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Observational Study

## Risk factors for low high-density lipoprotein among Asian Indians in the United States

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**Author contributions:** All authors contributed equally to this work, read and approved the final manuscript; Misra R and Patel TG designed the research and completed the data collection; Misra R supervised the project, carried out the data analysis and drafted/edited the manuscript; Lucke-Wold B completed the literature review, created the tables and drafted/edited the manuscript; Patel TG drafted and edited the manuscript.

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**Data sharing statement:** The DIA study used an 18-page survey to assess various constructs and anthropometric and clinical data to assess prevalence and risk for diabetes. Clinical information and demographic questions pertaining to this study are referenced in the paper; details were also provided in the method section. The authors do not wish to share their data in such repositories because of the unique nature of this only large scale population-level data on immigrant Asian Indians in the US. However, the authors are willing to provide additional supporting files (in SPSS) on which the conclusions of the manuscript have

been based.

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### Abstract

#### AIM

To examine the differences in metabolic risk factors (RFs) by gender in the Asian Indian (AI) population in the United States.

#### METHODS

Using cross-sectional data from 1038 randomly selected Asian Indians, we investigated the relationship between metabolic syndrome (MetS) RFs, cardiovascular disease,



and diabetes.

## RESULTS

A greater percent of women in this group had increased waist circumference and low high density lipoprotein (HDL) levels than men, but AI males had increased blood glucose, increased blood pressure, and increased triglycerides compared to females. Those individuals who met the MetS criteria had increased cardiovascular disease. One of the biggest single RFs for cardiovascular disease and diabetes reported in the literature for AIs is low HDL.

## CONCLUSION

Our results show that lack of knowledge about diabetes, low physical activity, increased body mass index, and age were the factors most significantly correlated with low HDL in this population. Future studies and prospective trials are needed to further elucidate causes of the MetS and diabetes in AIs.

**Key words:** Asian Indians; Diabetes; Cardiovascular disease; Metabolic syndrome; Low high density lipoprotein

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**Core tip:** Low high density lipoprotein (HDL) in American Indians is a significant risk factor for the metabolic syndrome. In particular, women with lack of knowledge about diabetes, decreased physical activity, and who have an increased body mass are at increased risk of low HDL.

Lucke-Wold B, Misra R, Patel TG. Risk factors for low high-density lipoprotein among Asian Indians in the United States. *World J Diabetes* 2017; 8(6): 297-303 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v8/i6/297.htm> DOI: <http://dx.doi.org/10.4239/wjd.v8.i6.297>

## INTRODUCTION

South-Asians who live in the United States have an increased risk for developing the metabolic syndrome (MetS)<sup>[1]</sup>. A proposed reason is poor dietary habits consistent with sedentary western lifestyle<sup>[2]</sup>. Few studies have looked at this unique population, but data from the Indian Americans national study suggests that Asian Indians (AIs) may be more susceptible to certain components that make up the MetS<sup>[3]</sup>. For example, Vasudevan and colleagues found that obesity was prominent in people from South-Asian descent but was often times underdiagnosed<sup>[4]</sup>. Furthermore, AIs have increased risk for cardiovascular disease due to genetic predisposition and low high density lipoprotein (HDL)<sup>[5]</sup>. What is unknown however is if gender plays a significant role in increasing susceptibility for the MetS in this population. Furthermore, it is unknown what individual components of the MetS are more closely

associated with diabetes in this population.

In this paper, we investigate these important questions utilizing data collected from a cross-sectional survey in the United States. Although causative factors cannot be determined, this study provides valuable insight into the differences observed between genders in relation to individual components of the MetS. More importantly, it highlights, which components of the MetS are more closely correlated with diabetes in this population. Previous studies in India have found that women have lower HDL than men and that cardiovascular risk factors (RFs) such as diabetes, hypertension, and smoking are highly prevalent<sup>[6,7]</sup>. Herein we report that a greater percent of AI males have increased fasting glucose, blood pressure, and triglycerides compared to females and that a greater percent of AI females have increased waist circumference and decreased HDL compared to males.

