Review

Crisis of the Asian gut: associations among diet, microbiota, and metabolic diseases

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The increase of lifestyle-related diseases in Asia has recently become remarkably serious. This has been associated with a change in dietary habits that may alter the complex gut microbiota and its metabolic function in Asian people. Notably, the penetration of modern Western diets into Asia, which has been accompanied by an increase in fat content and decrease in plant-derived dietary fiber, is restructuring the Asian gut microbiome. In this review, we introduce the current status of obesity and diabetes in Asia and discuss the links of changes in dietary style with gut microbiota alterations which may predispose Asian people to metabolic diseases.

Key words: gut microbiota, Asian Microbiome Project, diet, obesity, diabetes, enterotype, bile acid

INTRODUCTION

Several hundred microbial species form a distinctive complex ecological community, namely the gut microbiota, in the digestive tract of a person. It influences the host's physiology and susceptibility to disease via direct contact with host cells [1] or via its collective metabolic activities [2]. Multiple intrinsic and extrinsic factors, such as diet, host genetics and physiology, drugs and disease, and living environments, are involved in shaping the gut microbiota and its metabolic performance [3]. Notably, diet is considered one of the key drivers of the gut microbial community, as it supplies nutrition and alters the environment for the microbes [4–7].

Asian diets vary remarkably within the continent and significantly differ from those on other continents, with their main characteristics being that they are high in carbohydrates, fiber, vitamins, and antioxidants but low in concentrated fat [8]. Traditional Asian diets are basically considered to contain foods with beneficial effects against metabolic diseases, and some are reported to be helpful in promoting and inhibiting the colonization of beneficial and non-beneficial gut bacteria, respectively [7, 9–12]. However, contemporary diets have recently influenced the dietary lifestyles of Asian people, as rapid development of global food service chains has distorted local eating lifestyles. For instance, a trend toward an increase in consumption of calorie-dense diets by Asian people, such as diets containing refined carbohydrates, fat, red meats, and low fiber contents, has been largely confirmed by several studies [13–15]. This occasionally distresses the gut microbiota of Asian people, eventually leading to dysfunction of their gut microbial communities [16–18].

The development of next-generation sequencing (NGS) technology and progress of computer- and database-assisted bioinformatics has revolutionized the genomic research fields in the past two decades [19]. This includes studies on the microbiome of the human digestive system, and we have gained insight into its variation among the peoples of the world, including Asian people. The enterotype has been proposed as a general concept to type the human gut microbiome throughout the world and was first introduced by Arumugam *et al.* [20], although it remains controversial in the aspect of inconsistency and lack of discreteness of the enterotyping [21]. Three enterotypes were originally characterized with high abundances of *Bacteroides*, *Prevotella*, and *Ruminococcus*, respectively, which are present regardless of ethnicity, gender, age, and body mass index (BMI) [20]. Following this first report, a number of studies addressed the links of various microbiome markers and enterotypes with host phenotypes [22].

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At present, we understand that the gut microbiota plays an indispensable role as an interface between foods and host health. Asia is the world largest populous continent, accounting for proximately 60% of the world population and containing a great diversity of ethnicities with large variations in culture and lifestyle, especially in diet [23]. It can be said that each ethnic group has its own dietary culture. In this context, Asia is an attractive field to study the interplay of the gut microbial community and diet together with their effects on host health. Notably, Asian people have specific physiological aspects involved in the vulnerability to metabolic diseases. This therefore warrants capturing of the current status of the Asian gut in association with host metabolic disorders.

In this review, we introduce the current status of metabolic diseases, such as obesity and type 2 diabetes (T2D), and the risk factors for them that are increasing and becoming recent social problems in Asia. We also discuss the associations between diet and gut microbiota that cause metabolic diseases in Asian people by drawing upon the latest studies, including our own data.

