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Diabetes and Cardiometabolic Risk in South Asian Youth: A Review

Risa M Wolf, MD[1], **Mohika Nagpal**[1], **Sheela N. Magge, MD, MSCE**[1]

[1]Department of Pediatrics, Division of Endocrinology and Diabetes, Johns Hopkins University School of Medicine

Abstract

South Asians are at increased risk for developing type 2 diabetes and cardiovascular disease at lower BMI compared to other ancestral groups. Many factors contribute to this increased risk, including genetics, maternal-fetal factors, diet, fitness, body composition, and unique pathophysiology. Increased cardiometabolic risk is also seen at younger ages in South Asian individuals as compared to their White counterparts. This risk persists in migrant communities outside of South Asia. With the growing prevalence of obesity, diabetes, and cardiovascular disease in the South Asian population, it is imperative that we better understand the mechanisms underlying this increased risk and implement strategies to address this growing public health problem during childhood and adolescence.

Keywords

South Asian; adolescent; type 2 diabetes; cardiovascular; cardiometabolic risk

Introduction

It is well established that South Asian (SA) individuals are at increased risk for developing diabetes and cardiovascular disease (CVD) at lower body mass index (BMI), as compared to other racial/ethnic groups.[1–3] While cardiovascular disease is the leading cause of death globally,[4,5] South Asian individuals (originating from India, Sri Lanka, Pakistan, Bangladesh, Nepal, Maldives, and Bhutan) represent 25% of the world's population and have the largest proportion of individuals affected by cardiovascular disease.[2] Multiple studies show that this increased cardiometabolic risk persists in South Asian migrant communities as well.[5–8] Highlighting this phenomenon, the American Heart Association published a Scientific Statement describing "Atherosclerotic Cardiovascular Disease in South Asians in the United States" in 2018.[8] Among various other risk factors, type 2 diabetes (T2D) appears to have a particular burden on CVD. Recent studies find emerging

Corresponding author and person to whom reprint requests should be addressed: Sheela N. Magge MD, MSCE, Department of Pediatrics, Division of Pediatric Endocrinology and Diabetes, Johns Hopkins University School of Medicine, 200 N. Wolfe Street, Room 3114, Baltimore, MD 21287, Phone: 410-955-6463, Fax: 410-955-9773, smagge3@jhmi.edu.

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vulnerabilities for youth-onset T2D in the SA population,[1,6] as well as risk factors for CVD developing in adolescence. In this review, we discuss risk factors and associated mechanisms underlying elevated cardiometabolic risk, including obesity and adipose distribution, potential metabolic differences, hypertension, and fatty liver disease, among South Asian adolescents. A summary of clinical studies related to cardiometabolic risk in SA youth and adults are referenced in Tables 1 & 2, respectively.

Maternal/Prenatal Risk Factors

Family history as well as maternal factors during pregnancy are known to play a significant role in the risk for metabolic alterations in youth. A family history of T2D increases the risk of glucose intolerance and metabolic syndrome among all youth, further increased if both biological parents have T2D.[9] In SA youth, maternal diet during pregnancy also plays an important role.[10–13] Likely related to the increased prevalence of vegetarianism, Indian mothers are observed to eat fewer calories and less protein than Western mothers,[1,6,9] which has been associated with intrauterine growth retardation and lower newborn birth weight.[14,15] On the other hand, overnutrition in pregnant mothers can be equally problematic, associated with suboptimal developmental trajectory and increased risk of CVD in adulthood.[16] In particular, exposure to a high-fat diet predisposes offspring to metabolic syndrome-associated conditions such as hyperlipidemia and insulin resistance.[16,17] In addition, vitamin D deficiency during gestation is associated with the developmental origin of insulin resistance and T2D.[18,19] In a longitudinal birth cohort study conducted in Mysore, India, comparing children of vitamin D-sufficient mothers to those of vitamin D-deficient mothers (25OHD <50 nmol/l), the children of vitamin D-deficient mothers had higher fasting insulin concentrations and increased insulin resistance at 9.5 years of age for both sexes, and lower muscle mass.[18] Pregnant Indian women, in particular, display a high prevalence of vitamin D deficiency; more than 60% of the pregnant women studied in the longitudinal study had serum vitamin D concentrations less than 50nmol/L at 30 weeks gestation.[18] The mechanisms by which vitamin D has an effect on offspring are not clear, although vitamin D is thought to act on pancreatic beta-cells to affect insulin secretion, and potentially affect muscle tissue differentiation and growth in offspring.[18,20]

In a seminal study in 2003, Yajnik et al. compared mothers and their newborns in Pune, India to mothers and newborn White infants in Southampton, England. Indian newborns had decreased birth weight but higher percent body fat as compared to White British newborns, known as the *Thin-Fat Indian Baby paradox*.[19] This paradox supported the Thrifty Phenotype Hypothesis, which states that fetal undernutrition increases the risk of later T2D and CVD due to the resulting metabolic abnormalities.[21,22] In addition to low birth weight, the standard indicator of undernutrition, Indian infants also have smaller at-birth body composition measurements, with fat preservation of the subscapular skinfolds (subcutaneous) and abdominal circumference (visceral fat) in comparison to White infants.[22] These findings are compounded by the “double burden of malnutrition” in South Asia, in which initial undernutrition in low and middle-income countries worldwide leads to obesity later in childhood and adulthood.[23,24] Similar patterns have been described in SA immigrants, with SA children exhibiting increased adiposity as measured by skinfolds, waist

circumference, and dual-energy X-ray absorptiometry (DXA) for a given BMI, compared to White children.[25–31]

Adipose Distribution

Many SA countries face a double burden of malnutrition and childhood obesity,[13,15] with trends showing an increase in the prevalence of overweight and obesity in SA children and adolescents.[32] Recent estimates from epidemiological studies show higher prevalence of obesity overall (India 11.7%, Bangladesh 5.6%, Pakistan 14–18%, in 2009), and particularly in urban and affluent areas.[32–34] Evidence suggests that for any given BMI, SA populations have higher percentage body fat, higher visceral fat by CT-scan, unfavorable lipid profile and greater risk for T2D and CVD compared to their counterparts from other ancestries.[1,35–38] Lower BMI screening cutoffs for overweight and obesity have been suggested by the World Health Organization for SA populations (≥23 kg/m^2 and ≥25kg/m^2, respectively compared to the standard ≥25kg/m^2 and 30kg/m^2), but a clear cutoff could not be determined for all Asians and thus international cutoffs have remained the same.[39–41] In 2015, the American Diabetes Association recommended that screening for diabetes be considered in all Asian American adults with a BMI ≥ 23 kg/m^2.[40]

