on 1979 American Diabetes Association [ADA] diagnostic criteria). We defined undiagnosed diabetes as individuals with fasting blood glucose of 7.0–7.6 mmol/l, based on the 1997 ADA diagnostic criteria. Individuals with prevalent diabetes (n = 1,232), treated dyslipidemia (n = 328), or a history of coronary heart disease (n = 470) were excluded because therapies for glucose control and the associated hypertension and/or dyslipidemia might affect the outcome, masking the relationship between IRS and carotid IMT. Prevalent coronary heart disease was defined as evidence of myocardial infarcation on first visit, electrocardiogram or history of myocardial infarction, coronary artery bypass surgery, or angioplasty. These exclusions left 11,790 participants for analysis. There were 2,969 individuals with treated hypertension. Because there were quite a number of treated hypertensive individuals, the analyses presented include them to increase power; nearly identical results were obtained when these individuals were excluded from analysis.

Assessment of exposures. A baseline physical examination was performed on each participant between 1987 and 1989 to ascertain cardiovascular conditions and measure risk factors (18). Participants were asked to fast for 12 h; actual fasting times were recorded. Venipunctures were performed in the morning using a 21-gauge butterfly needle with the participant seated. After standardized processing at the clinical site, samples were separated into aliquots, frozen at −70°C, and shipped on dry ice to the appropriate ARIC Central Laboratory. Glucose was measured using the hexokinase method, and insulin was measured by radioimmunoassay (125-I Insulin 100 test kit; Cambridge Medical Diagnostics, Billerica, MA). Total cholesterol and triglycerides were measured using enzymatic methods. HDL cholesterol was measured after Dextran magnesium precipitation of apoB-containing lipoproteins. LDL cholesterol was calculated using the formula of Friedewald et al. (19). Patients with triglyceride levels ≥4.52 mmol/l were excluded.

Anthropometry was performed in the fasting state with the urinary bladder empty. Participants wore lightweight, nonconstricting underwear and scrubsuits. Height (without shoes) was measured using a wall-mounted ruler. Weight was measured using a balance scale (Detecto model 437) that was zeroed daily.

Blood pressure was measured in the right arm after the participant had been seated for 5 min, using a random-zero sphygmomanometer and an appropriately sized cuff. Three measurements were taken; the mean of the second and third measurements was used to characterize blood pressure at the visit.

Active smoking was assessed by a 12-item questionnaire. Responses permitted coding of current, ever, and never smokers. At the baseline examination, medication usage in the 2 weeks preceding the examination was determined by having participants bring their medications to the field center to be recorded and coded by study personnel certified to perform this function.

Assessment of subclinical atherosclerosis. Atherosclerosis was assessed using B-mode ultrasound to measure carotid artery IMT. The ultrasound methods used in ARIC were based on the technique developed by Pignoli et al. (20) and used a scanning protocol common to the four field centers, with central reading of ultrasound studies according to a standardized protocol (21). The measurement used in the analysis included the average carotid IMT of the far wall of six sites: left and right carotid bifurcation, left and right common carotid, and left and right internal carotid. Estimated site-specific reliability coefficients were 0.77, 0.73, and 0.70 for mean carotid far-wall IMT at the carotid bifurcation and the internal and common carotid arteries, respectively (22).

Determination of the presence of IRS components. The following cut points were used to define the presence of each IRS component: hyperinsulinemia was defined as a fasting insulin ≥110 pmol/l; hypertriglyceridemia as triglycerides ≥2.26 mmol/l; obesity as a BMI ≥25 kg/m^2; hyperglycemia as a fasting glucose ≥5.5 mmol/l; low HDL cholesterol as ≤1.04 mmol/l; and hypertension as a systolic blood pressure ≥140 mmHg or a previous diagnosis of hypertension.

