Prevalence of the Metabolic Syndrome Among a Racially/Ethnically Diverse Group of U.S. Eighth-Grade Adolescents and Associations With Fasting Insulin and Homeostasis Model Assessment of Insulin Resistance Levels

STUDIES TO TREAT OR PREVENT PEDIATRIC
   TYPE 2 DIABETES (STOPP-T2D)
PREVENTION STUDY GROUP*

OBJECTIVE — The purpose of this study was to report the prevalence of the International Diabetes Federation (IDF)–defined metabolic syndrome and its components among a cross-sectional sample of racially/ethnically diverse eighth grade youths and examine the association between the presence of the syndrome and participant fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) levels.

RESEARCH DESIGN AND METHODS — Data were from a cross-sectional study with 1,453 racially/ethnically diverse eighth grade students from 12 middle schools in three U.S. states (Texas, North Carolina, and California). Height, weight, waist circumference, and blood pressure were recorded. Fasting blood samples were analyzed for triglycerides, HDL cholesterol, glucose, and insulin; HOMA-IR was calculated. Sex, race/ethnicity, and pubertal stage were self-reported. IDF criteria were used to determine the prevalence of the metabolic syndrome. The odds ratio for being classified with the syndrome was calculated by quintiles of fasting insulin and HOMA-IR.

RESULTS — Of the sample, 138 students (9.5%) were classified with metabolic syndrome. Hispanics were more likely to have high abdominal adiposity and high triglycerides. Male adolescents were more likely to have high triglycerides, low HDL cholesterol, high blood pressure, and high fasting glucose. Participants in the highest insulin quintile were almost 200 times more likely to be classified with the syndrome than participants in the lowest quintile with comparable associations for HOMA-IR quintiles.

CONCLUSIONS — In a racially/ethnically diverse sample of U.S. adolescents, 9.5% of participants were identified with the metabolic syndrome using the IDF criteria. The likelihood of metabolic syndrome classification significantly increased with higher insulin and HOMA-IR values.

The metabolic syndrome is associated with an increased risk of development of type 2 diabetes and cardiovascular disease (CVD) (1–3). Although a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes raised concerns about whether the presence of the syndrome conveys a risk of heart disease beyond that of the individual components (3), it is clear that adults with metabolic syndrome are more likely to develop CVD. Metabolic syndrome risk factors (4,5) in childhood have also been shown to predict the likelihood of possessing the metabolic syndrome and type 2 diabetes in adulthood (4). Determination of pediatric prevalence rates has been hampered by the lack of a consistent definition for metabolic syndrome in children, with investigators creating their own definitions (6–9).

The International Diabetes Federation (IDF) proposed a definition that can be applied globally. According to the IDF criteria, an adolescent has metabolic syndrome if he or she has abdominal obesity (waist circumference ≥90th percentile) and two of the following: triglycerides ≥ 1.7 mmol/l; HDL cholesterol <1.03 mmol/l; blood pressure ≥ 130 mmHg systolic or ≥85 mmHg diastolic; or glucose ≥5.6 mmol/l (10). A recent analysis of the National Health and Nutrition Examination Survey (NHANES) reported that 4.5% of U.S. 12- to 19-year-old adolescents were classified with the syndrome (11) using the IDF criteria. There is a need to apply these new criteria to alternative datasets to compare metabolic syndrome prevalence rates across studies and facilitate monitoring of temporal trends.

Although metabolic syndrome has been referred to as the insulin resistance syndrome (12), the IDF criteria do not include either fasting insulin level or the homeostasis model of insulin resistance (HOMA-IR) (13). There has been debate about the extent to which the metabolic syndrome defines the risk of CVD associated with insulin resistance beyond the risk associated with classic CVD risk factors (obesity, HDL, triglycerides, and blood pressure) (3). Therefore, it would be useful to understand the extent to which the presence of the syndrome is associated with insulin resistance. This article reports *1*) the prevalence of the IDF-defined metabolic syndrome among a

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cross-sectional sample of ethnically diverse eighth grade youths, 2) the components of the syndrome among those participants, and 3) the association between the presence of the syndrome and participant fasting insulin and HOMA-IR levels.

