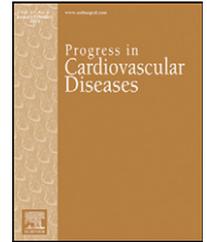


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Lifestyle Choices Fuel Epidemics of Diabetes and Cardiovascular Disease Among Asian Indians

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ABSTRACT

Within the next 15 years, India is projected to overtake China as the world's most populous nation. Due to the rapid pace of urbanization and modernization fueling population growth, in conjunction with a genetic predisposition to insulin resistance, India is suffering a rising epidemic of non-communicable diseases (NCDs), including coronary artery disease (CAD), type 2 diabetes mellitus (T2DM), and stroke. In addition to the genetic predisposition, major negative lifestyle factors are contributing to the alarming outbreak of cardiovascular disease (CVD) among the Asian Indian population; these factors include: 1) a diet high in added sugar, refined grains and other processed foods, 2) physical inactivity, 3) vitamin D deficiency (VDD), and 4) smoking/pollution. These risk factors are all highly modifiable, and steps to improve these issues should be taken urgently to avoid a worsening NCD crisis among the inhabitants of the South Asian subcontinent as well as for people with Asian Indian ethnicity worldwide.

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Exponential progress in science and technology has drastically altered daily human existence around the globe. In a few generations the world has moved from physically active lifestyles and agrarian diets to sedentary habits and processed fast food. Increased use of tobacco in certain parts of the world and heightened psychosocial stress along with low physical activity (PA) have added to this risk factor burden, which has fueled the emerging epidemics of type 2 diabetes mellitus (T2DM), high blood pressure, stroke, and coronary artery disease (CAD).¹

Within the next 15 years, India is projected to overtake China as the world's most populous nation.^{2,3} Accordingly, India's influence over the global community continues to grow, especially in the United States (US). Over the past 50 years, the number of Indian-born immigrants in the US has risen 150-fold.³ With approximately 3 million Asian Indian immigrants residing in the US, India is tied with China as the second largest immigrant group in the US by nation of origin, behind only Mexico.³

Statement of Conflict of Interest: see page 511.

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
CV = cardiovascular
CVD = cardiovascular disease
HFCS = high fructose corn syrup
MetS = metabolic syndrome
NAFLD = non-alcoholic fatty liver disease
NCD = non-communicable disease
PA = physical activity
RR = risk ratio
T2DM = type 2 diabetes mellitus
US = United States
VDD = vitamin D deficiency
WHO = World Health Organization

Due to the rapid pace of urbanization and modernization among the Asian Indian populace, perhaps exacerbated by their genetic predisposition to T2DM,^{4,5} India is in the throes of an especially pernicious outbreak of non-communicable diseases (NCDs), with the prevalence of CAD, T2DM, and stroke rising by upwards of 100% over the past 2 decades.^{6–8} Cardiovascular (CV) disease (CVD) now accounts for 25% of deaths on the South Asian subcontinent (defined as the peninsula south of the Himalaya Mountains, which is currently comprised of the fol-

lowing countries: India, Nepal, Bhutan, Pakistan, and Bangladesh). Today about 50% of the total Indian population (1.22 billion people) is 24 years of age or younger.⁹ In the next decade, India is projected to account for more than 20% of the CAD deaths worldwide.^{7,10,11} In an age-adjusted analysis of CAD mortality in Canada during a 15-year span, Asian Indians had the highest death rate due to CAD compared to other ethnicities including Chinese and European.¹² Furthermore, the recent atherosclerotic CVD risk assessment guidelines recognize that the standard risk factors under-measure risk in the Asian Indian population.^{13–15}

Our hypothesis is that the South Asian susceptibility to T2DM and CVD is due to: 1) a diet that is very high in various processed foods, particularly refined carbohydrates; 2) an inherent susceptibility to metabolic syndrome (MetS) even with a modest excess of intra-abdominal adiposity, especially combined with a diet high in added sugars and other refined carbohydrates; 3) a very high prevalence of vitamin D deficiency (VDD); 4) a growing cohort of smokers (up to 120 million); and 5) a progressively more sedentary lifestyle.