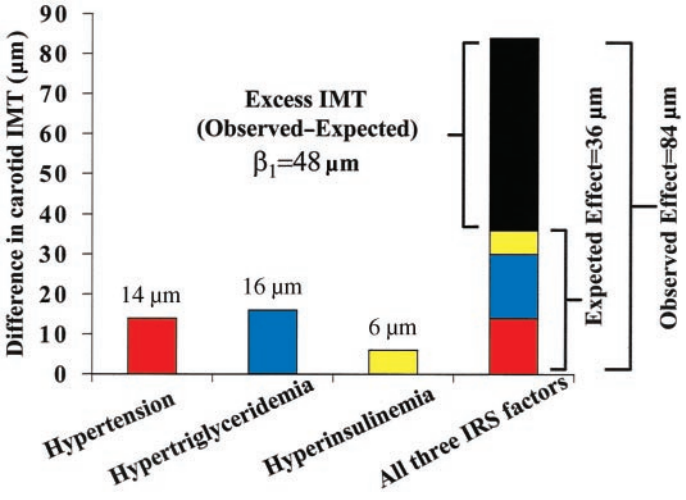

FIG. 1. An example of the calculation of excess carotid IMT for an IRS grouping from the linear regression models. The independent effect of each individual IRS component (hypertension in red, hypertriglyceridemia in blue, and hyperinsulinemia in yellow) on carotid IMT is displayed, along with the observed effect of the grouping of all three components on carotid IMT. The excess carotid IMT (black) is the difference between the observed IMT in the presence of the grouping and the expected IMT from the main effects of each component. Adjustment was made for age, sex, race, LDL cholesterol, fasting insulin, fasting glucose, HDL cholesterol, triglycerides (log-transformed), BMI (including a quadratic term to model its relationship to IMT), systolic blood pressure, use of antihypertensive medications, and smoking status.

Statistical analysis

Assessment of interaction: estimation of excess IMT associated with the IRS groupings. Excess carotid IMT associated with IRS component grouping was assessed using linear regression models. In all models, a grouping was considered to be associated with excess IMT if there was interaction among its components with regard to IMT on a linear (i.e., additive) scale. In other words, excess IMT was defined as the difference between the actual IMT versus the IMT predicted by adding the effects of the individual components. This was also our measure of the synergistic effect of a particular grouping on atherosclerosis. An example of the calculation of the adjusted (see below) excess carotid IMT is displayed in Fig. 1. In this example, the presence of hypertension, hypertriglyceridemia, and hyperinsulinemia each contributes 14, 16, and 6 μm of IMT, respectively. Therefore, the presence of all three components would be expected to contribute 36 μm of IMT; however, 84 μm of IMT are observed, resulting in 48 μm of excess IMT when all three components occur together.

The linear regression equations took the following form:

$$Y = \beta_o + \beta_1 x_1 + [\beta_2 x_2 + \ldots\ldots\ldots\ldots \beta_7 x_7] + [\beta_8 x_8 + \ldots\ldots\ldots\ldots \beta_{13} x_{13}] + \varepsilon$$

where Y = mean carotid IMT in micrometers; β_o = constant; β_1 = coefficient for the IRS grouping interaction term, interpreted as the excess carotid IMT for individuals with a given IRS component grouping compared with individuals without that grouping. If the IRS grouping was present, $x_1 = 1$; if the IRS grouping was absent, $x_1 = 0$. There were 57 possible groupings of two or more IRS components from a field of six components (hyperinsulinemia, hyperglycemia, hypertension, hypertriglyceridemia, low HDL cholesterol, and obesity), giving rise to 57 distinct models and 57 corresponding interaction (β_1) coefficients.

β_2– β_7 represent coefficients for the individual IRS components as covariables. These variables were included in all models for each cluster evaluated. In one set of models, x_2– x_7 were modeled as continuous variables (fasting insulin, fasting glucose, systolic blood pressure, triglycerides, HDL cholesterol, and BMI). To normalize their distribution, triglycerides were log transformed. Because BMI demonstrated a linear relationship to carotid IMT up to a BMI of 26 kg/m^2 and a flat relationship above that, adjustment for BMI included a quadratic term. In a second set of models, x_2– x_7 were modeled as categorical variables, indicating the presence or absence of each component (hyperinsulinemia, hyperglycemia, hypertension, hypertriglyceridemia, low HDL cholesterol, and obesity).

