See corresponding article on page 698.

Lifestyle for the prevention of type 2 diabetes: what is the role of genetic risk information?

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The prevalence of diabetes has been continuously increasing over the past 3 decades, globally but particularly in low-income and middle-income regions (1). There are 463 million adults (aged 20–79 y) estimated to be living with diabetes in 2019, with the largest number found in developing countries in Asia, such as China (116.4 million) and India (2). In the context of globalization, large proportions of populations in these less developed regions are undergoing urbanization and a host of environmental and nutritional transitions. The drastic shifts in lifestyle characterized by sedentary-style behaviors and Western-pattern diets are recognized as a major driver of the growing epidemic of diabetes (3).

Most (>90%) cases of adult diabetes are type 2 diabetes (T2D), which is a complex disease concordantly determined by environmental and genetic factors. Being facilitated by the extension of the inventory of T2D-risk variants by large-scale genome-wide association studies, a body of research, conducted predominantly in populations of European ancestry, has assessed the potential role of gene–environment interactions in the development of T2D (4). Currently, however, interpretation of these findings is complicated and their application in public health practice remains limited because relevant studies *1*) have mostly evaluated potential interplays between individual lifestyle factors (e.g., obesity, physical activity, or individual foods or nutrients) prone to confounding by each other and individual genetic variants; *2*) are often underpowered owing to relatively small sample sizes; *3*) have potential concerns of multiple testing leading to false positive findings as well as selective reporting bias because of only reporting selective findings; and *4*) have few cases of replications (4).

In this issue of the *Journal*, Li et al. (5) examined independent and joint associations of combined lifestyle, genetic susceptibility to T2D, and incident T2D in the China Kadoorie Biobank (CKB) and the Singapore Chinese Health Study (SCHS), 2 prospective studies of (ethnic) Chinese participants. Genetic risk scores (GRSs) were computed by summing 49 (for the CKB) or 37 (for the SCHS) single nucleotide polymorphisms which have been associated with T2D in Chinese. Scores of unhealthy lifestyle were derived based on BMI (plus waist-to-hip ratio in the CKB) in addition to 4 behavioral factors (i.e., physical activity, diet quality, smoking, and drinking habits). Pooling data from the 2 cohorts, the results of Li et al.'s analysis expectedly showed that participants with the bottom quintile of the unhealthy lifestyle scores had 70% lower risk of T2D than those in the top quintile. With respect to genetic susceptibility, participants in the top quintile of the GRSs were estimated to have 90% higher risk of T2D than those in the bottom quintile. Perhaps more importantly, Li et al. further highlighted that a combination of healthy lifestyles was similarly associated with lower risk of T2D across all categories of genetic risk. The lack of gene–environment interaction observed by Li et al. is not surprising given the limited evidence that these T2D-associated genetic variants might be involved in the relation between lifestyle factors and risk of T2D or risk factors [with the exception of the fat mass and obesity–associated (*FTO*) genotype, which has been shown to interact with diet/lifestyle intervention on regulating weight loss (6)].

Li et al.'s analyses are notable for the inclusion of 2 nationwide cohorts with ethnically comparable participants, the utilization of broadly consistent (albeit slightly variable) definitions for lifestyle and genetic susceptibility, and the adjustment for similar potential confounders. The large population sample size also provided adequate statistical power to detect potential gene–lifestyle interactions had these been present. These factors are all helpful for addressing the aforementioned limitations of most previous analyses on gene–environment interactions in relation to risk of T2D. In line with the results of Li et al.'s analyses, recent findings from a large prospective study of a UK population also suggest that lifestyle combination and genetic predisposition were associated with risk of T2D independently of each other (7). Of note, in both analyses, adiposity was assigned a weight almost equal to those of other individual lifestyles in deriving the lifestyle score. Because excess adiposity is the

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major contributor to T2D, it is unlikely that an equal amount of health benefits is achievable from weight regulation and from modification of other individual behavioral factors. In addition, obesity is largely a result of unhealthy lifestyles and, therefore, may capture overlapping information with other lifestyle factors. Distinguishing between adiposity and other behavioral factors may be particularly important for studies of Asian populations who are at greater risk of T2D than Western populations at a given BMI (8).

Another interesting question unexplored by Li et al. relates to potential ethnic differences in the associations of genetics and lifestyle with risk of T2D. Li et al. included mostly Chinese Han individuals, yet China of course consists of ethnically and dietary diverse populations with varying disease risks. National surveys conducted in mainland China have shown considerable ethnic differences in the prevalence of diabetes (e.g., ranging from 4.3% for Tibetan to 15.0% for Manchu in 2013) (9), which might suggest that genetic, behavioral, and socioeconomic determinants of T2D are variably distributed across the country. Thus, future ethnicity-specific investigations may provide opportunities for identifying novel risk factors and may facilitate the establishment of more efficient prevention guidelines for subgroups of the population.

Group-based lifestyle interventions have proven highly effective for the prevention of T2D among high-risk adults. As demonstrated in a landmark trial including Chinese people with impaired glucose tolerance, lifestyle interventions including counselling for physical activity, diets, and body weight over 6 y resulted in substantially reduced risk of T2D and the related complications during the subsequent 24 y (10).

Although T2D could be a consequence of complex genetic and environmental interactions, the potential role of genetics in the lifestyle–T2D association remains unclear and the corresponding clinical or public health relevance is still uncertain. Findings from the analyses by Li et al. (5) and others (7) consolidate the knowledge that prevention of T2D should rely on avoidance of excess adiposity and adherence to healthy lifestyles (e.g., regular physical activity, nonsmoking, and healthful eating patterns), and that these strategies are generalizable to global populations regardless of genetic risk categories.

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