## MATERIALS AND METHODS

### Sample and data collection

The sample consisted of 1038 randomly selected AIs aged  $\geq 18$  years from seven United States cities (Houston, TX; Phoenix, AZ; Washington, DC; Boston, MA; San Diego, CA; Edison, NJ and Parsippany, NJ); sampling frame and data collection methodology was previously reported<sup>[8]</sup>. All participants consented for the study prior to completing phone interviews and subsequent anthropometric/fasting blood work. In order to protect anonymity, participant codes were created based on letter codes and numbers unique to each participant. Non-participants did not differ in gender, educational level, family history of diabetes and cardiovascular disease, or smoking status, but were significantly older than participants. Survey data were collected via telephone interviews by trained, multilingual AI staff; the response rate was 37%. All participants completed blood work (after a 10 h fast) and anthropometric measurements. Blood samples were centrifuged to separate plasma or serum, and shipped on ice to three core laboratories for biochemical analysis (Atherotech Laboratory (Birmingham, AL), Diabetes Diagnostic Laboratory (Columbia, MO), and Translational Metabolism Unit, Baylor College of Medicine (Houston, TX)). The Institutional Review Board of Texas A and M University approved the study.

### Measures

**Demographic information:** Demographic information included age, gender, marital status, education, income, and access to conventional health care (health insurance coverage). Income was assessed as a categorical variable with response options ranging from  $< \$10000$  to  $\geq \$150000$ . Body mass index (BMI) was calculated from height and weight ( $\text{kg}/\text{m}^2$ ).

**Knowledge of MetS RFs:** Knowledge of 11 MetS RFs (age, high cholesterol, DM, male gender, menopause,

fat intake, overweight/obesity, family history, sedentary lifestyle, smoking, and stress) was assessed. Response options for each RF were 0 = no and 1 = yes. A MetS knowledge score was computed by summing the number of correct answers (Cronbach's  $\alpha = 0.78$ ); a higher score indicated greater knowledge.

**Fasting glucose:** Fasting capillary glucose (mg/dL) was measured using Accucheck Advantage (Roche Diagnostics, Indianapolis, IN). Although fasting serum glucose was collected and stored, analysis indicated abnormal levels with large standard deviations from the capillary glucose for one-third of the respondents. Hence fasting capillary glucose was used for calculating CMetS in the current analysis.

**RFs for MetS:** Plasma samples were assayed for TG, HDL using the vertical auto profile test at the Atherotech Laboratory (Birmingham, AL) as described previously<sup>[9]</sup>. The LDL-R subfraction was determined by subtracting Lp(a) and IDL from total LDL.

**Waist circumference:** For males/females, the cut-off of WC = 35.4/31.5 inches was used to define elevated WC in this study, based on the IDF criteria for South Asians; also it has a high sensitivity (0.901/0.923) and specificity (0.836/0.768) for identifying South Asians with BMI  $\geq 25$  kg/m<sup>2</sup><sup>[10]</sup>.

### Definitions

**MetS:** MetS was assessed according to the Harmonization criteria, *i.e.*, presence of  $\geq 3$  of the MetS RFs: central obesity, elevated triglycerides ( $\geq 150$  mg/dL), low HDL ( $< 40$  mg/dL in males,  $< 50$  mg/dL in females, or specific treatment for these lipid abnormalities), elevated BP ( $\geq 130/\geq 85$  mmHg or treatment of previously diagnosed hypertension), and elevated fasting glucose ( $\geq 100$  mg/dL or previously diagnosed type 2 diabetes). Central obesity was defined as ethnicity-specific elevated WC (for South Asians:  $\geq 35.4$  inches for males,  $\geq 31.5$  inches for females, where South Asian included Chinese, Malay and Asian-Indian populations)<sup>[11]</sup>.

**Diabetes:** Diabetes was defined as fasting blood glucose  $\geq 126$  mg/dL or a self-report of previously diagnosed diabetes. Impaired fasting glucose was defined as fasting blood glucose between 100-125 mg/dL.

### Statistical analysis

All analyses were performed using IBM SPSS version 24.0 (Chicago, IL) by the authors. The statistical analysis was reviewed by an expert biostatistician at WVU for adequacy, appropriateness, homogeneity of the data including missingness prior to the multivariate analysis. Basic descriptive statistics were obtained for demographic variables and MetS RFs. Analysis of variance was used to examine the difference in MetS RFs by gender for the total sample and by those with

type 2 diabetes mellitus (T2DM). The acceptance level for statistical significance was  $\alpha = 0.05$ . Multiple logistic regression analysis was used to predict low HDL controlling for traditional RFs such as age, gender, BMI, lifestyle behaviors, family history of chronic diseases, and MetS knowledge, and diabetes status. Sample size calculations indicated that 656 participants would provide over 80% power to detect important differences in HDL risk.

## RESULTS

### MetS variables

Lauderdale *et al.*<sup>[12]</sup> found that the MetS was significantly higher at all BMIs in Asian Americans vs non-Hispanic Whites. In those surveyed for our study, 62.7% had elevated fasting blood glucose (651/1038), 28.7% had elevated blood pressure (298/1038), and 41.3% had elevated triglycerides (429/1038). Sixty percent had an elevated waist circumference (623/1038) and 35.9% had low levels of HDL cholesterol (373/1038). These values were similar to those reported by Misra *et al.*<sup>[13]</sup> from AIs living in northern California.