NCD epidemic's adverse economic impact

NCDs adversely affect not only health, but also productivity and economic well-being.⁸ Because CVD manifests at younger ages among Asian Indians compared to other ethnicities, a larger proportion of deaths occur during working-age years^{7,16} (Fig 1). In Western nations mortality from CVD occurs mainly in the elderly, with only 23% of CV fatalities occurring in

people under age 70.^{7,8,17} In contrast, among the Asian Indian population, 52% of CV deaths occur in individuals under age 70.¹⁸ This high rate of premature death from CVD results in enormous losses of productivity.¹⁷ By 2020 India is projected to have a higher incidence of CVD and stroke than those of established market economies. Recent data indicate that developing countries already have 7 times as many disabled citizens from stroke as do established market economies.¹⁰ Unless preventive measures are undertaken, India is likely to lose \$2.2 trillion economically by the year 2030 from death and disability caused by CVD alone.⁸

Contributing conditions

Predisposition to T2DM

Currently India has 67 million people with T2DM; a number that is projected to double by the year 2030^{8,19} (Fig 2). This is in part related to the large scale migration of people from the rural outskirts into the urban centers of India. Waist circumference, a key risk factor for T2DM as well as many other NCDs, is rapidly expanding among the urban South Asians. As a consequence, the prevalence of T2DM increased 10-fold over the past 40 years in urban India.²⁰ Individuals with T2DM die on average of about 10 years earlier than those who are non-diabetic, and approximately 2 out of every 3 persons with T2DM die from CVD.^{6,8,10,20,21} As recently suggested by a one author of this review (JDD), added sugars (sucrose—also known as table sugar and high fructose corn syrup [HFCS]), may be involved in the development of T2DM, which may be especially applicable among individuals genetically predisposed to MetS and T2DM.²² In fact, in some studies these dietary substances are the only factors independently and significantly associated with the prevalence of T2DM after fully adjusting for other covariates (although many studies do not adequately assess PA).²³ These data suggest that the overconsumption of added sugars and other refined carbohydrates, especially among sedentary individuals, is likely one of the principle causative dietary factors driving the high prevalence of T2DM-related morbidity and premature mortality seen among Asian Indians.

India is already the world leader in residents diagnosed with impaired glucose tolerance and impaired fasting glucose, and approximately one-third of adults in India have MetS.²⁴ All 3 of these conditions are precursors to T2DM. The native people of the South Asian subcontinent are especially susceptible to the adverse metabolic effects of excess body fat, especially when it is inside the abdominal cavity, which may be increased from consumption of excess caloric loads, including added fructose.^{5,6,25,26} Among adults in India obesity (defined as a body mass index [BMI] >30 kg/m²) is rare; whereas about 1 in 3 US adults qualifies as being obese by this definition.⁸ Indeed, among the major nations, India has the lowest rate of obesity in the world²⁷ (Fig 3). Even so, the rates of T2DM and CAD are rising rapidly among Asian Indians.^{23,25} Compared to individuals with European ancestry, people with South Asian ethnicity often develop pre-diabetes

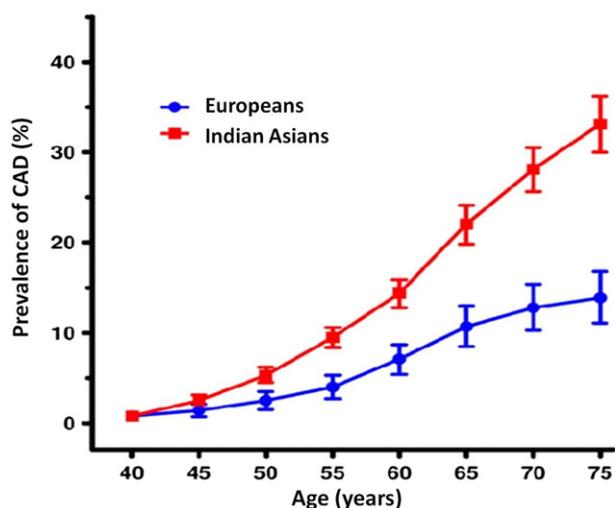


Fig 1 – Prevalence of coronary heart disease (95% confidence interval [CI]) among 16,774 UK Asian Indian and 7032 European participants in the LOLIPOP study. On average, Indian Asians develop CAD about 10 years younger than Europeans.^{7,16}

or frank T2DM with much more modest increases in weight²⁸ (Fig 4). Healthy waist circumferences for most adult populations are less than 88 cm for women, and less than 102 cm for men.²⁸ However, recent guidelines for optimal health specify that for people of Asian Indian ethnicity the adult waist circumferences should be less than 85 cm for women and less than 90 cm for men.²⁸