RESEARCH DESIGN AND METHODS

The data presented here are from a pilot study conducted by the Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D) Prevention Study Group. STOPP-T2D Prevention is a National Institute of Diabetes and Digestive and Kidney Diseases multisite study designed to reduce the prevalence of risk factors for type 2 diabetes among middle school children. Data were collected at three field centers in Texas (Baylor College of Medicine), California (University of California, Irvine), and North Carolina (University of North Carolina at Chapel Hill). The STOPP-T2D coordinating center is at The George Washington University Biostatistics Center (Washington, D.C.). The four institutional review boards approved this study.

Participant recruitment methods and inclusion criteria have been reported elsewhere (14). In brief, participants were eighth grade students recruited from 12 schools (4 per field center), in which at least 50% of the participants were from a race/ethnicity that has an increased risk of development of type 2 diabetes (black, Native American, or Hispanic). Schools were also required to have at least 50% of their enrolled students eligible for free or reduced price school lunch. All eighth grade students who provided written parental consent and childhood assent and who did not have a diagnosis of either type 1 or type 2 diabetes were eligible to participate. Participants received 50 USD and a free breakfast for participating in the study.

Participant race/ethnicity and sex were obtained by self-report. Pubertal development was self-assessed using the Pubertal Development Scale (15). Height was measured to the nearest 0.1 cm on a stadiometer (PE-AIM-101; Perspective Enterprises, Kalamazoo, MI) with the participants shoeless and the head in the Frankfort plane. Body weight was measured to the nearest 0.1 kg using a precalibrated electronic scale (SECA Alpha 882; Vogel & Halke, Hamburg, Germany) with the participants shoeless and pockets empty. BMI (weight in kilograms divided by the square of height in meters) and BMI percentiles were then calculated using Centers for Disease Control and Prevention age- and sex-specific percentiles, and participants were grouped as normal weight (BMI <85th percentile), overweight (85th percentile ≥ BMI <95th percentile), and obese (BMI ≥95th percentile). Waist circumference was assessed to the nearest 0.1 cm at the lateral border of the right iliac crest according to the NHANES protocol with use of a weighted measuring tape by research assistants who were within 90% agreement with a criterion observer during a prestudy training procedure. Blood pressure was recorded three times using an automated blood pressure monitor (Omron HEM-907; Omron Healthcare, Vernon Hills, IL). The initial measurement was taken after the participant had been seated quietly for 5 min, and each subsequent value was recorded 1 min after the preceding measurement. The mean of the second and third measurements was used in all analyses.

Participants were called the night before the blood sampling and were reminded that they needed to fast before the test. At the beginning of the blood sampling, participants were asked when they last ate, and any participant who reported eating or drinking after midnight was considered nonfasting and was asked to return another day when he or she would still receive the incentive. No participants reported taking any lipid-lowering or antihypertensive medications. Fasting venous blood samples were obtained by experienced phlebotomists. Blood was collected in 2-ml Vacutainers (Becton Dickinson, Franklin Lakes, NJ). Vacutainers containing sodium fluoride and sodium heparin were used to collect blood for glucose and insulin samples, respectively. Cholesterol samples were collected in EDTA tubes. Blood was spun and separated into serum and plasma, frozen, packed in dry ice, and shipped to the Northwest Lipid Metabolism and Diabetes Research Laboratory at the University of Washington. Measurement of lipoprotein fractions (for HDL cholesterol) and triglycerides were performed enzymatically using a Hitachi 917 autoanalyzer and Centers for Disease Control and Prevention standardized procedures. The interassay coefficients of variation (CVs) are consistently <1.5% for total cholesterol and triglycerides and <2% for HDL cholesterol for this laboratory. Glucose was assessed using the same analyzer and reagent from Roche Diagnostics. Insulin was determined using a double-antibody radioimmunoassay (16). The between-assay CVs of the two low- and high-insulin quality control samples were 6.9 and 4.6%, respectively. The CV on blind split duplicates was consistently <8.0%. HOMA-IR was computed according to the formula: (glucose × insulin)/22.5 (13).