β_8– β_{13} represent coefficients for demographic (age, race, sex) and behavioral (smoking status) covariables and other metabolic covariables (LDL

cholesterol and antihypertensive medication use). These covariables were the same in all multivariate models.

To minimize the risk of type 1 error, we recalculated *P* values for the 57 groupings using a Bonferroni correction for multiple comparisons (23). Absolute carotid IMT was calculated as the mean IMT for individuals with a given IRS grouping, to determine whether this relationship was qualitatively similar to the relationship between the IRS grouping and excess IMT.

Subsidiary analyses. To assess the robustness of the association between IRS and carotid IMT, we conducted parallel analyses using alternative models. Because carotid IMT was right skewed in this population, quantile linear regression, which estimates the median of the dependent variable and is less sensitive to the effects of outliers, was performed (24).

Analyses were conducted to determine the relationship between the IRS components and carotid IMT in the presence of two additional established cardiovascular risk factors that are not related to this syndrome: smoking and elevated LDL cholesterol. This analysis was used to determine if the synergistic effect of IRS component grouping was unique in its relationship to carotid IMT compared with grouping of non–IRS-related factors. High LDL cholesterol was defined as an LDL level ≥3.38 mmol/l (25). A categorical interaction term was created for the presence of current smoking and each of the six IRS components. These individual interaction terms were entered into separate multiple linear regression models. As an example, the β coefficient for one of these interaction terms represented the excess carotid IMT associated with the presence of smoking and hypertension, adjusting for the same variables outlined previously. Similarly, a categorical interaction term was created for the presence of high LDL cholesterol and each of the six IRS components. Statistical interaction was also assessed for selected IRS groupings in the presence of current smoking and high LDL cholesterol.

All statistical analyses were conducted using Stata 6 Software (College Station, TX).

RESULTS

Univariate analysis. As in previous ARIC analyses (26,27), higher levels of BMI, fasting glucose, fasting insulin, LDL cholesterol, triglycerides, and systolic blood pressure and lower levels of HDL cholesterol were all associated with significantly higher levels of carotid IMT (data not shown). Antihypertensive medication use, current smoking, and previously undiagnosed diabetes (fasting glucose ≥7.0 mmol/l) were also associated with significantly greater carotid IMT (all $P < 0.001$, data not shown).

Multivariate analyses

Groupings of IRS components and excess carotid IMT. Various groupings of the IRS components were evaluated in multiple linear regression models to determine their associations with excess carotid IMT. Table 1 displays the prevalence and mean absolute and excess carotid IMT for each individual IRS component and all 57 possible combinations of IRS groupings for the 11,790 middle-aged adults without diagnosed diabetes, treated dyslipidemia, or history of coronary heart disease. Each IRS component was associated with a similar mean absolute IMT, although hypertension, hypertriglyceridemia, and hyperglycemia were associated with significantly greater excess IMT (versus individuals without these traits).

Figure 2 displays the minimum, median, and maximum excess carotid IMT for individuals with two, three, four, five, and six component groupings of the IRS, versus individuals without those groupings. The minimum, median, and maximum excess IMT represent a summary of the range of values present within the 15 possible combinations of two components, 20 possible combinations of three, 15 possible combinations of four, 6 possible combinations of five, and 1 possible combination of all six. For groupings of two, three, four, and five IRS components, the groupings associated with the maximum excess IMT were hypertension and hypertriglyceridemia (26 μm; 95% CI 9.4–42); hypertension, hypertriglyceridemia, and hyperinsulinemia (48 μm; 95% CI 26–70); hypertension, hypertriglyceridemia, hyperinsulinemia, and low HDL cholesterol (64 μm; 95% CI 37–91); and hypertension, hypertriglyceridemia, hyperinsulinemia, low HDL cholesterol, and hyperglycemia (71 μm; 95% CI 41–101), respectively. The excess IMT for individuals with all six components was the same as the maximum excess IMT for individuals with hypertension, hypertriglyceridemia, hyperinsulinemia, low HDL cholesterol, and hyperglycemia (71 μm; 95% CI 40–102). The only difference between these two definitions was the addition of obesity, which did not contribute more information to the model. Eighteen of 57 groupings were significantly associated with excess IMT after Bonferroni correction of the *P* value for multiple comparisons, including the groupings associated with the maximal excess IMT.