CURRENT STATUS OF OBESITY AND DIABETES IN ASIAN PEOPLE

Prevalence of obesity and diabetes in Asia

Economic development and the ubiquity of low priced, highly processed diets in the past half century in Asian countries has been critically associated with an epidemic of obesity and diabetes among Asian people. Indeed, people in Asia have tended to shift away from traditional plant-based diets to calorie-dense foods rich in fat, animal protein, and simple sugars that lead to excessive weight gain and unhealthiness [13–15]. A study released by the Asian Development Bank Institute (ADBI) indicated that the obese population (BMI >25) in Asia has reached about one billion, corresponding to two out of every five adults [24]. The obese populations differ among the regions of Asia, with the population being extremely high in the Pacific region, exceeding 50%, and the rate in Central Asia following closely behind this. On the other hand, the rate was originally low in Southeast Asia (19% of total population on 1990), but it increased from 1990 to 2013 to 38.6%, whose increasing rate was highest in Asia. In particular, Malaysia is the fattest country in Asia at present (46% of total population has a BMI >25), with the nation particularly consuming high amounts of sugar in the form of various sugary drinks, an average of about 3 kg per person

per year as reported by the World Health Organization (WHO) (https://www.who.int/malaysia/news/commentaries/detail/sugary-drinks-tax-important-first-step-but-obesity-in-malaysia-demands-further-action). It should also be noted that Asia has recently become the epicenter of a diabetes epidemic [25]. The International Diabetes Federation stated that at least 463 million people among the total world population in 2019 were suffering from diabetes and that more than half of the affected people lived in Asia [26]. Moreover, five Asian countries are ranked among the world's top ten countries for the number of adults (20–79 years) with diabetes, and six Asian countries are among the top ten for impaired glucose tolerance (IGT; Table 1). The abovementioned points indicate that metabolic diseases are a serious concern in Asian people.

Specific phenotypes of Asian people leading to the risk of obesity and T2D

Abdominal obesity is one of the common phenotypes among Asian people. Normally, Asian people have lower BMIs compared with other ancestry groups but have higher body fat distributions, which causes susceptibility to metabolic abnormalities related to obesity, such as metabolic syndrome (MetS), cardiovascular diseases (CVDs), and T2D [27]. A study by Deurenberg et al. indicated that the body fat percentage of Asian people is around 3–5% higher than that of Caucasian people with the same BMI [28], and this condition is termed the Y-Y paradox [29]. Comparison between populations of the same sex, age, and BMI suggested that Filipino people with a higher body fat percentage show higher risks for T2D and MetS than Caucasians [30]. People from China and India are highly predisposed to abdominal obesity. Jia et al. reported that one-third of Chinese adults are overweight or obese and that 10–20% of all adults are affected by MetS [31]. Moreover, Chinese people tend to have an apple-shaped body rather than pear-shaped body, which represent abdominal obesity and generalized obesity, respectively [32]. Similar to China, obesity in India generally results from abdominal obesity. Ahirwar and Mondal presented a study released by the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) in 2015 stating that the prevalence rate of abdominal obesity in India is higher than that of general obesity, with the rates varying among the regions from 16.9% to 36.3% and 11.8% to 31.3%, respectively [33]. Moreover, abdominal obesity is one of the critical risk factors for the development of CVDs in Indian people [33].

Table 1. Top ten countries worldwide for the number of adults (20–79 years old) with diabetes and impaired glucose tolerance (IGT) in 2019

Rank	Diabetes		Impaired glucose tolerance (IGT)	
	Country	Number of people (millions)	Country	Number of people (millions)
1.	China	116.4	China	54.5
2.	India	77.0	USA	37.4
3.	USA	31.0	Indonesia	29.1
4.	Pakistan	19.4	India	25.2
5.	Brazil	16.8	Brazil	15.1
6.	Mexico	12.8	Mexico	12.6
7.	Indonesia	10.7	Japan	12.1
8.	Germany	9.5	Pakistan	8.8
9.	Egypt	8.9	Thailand	8.3
10.	Bangladesh	8.4	Nigeria	8.2

*Data from the International Diabetes Federation (2019) [26].

Obesity can be linked with an increased risk of T2D, namely diabesity [34]. Accumulation of body fat is associated with inflammation and is one of the major contributing factors to T2D [35]. In obese individuals, excessive calorie intake results in fat accumulation in adipose tissues and lipotoxicity in non-adipose tissues, which activate the production of nonesterified fatty acids (NEFAs), glycerol, and pro-inflammatory cytokines, whereas antidiabetic hormones, such as leptin and adiponectin, are also secreted from adipose tissues. The former action causes impaired insulin function as well as low-grade inflammation, resulting in a loss of insulin sensitivity, which is referred to as insulin resistance, and long-term insulin resistance leads to a constantly elevated systemic glucose concentration and ultimately drives the development of T2D. It should be noted that not all obese individuals develop T2D, and this is possibly explained by specific anti-T2D metabolic phenotypes, such as the increased adipose tissue capacity for lipogenesis in metabolically normal obese people [36, 37]. On the other hand, in Asia, diabesity has been increasing gradually, although lean diabetes is still highly prevalent [26, 38–40].