The risk for obesity, T2D, and CVD begins early. As described, SA babies are often born at a low birth weight but with greater adiposity than other ethnic groups, and this contributes to risk for development of insulin resistance, T2D and CVD.[19,22] In a study examining abdominal adiposity by whole body MRI in healthy full term Asian Indian (n=30) and white European newborns (n=39), investigators found that differences in adipose tissue partitioning exist at birth.[22] Asian Indian newborns had significantly greater adiposity overall, particularly more abdominal, visceral, and subcutaneous fat, with less non-abdominal superficial subcutaneous adipose tissue.[22] This central adiposity is strongly correlated with insulin resistance and T2D, in addition to other CVD risk factors, including dyslipidemia.[2,42] In addition, children born small with higher rates of postnatal growth are also predisposed to insulin resistance.[43] In a Sri Lankan study of 309 children ages 5–15 years, children born in the lowest birth weight tertile with rapid postnatal weight gain and in the highest current BMI tertile had increased insulin resistance compared to other BMI tertiles. However, children born into the lowest birth weight tertile who remained in the lowest current BMI tertile avoided this increased risk.[43] This again highlights the double burden SA countries face with malnutrition yet increasing obesity rates, and reinforces the importance of a healthy diet even for low-birth weight children, in order to prevent development of insulin resistance later in life.

Insulin Resistance, Fatty Acid Metabolism, and T2D

Regardless of BMI classification, SA adults in the U.S. have the highest BMI-specific prevalence of T2D among all ethnic groups, about 17.4%.[36,39,44] The Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study, a longitudinal population health study investigating CVD risk in South Asian adults in the U.S., compared the prevalence of T2D in the MASALA cohort to the prevalence among the four ethnic groups of the MESA study. Investigators found an age-adjusted T2D prevalence of 23% in

SA, versus 6% in Whites, 18% in African Americans, 17% in Latinos, and 13% in Chinese Americans.[45] However, the mechanisms behind this increased diabetes prevalence among SA have not been fully elucidated.

The increase in visceral adiposity described in SA is associated with increased insulin resistance and cardiometabolic risk. Raji et al compared healthy, normal weight Asian Indian adult immigrants in the U.S. to age- and BMI- matched White controls, using hyperinsulinemic euglycemic insulin clamp studies to measure insulin resistance, and CT-scans to assess body composition.[3] Asian Indians had increased insulin resistance, were hyperinsulinemic, and had increased total, visceral, and subcutaneous fat compared to Whites. Moreover, the increased fat was inversely related to insulin-mediated glucose disposal. SA in Canada were found to have an unfavorable adipokine profile, with increased leptin and decreased adiponectin compared to Whites. Moreover, the increase in insulin resistance by HOMA-IR seen for a given decrease in adiponectin, was greater in those of SA ancestry.[46] Another study comparing young, lean, healthy adults of various ethnicities, used oral glucose tolerance tests to calculate the whole body insulin sensitivity index, and found that Asian Indians had 2–3 fold higher prevalence of insulin resistance compared to other ethnic groups, predominantly due to increased insulin resistance among Asian Indian men.[47] However, data on insulin secretory capacity in SA has not been as clear, with conflicting evidence of both decreased pancreatic beta-cell secretory capacity[45] as well as preserved beta-cell function.[48]

Altered fat distribution may also impact free fatty acid flux in South Asians. Adipose tissue expansion can occur by adipocyte hypertrophy or hyperplasia, which has implications on metabolic health.[49] With weight gain, lower subcutaneous body fat proliferates by hyperplasia, whereas abdominal subcutaneous adipose has a hypertrophic response.[50,51] Hypertrophic adipose is dysfunctional and associated with increased insulin resistance.[52] Fat biopsies have identified increased adipocyte hypertrophy in SA vs Whites, a difference that explains higher insulin and lower adiponectin in SA.[53] After an overnight fast, fatty acid release originates to a greater extent from abdominal rather than lower body adipose, with ~50% lower release rates from lower body adipose stores.[50,54] Although at least 50–60% of hepatic free fatty acid (FFA) delivery comes from SC fat, in vivo studies demonstrate that a greater proportion of FFA delivery to the liver originates from visceral fat in those who have more visceral fat, and this effect is greater in women than men. Thus, abdominal adipose may be detrimental to health by exposing the liver to relatively more FFA, and sex may be important to consider.[55] Few published studies have investigated FFA flux in SA in response to a glucose load. In 2004, Abate et al used area under the curve (AUC) to show that Asian Indian men had a hyperinsulinemic insulin response, but decreased FFA suppression by insulin, during an oral glucose tolerance test (OGTT) compared to White men.[56] Another study in 2010 also found increased insulin AUC on OGTT in SA compared to Europeans, but did not find a difference in FFA flux.[57] Thus, the role in FFA metabolism in the increased cardiometabolic risk in SA is unclear.

A current NIH-funded study led by the senior author of this review is attempting to address some of these knowledge gaps. The Cardiometabolic Health in Adolescents of South Asian Ancestry - (the CHAriSmA study) is investigating the association between ectopic fat