Two patterns emerge from this analysis. First, the groupings most strongly associated with excess carotid IMT all included hypertension and hypertriglyceridemia. Second, the groupings with more IRS components were less prevalent in the study population (see Table 1).

The groupings associated with the minimum excess IMT for the two-, three-, four-, and five-component groupings were hypertension and hyperglycemia (0.46 μm; 95% CI −10 to 11); hypertension, hyperglycemia, and low HDL cholesterol (−6.2 μm; 95% CI −21 to 9); hypertension, hyperglycemia, low HDL cholesterol, and obesity (−2.0 μm; 95% CI −17 to 14); and hypertension, hyperglycemia, low HDL cholesterol, obesity, and hyperinsulinemia (14 μm; 95% CI −6 to 34). The IRS groupings associated with the minimum excess IMT all included hypertension and hyperglycemia but did not include hypertriglyceridemia.

When modeling the IRS covariables as categorical variables (hyperinsulinemia, hyperglycemia, hypertension, obesity, low HDL cholesterol, and hypertriglyceridemia) in multiple linear regression models, the associations were attenuated somewhat, but still demonstrated a similar pattern. For example, the maximum excess IMT for individuals with hypertension, low HDL cholesterol, hyperinsulinemia, hypertriglyceridemia, and hyperglycemia was 56 μm (95% CI 24–87) with categorical covariate adjustment vs. 71 μm (95% CI 41–101) with continuous covariate adjustment.

Quantile linear regression, which estimates the median of the dependent variable and is therefore less sensitive to the effects of outliers, yielded attenuated but similar results, indicating the robustness of the associations. The excess IMT for individuals with all six IRS components versus those without these components was 33 μm (95% CI 8.7–62) using quantile linear regression, compared with 71 μm using conventional linear regression.

In unadjusted analyses, IRS groupings associated with the greatest excess IMT were also associated with the greatest absolute carotid IMT (see Table 1). Individuals with hypertension and hypertriglyceridemia had an absolute IMT of 818 μm and individuals with all six components had an absolute IMT of 877 μm.

Other cardiovascular risk factors. To determine whether the synergy observed with regard to carotid IMT was specific to components of the IRS, we conducted subsidiary analyses of two established cardiovascular risk

TABLE 1
Prevalence, mean absolute carotid IMT, and excess carotid IMT for each IRS component and the 57 possible combinations of IRS groupings for 11,790 middle-aged adults