Asian people are known to have specific physiological aspects involved in vulnerability to glucose homeostasis. For example, Asian people have a high risk of insulin resistance caused by dysfunctional pancreatic insulin secretion [41–43]. A number of studies have shown that slight defects in insulin secretion capacity are indicated in healthy Asian people when assessed by their glucose tolerance [41, 42]. Reduced pancreatic β-cell mass is normally found in Asian people, particularly East Asians. A study by Yoon *et al.* suggested that the impaired insulin secretion of T2D patients results from an inadequate pancreatic β-cell mass and/or functional defects within the β-cells themselves [43]. Moreover, Kodama *et al.* speculated that even a small decrease in insulin secretory function in East Asians leads to a rapid decrease in the threshold level of insulin resistance and the development of T2D and that this instability and the vulnerability of glucose homeostasis due to their lower β-cell function has increased the prevalence of diabetes in East Asia in recent decades [44].

GUT MICROBIOTA OF ASIAN PEOPLE ASSOCIATED WITH LIFESTYLE DISEASE

Gut microbiota of Asian children with a change in their dietary lifestyle

We investigated the gut microbiomes of school-aged children in five Asian countries, including Japan, China, Taiwan, Indonesia, and Thailand [45]. Urban and rural cities were chosen in each country that highly reflected the microbiome profiles of the respective countries and residents, at least in part, which we thought they might reflect the differences in dietary habits [45]. Among the subjects, two enterotype-like clusters were observed, which were defined by a high abundance of *Prevotella* (P type) or high abundance of *Bacteroides* and *Bifidobacterium* (BB type; Fig. 1A and 1B). Whole shotgun metagenomics data for each microbiome type indicated that the P type microbiome is enriched with genes encoding plant-polysaccharide degrading enzymes, such as amylase and pectinase, while the BB type microbiome is enriched with genes involved in bile acid metabolism, such as
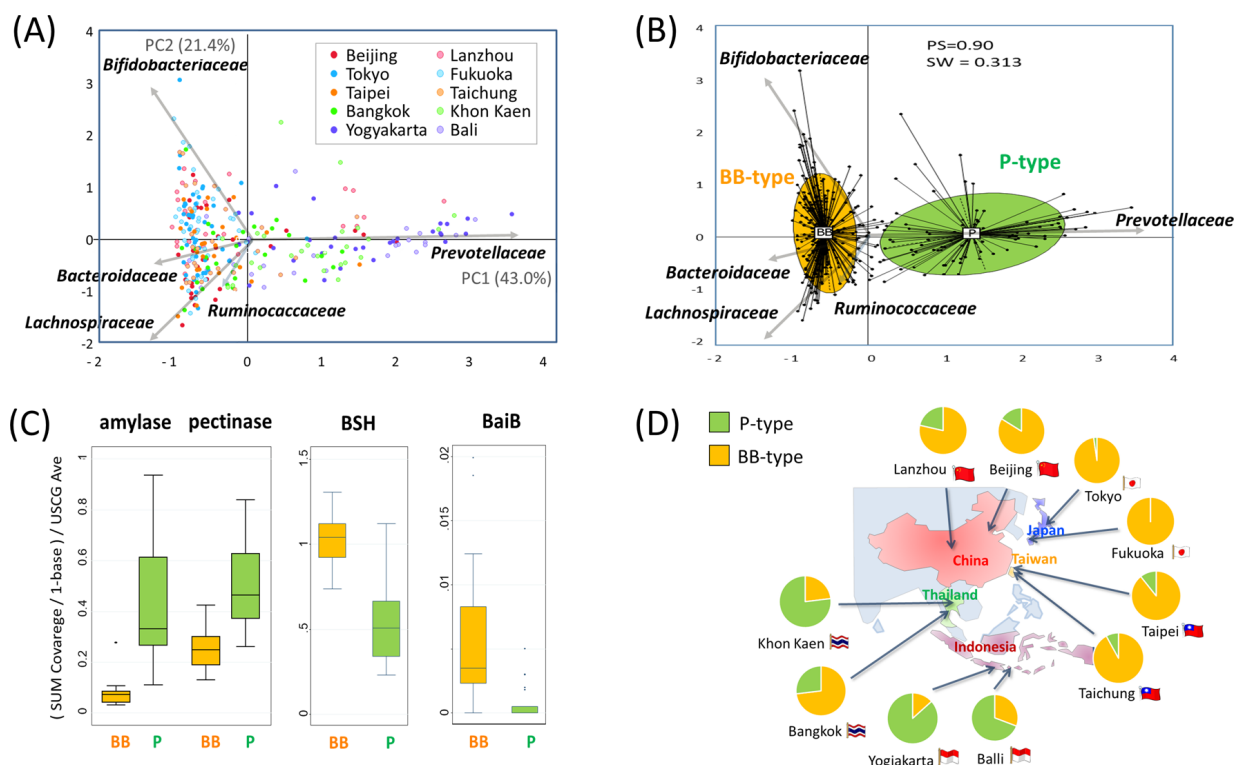