Statistical analysis

Descriptive statistics including means, SDs, and percentages were calculated for all variables. Generalized estimating equation models that took into account the clustering of observations within schools were used to test for differences in the percentage of students with metabolic syndrome as defined by each measurement, the mean number of metabolic syndrome abnormalities, and mean insulin levels and HOMA-IR for those with and without metabolic syndrome. Equal correlation between all interschool observations (exchangeable) was chosen as the covariance structure. Associations between sex and race/ethnicity and each of the metabolic syndrome components were determined using logistic regression models. Logistic regression generalized estimating equation models were used to predict metabolic syndrome by quintile of insulin and HOMA-IR before and after adjustment for sex, pubertal stage, and racial/ethnic group. To explore whether results differed by racial/ethnic groups, the models with the interaction between racial/ethnic group and our primary exposure variables (insulin or HOMA-IR) were rerun. Unfortunately, none of these models would converge because there was collinearity between school and race, with some schools almost exclusively comprising a single racial/ethnic group. As participants were clustered within schools and the data are from a cluster-designed trial, it is not appropriate to rerun the analysis independent of school, and therefore these analyses could not be performed. All descriptive data from this pilot study of a multisite trial are considered exploratory and thus all *P* values are presented without adjustment for multiple comparisons. SAS statistical software (version 9.1; SAS Institute, Cary NC) was used for all statistical analyses.

RESULTS

A total of 1,740 eighth grade students participated in the study. After exclusion of 135 students with incomplete data required for the various metabolic syndrome definitions and 8

Table 1—Descriptive values for all participants and stratified by presence or absence of the metabolic syndrome

| | | | | | | IDF-defined metabolic syndrome | | | | | | | | | | |
| | All participants | | | | | No | | | | | Yes | | | | | |
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	P
Waist circumference (cm)	1,453	80.5	14.1	56	154	1,315	78.1	12.2	56	130	138	103.2	10.7	85	154	<0.001
HDL (mg/dl)	1,453	47.3	11.9	19	94	1,315	48.5	11.7	22	94	138	35.0	5.1	19	55	<0.001
Triglyceride (mg/dl)	1,453	77.6	43.6	13	375	1,315	71.6	35.4	13	312	138	134.6	67.0	36	375	<0.001
Diastolic blood pressure (mmHg)	1,453	65.6	8.8	43	110	1,315	64.8	8.3	43	110	138	73.2	10.0	48	98	<0.001
Systolic blood pressure (mmHg)	1,453	114.1	10.5	83	156	1,315	113.3	10.1	83	156	138	121.7	11.3	96	153	<0.001
Fasting glucose (mg/dl)	1,453	97.9	7.2	75	123	1,315	97.4	7.1	75	123	138	103.1	6.2	84	123	<0.001
BMI (kg/m^2)	1,453	24.2	5.8	14	56	1,315	23.4	5.1	14	50	138	32.5	5.1	24	56	<0.001
Fasting insulin (μU/ml)	1,444	30.2	19.2	3	209	1,308	27.6	16.3	3	209	136	55.3	25.6	16	160	<0.001
HOMA-IR	1,444	7.4	4.9	1	48	1,308	6.7	4.1	1	48	136	14.2	6.9	4	46	<0.001

*Logistic regression models testing for differences in mean values for participants classified with and without the IDF-defined metabolic syndrome. Min, minimum; Max, maximum.

students who had diabetes at the time of the blood sampling, a total of 1,597 students remained. Because standardized cut points for waist circumference are only available for white, black, and Hispanic children (17), an additional 144 students with any other race/ethnicity were excluded, leaving 1,453 students for these analyses.

Of the 1,453 eighth grade participants included in the analyses, 828 (57%) were female, 844 (58%) were Hispanic, 367 (25%) were black, and 242 (17%) were white. Fifty percent (733) were normal weight (BMI <85th percentile), 20.9% were overweight (85th ≤ BMI < 95th percentile), and 28.6% were obese (BMI ≥95th percentile). Only 122 (8.5%) of the participants were Tanner stage I or II, 370 (25.6%) were Tanner stage III, 853 (59.1%) were Tanner stage IV, and 98 (6.8%) were Tanner stage V with 10 students having missing values for Tanner stage. Mean values for each of the metabolic syndrome components and BMI are presented for all participants and separately for participants with and without the syndrome in Table 1. The *P* values in Table 1 are for regression models testing for differences in the mean values for each risk factor between participants classified with and without the syndrome. Mean values for each risk factor were significantly higher among participants who were classified with the syndrome (Table 1).

