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Introduction

This study examines the association between obesity and risk of type II diabetes (T2D) in a large multiethnic observational study. We examined effect modification of the obesity-T2D association by race and physical activity.

The present study also examines the relationship between genotypes and T2D risk in a nested case-control study.

Methods

The Global Epidemiology Study. The Global Epidemiology Study (GES) is a multinational study to assess disease risk factors. Subjects were recruited to the GES from countries including the United States, Tunisia, Poland and India. The GES is linked to the Global Repository that houses biomaterial. For diabetes, subjects provided informed consent and were asked about diet and health behaviors during in-person interviews using the same translated survey instrument.

Epidemiology Study. We examined the association between obesity and type II diabetes risk among 11,455 type II diabetes cases and 12,837 disease-free controls including 3,369 Indian cases and 2,687 Indian Controls.

SNPlates - Nested Case-Control Study. The diabetes SNPlates are a nested case-control study within the GES study. The cases consist of 360 subjects diagnosed with T2D and 360 controls matched to cases on age (\pm 5 years), race, gender and BMI in 1:1 ratio. Selection of cases and controls was independent of genotype.

Covariate data. Data from the baseline questionnaire and medical assessment included data on age, gender, race, diet, physical activity, smoking and alcohol consumption.

Genotyping. DNA was extracted from lymphocytes of study participants and the samples genotyped. Genotyping was conducted by high-throughput chip-based matrix-assisted laser desorption time-of-flight mass spectrometry utilizing the MassEXTEND reaction (Sequenom, Inc. San Diego, CA). PCR primers and extension primers were designed using SpectroDESIGNER software (Sequenom, Inc.) and synthesized at BioServe.

Statistical Analyses:

- Cross tabulations with Chi square tests and t-tests were conducted to determine the association between diabetes status and potential confounders
- Unconditional logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). The variables used in the multivariate analyses were age, pack-years of smoking and BMI as continuous variables and race as a categorical variable.
- Potential confounding of the association between obesity or genotype and T2D risk was explored using Spearman rank correlation analyses and multivariate logistic regression models, including stepwise regression models. If the potential confounder caused a >20% change in the β coefficient, it was kept in the model for further analyses.
- All p-values shown are 2-sided.
- All statistical analyses were performed using the software package STATA (STATA Corporation, College Station, TX).

Discussion

We observed a consistent increase in T2D risk with increased Body Mass Index (BMI). The increase in diabetes risk was observed in all race groups including Caucasian-Americans, Polish-Caucasians, South-Indians and North-Indians. However, the magnitude of the association was lower among Indian individuals. In table 3 we show that diabetes risk can be potentially reduced in healthy-weight, over-weight and obese individuals with increased physical activity among American and Polish (data not shown) Caucasian individuals. However, among South Indian and North Indian (data not shown) individuals increased physical activity did not reduce T2D risk. In summary, our study shows that obesity is strong risk factor for T2D and that exercise may reduce risk among Caucasians but not Indians.

The association between genotype and T2D risk is being extensively studied. However, less focus has been placed on people of the Indian subcontinent. We show here that genotype distribution among Indian Dravidians is different from that reported for Asians in NCBI [rs1111875: AA=0.47, AG=0.47, GG=0.06, rs1153188: TT=0.96, AT=0.04, rs12779790: AA=0.78, AG=0.20, GG=0.02]. The HHEX homeobox gene SNP (rs1111875) has been shown to be associated with risk for type-2 diabetes in several studies including Caucasians and Japanese. We show that a significant association exists between rs1111875 and T2D among Dravidian Indians. The SNP near the Dermcidin gene (rs1153188), an antimicrobial peptide gene, and the SNP located between the CDC123 and CAMK1D genes (rs12779790), were also marginally associated with T2D risk. The Hardy-Weinberg Principle was tested with χ^2 tests and all genotypes were found to be in equilibrium.