### Variables by gender

Recent evidence indicates that AIs have genetic single nucleotide polymorphisms that make them susceptible to developing the MetS in the context of poor diets and western sedentary lifestyles<sup>[14]</sup>. What has not been adequately investigated however is the role of gender as increasing risk for metabolic criteria. We report in Table 1 significant differences between male and females for individual components of the MetS. Interestingly, males were more likely to have elevated blood glucose, elevated blood pressure, and elevated triglycerides compared to females whereas females were more likely to have elevated waist circumference and low HDL cholesterol.

### Heart disease and T2DM

Trude *et al.*<sup>[15]</sup> reported that AIs had a 7.8% prevalence of cardiovascular disease. In our cohort, we found that 7.2% of survey participants had been diagnosed with cardiovascular disease. MetS can increase the risk for cardiovascular disease and subsequent adverse outcomes<sup>[16]</sup>. Similarly, diabetes is increasingly prevalent in this population. Seventeen point four percent of survey participants had diabetes and 32.9% of participants had pre-diabetes. Like cardiovascular disease, diabetes increases the risk for long-term morbidity and mortality<sup>[17]</sup>.

### Diabetes and individual components of the MetS

Anjana *et al.*<sup>[18]</sup> found that low HDL in Indians is a predictor for the progression to T2DM. In Table 1, we report that a greater percentage of AI females had low HDL than males. In Table 2, we look specifically at participants with diagnosed or undiagnosed T2DM. The majority (60.71%) of females diagnosed with diabetes

**Table 1** Significant differences between male and females for individual components of the metabolic syndrome

Variable	% Male Meeting Criteria	% Female Meeting Criteria	Significance
Elevated blood glucose: $\geq 100$ mg/dL or previous diagnosis of diabetes	71.77%	59.69%	(F1, 971) = 15.64 $P < 0.001$
Elevated blood pressure: $\geq 130/\geq 85$ mmHg or previous diagnosis of hypertension	38.32%	31.45%	(F1, 836) = 4.16 $P = 0.042$
Elevated triglycerides: $\geq 150$ mg/dL	48.65%	33.49%	(F1, 1011) = 23.65 $P < 0.001$
Elevated Waist Circumference: $\geq 35.4$ inches for males, $\geq 31.5$ inches for females	56.41%	67.78%	(F1, 1018) = 13.59 $P < 0.001$
Low HDL: Low HDL $< 40$ mg/dL in males, $< 50$ mg/dL in females or previous treatment for low HDL	34.48%	42.30%	(F1, 987) = 6.26 $P = 0.012$

HDL: High density lipoprotein.

had low HDL compared to only 39.32% of males. Hence, further investigation is warranted to determine if low HDL in females might contribute to the onset and progression of diabetes in this population.

#### Multivariate analysis of RFs for low HDL

Mani *et al.*<sup>[19]</sup> found that low HDL is a primary predictor of progression towards diabetes and the MetS. We were interested in what factors were significantly associated with low HDL in our AI population (Table 3). A significant effect was found for age of respondent ( $P = 0.03$ ), physical activity level ( $P = 0.014$ ), knowledge about diabetes risk factors ( $P = 0.017$ ), and the BMI ( $P = 0.01$ ). Other groups have shown similar correlations between these risk factors and low HDL in other populations with high prevalence of the MetS<sup>[20]</sup>.

## DISCUSSION

Cardiovascular disease mortality is significantly higher among AIs and MetS, a proxy to predict the development of CVD, is of concern in this high-risk group. A study in South Asia recently found that ethnic Chinese had the lowest incidence of the MetS whereas ethnic Indians had the highest rate<sup>[21]</sup>. The MetS in this population can lead to an increase in vascular inflammatory markers such as C reactive protein, which can accelerate the progression of T2DM<sup>[22]</sup>. Indians as a whole have increased risk for developing diabetes due to genetic predisposition for poor insulin secretion<sup>[23]</sup>. This predilection for diabetes is even present in AIs with low body weight<sup>[24]</sup>. Little is known about gender differences in individual MetS components among AIs; our results highlight significant differences among male

