



Mumbai's Linking road, a congested artery at the heart of the city's eternal traffic jam, offers a disturbing snapshot of the way that growing wealth is compromising India's health. Roadside carts selling traditional fried sweets and samosas jostle with fast-food joints selling burgers and fries, and shopping malls are full of shops selling myriad labour-saving appliances.

JAGADESH N. V./REUTERS/CORBIS

India's embrace of the worst of both Eastern and Western ways is sending lifestyle illnesses such as obesity and diabetes skyrocketing. In 2011, India had 62.4 million people with type 2 diabetes, compared with 50.8 million the previous year, according to the International Diabetes Federation (IDF) and the Madras Diabetes Research Foundation. As the economy started growing, so did the incidence of diabetes. The nationwide prevalence of diabetes in India now tops 9%, and is as high as 20% in the relatively prosperous southern cities. By 2030, the IDF predicts, India will have 100 million people with diabetes.

Health experts are alarmed because, although the onset of type 2 diabetes tends to affect people in the West in their 40s and 50s, the disease strikes Indians much younger. Indians as young as 25 are being diagnosed with the disease, a trend that threatens to seriously hamper the country's economic development.

The rise of type 2 diabetes in India's cities was to some extent expected. And in fact, until the 1980s, the urban prevalence of diabetes was at least double the rural prevalence. But the recent surge in diabetes has spilled out of the cities into the countryside. The spike in rural areas has been shocking, says Nikhil Tandon, an endocrinologist at the All India Institute of Medical Sciences in New Delhi (see 'India's diabetes boom'). "Villages in wealthier southern states like Tamil Nadu and Kerala are seeing prevalence hit double digits, which is enormous," he says. "If it was confined to affluent India, you could still put a lid on it, but now it's rising quickly all over the country."

#### THRIFTY GENES

Health experts in countries like the United States have for years been lamenting the trend towards overeating and lack of physical exercise, and the resulting rise in obesity, diabetes and heart disease. Indians seem to be even more vulnerable to these lifestyle changes. The culprit may be what is called the 'thrifty genotype', whereby millennia of evolution have shaped the genetic profile to cope with hardship. According to this theory, some of the world's populations, including Indians, are genetically adapted to an environment in which calories are scarce. As a result, their bodies can't cope in times of over-indulgence, and it takes only a small increase in daily calories (or a small drop in calorie expenditure) for their metabolism to tip over into diabetes.

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#### PUBLIC HEALTH

# India's diabetes time bomb

*Epigenetics and lifestyle are conspiring to inflict a massive epidemic of type 2 diabetes in the subcontinent.*

BY PRIYA SHETTY

But the idea of a thrifty genotype doesn't fully explain the prevalence of type 2 diabetes among certain populations, says Antonio Gonzalez-Bulnes, a geneticist at the National Institute for Agriculture and Food Research and Technology (INIA), Spain. He points out that although this genotype has been identified in rat models and in particular ethnicities around the world, such as South Pacific islanders, these groups haven't always had higher rates of metabolic disease. C. Ronald Kahn, director of the Joslin Diabetes Center in Boston, Massachusetts, emphasizes that "we still need to regard it as a hypothesis, since no genes have been specifically identified that contribute to the phenotype".

Instead, researchers like Gonzalez-Bulnes and Tandon are interested in a related idea of a 'thrifty phenotype': that being deprived of nutrients in the womb, but then exposed to a high-calorie and low-exercise life, leads to a person to develop diabetes. The supposed mechanism is epigenetic; the fetal environment triggers changes in DNA methylation, which is responsible for switching genes on or off. The environment *in utero* thereby affects the expression of genes that code for enzymes that regulate blood sugar or tell our brains when we have eaten enough. "The mother's nutrition, or even her smoking or alcohol consumption, can change the way the baby's genes react to the environment: a poor or excessive diet and sedentary lifestyle," says Paul Zimmet, head of international research at the Baker IDI Heart and Diabetes Institute in Melbourne, Australia, and one of the first to predict the Indian diabetes epidemic.

Several epigenetic studies back up the idea that the *in utero* environment has a life-long influence on health. In one study of the Dutch Hunger Winter of 1944, in which thousands of people starved during a German blockade, children born to women who were pregnant during the famine were far more likely to develop obesity or diabetes; this finding was backed up by studies of children born during the Chinese famine of 1959–61.

### IN THE WOMB

The problem of the thrifty phenotype begins before the child is born. A fetus growing in a malnourished mother will need to grab all the glucose it can for its development. It does this by making its muscles resistant to insulin; since insulin is responsible for allowing fat and muscles to store sugar, insulin resistance forces the sugar to circulate in the blood instead. But when food is freely available, this inability to store glucose can send blood sugar levels soaring and trigger the onset of type 2 diabetes.