Fatty liver disease among Asian Indians

People of South Asian ethnicity appear to have an increased predisposition to non-alcoholic fatty liver disease (NAFLD), also called hepatic steatosis,¹⁶ which has been described as the hepatic manifestation of the MetS.²⁹ NAFLD is among the most potent risk factors for CAD,^{29,30} and may be exacerbated by a high-sugar diet, abdominal adiposity, and low PA, all of

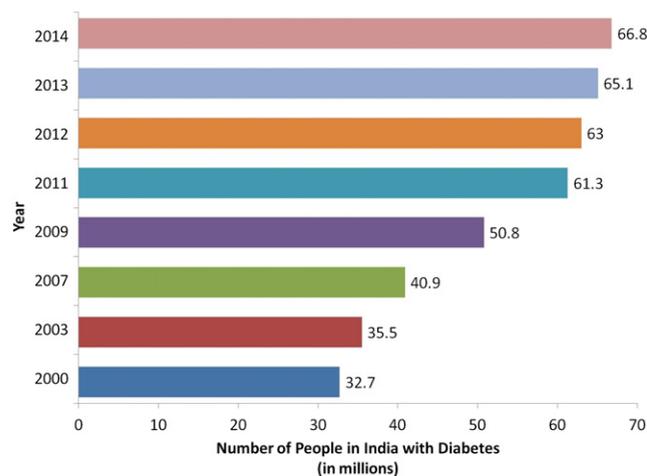


Fig 2 – Number of patients diagnosed with diabetes in India from 2000 to 2013. Projections call for the number of Asian Indians with diabetes to reach over 100 million by 2030.^{8,19}

which are increasingly pervasive in the modern Asian Indian lifestyle.^{12,24,26,29} Recent studies show that about 1 out of every 3 adults from the Asian Indian urban population is afflicted by fatty liver,^{31–34} though the vast majority are asymptomatic and unaware of its presence. This is similar to the prevalence of fatty liver disease in the US population, where NAFLD is present in about 30% of adults.^{32–35} Patients with NAFLD are not only predisposed to CAD and cirrhosis, but to liver cancer and exogenous malignancies outside of the liver.²⁹

A recent prospective study demonstrated that individuals with NAFLD are very likely to have CAD with high-risk features by coronary angiography.³⁰ Of the 440 patients studied, NAFLD was present in 40%. The individuals with NAFLD were approximately 3 times more likely than those without NAFLD to harbor high-risk coronary plaque (59% versus 19% respectively). Furthermore, the presence of fatty liver predicted ominous coronary anatomy independent of the standard CAD risk factors. This pathophysiological link between NAFLD and high-risk coronary plaque is theorized to occur because of shared risk factors and also systemic inflammation induced by the excess fatty deposits in the liver.

It remains unknown which therapies are most effective for regressing NAFLD, but weight loss (especially mobilizing excess intra-abdominal fat), coffee consumption, exercise, avoidance of alcohol, intermittent fasting, L-carnitine, and a diet low in sugar and other refined carbohydrates have demonstrated efficacy for reducing intra-hepatic fat.³⁶

Smoking and air pollution

According to WHO estimates, approximately 12% of the world's smokers are in India.³⁷ A recent case-control study evaluating the impact of smoking among Asian Indian males and females found that 5% of female subjects and 37% of male control subjects between the ages of 30 and 69 years were smokers.³⁸ In this age group, smoking was associated with an increased risk of death from any cause among both women (risk ratio [RR], 2.0; 99% confidence interval [CI], 1.8–2.3) and men (RR, 1.7; 99% CI, 1.6–1.8).³⁸ Daily smoking of even a small amount of tobacco was associated with increased mortality. Smoking was associated with a reduction in median survival of 8 years for women (99% CI, 5–11) and 6 years for men (99% CI, 5–7).³⁸