Categorical IRS Component								
Hyperinsulinemia	Hypertension	Low HDL cholesterol	Hypertriglyceridemia	Obesity	Hyperglycemia	Prevalence (%)	Mean Absolute IMT (μm)	Excess IMT (μm)
Individual IRS components								
X						18	760 ± 187	6 (−6, 17)
	X					30	777 ± 200	14 (3, 24)
		X				24	770 ± 191	6 (−3, 15)
			X			10	773 ± 200	16 (4, 29)
				X		63	744 ± 175	6 (−5, 16)
					X	42	765 ± 187	13 (4, 22)
Two-component IRS groupings								
	X				X	16	785 ± 201	0.5 (−10, 11)
X				X		16	760 ± 183	2 (−10, 13)
	X			X		23	777 ± 189	2 (−8, 12)
X	X					8.8	781 ± 202	6 (−7, 19)
X					X	12	770 ± 193	7 (−5, 19)
		X		X		19	775 ± 188	8 (−1, 17)
	X	X				7.6	806 ± 217	8 (−4, 21)
		X			X	13	784 ± 196	11 (1, 22)
				X	X	32	765 ± 187	13 (4, 22)
		X	X			5.9	785 ± 208	16 (2, 30)
X		X				7.2	788 ± 207	18 (5, 32)
			X	X		8.1	782 ± 199	19 (6, 31)
			X		X	5.8	790 ± 210	20 (6, 34)
X			X			3.7	795 ± 217	26 (9, 43)
	X		X			4.1	814 ± 234	26 (9, 42)
Three-component IRS groupings								
	X	X			X	4.8	800 ± 205	−6 (−21, 9)
X	X			X		8.5	780 ± 196	3 (−10, 16)
	X			X	X	13	789 ± 196	3 (−7, 14)
X				X	X	11	770 ± 192	7 (−5, 19)
	X	X		X		6.5	806 ± 209	8 (−5, 21)
X	X				X	6.4	790 ± 204	10 (−4, 24)
X		X			X	5.2	792 ± 210	13 (−2, 28)
		X		X	X	11	788 ± 197	13 (2, 24)
X		X		X		6.8	787 ± 201	16 (3, 30)
		X	X	X		5.1	791 ± 205	19 (4, 34)
X	X	X				3.3	812 ± 230	22 (4, 39)
	X		X	X		3.5	817 ± 227	23 (6, 40)
		X	X		X	3.7	801 ± 214	24 (8, 41)
X			X	X		3.5	795 ± 220	25 (8, 42)
			X	X	X	5.0	798 ± 213	25 (10, 40)
	X	X	X			2.4	828 ± 245	27 (7, 48)
	X		X		X	2.8	828 ± 242	32 (13, 51)
X			X		X	2.6	811 ± 232	34 (14, 54)
X		X	X			2.4	812 ± 230	36 (16, 56)
X	X		X			2.0	834 ± 249	48 (26, 70)
Four-component IRS groupings								
	X	X		X	X	4.3	803 ± 206	−2 (−17, 14)
X	X			X	X	6.1	790 ± 205	10 (−4, 25)
X	X	X			X	2.6	809 ± 223	12 (−8, 32)
X		X		X	X	5.0	793 ± 212	14 (−0.7, 30)
X	X	X		X		3.2	808 ± 218	17 (−0.3, 35)
	X	X	X	X		2.1	829 ± 234	26 (5, 47)
	X	X	X		X	1.7	835 ± 245	29 (5, 52)
		X	X	X	X	3.3	809 ± 220	29 (11, 46)

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TABLE 1
Continued

Categorical IRS Component								
Hyperinsulinemia	Hypertension	Low HDL cholesterol	Hypertriglyceridemia	Obesity	Hyperglycemia	Prevalence (%)	Mean Absolute IMT (μm)	Excess IMT (μm)
X			X	X	X	2.4	813 ± 236	34 (14, 55)
	X		X	X	X	2.5	835 ± 244	35 (15, 55)
X		X	X	X		2.3	813 ± 233	36 (15, 56)
X		X	X		X	1.7	827 ± 246	43 (20, 66)
X	X		X	X		1.9	835 ± 252	47 (24, 69)
X	X		X		X	1.5	854 ± 260	63 (38, 88)
X	X	X	X			1.3	857 ± 267	64 (37, 91)
Five-component IRS groupings								
X	X	X		X	X	2.5	811 ± 224	14 (−6, 34)
	X	X	X	X	X	1.6	842 ± 248	33 (7, 57)
X		X	X	X	X	1.6	829 ± 250	43 (19, 67)
X	X		X	X	X	1.4	857 ± 263	63 (37, 89)
X	X	X	X	X		1.2	858 ± 268	64 (36, 91)
X	X	X	X		X	1.0	871 ± 277	71 (41, 101)
Six-component IRS groupings								
X	X	X	X	X	X	1.1	868 ± 277	71 (40, 102)