The maternal link may help explain why the diabetes epidemic is being seen all over India, in both rural and urban areas, says Caroline Fall, a paediatric epidemiologist at the University of Southampton, UK. India already has a problem with babies being born underweight — 40%

of 20 million babies born weighing less than 2.5 kilograms in the developing world are born in India. Fall points out that low birthweight (a marker of poor maternal and fetal nutrition)



Doctors and students "walk together to keep diabetes away" at a rally on World Diabetes.

does not differ that much between cities and villages in India. "You don't need to have severe maternal malnutrition to produce the problem of obesity and diabetes in later life," Fall says.

If poor maternal nutrition could cause diabetes, might improving it prevent the disease? Fall is investigating the effect of micronutrients such as folate and vitamin B12 in pregnancy on the child's development of diabetes. This link has been proven in animal models, says Fall. She is now trying to see if there is a similar effect in humans, through a study of maternal nutrition in 5,000 women living in a Mumbai slum.

**"The question is whether the Indian government is prepared to put in the resources."**

children whose mothers took nutritional supplements during pregnancy had lower insulin resistance<sup>2</sup>. Similar results have been found in the Gambia, says Fall. And studies by Tandon and others of the New Delhi Birth Cohort, which is following people born between 1969

and 1972, reinforce the link. According to Tandon, "those who were born small relative to their peers and then gained weight rapidly — not necessarily becoming obese — are the ones who later in life had the highest risk of developing metabolic diseases"<sup>3</sup>.

Tandon's findings tie in with previous observations that Indians don't need to be as overweight as people of other ethnicities to develop diabetes. The reason lies in Indians' natural body composition, says Fall. Pound for pound, she says, "Indians have less lean mass, more body fat, and more central fat than a white Caucasian. All of these very much increase the risk of diabetes." This difference in body type affects standard measurements such as body mass index (BMI): according to Fall, an Indian with a BMI of 23 has the same amount of body fat as a British Caucasian person with a BMI of 25. Thus, the BMI threshold that serves as a warning sign for developing diseases like type 2 diabetes is much lower in Indians.

Moreover, says Fall, the Indian susceptibility starts before birth. Even without poor maternal nutrition, "a lower muscle growth but higher fat growth *in utero* makes babies more vulnerable," she says. "This is why we think diabetes hits earlier in India — they are more vulnerable from the start. If babies were well nourished in the womb, it might mean that they were not so biologically susceptible to changes in diet and lifestyle, and therefore more immune to diseases like diabetes."

In addition to improving maternal nutrition, Fall wants to see routine screening for gestational diabetes (high blood glucose in pregnant women) because the condition is known to prime the child to be insulin-resistant and significantly increases the chance that the child will develop diabetes later in life. She points out that gestational diabetes is 5 or 10 times more common in Indian cities than in the United Kingdom.

Tandon points out that the focus on mothers and babies has a corollary: it means that "the problem cannot just be solved by taking 30- or 40-somethings and getting them to exercise," he says. "We've missed the boat if we do that."

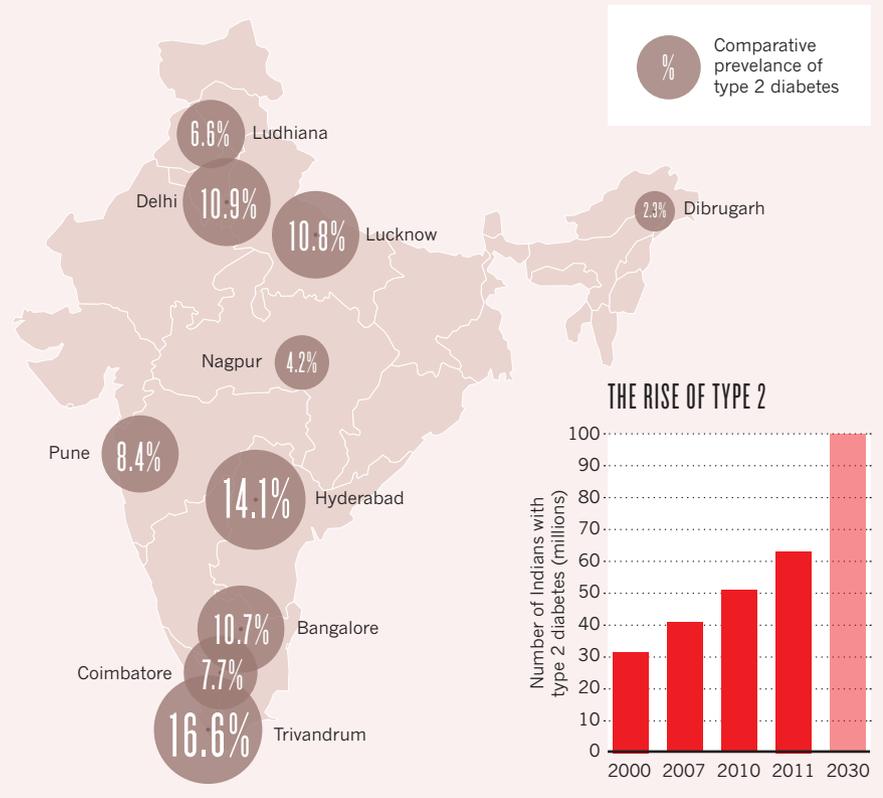
### TOO LITTLE ACTION

Screening for gestational diabetes could be implemented as part of a national diabetes prevention plan in India, though that is still being developed slowly. Preventing diabetes should be a high priority for India but there is little evidence that any major initiatives are under way in that direction," says Zimmet. He adds that while "diabetes is now regarded as a very serious problem by the Indian government, the question is whether they are prepared to put in the resources that are needed to turn around the epidemic".