In a related issue, air pollution has been increasingly problematic in India. Poor air quality both indoors (due to solid fuel use for cooking) and outdoors (due to automobiles, industrial pollution, etc.) has been shown to adversely affect life expectancy in Asian Indians, and increase morbidity/mortality especially from respiratory diseases and CVD.³⁹

Data from the WHO indicate that among the 20 cities in the world with the worst air pollution, 13 are in India; in fact Delhi is the single worst polluted city on Earth.³⁹ Correspondingly, India as a nation has the highest death rate from chronic respiratory disease in the world. About 50% of India's population today lives in regions with air quality that does not meet minimum safety limits set by the Indian National Ambient Air Quality Standard.³⁹ Experts estimate that improving the air pollution levels in these regions to meet the standard would improve life expectancy in the affected populations by an average 3.2 years.³⁹

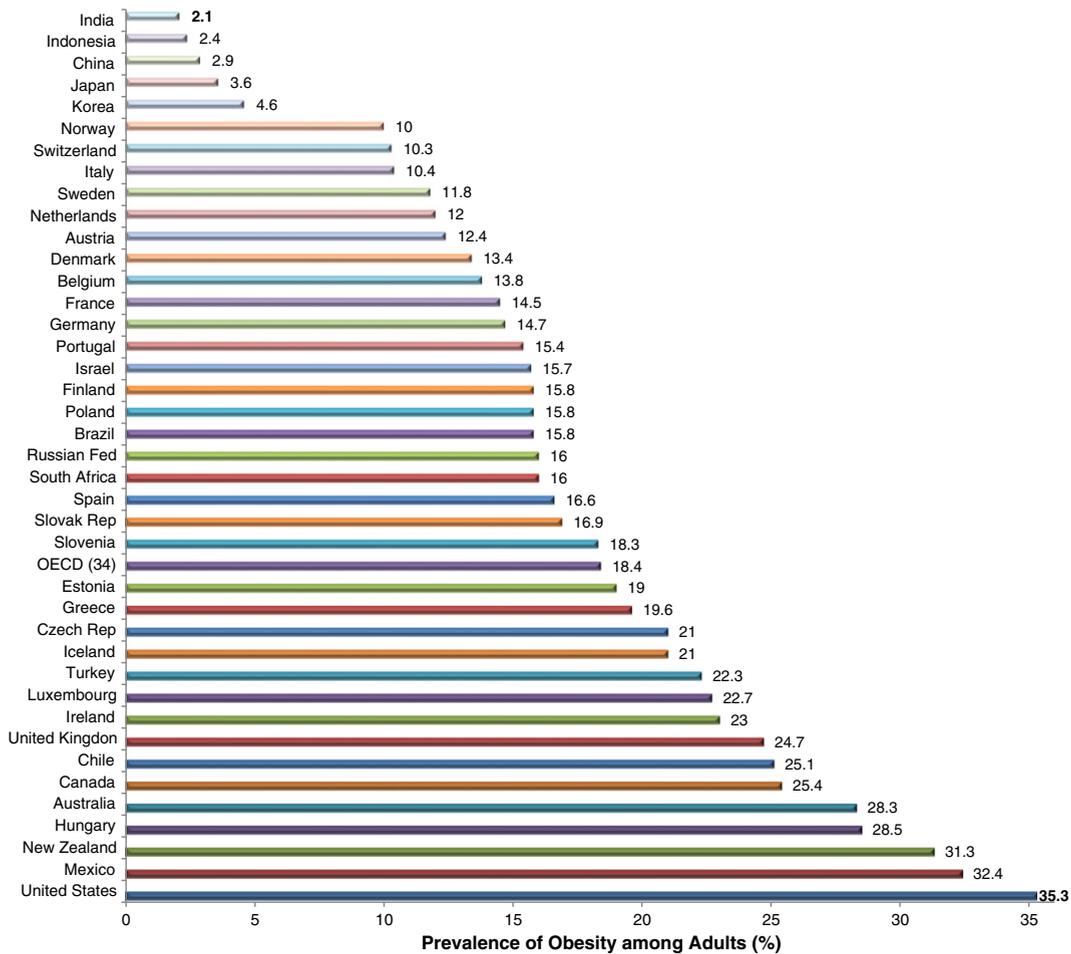


Fig 3 – Rates of obesity among adults in various countries from The Organization for Economic Co-operation and Development.²⁷