*Data are means ± SD or β (95% CI) unless indicated otherwise. Adjustment was made for age, sex, race, LDL cholesterol, fasting insulin, fasting glucose, HDL cholesterol, triglycerides (log transformed), BMI (including a quadratic term to model its relationship to IMT), systolic blood pressure, use of antihypertensive medications, and smoking status.

factors that are not related to the IRS: cigarette smoking and LDL cholesterol. Among current smokers, there was significantly greater excess carotid IMT in the presence of hypertension (32 μm; 95% CI 18–45) and hyperglycemia (15 μm; 95% CI 3.4–27). The magnitude of the excess IMT for these risk factor groupings was similar to that of the two-component IRS grouping containing hypertension and hypertriglyceridemia (26 μm).

There was a statistically significant interaction between smoking and the six-component IRS grouping. Current smokers with this grouping had 106 μm of excess IMT (95% CI 32–179), compared with 9 μm of excess IMT associated with the six-variable grouping in never smokers (95% CI −32 to 50).

In individuals with high LDL cholesterol, there was significantly greater excess carotid IMT in the presence of hypertension (14 μm; 95% CI 4.0–24). The magnitude of the interaction was smaller than that of the two-component IRS grouping containing hypertension and hypertriglyceridemia (25 μm). There was not a statistically significant interaction between the IRS grouping containing all six components and high LDL cholesterol on IMT.

DISCUSSION

We found strong independent associations between selected groupings of IRS components and excess carotid IMT, indicating synergy for atherosclerosis risk beyond what would have been expected from merely additive effects. This synergy was positively associated with an increased number of certain IRS components in the grouping, was strongest in groupings that contained hypertension and hypertriglyceridemia, and was robust under diverse analytic approaches. However, synergy was not unique to grouping of IRS components, as similar magnitudes of excess carotid IMT were found when smoking (a non-IRS cardiovascular risk factor) was grouped with certain IRS components.

Our study has two strengths that lend weight to these conclusions. First, the ARIC population provided a large enough sample size to evaluate all possible IRS groupings in relation to a clinically relevant outcome measure—namely, subclinical atherosclerosis, which has been shown to be predictive of incident coronary heart disease (CHD) (27,28). Second, ARIC has data on multiple cardiovascular risk factors, allowing the independent association between the IRS and carotid IMT to be determined in multivariate analyses.

Nonetheless, several limitations should be kept in mind when interpreting our data. First, because this analysis was cross-sectional, a temporal relationship between IRS and atherosclerosis cannot be firmly established. It has been previously demonstrated, however, that one component of IRS, hyperinsulinemia, predicts the development of type 2 diabetes, low HDL cholesterol, hypertriglyceridemia, and hypertension (29,30), which are known risk factors for atherosclerosis and cardiovascular disease.

Second, we did not examine other emerging components of the IRS, most notably the fibrinolytic factors, that are also related to atherosclerosis (31). Third, multiple analyses using 57 groupings raise concern about type 1 error. However, the main hypothesis was that a general pattern of association would exist between IRS groupings and IMT. Furthermore, several of the stronger associations held even after correction for multiple comparisons. Fi-