Results

Table 1. Crosstabs of Demographics and Health Behavior Indicators

Characteristic	South Indian Controls	South Indian Cases	P-Value	North Indian Controls	North Indian Cases	P-Value	Polish Caucasian Controls	Polish Caucasian Cases	P-Value	Caucasian American Controls	Caucasian American Cases	P-Value
Age (Years)*	50.22 (9.80)	57.11 (11.0)	<0.0001	48.67 (9.8)	58.21 (11.4)	<0.0001	56.12 (6.26)	58.34 (13.09)	<0.0001	56.35 (13.11)	61.26 (13.32)	<0.0001
Gender												
Male	1447 (57.5%)	1903 (62.7%)		111 (64.5%)	195 (58.2%)		485 (41.07%)	639 (59.09%)		2312 (49.01%)	1971 (50.71%)	
Female	1068 (42.5%)	1131 (37.3%)	<0.0001	61 (35.5%)	140 (41.8%)	<0.17	696 (58.93%)	923 (40.91%)	<0.934	2405 (50.99%)	1916 (49.29%)	<0.12
Smoking												
No	1385 (55.0%)	1943 (63.9%)		110 (64.0%)	232 (69.3%)		694 (58.76%)	964 (61.56%)		2391 (50.60%)	1699 (43.60%)	
Yes	1135 (45.0%)	1097 (36.1%)	<0.0001	62 (36.0%)	103 (30.75%)	<0.23	487 (41.24%)	602 (38.44%)	<0.14	2325 (49.40%)	2197(56.40%)	<0.0001
Alcohol												
No	2153 (85.8%)	2692 (88.8%)	<0.001	133 (77.8%)	286 (85.9%)	<0.3	710 (60.12%)	1261 (80.83%)	<0.0001	2640 (56.27%)	2962 (76.36%)	<0.0001
Yes	357 (14.2%)	338 (11.2%)		38 (22.2%)	47 (14.1%)		471 (39.88%)	299 (19.17%)	<0.0001	2052 (43.73%)	917 (23.64%)	<0.0001
Vegetables (servings/day)*	5.31 (2.8)	4.68 (3.5)	<0.0001	5.17 (2.8)	4.59 (3.4)	<0.06	1.33 (0.66)	1.23 (0.65)	<0.0001	2.10 (1.27)	2.20 (1.30)	<0.0004
Fruits (servings/day)*	0.73 (1.1)	1.12 (1.4)	<0.0001	1.09 (1.3)	1.59 (1.6)	<0.0005	1.30 (0.79)	1.18 (0.67)	<0.0001	1.74 (1.17)	1.85 (1.30)	<0.0001
Wholegrains (servings/day)*	13.51 (4.3)	11.48 (5.8)	<0.0001	13.31 (4.6)	11.01 (5.5)	<0.0001	0.73 (0.76)	1.59 (0.86)	<0.0001	1.74 (1.26)	1.93 (1.43)	<0.0001
Dairy prod. (servings/day)*	3.36 (2.3)	2.98 (2.6)	<0.0001	3.48 (2.5)	3.2 (2.8)	<0.30	1.49 (0.99)	1.57 (0.73)	<0.02	1.77 (1.29)	1.74 (1.21)	<0.24
Red meat (Times/week)*	0.92 (1.13)	1.28 (1.73)	<0.0001	1.01 (1.4)	0.95 (1.5)	<0.67	3.37 (1.70)	2.03 (1.39)	<0.0001	3.09 (2.39)	3.32 (2.48)	<0.0001
Fish (Times/week)*	0.44 (0.8)	0.82 (1.7)	<0.0001	0.50 (0.8)	0.55 (1.3)	<0.6	1.15 (0.83)	1.18 (0.67)	<0.23	1.41 (1.22)	1.27 (1.16)	<0.0001
Exercise (Minutes/week)*	105.20 (189.3)	152.71 (263.5)	<0.0001	134.22 (192.6)	91.30 (126.0)	<0.003	203.07 (304.09)	113.15 (313.72)	<0.0001	210.79 (359.57)	138.29 (322.13)	<0.0001
BMI, Kg/m ² *	23.29 (4.2)	24.87 (4.1)	<0.0001	24.45 (4.4)	25.98 (4.1)	<0.0001	25.95 (3.53)	28.92 (5.15)	<0.0001	27.63 (5.55)	32.30 (7.25)	<0.0001

* Mean [Standard Deviation]