deposition (visceral, intramyocellular, and hepatic fat) by magnetic resonance imaging and spectroscopy (MRI/MRS), and fatty acid flux (calculated using the MINIMAL model of FFA kinetics during 3-hour OGTT[58]), in SA vs African American vs White adolescents. In addition, glucose-potentiated arginine stimulation testing is being used to measure pancreatic beta-cell secretion and its association with FFA flux, testing whether increased FFA may be associated with impaired beta-cell function in SA.[59] Lipoprotein particle analysis, adipocytokines, and aortic stiffness (by pulse wave velocity) are also being measured in the groups. By studying adolescents, the investigators hope to uncover early, ancestry-related pathophysiologic differences among ethnic groups, before environmental factors may affect disease phenotype. Additional mechanistic research will be needed to clarify the pathophysiology behind differing cardiometabolic risk profiles in different ancestry groups.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease resulting from the deposition of ectopic fat in the liver. It is the hepatic manifestation of metabolic syndrome, and commonly associated with CVD. The prevalence of NAFLD in South Asian countries has been rising, with prevalence rates ranging from 18–87% in SA adults, and up to 87% in some urban Indian cohorts.[60,61] NAFLD in South Asians has been worsening due to urbanization, sedentary lifestyle and a Western diet.[62] In contrast to other populations, NASH (non-alcoholic steatohepatitis)/NAFLD can affect non-obese Asian individuals, known as the “Asian paradox” or “lean NAFLD.” Even non-obese, NAFLD is an independent risk factor for development of atherosclerosis and CVD.[63] NAFLD is also associated with prediabetes and diabetes. Hepatic triglyceride content measured by MRS was significantly associated with insulin resistance in Asian Indian men.[47] In addition, in a study in Eastern India, the prevalence of prediabetes and diabetes increased six-fold among NAFLD patients. These patients also had markedly larger waistlines, hypertension, and increased insulin resistance as compared to the general population.[63] Further, the age of presentation of NAFLD is younger among SA as compared to their Western counterparts.[60] Increased dietary intake of fat is associated with NAFLD development and progression, so it is thought that “Westernizing” dietary patterns in Asia, particularly among youth, may be contributing to this earlier NAFLD development.[64] Current data and prevalence rates of NAFLD in SA adolescents is limited to a study completed at a school in India, which found that 62% of students (elementary and middle school level) who were overweight or obese had NAFLD by ultrasound, and that systolic hypertension was an independent risk factor for NAFLD.[65] Moreover, the rs738409 polymorphism in the patatin-like phospholipase domain-containing protein-3 (PNPLA3) gene, known to be associated with NAFLD in other ethnic groups,[66,67] has been found to be associated with NAFLD in Asian Indians as well.[68] NAFLD, obesity, and hypertension are all risk factors hypothesized to influence the development of T2D and CVD.

Hypertension, Dyslipidemia, Inflammation, and CVD

In one of the few longitudinal studies of SA adults, the SABRE study in the U.K. found that SA had increased diabetes and strokes compared to Whites, and increased coronary heart

disease compared to Black Caribbeans and Whites. Traditional risk factors, such as smoking and hypertension, could not explain this increased risk.[4] According to large population-based epidemiological studies, multiple CVD risk factors develop at a young age among the SA population, including hypertension and dyslipidemia, rising in incidence with increasing age.[69] In SA, data suggests that coronary heart disease occurs at least 10 years earlier as compared to other ethnic groups.[69] The presence of dyslipidemia in SA, specifically increased triglycerides, decreased HDL-cholesterol, and increased highly atherogenic lipoprotein (a), are risk factors for CVD.[70–72] The INTERHEART study showed that Asians have increased CVD risk at lower LDL-C than non-Asians, and for any given LDL-C, SA had higher apolipoprotein B, indicative of higher atherogenic lipoproteins. In addition, while higher HDL-C was still associated with decreased risk for an acute myocardial infarction, the protective effect was less in SA vs other Asian groups.[69] Hypertension and hyperglycemia are frequently seen together in the SA population, both contributing to CVD risk in this population.[73] Migrant SA communities also have increased hypertension, with studies in the UK and Canada showing that SA had higher blood pressures compared to Whites,[74,75] and the UK study showing that the increased blood pressure in SA was associated with central adiposity.[72] A large epidemiologic study in India found a low prevalence of CVD risk factors in adolescence, but that the risk factors for CVD, including smoking, hypertension, dyslipidemia, diabetes and metabolic syndrome, rapidly escalated by age 30–39 years in Urban Asian Indians.[69] Inflammatory factors, such as C-reactive protein (CRP) are also increased in SA compared to European adults, and felt to contribute to CVD risk.[76] Homocysteine, a known risk factor for vascular disease, is higher in SA compared to White adults, and has been associated with vitamin B12 and folate deficiency.[77] Although homocysteine is an independent risk factor for CVD in SA, attempts at decreasing homocysteine levels have not shown CVD benefit.[78] Thus, further studies will be needed to understand the pathophysiologic mechanisms involved.

Diet & Lifestyle

Diet & Nutrition

SA diets are known to be higher in carbohydrates and fats, and lower in protein, with high carbohydrate intake associated with insulin resistance.[13,15] With urbanization and the changing lifestyle of SA, dietary intake has changed. In India, for example, the change in food consumption patterns has included increased intake of processed foods, and increased caloric and fat intake.[79] Urban Asian Indian adolescents have high saturated fatty acid and high total fat intakes compared to rural Asian Indian adolescents, likely contributing to the increasing prevalence of obesity and insulin resistance in the former population.[13] While protein intake has not changed significantly over the last decade in India, Asian Indians already have lower protein intake relative to North Americans. Further, in comparison to immigrant Indians in the United States, adolescents and young adults in India have lower protein intake.[13] This lower protein intake in Asian Indians may affect skeletal muscle mass and cause sarcopenia (discussed below).

The patterns of dietary changes in adult SA immigrants in the United States have been studied in the MASALA Study.[10–12] Using validated food frequency questionnaires, the

investigators identified 3 major dietary patterns; greater intake of 1) animal protein and 2) fried snacks, sweets, and high-fat dairy dietary patterns were associated with adverse metabolic risk, whereas a pattern of increased 3) fruits, vegetables, nuts, and legumes was associated with decreased hypertension and metabolic syndrome.[12] In addition, as South Asian immigrants lived in the U.S. longer, dietary benefits varied, with an increased intake of saturated and trans fats, but decreased rice intake and decreased glycemic load.[11] Metabolomics data among 145 Asian Indians in the study demonstrated that compared to a vegetarian dietary pattern, a Western/nonvegetarian dietary pattern was associated with increased branched-chain amino acids, aromatic amino acids, and short-chain acylcarnitines, which were related to an adverse cardiometabolic profile.[10]

Studies in SA adolescents in the U.S. are limited, but one descriptive cross-sectional study of 56 first-generation, urban Indian American adolescents showed intake of saturated fats exceeded recommended amounts, with insufficient intake of fiber and certain vitamins. However, intake of high-cholesterol and sweet foods was lower among adolescents who lived in the U.S for a longer period of time. This small study did not find any associations of dietary patterns with health characteristics but this is another area in need of future investigation.[80]