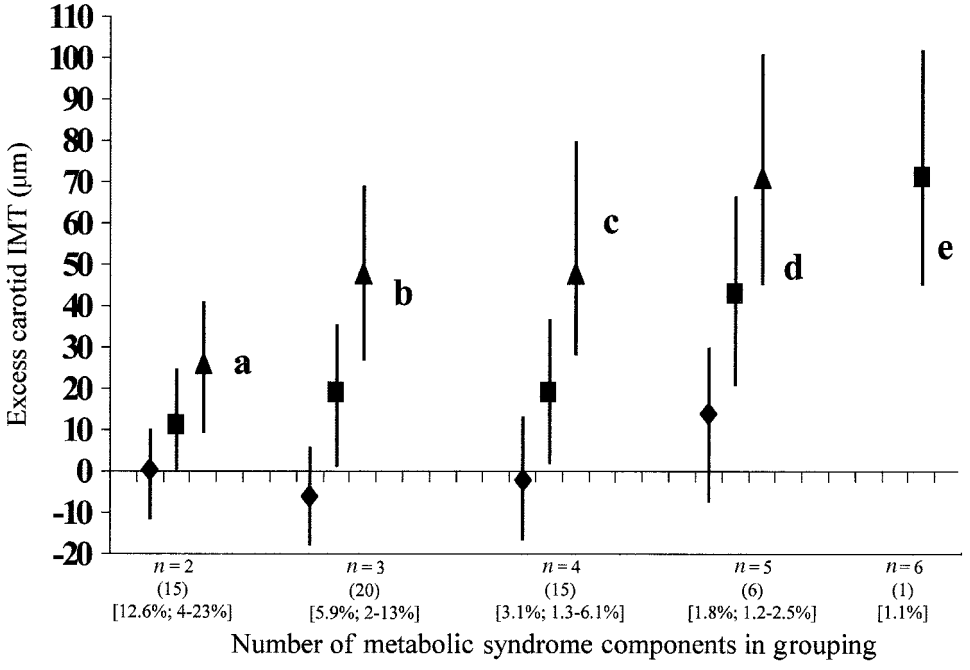

FIG. 2. Excess carotid IMT related to selected groupings of IRS components with continuous adjustment of covariates. Minimum (●), median (■), and maximum (▲) excess carotid IMT and 95% CIs for individuals with two, three, four, five, and six component groupings of the IRS components are displayed. Values on the *x*-axis represent (*n* of possible combinations tested) [average prevalence and range of prevalence of groupings within *n* category]. The prevalence range of the two-, three-, four-, and five-component groupings were 4–23%, 2–13%, 1.3–6.1%, and 1.2–2.5%, respectively. The components of the groupings associated with the greatest excess IMT and their prevalences are a = hypertension + hypertriglyceridemia (4.1%); b = hypertension + hypertriglyceridemia + hyperinsulinemia (2.0%); c = hypertension + hypertriglyceridemia + hyperinsulinemia + low HDL (1.3%); d = hypertension + hypertriglyceridemia + hyperinsulinemia + low HDL + hyperglycemia (1.0%); e = hypertension + hypertriglyceridemia + hyperinsulinemia + low HDL + hyperglycemia + obesity (1.1%). All models were also adjusted for age, sex, race, LDL cholesterol, fasting insulin, fasting glucose, HDL cholesterol, triglycerides (log transformed), BMI (including a quadratic term to model its relationship to IMT), systolic blood pressure, use of antihypertensive medications, and smoking status.

nally, the definitions of the 57 groupings were not mutually exclusive (e.g., the 131 individuals with all six components were a subset of the 520 individuals with hypertension and hypertriglyceridemia). Thus, direct comparisons across grouping sizes are difficult to interpret. Instead, these analyses are intended to show a general pattern (i.e., rising excess IMT and decreasing prevalence as grouping size increases).

Only a few previous studies have evaluated the IRS in relation to a clinically relevant outcome, such as IMT (32,33). In one study, carotid IMT was positively correlated with fasting glucose, BMI, total cholesterol, and dyslipidemia (32), and in a second study, the thicker IMT in diabetic subjects was mediated through a cluster of hyperglycemia and dyslipidemia (33). These studies, however, had small sample sizes and did not evaluate synergy among IRS components.