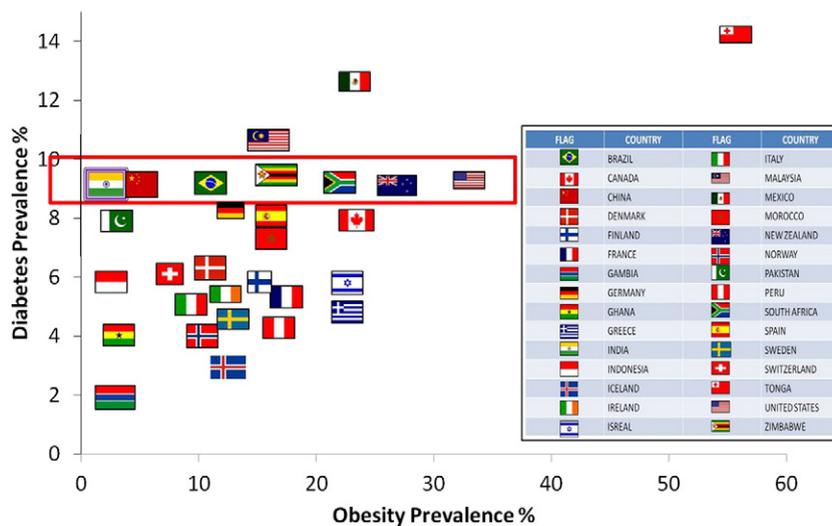


Fig 4 – Relationship between obesity rates and diabetes prevalence among various countries worldwide. Although the rates of diabetes tend to increase as the prevalence of obesity rises, a great deal of variability exists. For example, the countries in the red box (from left to right: India, China, Brazil, Zimbabwe, South Africa, New Zealand and US) all have a similar prevalence of diabetes (about 9%) despite obesity rates varying from about 2% in India to 35% in the US.^{23,25}

Physical inactivity

Exercise confers numerous health benefits, regardless of whether the PA is performed as part of one's occupation, or during activities required for daily living, or in the course of recreational pursuits.⁴⁰ Today, in Europe and the US approximately 30–50% of individuals lead sedentary lives.^{41–43} In India the prevalence of physical inactivity has traditionally been much lower; just 1 decade ago only 9% of men and 15% of women led sedentary lives.⁴⁴ However, in 2014 a large nationwide survey of India documented a dramatic decrease in PA, with about 50% of adults reporting physical inactivity.⁴⁵ In India a sedentary lifestyle is more prevalent in urban affluent regions compared to rural impoverished areas.⁴⁵ Regardless, about 90% of adults in both urban and rural areas do virtually no recreational exercise during their leisure time. This very high prevalence of inadequate recreational PA is noted among both genders and is present across all adult age groups.⁴⁵

For optimal health, the WHO guidelines call for at least 150 minutes or moderate or 75 minutes of vigorous PA each week. Currently in India as in the US, 1 out of every 2 adults fails to meet these recommendations.^{41–43,45} Historically, adults in India performed most of their PA as part of their occupational demands. Thus, as modern mechanization displaces the work force from manual labor to sedentary jobs, the widespread tendency to avoid PA in leisure time becomes an even more significant problem. Clearly, it is of paramount importance to emphasize the need to include exercise as part of recreational pursuits, and to build the infrastructure to support these activities.