The early signs are that it has at least set the wheels in motion. In its latest 5-year plan, the Indian government has dedicated a significant chunk of funding for non-communicable

## INDIA'S DIABETES BOOM

The Western diet and lifestyle that have accompanied India's growing prosperity has brought an alarming rise in cases of type 2 diabetes. Nationwide, prevalence of T2D is more than 9%. The epidemic is not surprising in urban areas. However, the disease is now also becoming common in rural villages, especially in wealthy southern states.



diseases such as diabetes. On chronic diseases overall, it will spend 580 billion rupees (US\$11.6 billion) — six times what was allocated in the previous 5-year plan<sup>4</sup>. Progress is slow, however. India's National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases and Stroke (NPCDS), launched in 2008, has made little headway

**“Unless we streamline patient flow, it will be very difficult to handle the growing number of people with chronic diseases.”**

respond to *Nature Outlook's* requests for comment on the diabetes epidemic.)

India's national programme on diabetes might be at a nascent stage, says Tandon, but he nevertheless finds it “reassuring” that in 100 districts, the government will be targeting programmes at schoolchildren to help reduce diabetes and other health risks in later life. The department of health is also rolling out a much-needed nationwide prevalence study, he

in either strengthening infrastructure or implementing prevention plans, other than developing a website (healthy-india.org) to educate people about risk factors for chronic diseases such as diabetes. (India's Ministry of Health did not

says, which should help provide a cohesive picture — most data currently available are from fragmented regional studies, predominantly in cities.

One big barrier to improving diabetes care, says Tandon, is India's chaotic patient referral system. “The lack of systemic processing of patients has been a bugbear of the Indian healthcare system,” he says. Patients aren't first seen by primary care workers, and then referred to secondary or tertiary care. Because 80% of healthcare in India is private, many people bypass general practitioners and go straight to the specialists, a habit that overburdens their clinics. “Unless we streamline patient flow in the future, it will be very difficult to handle the growing numbers of people with chronic diseases,” says Tandon.

Tackling most epidemics starts with screening, but this is difficult given India's ailing healthcare system and the inability of most people to afford glucose tests. The World Health Organization has recommended HbA1c as a proxy for blood glucose level, as the test is cheaper and quicker than a glucose-tolerance test. Fall points out that this method tends to create a lot of false alarms in India because of the country's unusually high prevalence of iron-deficiency anaemia, a condition that elevates HbA1c levels.

Although better screening would be desirable, Zimmet argues that the top priority needs to be prevention. He points out that India won't have the resources to treat growing numbers. “Rather, India needs to look to the future, and that may be 20 or 30 years down the track, to reducing the burden. Attention to maternal and child health may be an important way of eventually stemming the epidemic.”

For India to effectively fight the onslaught of diabetes will require more than government programmes, however. Indian society's nonchalant attitude towards the disease must change as well. “Almost 50% don't follow any diet and exercise regime despite our advice, and 25% of the rest will follow it initially but then abandon it,” says Anoop Misra, head of diabetes and metabolic diseases at Fortis Hospital in New Delhi. People believe that since they don't have symptoms from their high-sugar levels, “they don't need to worry about something that won't harm them until a decade later”, says Misra.

Tandon agrees, saying that studies of diabetes awareness, especially in urban areas, have shown “pathetic” results<sup>5</sup>. “If you're only worried about peeing a bit more in the night, without realizing that this is a disease that could blind you, knock your kidneys out or give you a heart attack, you won't worry too much.”

Ignorance about diabetes can be lethal when combined with the fact that many patients first seek out alternatives such as homeopathy or the traditional Indian medicine known as ayurveda, says Misra. He estimates that about 10–15% of his patients first tried traditional medicines — a detour that can delay their treatment through conventional medicine by up to a year.

The Indian government has been trying to raise awareness with television advertisements and posters about diabetes in doctor's clinics and hospitals. Tandon welcomes these efforts. But considering the momentous cultural and political shifts required, he's cautious about how quickly change will come. “It's still an incredibly long haul.”

The middle-aged, middle-class people passing through Mumbai's shopping mecca consider themselves to be part of the new, prosperous India. But as the epidemic of type 2 diabetes takes hold, many of them face a chronic condition — and a fate that could signal a warning for other parts of the world that are starting to enjoy abundant food and freedom from labour. ■

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