Physical Activity & Cardiorespiratory Fitness

Exercise and physical activity are known to reduce the risk of diabetes, particularly in the SA Indian population.[81] However, physical activity levels in SA and migrant SA individuals are low. Further, cardiorespiratory fitness, defined as the ability of the cardiovascular and respiratory systems to supply oxygen to working muscles during physical activity, is suggested to be lower in SA compared to white Europeans. A European study of SA men without T2D compared to Whites, matched for BMI, showed that SA men had decreased cardiorespiratory fitness, which could not be explained by decreased physical activity. This decreased fitness explained 68% of their insulin resistance, measured by HOMA-IR.[82] Moreover, SA adults require 232 min/week of moderate intensity physical activity vs. 150 min/week in Whites, in order to obtain the same cardiometabolic risk score.[83] While decreased cardiorespiratory fitness does not account for differences in physical activity, it is associated with levels of physical activity and is an important risk factor for T2D. In a study of SA children residing in the United Kingdom (UK), SA youth participated in significantly less physical activity than their White peers, indicating that the lower physical activity level seen in SA adults begins in childhood.[84] In this study, lower physical activity was attributed to difference in after-school activity participation. Other studies in SA children in the UK have shown lower levels of physical fitness as compared to their White counterparts.[85] This could be an area for future intervention studies and public health efforts, as increased physical activity during childhood may improve physical fitness and future metabolic health in SA.

Sarcopenia

The combination of genetic factors, lower protein diet, and decreased physical activity may contribute to the lower skeletal muscle mass seen in SA as compared to White individuals.[53] Studies have shown lower thigh muscle cross-sectional areas in SA men and women

compared to European counterparts, which are negatively associated with hemoglobin A1c.[86,87] In a study comparing SA to Europeans, SA had greater abdominal visceral fat and thigh subcutaneous adipose tissue, but less thigh muscle as compared to Europeans. This lower muscle mass, also called pre-sarcopenia, is independently associated with diabetes in South Indians and thus may exacerbate diabetes risk.[88] While the mechanism for muscle mass loss in diabetes is not well understood, low body protein and abnormal glucose metabolism may play a role.[88] Dietary interventions to increase dietary protein content, increase satiety, and preserve lean mass have been suggested for individuals with sarcopenia.[86,88]

Genetic Markers

The identification of genes associated with cardiometabolic risk have been predominantly studied in European and other White populations. However more recent studies have examined gene-environment interactions with obesity, diabetes, and CVD in SA adult populations.[89–92] Ahmad et al studied 95 BMI-associated genetic variants previously identified in European-ancestry populations in 16,157 Pakistani adults, and identified 73 genetic variants in Pakistanis that were directionally consistent with BMI associations in Europeans.[92] Using the heterogeneity of variance (HeVa) approach as an extension of conventional GWAS studies, the FLJ33534 rs140133294 gene variant was associated with BMI and smoking in the same Pakistani population.[91] In non-smokers, the minor T-allele variant was positively associated with BMI, and in current smokers, the same allele was negatively associated with BMI.[91] A common variant of the fat mass and obesity (FTO) gene, rs1558902, was strongly associated with adiposity in South Asians.[93] Despite genetic susceptibility to obesity with another FTO variant, rs1421085, Reddon et al further demonstrated that vigorous physical activity could ameliorate obesity and minimize the risk for adiposity in individuals of SA ancestry with this variant.[94] Another two FTO associated genetic variants (rs8050136 and rs11076023) were also found to be associated with dietary intake in Asian Indians.[95] Further genetic associations have been made linking TCF7L2 rs12255372 with dietary fat intake and HDL-C levels in the Asian Indian population, where those with the highest fat intake had lower HDL-C, compared to homozygous carriers.[96] Since elevated homocysteine levels are considered a risk factor for diabetes, obesity and CVD, studies have investigated the relationship of genes in the homocysteine metabolism pathway with obesity. In a study of urban Indian children, the AMD1 variant (rs2796749) in the homocysteine metabolism pathway was associated with plasma leptin levels and obesity.[97] It has also been suggested that an epigenetic shift induced by a suboptimal intrauterine environment may be contributing to the increased adiposity seen in SA.[22] Further understanding of the complex integration of genetic and environmental factors and their influence on obesity, diabetes and CVD will provide future opportunities for prevention and treatment of these diseases.

Conclusion & Future Directions

The increased T2D and CVD risk seen at lower BMI and younger age in South Asians compared to other ethnicities is thought to originate from increased visceral fat in SA, contributing to increased insulin resistance, dyslipidemia, inflammation, and ectopic fat deposition. Longitudinal population studies such as the MASALA study hope to shed light

on risk factors and pathology in order to better inform prevention and treatment. Smaller mechanistic studies, such as the CHAriSmA study hope to provide insights as to the pathophysiologic underpinnings of increased risk in the SA population. A better understanding of the physiology involved, may allow a more personalized, population-specific approach to treatment. Other studies of the impact of differential body composition on cardiometabolic risk will be critical to developing ancestry-specific prevention and treatment strategies. In the meantime, it is imperative to implement aggressive screening and prevention strategies for SA around the world, focusing on healthy diet and increased physical activity at an early age.

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Table 1:

Pediatric Studies

Author (publication year)	Design	Population Group (Region)	Age range (years)	Primary Outcome(s)	Conclusions
Maternal/Prenatal Influences					
Yajnik CS (2003)[19]	Cross-sectional	Mothers and infants from rural Pune, India and Southampton, England *Indigenous*	Term infants n=631 in Pune, India n=338 in Southampton, England	Indian babies were smaller by anthropometric measurements, with lower weight and muscle mass, but preserved body fat by skinfold measures.	Rural Indian newborns have decreased birth weight and decreased muscle mass, but higher percent body fat as compared to White British newborns. Indian mothers also had decreased BMI compared to British mothers.
Modi (2009)[22]	Observational Case-control	Pune, India London, England *Indigenous*	Newborn age babies n=30 Pune, India n=39 London, England	Asian Indian neonates had greater absolute adiposity (by MRI) in visceral ($p<0.001$), deep subcutaneous ($p<0.01$), and superficial subcutaneous ($p=0.01$), and less non-abdominal superficial subcutaneous ($P<0.01$) adipose tissue, compared to White British newborns.	Asian Indian newborns have greater adiposity overall than White British infants.
Krishnaveni GV (2011)[18]	Longitudinal birth cohort	Mysore, India Children of vitamin D-deficient mothers (25OHD <50 nmol/l) and children of vitamin D-sufficient mothers (25OHD≥50 nmol/L) *Indigenous*	n=568 Mothers at 28–32 weeks gestation Offspring at ages 5 y (n=506) and 9.5 y (n=469)	Children of Vit D deficient mothers had decreased muscle mass by arm muscle area ($p<0.05$) at 5 & 9.5y, higher fasting insulin resistance ($p=0.04$) at 9.5 y, increased HDL-cholesterol in boys at 9.5 y.	Vitamin D-deficiency during pregnancy was associated with lower muscle mass and higher fasting insulin in offspring during childhood.
Anand (2016)[25]	Cross-sectional	South Asian and White pregnant women and newborns in Canada *Migrant*	Pregnant women and their full-term newborns n=401 South Asian n=389 White	SA mothers were younger ($p<0.001$), had lower pre-pregnancy BMI ($p<0.0001$), and had increased gestational diabetes ($p=0.005$) compared to White mothers. SA newborns had lower birthweight ($p<0.001$), greater skinfold thickness ($p<0.001$), and higher waist circumference ($p<0.001$) compared to White newborns.	SA newborns have lower birthweight but increased adiposity compared to White infants. Increased newborn adiposity was associated with maternal body fat and glucose.
Adipose Distribution					
Warraich (2009)[34]	Cross-sectional	Adolescents attending privately funded and government-funded schools in Karachi, Pakistan *Indigenous*	Pakistani children grades 6–8 n=284	Prevalence of underweight was 52%; Prevalence of obesity was 6%. Among underweight, 63.3% from lower socioeconomic status group. Among obese, 70% from higher socioeconomic status group.	Obesity and overweight increase with socioeconomic status. There is a dual burden of obesity and undernutrition among Pakistani school children.
Gupta (2010)[13]	Cross-sectional	Urban Asian Indian adolescents compared to rural Asian Indian and rural American adolescents. *Indigenous*	Adolescents/young adults aged 13–25 y n=1236 Urban Indian n=2579 Rural Indian n=2974 American adolescents (NHANES)	Macronutrient, micronutrient, food intake pattern, anthropometric and lipid measures obtained. Absolute daily intake of total fat was ~4x higher than RDA for Asian Indians in urban Indian group. Urban adolescents had	Urban Asian Indian adolescents had higher total and saturated fatty acid intake, and low MUFAs and omega-3 PUFAs, compared to rural Indian adolescents, which could be the cause

Author (publication year)	Design	Population Group (Region)	Age range (years)	Primary Outcome(s)	Conclusions
				inappropriately high intake of total fat compared to rural Indian adolescents.	of increased obesity and insulin resistance in rural Indian adolescents.
Gupta (2011)[33]	Cross-sectional, longitudinal	Adolescents attending privately funded and government-funded schools in New Delhi, India *Indigenous*	Indian adolescents aged 14–17 y n=8,401	From 2006 to 2009, obesity increased from 9.8 to 11.7% (p<0.01), underweight decreased from 11.3 to 3.9% (p<0.001).	Over a 3-year period, there was an increase in overweight and obesity in Indian adolescents, most commonly in male students attending private schools and from affluent families.
Bulbul (2014)[32]	Cross-sectional	Children in Bangladesh *Indigenous*	Bangladeshi children from urban and rural schools aged 6–15 y n=10,135	Prevalence of obesity and overweight in students was greater in urban schools compared to rural schools (5.6%, 10.6%, v 1.2%, 8.6%, respectively). Lower prevalence of underweight in urban schools compared to rural schools (16.1 v 19.2%).	There is a dual burden of obesity and undernutrition among Bangladeshi school children.
Mehta (2002)[35]	Cross-sectional	Adolescent males at a boys' high school in the U.S. *Migrant*	American males aged 15–16 y. n=139 46% Caucasian, 41% East Asian, 13% South Asian.	SA boys had higher mean WHR than East Asians (p<0.01), higher mean %TBF than Caucasians when adjusting for BMI, and lower BMI than other groups.	BMI and %TBF are related to ethnicity in male adolescents of similar age.
Rosenbaum (2013)[27]	Cross-sectional	Middle school students in New York, U.S. *Migrant*	Youth aged 10–15 y n=994 12% African American, 14% East Asian, 13% South Asian, 9% Caucasian, 44% Hispanic, 8% other	Fractional body fat content and %TBF was significantly greater at any BMI among SA adolescents.	Ancestry- specific differences in risk factors for T2D and adiposity-related comorbidities exist in youth. SA youth have higher %TBF at similar BMIs, and less insulin sensitivity compared to other ethnic youth cohorts.
Insulin Resistance, Fatty Acid Metabolism, and Type 2 diabetes					
Misra (2004)[42]	Cross-sectional	Healthy, post- pubertal children in urban Indian cities *Indigenous*	Children aged 14–18 y n=155 males n=95 females	Fasting insulin correlated with BMI, %TBF, waist circumference, central and peripheral skinfold thicknesses, and sum of four skinfold thicknesses in both sexes. Increased fasting insulin was associated with increased skinfold thickness.	Insulin resistance is associated with excess body fat, abdominal adiposity and excess truncal subcutaneous fat in urban Asian Indian children.
Wickramasinghe (2017)[43]	Cross-sectional	Children in urban Sri Lanka *Indigenous*	Children aged 5–15 y n=133 boys n=176 girls	Fasting and 2-hour insulin levels and HOMA-IR were not affected by birth weight, but were highest among those in highest current BMI tertile.	Children born small who became obese had the highest risk of insulin resistance.
Ehtisham (2005)[31]	Cross-sectional	South Asian and white European adolescents in Birmingham, UK *Migrant*	Adolescents aged 14–17 y n=138	SA adolescents have more body fat (boys, p<0.001; girls p<0.01), and greater insulin resistance (boys, p<0.05) than their white counterparts.	SA adolescents are less insulin sensitive, and have more body fat than white European adolescents, which may contribute to risk of developing T2D.
Whincup (2010)[30]	Cross-sectional, survey	Children in London, Birmingham, Leicester, UK *Migrant*	Children aged 9–10 y n=1306 South Asian n=1153 white European	SA children had higher HbA1c, fasting insulin, triglycerides, and lower HDL-cholesterol levels than their white counterparts.	SA youth have early onset of risk factors for T2D.