Table 2. Obesity and Diabetes Risk

Body Mass Index	South Indian OR (95% CI) [Cases/Controls]	North Indian OR (95% CI) [Cases/Controls]	Polish-Caucasian OR (95% CI) [Cases/Controls]	Caucasian-American OR (95% CI) [Cases/Controls]
18.5 to 24.9 [Healthy weight]	1.0 (ref) [1528/1468]	1.0 (ref) [122/93]	1.0 (ref) [223/464]	1.0 (ref) [412/1581]
25.0 to 29.9 [Overweight]	1.66 (1.46-1.90) [1025/603]	2.55 (1.59-4.08) [155/47]	2.02 (1.64-2.49) [566/570]	2.19 (1.90-2.53) [1022/1808]
30 or higher [Obese]	2.10 (1.68-2.63) [358/144] p-trend<0.001	2.00 (1.02-3.90) [50/19] p-trend<0.001	9.35(7.22-112.10) [569/140] p-trend<0.001	8.04 (6.99-9.25) [2142/1279] p-trend<0.001

p-value for trend estimated from logistic regression models. Odds Ratios adjusted for age, gender, and smoking pack-years.

Table 3. Obesity, Exercise and Diabetes Risk Stratified by Race

Dravidian South Indian	Healthy-Weight OR (95% CI) [Cases/Controls]	Over-Weight OR (95% CI) [Cases/Controls]	Obese OR (95% CI) [Cases/Controls]
Exercise (Minutes/week) Tertile 1: 0 Tertile 2: 0-150 Tertile3: >150	1.0 (ref) [700/916] 2.39 (1.87-3.06) [239/134] 1.93 (1.63-2.30) [589/418] p-trend<0.0001	1.0 (ref) [436/364] 2.51 (1.75-3.59) [163/58] 2.16 (1.68-2.76) [425/180] p-trend<0.0001	1.0 (ref) [202/100] 2.29 (1.22-4.31) [63/18] 2.57 (1.47-4.49) [92/26] p-trend<0.0001
Caucasian-American	Healthy-Weight OR (95% CI) [Cases/Controls]	Over-Weight OR (95% CI) [Cases/Controls]	Obese OR (95% CI) [Cases/Controls]
Exercise (Minutes/week) Tertile 1: 0 Tertile 2: 0-150 Tertile3: >150	1.0 (ref) [121/269] 0.61 (0.44-0.84) [135/524] 0.43 (0.32-0.59) [142/772] p-trend<0.0001	1.0 (ref) [287/345] 0.75 (0.60-0.94) [358/630] 0.55 (0.44-0.69) [334/817] p-trend<0.0001	1.0 (ref) [892/371] 0.72 (0.60-0.85) [695/428] 0.46 (0.38-0.55) [478/462] p-trend<0.0001

Adjusted for age, gender, race and smoking packyears.

Table 4. Genotype and Diabetes Risk in Dravidian South Indians

HHEX: rs1111875	Controls	Cases	OR _{crude}	OR _{adjusted*}
Homozygous WT [GG]	141 (40%)	101 (29%)	1.00 (Ref.)	1.00 (Ref.)
Heterozygous [AG]	157 (44%)	179 (50%)	1.59 (1.14-2.22)	1.75 (1.23-2.46)
Homozygous VT [AA]	58 (16%)	75 (21%)	1.81 (1.18-2.77)	2.11 (1.35-3.29)
Total	356	355		
P _{chiz} =0.006				
DCD: rs1153188	Controls	Cases	OR _{crude}	OR _{adjusted*}
Homozygous WT [TT]	241 (69%)	214 (61%)	1.00 (Ref.)	1.00 (Ref.)
Heterozygous [AT]	93 (27%)	125 (35%)	1.51(1.09-2.10)	1.44 (1.03-2.01)
Homozygous VT [AA]	15 (4%)	13 (4%)	0.98 (0.45-2.10)	0.88 (0.40-1.91)
Total	349	352		
P _{chiz} =0.040				
CDC123/CAMK1D: rs12779790	Controls	Cases	OR _{crude}	OR _{adjusted*}
Homozygous WT [AA]	284 (81%)	260 (74%)	1.00 (Ref.)	1.00 (Ref.)
Heterozygous [AG]	62 (18%)	85 (24%)	1.50 (1.04-2.16)	1.45 (0.99-2.12)
Homozygous VT [GG]	4 (1%)	7 (2%)	1.91(0.55-6.61)	1.83 (0.51-6.53)
Total	350	352		
P _{chiz} =0.065				

* Logistic regression model adjusted for age, gender, BMI and packyears of smoking