**Table 2** Specifically at participants with diagnosed or undiagnosed type 2 diabetes mellitus

Variable	% Males with diagnosed Diabetes who Meet the Criteria	% Female with diagnosed Diabetes who Meet the Criteria	Significance
Elevated blood pressure: $\geq 130/\geq 85$ mmHg or previous diagnosis of hypertension	54.95%	54.72%	(F1, 162) = 0.001 $P = 0.977$
Elevated triglycerides: $\geq 150$ mg/dL	57.63%	51.72%	(F1, 174) = 0.545 $P = 0.462$
Elevated Waist Circumference: $\geq 35.4$ inches for males, $\geq 31.5$ inches for females	80.00%	80.70%	(F1, 175) = 0.012 $P = 0.913$
Low HDL: Low HDL $< 40$ mg/dL in males, $< 50$ mg/dL in females or previous treatment for low HDL	39.32%	60.71%	(F1, 171) = 7.185 $P = 0.008$

HDL: High density lipoprotein.

and female AIs for the five MetS criteria in a large Asian Indian sample in the United States. The results have broad-reaching implications for public health education, primary prevention, and improving unhealthy behavior.

A greater percentage of AI males had increased blood glucose, increased blood pressure, and increased triglycerides compared to females. Interestingly however, females had increased waist circumference and lower HDL compared to males. Recent evidence suggests that low HDL has a strong genetic component and can significantly increase the risk for cardiovascular disease, diabetes, and mortality<sup>[25]</sup>. Although this study is cross-sectional in design, it does show an important finding in that AI women with diabetes are much more likely to have low HDL than males.

Our study results showed that the obesity was associated with low HDL levels among AIs. One plausible explanation might be the westernized lifestyle adapted upon immigration or acculturation to the United States society. In addition, the increased vulnerability to metabolic diseases including the MetS may be due to the unique body composition, which is marked by increase in abdominal obesity and percent body fat. This is termed the "Yudkin Yajnik paradox" where AIs with low BMI have higher percent body fat than African Americans and Europeans increasing their risk for metabolic diseases<sup>[26]</sup>. The typical AI phenotype is one of higher percent body fat, higher truncal, sub-cutaneous, and intra-abdominal fat, and less lean body mass<sup>[27]</sup>. These features are even noted in AI neonates<sup>[28]</sup>. These genetic findings coupled with biochemical indicators such as high levels of inflammatory markers, low levels of adiponectin, the co-existence of hyperinsulinemia, insulin resistance, hypertriglyceridemia, abnormal lipid profiles, endothelial dysfunction and hyperhomocysteinemia

**Table 3** Significant factors associated with low high density lipoprotein in Asian Indian population

		Variables in the Equation					95%CI for EXP(B)	
		B	SE	Wald	df	Sig.	Exp (B)	
								Lower Upper
Step 1 <sup>a</sup>	Diab_Category			0.229	2	0.892		
	Diab_Category(1)	-0.089	0.341	0.068	1	0.795	0.915	0.469 1.787
	Diab_Category(2)	0.057	0.252	0.051	1	0.821	1.059	0.646 1.737
	Gender(1)	-0.294	0.236	1.562	1	0.211	0.745	0.470 1.182
	Age of respondent	0.028	0.010	8.793	1	0.003	1.029	1.010 1.048
	Physicalact	1.004	0.409	6.034	1	0.014	2.730	1.225 6.082
	Nutrition	0.100	0.407	0.061	1	0.806	1.105	0.498 2.453
	TobaccoUse_Rec(1)	-0.513	0.508	1.019	1	0.313	0.599	0.221 1.621
	FamHistory	0.148	0.226	0.425	1	0.515	1.159	0.744 1.807
	Income_Rec			3.456	2	0.178		
	Income_Rec(1)	0.451	0.305	2.180	1	0.140	1.570	0.863 2.857
	Income_Rec(2)	0.424	0.254	2.801	1	0.094	1.529	0.930 2.513
	Lifestyle	-0.389	0.258	2.268	1	0.132	0.678	0.408 1.124
	Knowledge of CVD risk	0.099	0.067	2.191	1	0.139	1.104	0.968 1.259
	Knowledge of DM risk	-0.230	0.097	5.652	1	0.017	0.795	0.658 0.960
	BMI_Up	-0.077	0.03	6.560	1	0.010	0.926	0.873 0.982
	Constant	2.182	1.194	3.338	1	0.068	8.864	

<sup>a</sup>Variable(s) entered on step 1: Diab\_Category, gender, age of respondent, physicalact, nutrition, TobaccoUse\_Rec, FamHistory, Income\_Rec, Lifestyle, Knowledge of CVD risk, Knowledge of DM Risk, BMI\_Up. CVD: Cardiovascular disease; BMI: Body mass index; DM: Diabetes mellitus.