Vitamin D deficiency

Vitamin D is a pro-hormone aiding in absorption of calcium and promoting overall bone and muscle health. Certain substances such as fatty fish, mushrooms, and fortified foods are all rich in vitamin D. For most of the world's population, however, the chief source of vitamin D is exposure to sunshine—the epidermis endogenously synthesizes vitamin D when UV rays contact bare skin. Because India, located between 8°N and the 38°S parallel, straddles the Equator, VDD among the Asian Indian population historically has been assumed to be rare. Surprisingly, in the past several years studies indicate that VDD is now present among 50–90% of India's population.⁴⁶ VDD has been associated with significant morbidity and increased rates of NCDs including T2DM and CAD.^{47,48} Furthermore, supplementation with oral vitamin D₃ in individuals with VDD has been shown to improve insulin resistance and glucose tolerance, in addition to lowering concentrations of both fasting plasma glucose and insulin.⁴⁹

Most of the evidence linking VDD to NCDs is observational. Because correlation does not necessarily imply causation, the question of whether or not normalization of VDD will prevent or even improve T2DM and/or CAD remains unanswered. Nonetheless, VDD is common among Asian Indians and normalization of low vitamin D levels with oral supplementation has been demonstrated to strengthen bones and

muscles, and reduce the incidence of falls.⁵⁰ Thus, daily dietary supplementation with 2000 IU of oral vitamin D₃ would appear to be an inexpensive, safe and logical recommendation for many adults of South Asian ethnicity.

Measures to combat rising burden of disease

Excess sugars and refined carbohydrates problematic for Asian Indians

Refined sugar was invented in India, where the process of crystallizing sugar granules from sugarcane juice was developed about 350 AD.⁵¹ The consumption of sweets is a common denominator for many important traditions in the Indian culture, and to “sweeten the mouth” after each meal is considered customary. Thus, sugar has been and continues to be not only a source of calories but also a fundamental aspect of the traditional Indian way of life. Presently, India is the largest consumer of sugar in the world.⁵¹ However, the consumption of foods containing added sugar and processed carbohydrates may be a considerable threat to the future health and wellness of the increasingly sedentary Asian Indian people with their innate genetic predisposition to MetS and T2DM.^{5,52}

Recent large and comprehensive analyses of populations from 165 to 173 countries showed that the per capita sugar consumption is correlated with the prevalence of T2DM among the various nations.^{23,53} The correlation between sugar consumption and adjusted risk of T2DM was especially robust among South Asian populations, where even a modest increase in sugar intake (for example, 150 extra calories of added sugar) correlates with a significantly heightened risk for T2DM^{23,53} (Fig 5).

The customary diet of India was already high in sweets, but this was less problematic as the sugar came from whole-foods (such as fruit that contains fiber, water, antioxidants, and other substances that buffer the sugar load) and was generally consumed in the ancestral rural environments of South Asia where obesity and sedentary lifestyles were

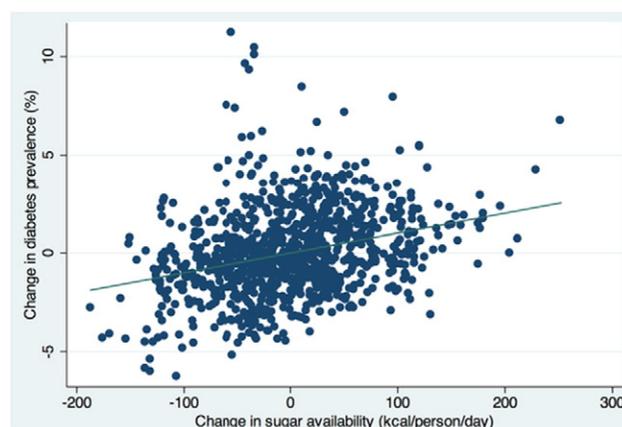


Fig 5 – Adjusted association of sugar availability (kcal/person/day) with diabetes prevalence. Every 150 kcal/person/day increase in sugar availability was associated with an absolute increase in diabetes prevalence by 1.1% ($p < 0.001$).^{23,53}