Of the participants, 138 students met the IDF criteria for metabolic syndrome. The prevalence of each component of the syndrome is shown for each sex stratified by race/ethnicity in Table 2. There were significant (*P* < 0.05) racial/ethnic differences in the presence of high waist circumference with the highest levels among the Hispanic male adolescents (25 vs. 21 and 16%), and a similar pattern was also evident for the female adolescents. Fewer black male adolescents had high triglycerides than white or Hispanic male adolescents (3 vs. 9 and 10%). The same pattern was also evident for low HDL cholesterol, in cholesterol, which fewer black male adolescents (21%) had low HDL cholesterol than either Hispanic (41%) or white (46%) male adolescents. Similarly, fewer black female adolescents (11%) had low HDL cholesterol than white (22%) or Hispanic females adolescents (27%) (Table 2).

Thus, 138 participants were classified with metabolic syndrome. Of the 1,453

Table 2—Presence of each individual metabolic risk factor percentage within sex stratified by race/ethnic group

| | Waist ≥90th percentile NHANES | | Triglycerides ≥150 mg/dl | | HDL cholesterol ≤40 mg/dl | | High blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg | | Fasting glucose ≥100 mg/dl | |
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Male										
Black	112 (79)	30 (21)	138 (97)	4 (3)	112 (79)	30 (21)	114 (80)	28 (20)	67 (47)	75 (53)
Hispanic	272 (75)	93 (25)	329 (90)	36 (10)	217 (59)	148 (41)	320 (88)	45 (12)	140 (38)	225 (62)
White	99 (84)	19 (16)	107 (91)	11 (9)	64 (54)	54 (46)	98 (83)	20 (17)	55 (47)	63 (53)
	P = 0.0337		*P* = 0.0012		*P* < 0.0001		*P* = 0.066		*P* = 0.0513	
Female										
Black	188 (84)	37 (16)	225 (100)	0 (0)	201 (89)	24 (11)	215 (96)	10 (4)	182 (81)	43 (19)
Hispanic	355 (74)	124 (26)	436 (91)	43 (9)	348 (73)	131 (27)	450 (94)	29 (6)	330 (69)	149 (31)
White	107 (86)	17 (14)	120 (97)	4 (3)	97 (78)	27 (22)	119 (96)	5 (4)	93 (75)	31 (25)
	P = 0.0065		*P* = *		*P* < 0.0001		*P* = 0.1485		*P* = 0.1055	
Total	1,133 (78)	320 (22)	1,355 (93)	98 (7)	1,039 (72)	414 (28)	1,316 (91)	137 (9)	867 (60)	586 (40)

Data are n (%). P values represent tests for ethnic/racial differences within sex in the proportion of participants classified with and without the IDF-defined metabolic syndrome. *Model could not be assessed due to an empty cell.

Table 3—*Logistic regression model predicting prevalence of metabolic syndrome by quintiles of insulin and HOMA-IR values, adjusted for sex, pubertal stage, and racial/ethnic group*

	OR (95% CI)	Z	P
Insulin quintile group			
Insulin: 39.1+ µU/ml	199.64 (31.29–1,273.70)	5.60	<0.001
Insulin: 29.1–39.0 µU/ml	30.23 (4.25–215.00)	3.41	0.0007
Insulin: 23.1–29.0 µU/ml	10.29 (1.60–65.99)	2.46	0.0139
Insulin: 17.1–23.0 µU/ml	2.20 (0.52–9.28)	1.08	0.2817
Insulin: ≤17.0 µU/ml	Referent	—	—
HOMA-IR quintile group			
HOMA-IR: 10.0+ HOMA units	210.88 (31.10–1,429.73)	5.47	<0.0001
HOMA-IR: >7.0–10.0 HOMA units	36.70 (4.97–271.05)	3.61	0.0003
HOMA-IR: >5.5–7.0 HOMA units	6.62 (0.89–49.04)	1.92	0.0548
HOMA-IR: >4.0–5.5 HOMA units	2.26 (0.48–10.56)	1.12	0.2607
HOMA-IR: ≤4.0 HOMA units	Referent	—	—

participants with complete data only 320 (22.0%) had the mandatory waist circumference greater than the 90th percentile. Of the participants who had the syndrome, 125 (90.6%) had low HDL cholesterol, 110 (79.7%) had high fasting glucose, 44 (31.9%) had high blood pressure, and 53 (38.4%) had high triglycerides. Eight participants (5.8% of those with syndrome) had all five risk factors, 40 (29.0%) had four risk factors, and 90 (65.2%) had three risk factors (data not in tabular form).