Author (publication year)	Design	Population Group (Region)	Age range (years)	Primary Outcome(s)	Conclusions
Non-alcoholic fatty liver disease					
Pawar (2016)[65]	Cross-sectional	Students in a convent in Southern Mumbai, India *Indigenous*	Students aged 11–15 y n=616	32% of the students were overweight or obese; 62% of the overweight/obese students had NAFLD measured by ultrasound.	NAFLD is common in overweight and obese Indian children. Screening for NAFLD is recommended in this high-risk group.
Hypertension, Dyslipidemia, Inflammation, and CVD					
Gupta (2009)[69]	Population-based epidemiological study	Adolescents and young adults in urban North India *Indigenous*	Adolescents/young adults aged 15–39 y n= 2051	Obesity (BMI, waist circumference, WHR), glycemia (fasting glucose, metabolic syndrome) and dyslipidemia showed increasing trends with age ($p<0.01$).	Low prevalence of multiple CVD risk factors (smoking, hypertension, dyslipidemia, and diabetes and metabolic syndrome) in adolescents, rapidly increased by age 30–39 years in Urban Asian Indians.
Diet and Lifestyle					
Eyre (2013)[84]	Cross-sectional	Children in Coventry, UK *Migrant*	South Asian and European children in the UK aged 8–9 y n=65 South Asian n=96 White European	73% White European children and 35% SA achieved the recommended 60-min daily moderate to vigorous physical activity.	SA children were less active than European peers.
Nightingale (2016)[85]	Cross-sectional	South Asian, Black African-Caribbean, and White European children in the UK *Migrant*	Children aged 9–10 y n= 407 South Asian n= 424 White European n= 413 Black African-Caribbean n= 381 Other	Estimated VO2 max was lower in SA children (boys and girls) compared to White European and Black African- Caribbean youth, even after adjusting for physical activity (daily steps).	SA children have lower levels of physical fitness than White European and Black African-Caribbeans in the UK, irrespective of amount of physical activity.
Martyn-Nameth (2017)[80]	Cross-sectional	First-generation South Asian adolescents in the urban American Midwest *Migrant*	Adolescents aged 13–21y n=56	Saturated fat intake exceeded U.S. RDA for age/gender groups, while potassium, magnesium, calcium, vitamin D, and fiber intake were insufficient.	Dietary patterns including high saturated fats and low potassium, magnesium, calcium, vitamin D and fiber, may increase future disease risk in SA adolescents.
Genetic Markers					
Tabassum (2012)[97]	Cross-sectional	Children from four zones in New Delhi, India *Indigenous*	Obese and nonobese children aged 11–17 y n=3,168	Seven variants in the homocysteine metabolism pathway were associated with childhood obesity ($p<0.05$), but only the variant *rs2796749* in AMD1 remained significant after multiple testing corrections ($p<0.001$).	AMD1 variant in the homocysteine metabolism pathway is associated with obesity and plasma leptin levels in children.

Table 2:

Adult Studies

Author (publication year)	Design	Population Group (Region)	Age range (years)	Primary Outcome(s)	Conclusions
Adipose Distribution					
Misra (2002)[36]	Cross-sectional	Adult males in India *Indigenous*	n=50 Non-diabetic, non-obese (BMI<25kg/m^2) males with primary hyperlipidemia n=50 non-diabetic, non-obese, normolipidemic males	BMI, waist- circumference, waist/hip ratio, skinfolds, sum of 4 skinfolds, and % TBF were higher in hyperlipidemic men compared to normolipidemic men (P<0.01)	Hyperlipidemic Asian Indian men, despite being non-obese, have an adverse anthropometric profile and excess %BF compared to normolipidemic males.
Anand (2011)[53]	Cross-sectional	South Asian and Caucasian adults in Canada *Migrant*	South Asian adults (36.8 y) and Caucasian adults (34.2 y) in Canada n=56 South Asian n=52 Caucasian	South Asians had higher fasting insulin, lower HDL-C, lower adiponectin, more body fat, lower lean muscle mass, and a greater deep to superficial adipose tissue ratio compared to their Caucasian counterparts.	SA have increased adipocyte area compared to Caucasians, which is related to ethnic differences in insulin, HDL-C, adiponectin, and ectopic liver fat deposition.
Eastwood (2014)[86]	Cross-sectional	South Asian and European adults in London *Migrant*	Aged 40–85 y n=669 White European n=514 South Asian	SA had greater abdominal visceral and thigh subcutaneous adipose tissue than White Europeans, but less thigh muscle. In SA, visceral adipose tissue was positively associated with T2D and CVD.	Greater visceral adipose tissue was positively associated with T2D and coronary heart disease in SA compared to Whites.
Insulin Resistance, Fatty Acid Metabolism, and Type 2 diabetes					
Vikram (2003)[2]	Cross-sectional	Adults in urban slums of New Delhi, India *Indigenous*	Adults, including non-obese and obese (BMI≥25kg/m^2) n=170 men (37.6y) n=469 women (38.5y)	Among non-obese Indian men and women, 66% and 88%, respectively, have at least one risk factor for CVD. Among non-obese, there were higher odds ratios for hypertension and hypertriglyceridemi a among those with increased %BF and among those with normal WC.	Asian Indians have excess cardiovascular risk at BMI (<25kg/m^2) and WC values considered normal.
McKeigue (1991)[75]	Cross-sectional	South Asian and European adults in London, UK *Migrant*	Adults aged 40–69 y n=561 women n=3193 men	SA adults had higher prevalence of diabetes (19% v 4%), higher blood pressure, higher insulin levels, higher TG, and lower HDL-C compared to their European counterparts. SA adults had higher mean waist-hip girth ratios and trunk skinfolds.	SA adults have a propensity for central obesity that is associated with an “insulin resistance syndrome” compared to their White European counterparts.
Banerji (1999)[38]	Cross-sectional	Healthy Asian Indian males in New York, US *Migrant*	Adults, aged 28–48 y n=20	Non-obese BMI was associated with a high %BF (33%). 66% of non-obese men were insulin resistant. Insulin action was inversely correlated with visceral fat, not total or abdominal subcutaneous fat.	Despite a non-obese BMI, Asian Indians have increased visceral fat, which is related to dyslipidemia and insulin resistance.
Raji (2001)[3]	Cross-sectional	Healthy Asian Indian immigrants vs healthy Caucasians in Massachusetts, US *Migrant*	Adults aged 20–65 y n=12 Asian Indians n=12 Caucasians	Asian Indians had fasting hyperinsulinemia (p<0.01), higher glucose and insulin during 2-hr OGTT (p<0.05), and reduced glucose disposal rate (p<0.01) during 2- hr euglycemic hyperinsulinemic clamp.	For similar BMI and age, Asian Indians had increased insulin resistance, dyslipidemia, total abdominal and visceral fat, and CVD risk, compared to Whites.
Abate (2004)[56]	Cross-sectional	Asian Indians and Caucasians in the U.S. *Migrant*	Adults n=79 Asian Indians (31 y) n=61 Caucasians (30 y)	Asian Indians have higher plasma NEFAs and leptin, and lower plasma adiponectin than Caucasians (p<0.001).	Insulin-resistant Asian Indians have higher leptin and NEFAs, and lower adiponectin than insulin-sensitive Caucasians, which may contribute to