Three recent studies have used factor analysis in an attempt to identify components of the IRS in relation to CHD events and stroke (8–10). Lehto et al. (10) identified a "hyperinsulinemia cluster" (increased BMI, triglycerides, and insulin and decreased HDL cholesterol), which was predictive of death from CHD in patients with type 2 diabetes. In another study, the insulin resistance factor (BMI, waist-to-hip ratio, triglycerides, fasting plasma glucose, and insulin) predicted CHD death and nonfatal myocardial infarction in elderly men (9). In a follow-up of the Helsinki Policemen Study, factor analysis produced an insulin resistance factor (BMI, subscapular skinfold, area under the curve [AUC] for insulin, AUC for glucose, mean blood pressure, and triglycerides) that independently predicted the risk of CHD (8). Whereas these studies identify several of the same IRS components (BMI, triglycerides, and insulin), they did not seek IRS component combinations associated with the maximum synergy for atherosclerosis.

Our analysis identified hypertriglyceridemia as a key component of the IRS that is closely associated with atherosclerosis. Several studies in diabetic and nondiabetic individuals have shown that triglyceride levels are positively correlated with direct measures of insulin resistance (14,15,34) and serum insulin levels (35,36). Insulin resistance leads to several abnormalities in lipoprotein metabolism that lead to elevated triglyceride levels and atherogenesis. These include *1*) failure of insulin to suppress plasma levels of nonesterified fatty acids, providing more substrate for triglyceride synthesis; *2*) stimulation of triglyceride synthesis and secretion through hyperinsulinemia-induced upregulation of fatty acid synthase and acetyl CoA carboxylase; *3*) suppression of lipoprotein lipase activity, leading to decreased clearance of atherogenic VLDL and chylomicron remnants; and *4*) transfer of triglycerides to LDL, leading to an increase in atherogenic small, dense LDLs (37).

We also identified hypertension as the other component of the IRS most strongly associated with atherosclerosis. With the exception of one-factor analysis (8), blood pressure has been identified as a separate factor from the insulin/obesity/lipid factors (5,9,10,38), suggesting different pathophysiological processes leading to hypertension

and insulin resistance. In two studies, however, the hypertension factor predicted CHD death, as did the insulin resistance factors (9,10). Our data show that independent of the significant main effect of hypertension on IMT, it also has a synergistic effect on IMT in the setting of other IRS-related risk factors, demonstrating the important contribution of hypertension to IRS-related atherosclerosis.

Although neither cigarette smoking nor high LDL cholesterol is related to the IRS, they are well-established cardiovascular risk factors and, in our study, appeared to independently contribute to excess IMT. Current cigarette smoking and high LDL cholesterol were associated with greater excess carotid IMT in the presence of hypertension, on a magnitude similar to that attributable to selected groupings of IRS components. This is consistent with previous studies showing that clustering of multiple cardiovascular risk factors, including elevated cholesterol, hypertension, and smoking, is associated with increased risk for cardiovascular disease (17,39,40). Endothelial dysfunction, altered lipid metabolism, and adrenergic stimulation induced by smoking can lead to vascular damage (41,42), augmenting atherosclerotic changes in the setting of hypertension and dyslipidemia. Further studies are needed, however, to confirm the impact of smoking on atherosclerosis in the IRS.

Studies of IMT beg the question of clinical interpretation, e.g., how significant is an excess IMT of 70 μm, as we found for individuals with all six IRS components, in the face of the significant main effects of each factor? Previous work by Hodis et al. (28) found that a 130-μm increase in absolute carotid IMT was associated with a 40% increased risk of myocardial infarction or coronary death. Therefore, an excess carotid IMT of 70 μm would be expected to predict an ~20% increased risk of myocardial infarction or coronary death. However, further research is needed to support this inference empirically.

Our study has the following implications. First, it further confirms previously reported associations between the IRS and atherosclerotic cardiovascular disease. Second, it provides a basis for using clinical parameters to identify individuals at high risk for IRS-related atherosclerosis. Third, it demonstrates that there is synergy between cardiovascular risk factors. Although this synergy is not unique to the IRS components, it nonetheless suggests that interventions aimed at the root cause of the IRS may confer benefits on cardiovascular disease prevention beyond that expected from treating these risk factors individually.

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