The mean fasting insulin and HOMA values for 136 participants (2 students with the syndrome were missing insulin values) with metabolic syndrome were 51.2 µU/ml and 12.9 HOMA units for those with three components, 61.5 µU/ml and 16.4 HOMA units for four components, and 70.9 µU/ml and 19.2 HOMA units for participants with all five risk factors (data not in tabular form).

Logistic regression models predicting the presence of the syndrome by quintiles of fasting insulin and HOMA-IR values after adjustments for sex, racial/ethnic group, and pubertal stage are shown in Table 3. The odds of metabolic syndrome increased rapidly with increasing insulin levels; students in the third insulin quintile group were 10 times more likely to have the syndrome than those in the lowest insulin quintile group and the odds ratio (OR) increased to about 200 times for those in the highest quintile group compared with those in the lowest quintile group ($P = 0.014$ and $P < 0.001$, respectively). Comparable ORs (157.4, 26.2, 9.9, and 2.1 for the four quintile groups) were obtained for unadjusted models (data not in tabular form). Participants in the highest HOMA-IR quintile

group were >200 times more likely to have the syndrome than those in the lowest quintile group ($P < 0.0001$). In the insulin model, female adolescents were less likely to be categorized with the syndrome than male adolescents ($P = 0.009$) and in both the insulin and HOMA-IR models, blacks were less likely to have the syndrome than whites (both $P < 0.01$). The unadjusted ORs for the HOMA-IR models were similar to those obtained for the adjusted model (182.6, 33.8, 6.5, and 2.2 for each of the four quintile groups, data not shown) (Table 3).

CONCLUSIONS — The data presented in this article show that 9.5% of a racially and ethnically diverse sample of U.S. eighth grade adolescents, 50% of whom were overweight or obese, had the metabolic syndrome on the basis of the new IDF criteria for children. The prevalence rate in this sample was roughly double the mean 4.5% prevalence rate that was reported in the NHANES 1999–2004 sample using the same criteria (11). A recent NHANES article (11) also reported that metabolic syndrome prevalence was highest (7.1%) among Mexican-American adolescents; the metabolic syndrome has also been shown to be higher among overweight adolescents (18). Thus, the increased prevalence in our sample probably reflected the high percentage of participants from racial/ethnic groups at increased risk of type 2 diabetes and the high prevalence of overweight/obesity among our participants.

The IDF criteria are based on expert opinion but have not been shown to predict future disease risk. Therefore, to facilitate comparison of our sample with published data we also applied four pre-

viously reported adolescent metabolic syndrome criteria to our data (6–9). The criteria of Weiss et al. (9) yielded a prevalence rate of 1.7%, those of Cruz et al. (7) yielded a rate of 6.1%, those of Cook et al. (6) yielded a rate of 11.6%, and those of de Ferannti et al. (8) yielded a rate of 14.3%. Thus, the IDF criteria produced a prevalence estimate that is approximately the mean of previously reported criteria, thereby providing concurrent validity to use of the IDF criteria as a reasonable method of classifying adolescents with metabolic syndrome.

More than 92% of students with the syndrome had low HDL cholesterol, whereas 80% had high fasting glucose levels, indicating that these two components were central to a participant being classified with the syndrome. Waist circumference is essential to the IDF criteria and has previously been shown to correlate strongly with HDL cholesterol ($r = -0.47$) and glucose ($r = 0.44$) among U.S. adolescents (19). Thus, the high percentage of participants with metabolic syndrome on the basis of low HDL cholesterol and high fasting glucose is also probably a reflection of the emphasis that the IDF criteria places on high waist circumference.