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Author (publication year)	Design	Population Group (Region)	Age range (years)	Primary Outcome(s)	Conclusions
					higher prevalence of T2D and CVD in SA.
Petersen (2006)[47]	Cross-sectional	Young adults in New Haven, Connecticut *Migrant*	Adults aged 17–39 y n=59 Asian Indians n=423 Caucasian, Other	Insulin resistance was 2-to 3-fold higher in Asian Indians compared to other ethnic groups. Asian-Indian men had a 3- to-4 fold increased prevalence of insulin resistance, which was associated with an increased hepatic lipid content.	Prevalence of insulin resistance is higher in Asian- Indian men as compared to other ethnic group, and is associated with increased hepatic fat.
Mente (2010)[46]	Cross-sectional	South Asian, Chinese, Aboriginal, and European adults in Canada *Migrant*	Adults, aged 50.3y (mean) n=317 South Asian n=312 European n=303 Chinese n=244 Aboriginal	Adiponectin concentrations are lower in SA ($p<0.001$), and leptin levels are higher in SA $p<0.001$). BMI and waist circumference were inversely associated with adiponectin in every group except SA.	SA have an unfavorable adipokine profile, similar to Aboriginal. SA have greater insulin resistance and lower adiponectin levels, as compared to other ethnic groups.
Hall (2010)[57]	Cross-sectional	South Asian and White European in the UK *Migrant*	Adults n =20 South Asian (26.9 y) n =19 White European (24.5 y)	SA have reduced insulin sensitivity by 26% ($p<0.01$), lower VO2max $p<0.01$), and reduced fat oxidation during submaximal exercise at the same relative, and absolute, exercise intensities.	SA have a more insulin resistant phenotype with reduced oxidative capacity and fatty acid utilization.
Kanaya (2014)[45]	Cross-sectional	South Asian, White, African American, Latino, and Chinese American adults in the U.S. *Migrant*	Adults, aged 44–84y n=799 South Asians n=2611 Whites n =1879 African Americans n =1492 Latinos n = 801 Chinese Americans	SA had higher age- adjusted prevalence of T2D (23%) than the MESA ethnic groups (6% in Whites, 18% in African Americans, 17% in Latinos, and 13% in Chinese Americans). HOMA-IR was higher among SA compared to other ethnic groups.	There is a higher prevalence of diabetes in SA. SA may have decreased β -cell function.
Non-alcoholic fatty liver disease					
Thakur (2012)[63]	Cross-sectional	Adults with and without NAFLD in India *Indigenous*	n=40 non-diabetic with NAFLD, age 42.1± 10.9y n=40 health controls without NAFLD, age 41.9± 10.7y	Participants with NAFLD had greater carotid intima-media thickness (cIMT) and higher prevalence of atherosclerotic plaques than controls.	In Asian Indians, NAFLD is associated with subclinical atherosclerosis and endothelial dysfunction independent of obesity and metabolic syndrome.
Singh (2015)[61]	Cross-sectional	Patients with and without NAFLD in Orissa, India *Indigenous*	Adults n=464 NAFLD patients n=181 controls	Participants with NAFLD had higher fasting blood sugar, HOMA-IR and TG.	Sedentary lifestyle, obesity, family history of metabolic syndrome and consumption of meat/fish, spicy foods and fried foods are risk factors associated with NAFLD.
Hypertension, Dyslipidemia, Inflammation and CVD					
Joshi (2007)[73]	Case-control study	South Asian adults and controls from other countries. *Indigenous*	n=1732 SA with first acute myocardial infarction (AMI) n=2204 SA controls n=10,728 non-SA cases n=12,431 non-SA controls	The mean age for first AMI was lower in SA (53y) than in other countries (58.8y) ($p<0.001$). SA had more risk factors including elevated apolipoprotein B(100)/apolipoprot ein A-I ratio, and history of T2D, than individuals from other countries.	SA adults have an earlier age of first AMI, explained by the higher risk factor levels at younger ages.
Karthikeyan (2009)[72]	Case-control study	Adults in Asian subgroups (South Asians, Chinese, Southeast Asians, and Japanese) *Indigenous*	n= 5731 Adults with first AMI n= 6459 controls	HDL-C was lower among SA compared to other Asians ($p<0.001$). Risk of AMI associated with LDL-C increases and HDL-C decreases was similar in all participants. In SA, apolipoprotein (Apo)A1 predicted AMI risk better than HDL-C.	South Asians have a lower baseline HDL-C, despite similar risk for AMI, and thus thresholds and targets for goal HDL-C in this population should be considered.