Fig. 1. Two enterotype clusters of school-age children in five Asian countries. (A) Principal component analysis (PCA) of 303 samples based on the family-level compositions of fecal microbiota. (B) Cluster analysis of the PCA plot in A. PS, prediction strength; SW, silhouette index. (C) Abundance of enzymatic genes encoded in the fecal metagenome of BB-type and P-type feces. (D) Distribution of P-type and BB-type samples in ten cities from five countries. Figure 1A and B are reproduced from Nakayama *et al.* [45] under a Creative Commons License CC BY 4.0.

bile salt dehydrogenase (BSH) and bile acid-coenzyme A ligase (BaiB), suggesting that the P type microbiome reflects a plant-based diet and that the BB type microbiome reflects a high-fat diet (Fig. 1C). Children from East Asian countries primarily harbored the BB type, whereas those from Southeast Asian countries primarily harbored the P type, except for children from Bangkok, Thailand (Fig. 1D). The gut microbiota of Thai children likely reflects a shift of dietary habits from a traditional to modern style that commenced in urban areas.

To address the impact of changes in dietary style, we performed two cross-sectional studies to compare the gut microbiota of urban and rural children: one was conducted on Leyte island in the Philippines (Fig. 2A) [16], and the other one was conducted on the capital and rural cities in Thailand (Fig. 3A) [17]. Interestingly, Rohrer's index was significantly higher in urban children in both countries; notably, the index in urban cities was around 145, which was the border between normal and obesity, whereas in rural cities, it was in the middle of the normal range, suggesting that urban children in these developing countries tend to suffer from obesity (Fig. 2B and 3B). This has attracted interest with respect to the condition of the gut microbiota of urban children compared with rural children who maintain a standard body mass under a traditional diet.