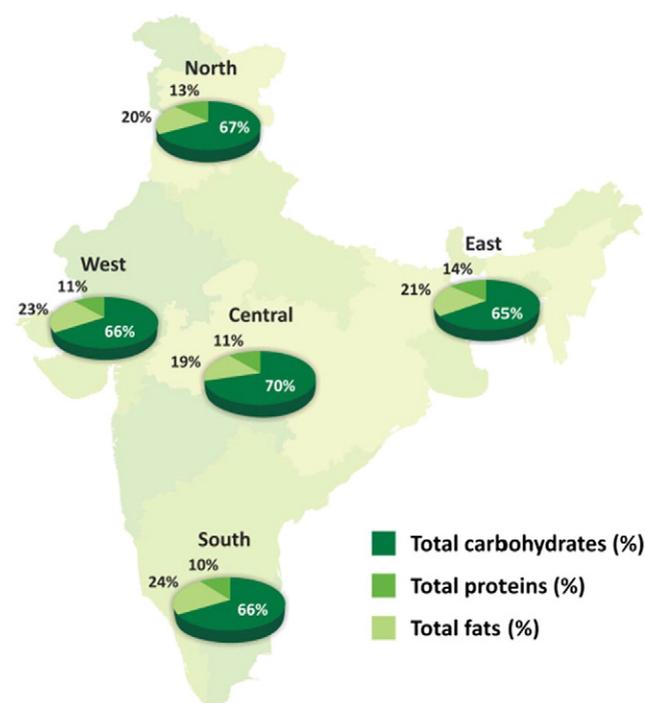


Fig 6 – Proportions of the macronutrients as a percent of total calorie consumption among individuals in India without type 2 diabetes mellitus.⁵⁴

virtually nonexistent. In contrast, about 70% of total calorie intake in the modern Asian Indian diet comes from carbohydrates, and mostly in the form of refined sugar, white flour, and white rice⁵⁴ (Fig 6). The World Health Organization (WHO) has described the risk of consuming excess added sugar as similar to the mortality risk from tobacco.^{55,56} Some data indicate that the incidence of T2DM doubles when the consumption of refined carbohydrates/added sugar reaches 330 g/day, which is the mean daily intake for an adult Asian Indian.^{53,56,57}

The average US adult consumes about 15% of daily calories in the form of added sugar, compared to 14% for Asian Indian adults.^{51,52,54} Other data suggest that the average intake is even higher—i.e., 152 pounds per person per year, with 13% of the US population consuming 25% or more of their total calories from added sugars.^{52,58,59} Consensus dietary guidelines for Asian Indians currently recommend restricting sugar intake to less than 10% of total calories consumed.⁶⁰ In an effort to curb the obesity epidemic that is blossoming worldwide, the WHO recently went even further and recommended reducing sugar intake to 5% of total calorie intake, or about 25 g of sugar per day for an average-sized person.⁶¹ The typical adult in India consumes 58 g of sugar daily.⁶²

In light of the heightened susceptibility of individuals with Asian Indian ethnicity to adverse metabolic effects from consumption of sugar and their propensity to develop T2DM and CAD with modest increases in abdominal fat, it may be particularly important for South Asians to restrict sugar intake to less than 5% of total calories, especially if PA levels are inadequate. For the average adult (using 2000 calories per day as a reference) this translates to not more than about 6 teaspoons per day, which is the amount of sugar in about 8 ounces of a

sweetened soft drink, for example.⁶³ Higher intakes of dietary sugar may be safer for those with high PA and those who do not have high risk of T2DM and MetS.

Sweetened beverages

Some studies have suggested that sugar-sweetened beverages, perhaps because they are widely available, heavily marketed, and usually contain HFCS, have been shown to be very strongly associated with risk of T2DM, even after statistical adjustment for total calorie consumption and abdominal obesity⁶⁴ (although most assessments have not accounted for the marked decline in PA that has been noted in recent decades).^{40–43} If these estimates are correct, each additional sugar-sweetened drink consumed on a daily basis raises the risk of developing T2DM by approximately 25%.^{64–66} Sugar-sweetened beverages, along with other added sugars and refined carbohydrates (particularly in the setting of low PA) also increase the risk of obesity, CAD and CV death.^{65–67} However, substantial evidence has not agreed with the links of dietary sugar with adverse health outcomes,^{68–75} especially with high PA.⁷⁴