More than 40% of all participants in this study had high fasting glucose levels, which is higher than the 10.8% that was reported for 12- to 19-year-old adolescents participating in the NHANES 1999–2002 survey (20). We have previously reported that the fasting glucose levels of the participants in this study increased with BMI group and that our fasting glucose levels are comparable to those of other studies that include subjects across the weight spectrum (14,21). The higher prevalence rate reported here therefore probably reflects differences in the criteria for high fasting glucose levels as the IDF criteria use the ≥100 mg/dl definition recommended by the American Diabetes Association (22), whereas the analysis of the NHANES dataset used a level of ≥110 mg/dl.

Similarly, only 53 (38.4%) of our participants with the syndrome had high triglycerides, but the triglyceride cut point of 150 mg/dl is considerably higher than the 110 mg/dl that has previously been used for this age-group (6). Thus, comparison of our findings with previous data are difficult because the risk categories for each of the metabolic syndrome criteria has not been consistent. These differences underscore the need to adopt

uniform definitions such as the IDF criteria to facilitate comparison of data from different studies.

Students in the highest quintile of insulin values were about 200 times more likely to be classified with metabolic syndrome than those in the lowest quintile group with comparable ORs for HOMA-IR quintiles. Similarly, the mean insulin and HOMA-IR values increased with the number of components. Thus, if future epidemiological research shows that metabolic syndrome identifies participants at increased risk of CVD above the risk provided by classic CVD risk factors because of insulin resistance, our findings suggest that the IDF criteria are likely to capture the increase in risk attributable to insulin resistance. The mean insulin value for our participants was 30.2 μU/ml, which is considerably higher than the level that has previously been reported in other U.S. samples (7,19), probably reflecting the high rate of obesity and the racial/ethnic diversity of our participants. The relationship between insulin and metabolic syndrome might be different in other samples. Nevertheless, the key implication is that youths with high insulin and HOMA-IR levels have a much greater risk of being classified with metabolic syndrome.

The specific metabolic syndrome components differed by race/ethnicity and sex. Hispanics were more likely to have high fasting glucose than the other racial/ethnic groups. The presence of low HDL was substantially lower among the black students than among the other two racial/ethnic groups. Male adolescents were more likely to have low HDL cholesterol, high blood pressure, and high fasting glucose than female adolescents. Collectively, these findings suggest that understanding the presence of the individual components of the syndrome by participant characteristics is important as prevention efforts may be more successful if they are tailored to the risk factors that are more likely to be present in each racial/ethnic and sex group.

Limitations

Insulin is not a standardized assay; assessment methods differ between laboratories (23), making comparison with other studies difficult. Insulin has also been shown to vary within individuals (24) and thus the categorization of participants' insulin levels based on a single insulin value should be interpreted with caution. HOMA-IR is a function of both insulin

and glucose, and glucose is included in the syndrome criteria. Therefore, caution is required when interpreting the associations with HOMA-IR. The data are cross-sectional, and it is not possible to identify the direction of causality among metabolic syndrome, insulin, and HOMA-IR. Participants were predominately from low-income households and from just three U.S. states; therefore, it is not possible to generalize the findings to other groups or to the wider population. Finally, the analyses identified the associations between the presence of the IDF-defined metabolic syndrome and fasting insulin and HOMA-IR levels. The association between fasting insulin levels and the presence of the metabolic syndrome highlights the importance of insulin resistance in the development of the syndrome. However, insulin or HOMA-IR cut points for the identification of metabolic syndrome were not identified, and our data should not be used to formulate clinical guidelines. Finally, the study is limited by the collinerality between school and racial/ethnic group in our samples, which prevented us from fully exploring racial/ethnic differences in associations, and therefore more work is needed to revaluate our findings in other datasets.

In summary, ~9.5% of a racially/ethnically diverse sample of U.S. adolescents were identified with IDF-defined metabolic syndrome. The likelihood of being classified with metabolic syndrome increased with higher insulin and HOMA-IR values, suggesting that the criteria might provide a method of identifying adolescents who could have an increased risk of CVD and type 2 diabetes because of insulin resistance.

APPENDIX — The members of the writing group for this article are R. Jago (chair), T. Baranowski, J. Buse, S. Edelstein, P. Galassetti, J. Harrell, F. Kaufman, B. Linder, and T. Pham.

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