To begin, we compared the daily diets and fecal microbiota of children living in an urban city (Ormoc) and rural city (Baybay) on Leyte island [16]. The results of a dietary survey and examination of fecal microbiota revealed that the children in Ormoc consumed modern high-fat foods, such as snacks and fast foods, with the associated total fat consumption accounting for 27.2% of their total energy intake, which corresponded closely to the similar level of children in Western countries. On the other hand, the children in Baybay maintained a traditional dietary style, including the daily consumption of regional fruits, green mangos and bananas, and their total fat consumption rate was 18.1% (Fig. 2C). Regarding microbiota, the children in these two cites harbored two distinctive gut microbiotas, namely BB type and P type microbiotas, respectively. A redundancy analysis indicated that the BB type microbiota in Ormoc is driven by high fat consumption, reflecting the introduction of Western foods (Fig. 2D). It is highly surprising that the two populations of these cities, which where of the same ethnicity and only 60 km apart from each other on the same island, had opposing enterotypes that appeared to be driven by the introduction of a Western diet. Interestingly, the fat consumption of the children in both cities on Leyte island showed a positive correlation with the Firmicutes-to-Bacteroidetes (F/B) ratio, which is known as a gut biomarker of obesity (Fig. 2E).
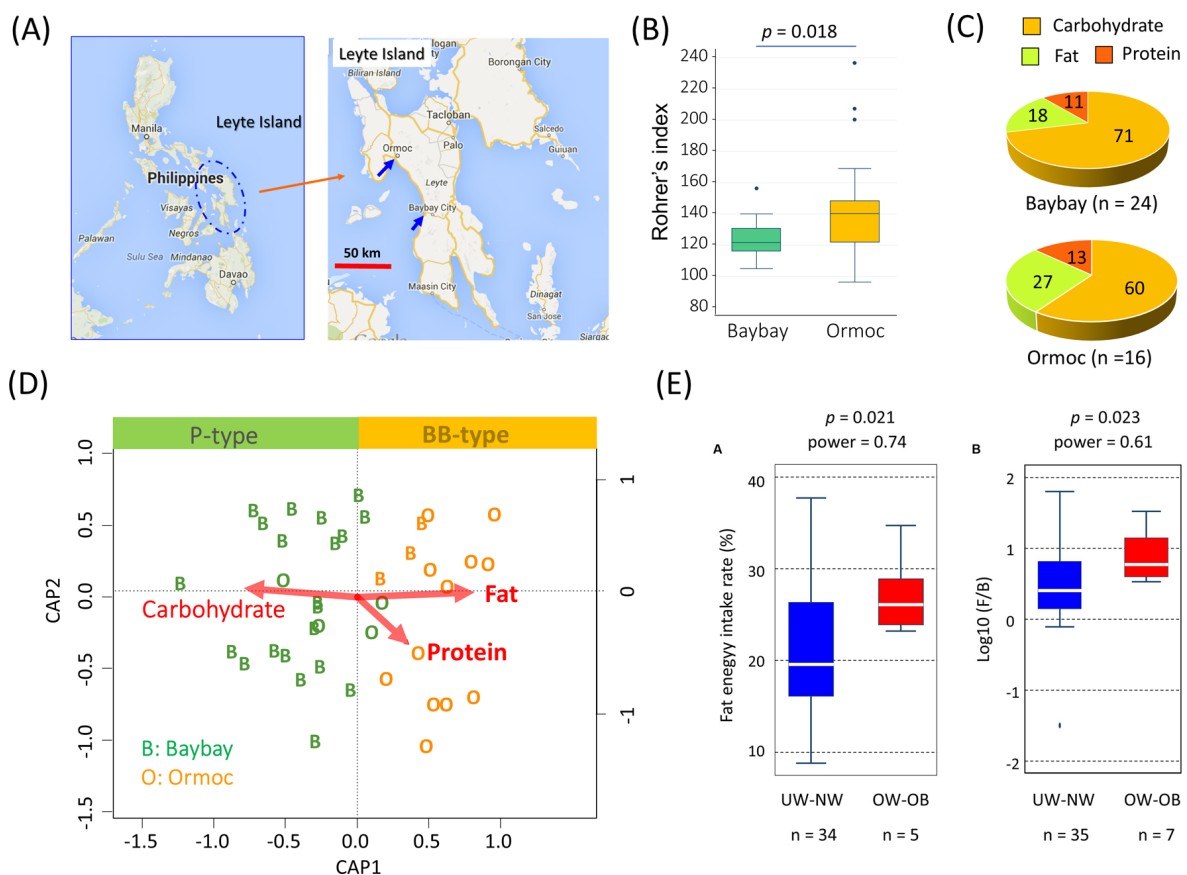
Fig. 2. Comparative cross-sectional study on the food-gut microbiota-host physiology of Leyte school-age children. Samples were collected from a rural city, Baybay (n=24), and urban city, Ormoc (n=16), on Leyte island. (A) Map showing the locations of Ormoc and Baybay cities on Leyte island. (B) Distribution of the Rohrer's indices of the subjects from Baybay and Ormoc. (C) Macronutrient consumption ratio of the subjects from Baybay and Ormoc. (D) Redundancy analysis for the Baybay (B) and Ormoc (O) subjects based on the bacterial compositions of their feces at the family level and their macronutrient consumption ratios. (E) A: Distribution of the fat energy intake ratio of the underweight (UW)-normal weight (NW) group and the overweight (OW)-obese (OB) group. B: Distribution of the Firmicutes to Bacteroidetes ratio (log10) of the UW-NW and OW-OB groups. Figures are reproduced from Nakayama *et al.* [16] under a Creative Commons License CC BY 4.0.