Nuts and unsweetened yogurt—heart-healthy substitutes for sweets

Nuts contain a valuable array of protein, fiber, essential fats, phytosterols, antioxidants, vitamins, and minerals. One handful (about 1 ounce) of nuts provides a nutritious and filling snack that is an excellent substitute for other processed options that are typically high in refined carbohydrates. Over 40 clinical trials have tested the effect of nut consumption on biomarkers of CV health, and have consistently reported improvements in blood glucose and lipid levels, as well as a decrease in inflammatory markers.^{76–78} A recent trial demonstrated that pistachio nuts when substituted for 20% of calories in a standard Asian Indian diet significantly improved not only glucose and total cholesterol, but also reduced abdominal obesity, lowered markers of inflammation and oxidative stress, and increased adiponectin.⁷⁹ The latter hormone is theorized to play a role in suppression of the metabolic derangement present in T2DM, MetS, atherosclerosis, NAFLD, and abdominal obesity.

Nuts also have a low glycemic index, contain no cholesterol, and have been strongly linked to good health outcomes.⁸⁰ Studies show that consuming 1–2 ounces of tree nuts per day will reduce risk of T2DM, myocardial infarction, stroke and CV death.^{76–78} The benefits of tree nuts might be of special relevance to Asian Indians, considering the high rates of MetS, T2DM, and CVD in this population.

A prospective observational study recently demonstrated that a higher intake of yogurt was associated with a lower risk of T2DM, whereas consumption of other dairy foods and beverages was not linked to lower rates of T2DM.⁸¹ Unsweetened yogurt contains beneficial probiotics along with calcium, vitamin D, protein and potassium, with relatively low levels of lactose because the fermentation process metabolizes much of the sugar. These impressive findings suggest that yogurt, which has traditionally played a central role the Asian Indian diet, should be encouraged as a healthy food choice; though it is important to avoid yogurts supplemented with added sugars.

Table 1 – Suggested steps for prevention of diabetes and CVD among Asian Indians.

<p>Reduce added sugar to <10% of calories (possibly <5% in high risk individuals).</p> <p>Reduce consumption of refined carbohydrates such as wheat flour, white rice, fried batter, and commercial baked goods.</p> <p>Encourage cessation of tobacco use.</p> <p>Increase exercise and PA, particularly during leisure time.</p> <p>Keep waist circumference less than 85 cm (33.5 inches) for women and less than 90 cm (35 inches) for men.</p> <p>Encourage consumption of unsweetened yogurt and tree nuts, such as pistachios.</p> <p>Consider measuring and normalizing blood levels of 25-hydroxy-vitamin D.</p>

Focus on prevention

Only 10% of people living in India have medical insurance; the remaining 90% pay for their health care and medications as “out of pocket” expenses,⁸ and over half of the 1.2 billion Asian Indians live on \$1–\$2 per day.⁸² Clearly, the intelligent response to this deepening NCD crisis is an emphasis on prevention, which by necessity will be focused on healthy eating, smoking cessation, and increased exercise. Devising a plan is very feasible, but successful deployment will be problematic. In India, as in the US, progress at a societal level will require policy changes. These could hypothetically include programs favoring healthy whole foods such as fruits, vegetables, nuts, and low-fat dairy over refined foods and beverages, along with government subsidies for healthy foods versus unhealthy foods.⁸³ In addition, other public health initiatives might include smoking bans, employer-sponsored personal health incentives, and increased opportunities for urban exercise (bicycle paths, parks, etc.) along with other efforts to promote PA.^{83–87} Table lists possible strategies for the prevention of diabetes and CVD among Asian Indians.

Conclusion

A constellation of data reviewed in this manuscript indicates that India is suffering a rising epidemic of NCDs, including CAD, T2DM, and stroke. In addition to the genetic predisposition, major negative lifestyle factors are contributing to the alarming outbreak of CVD among the Asian Indian population. Dietary and lifestyle changes, including promotion of PA and smoking cessation, along with reductions in intake of refined carbohydrates are urgently needed for the primary and secondary prevention of CVD in this high-risk population (Table 1).

Statement of conflict of interest

All authors declare that there are no conflicts of interest.

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