set the stage for chronic low grade inflammation that exacerbates morbidity and mortality among AIs. Since muscle mass is an indicator of insulin sensitivity, a lower muscle mass re-routes energy from large carbohydrate meals typical in the Asian Indian diet into hepatic lipogenesis compromising muscle glycogen synthesis. The outcome is atherogenic dyslipidemia<sup>[29]</sup>, a menacing combination that is metabolically linked to insulin resistance, promotes sub-clinical chronic inflammation, and is strongly associated with type 2 diabetes and cardiovascular disease. Underlying genetic factors such as gene variants and polymorphisms further exacerbate the risk for AIs. These factors include the ectonucleotide pyrophosphate phosphodiesterase 1 121Q variant implicated in negatively influencing insulin receptor signaling<sup>[30]</sup>, the *DOK5* gene<sup>[31]</sup> that increases the risk for diabetes in immigrant AIs<sup>[30]</sup>, apolipoprotein E gene polymorphisms and the Myostatin gene linked to abdominal obesity<sup>[32]</sup>, the AMDI variant in homocysteine metabolism that predisposes children to obesity<sup>[33]</sup>, and finally the PPAR-gamma polymorphisms that contribute to non-alcoholic fatty liver disease<sup>[34]</sup>. Research shows low HDL level is a strong and independent risk factor for cardiovascular disease<sup>[35]</sup>. A meta-analysis showed one mg/dL increase of HDL-C levels is associated with a 2%–3% decreased CVD risk<sup>[36]</sup>. It may be one of the primary reasons why AIs are disproportionately burdened by coronary artery disease at younger ages and in more severe forms<sup>[37,38]</sup>. Our results concur with prior studies that AIs have amplified low levels of HDL as compared to Non-Hispanic Whites and Europeans. Furthermore, the higher prevalence of low HDL among AI females (61%) than AI males in this study (39%) support prior literature on a higher prevalence among AI women ranging from 65%–79%<sup>[37,39,40]</sup> than among AI men 35%–67%<sup>[37,39-41]</sup>.

Low HDL can be exacerbated in the context of

sedentary habits and a poor diet in Indian populations<sup>[42]</sup>. We found that obesity, decreased physical activity, lack of knowledge about diabetes, and advanced age are significantly associated with low HDL in this population. AIs who have lived in the United States for greater than 10 years are more likely to have a sedentary lifestyle, increased obesity, and increased risk of diabetes type 2<sup>[43]</sup>. Ghai *et al.*<sup>[44]</sup> compared an AI cohort to a White non-Hispanic cohort. They noted that AIs were less likely to eat 5 servings of fruit and vegetables a day and less likely to engage in physical activity. They were more likely however to have a lower calorie diet, not smoke, and not consume alcohol<sup>[44]</sup>. The authors concluded that genetics in addition to lifestyle factors contributed to the development of the MetS in AIs.

Going forward, it will be important to isolate key genetic components that increase the susceptibility of low HDL in AI women. Once these components are identified, it will be possible to develop a tailored treatment approach and education with personalized medicine. Additionally, public health initiatives can provide an important element for training individuals to engage in health promoting behavior. Diabetes prevention and management programs can help individuals learn key skills on how to prevent and manage the MetS. These programs can be especially influential for the AI population<sup>[45]</sup>.

The MetS affects the AI population and may contribute to the increased prevalence of diabetes. Interestingly, we found a significant difference in metabolic components between men and women. A greater percent of women met the waist circumference and low HDL criteria than men. Furthermore, in this cohort we found a high prevalence of diagnosed cardiovascular disease, which has been linked to increased adverse vascular events. Understanding the genetic and environ-



mental components that contribute to the increased MetS in this population will be essential in order to improve and tailor public health and pharmacologic treatment approaches.

## COMMENTS

### Background

American Indians are prone to develop the metabolic syndrome (MetS) once they adapt a western lifestyle.

### Research frontiers

This article addresses the importance of low high density lipoprotein for the development of diabetes and the MetS in American Indians.

### Innovations and breakthroughs

Improving education about the MetS for this population will be beneficial.

### Applications

In particular, diabetes prevention and management programs will be highly important to implement for this population.

### Terminology

The authors specifically focused on the components of the MetS.

### Peer-review

The authors utilized data collected from a cross-sectional survey from 1038 randomly selected Asian Indians in the United States to investigate the relationship between metabolic syndrome risk factors, cardiovascular disease, and diabetes. The article implicates that one of the biggest single risk factors for cardiovascular disease and diabetes reported in the literature for Asian Indians is low high density lipoprotein. It is suitable to the Journal and could be helpful in clinic application.

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