Author (publication year)	Design	Population Group (Region)	Age range (years)	Primary Outcome(s)	Conclusions
Chambers (2000)[77]	Case-control study	Indian Asian and White European adult men in the UK *Migrant*	n= 257 Indian Asian men with coronary heart disease (CHD) n= 294 White European men with CHD n= 518 Indian Asian controls n= 507 White European controls	Fasting homocysteine levels were 8% higher in men with CHD compared to controls, in both ethnic groups. In health controls, fasting homocysteine levels are higher in Indian Asians than in White Europeans. Homocysteine was associated with CHD in both ethnic groups.	Plasma homocysteine is an independent risk factor for CHD in Indian Asians. Elevated homocysteine levels may be related to reduced Vit B12 and folate levels as a result of dietary intake.
Chambers (2001)[76]	Cross sectional study	Indian Asian and White European adult men in the UK *Migrant*	Healthy adults aged 35–60y n=518 Indian Asians n=507 White Europeans	Indian Asian men had C-reactive protein (CRP) levels 17% higher than European White men. CRP was associated with CVD risk factors, obesity and insulin resistance.	CRP levels are higher in healthy Indian Asians than White Europeans, and may contribute to increased CVD risk among Indian Asians.
Diet and Lifestyle					
Ramachandran (2006)[81]	Randomized control trial	Adults in urban India *Indigenous*	Adults (45.9 ± 5.7y) with impaired glucose tolerance randomized to control, lifestyle- modification, metformin treatment, or lifestyle- modification plus metformin group.	Relative diabetes risk reduction was 28.5% in the lifestyle modification (p=0.018), 26.4% in the metformin treatment (p=0.029), and 28.2% in the combined group (p=0.022).	Lifestyle modification and metformin therapy significantly reduced the incidence of diabetes, with no added benefit from combining them.
Anbalagan (2013)[88]	Cross-sectional	Adults in Chennai, India *Indigenous*	Adults in India aged 28–67 y with and without diabetes n=68 women n=84 men	The prevalence of presarcopenia is 39.5% in individuals with diabetes, and 15.8% among adults without diabetes. Diabetes was independently associated with presarcopenia (p=0.001).	Asian Indians with T2D have a higher prevalence of presarcopenia compared to age and sex-matched participants without diabetes.
Ghouri (2013)[82]	Cross-sectional	South Asian and White European adult men in the UK *Migrant*	Adults, aged 40–70y n=100 South Asian n=100 European	HOMA was 67% (p<0.001), and fasting glucose was 3% (p<0.0018) higher in SA compared to White Europeans. SA had lower VO2max, lower physical activity and greater total adiposity than Whites.	SA men have lower cardiorespiratory fitness that is associated with excess insulin resistance and fasting glycemia, compared with White European men in the UK.
Iliodromiti (2016)[83]	Cross-sectional	South Asian and White European adults living in the UK *Migrant*	Adults, aged 18–70 y n=148 South Asians n=163 White Europeans	South Asian adults would require ~230 minutes of moderate intensity exercise per week to match the cardiometabolic risk factor score of White European adults spending 150 minutes performing the same exercise.	SA men have lower cardiorespiratory fitness, compared to White Europeans in the UK.
Gadgil (2015)[12]	Cross-sectional	South Asians living in the U.S. *Migrant*	Adults aged 40–84 y without known CVD n=892	Associations between dietary patterns (validated food frequency questionnaires) and metabolic risk factors (HOMA-IR, lipids, anthropometric measures, BP, etc). Three major dietary patterns identified: 1. animal protein, 2. fried snacks, sweets, and high-fat diary, 3. fruits, vegetables, nuts, and legumes.	Highest vs lowest tertile of 1. animal protein and 2. fried snacks, sweets, and high-fat dairy dietary patterns were associated with adverse metabolic risk, whereas 3. fruits, vegetables, nuts, and legumes dietary pattern associated with decreased hypertension and metabolic syndrome.
Bhupathiraju (2018)[10]	Cross-sectional	Asian Indians living in the U.S. *Migrant*	Adults aged 45–79 y n=145	Association(s) between metabolomic profiles, dietary patterns by food- frequency questionnaire, and cardiometabolic risk markers, using principal components analysis.	“Western/nonvegetarian” dietary pattern in Asian Indians was associated with a metabolomic profile related to an adverse cardiometabolic profile

Author (publication year)	Design	Population Group (Region)	Age range (years)	Primary Outcome(s)	Conclusions
				"Western/nonveget arian" diet was associated with increased branched- chain amino acids, aromatic amino acids and short- chain acylcarnitines.	compared to those following a vegetarian dietary pattern.
Genetic Markers					
Ahmad (2015)[92]	Cross-sectional	Adults in Pakistan *Indigenous*	Adults in Pakistan, aged 53.8 ± 9.6y n=16,157 n=8232 controls n=7925 with myocardial infarction	73 out of 95 tested SNPs showed directionally consistent effects on BMI. Each additional BMI-raising allele of the genetic risk score was associated with a 0.04kg/m^2 higher BMI ($p<0.001$).	Most BMI-associated loci have directionally consistent effects on BMI in Pakistanis and Europeans. MC4R (rs6567160) and TMEM18 (rs13021737) were most strongly associated with BMI.
Ahmad (2016)[91]	Cross-sectional	Adults in Pakistan *Indigenous*	Adults in Pakistan, aged 53.8 ± 9.6y n=14,131	Genome-wide heterogeneity of variance analysis (GWHVA) showed intronic variant, rs140133294, in FLJ33544 gene associated with BMI variance. In tests of gene x lifestyle interaction, smoking most significantly modified the effects of *rs140133294* on BMI, with minor allele (T) associated with lower BMI in current smokers.	GWHVA identified a novel interaction between a variation at the FLJ33534 locus and smoking, in relation to BMI in Pakistani adults.
Reddon (2016)[94]	Longitudinal	Multi-ethnic participants from 21 countries	Adults, aged 52.7 y ± 11.4y n=17,423 (53.9% European, 18.9% Latino, 15.8% South Asian, 7.2% African, 2.9% Native American, 1.3% East Asian)	Increased physical activity was associated with decreased BMI at baseline/follow-up. FTO variants and obesity genetic risk score was associated with obesity measures at baseline and/or follow-up.	Physical activity can blunt the genetic effect of FTO variant rs1421085 on adiposity by 36–75% in a longitudinal multi-ethnic cohort.
Vimaleswaran (2016)[95,98]	Cross-sectional	Adults in urban Chennai, India *Indigenous*	Adults (24–52 y) n=734 T2D n=884 normal glucose tolerant	There was a significant interaction between FTO gene variant *rs8050136* and carbohydrate intake (% energy), where 'A' allele carriers have 2.46x increased risk of obesity than 'CC' genotype carriers.	Associations between FTO single nucleotide polymorphisms and obesity are influenced by carbohydrate intake, dietary fiber intake, and physical inactivity.
Bodhini (2017)[96]	Cross-sectional	Adults in urban Chennai, India *Indigenous*	Adults (30 – 61y) n=861 T2D n=821 normal glucose tolerant	Significant interaction between TCF7L2 *rs12255372* and fat intake on HDL-C, where 'T' allele carriers in the lowest total fat intake tertile have higher HDL-C ($P<0.001$), and those in the highest tertile had lower HDL-C ($p=0.017$).	The association between TCF7L2 SNP *rs12255372* and HDL-C may be modified by dietary fat intake.