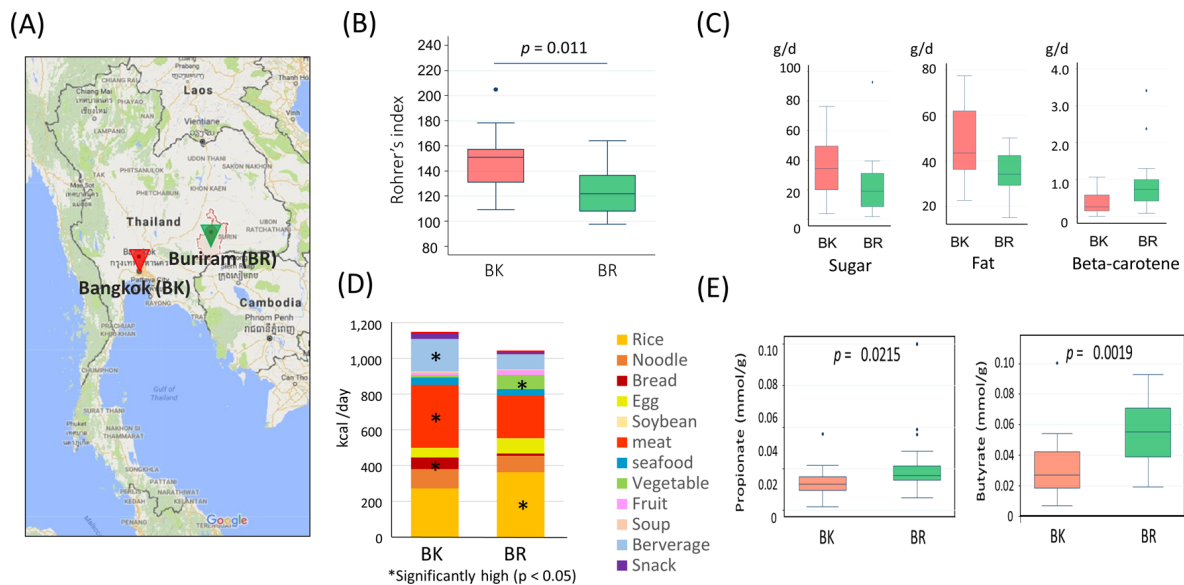
Fig. 3. Comparative cross-sectional study on the food-gut microbiota-host physiology of Thai school-age children. Samples were collected from a rural city, Buriram (n=28), and urban city, Bangkok (n=17), in Thailand. (A) Map showing the locations of Buriram and Bangkok in Thailand. (B) Distribution of the Rohrer's indices of the subjects from Bangkok (BK) and Buriram (BR). (C) Distribution of the daily consumed amounts of food components in individuals in BK and BR. (D) Stacked bar chart of the daily consumed amounts of each food component. The data are the averages for 15 BK children and 26 BR children. (E) Box plot showing the levels of fecal propionate and butyrate of the BK and BR children. Figures are reproduced from Kisuse *et al.* [17] under a Creative Commons License CC BY 4.0.

In our Thai study, different aspects were observed [17]. Comparison of the daily diet profiles of Thai children who lived in a rural city, Buriram, and an urban city, Bangkok, clearly indicated that the urban dietary lifestyle has penetrated into Bangkok. Dietary records showed that Bangkok children consumed more fat and simple sugars and much lower amounts of vegetables, whereas Buriram children maintained a traditional Thai plant-based diet (Fig. 3C and 3D). Comparative microbiomics did not show an enterotype shift like the Leyte children but did show slight changes in the abundance of *Peptostreptococcus*, which increased in the Buriram children. On the other hand, comparative metabolomics showed some distinct types among the children; one type showed a higher level of short-chain fatty acids (SCFAs) in a cluster mainly consisting of Buriram children, and the other type showed a higher level of amino acids and lower level of SCFAs in a cluster mainly consisting of Bangkok children. Taken together, the fecal butyrate and propionate concentrations were significantly lower in Bangkok children than Buriram children (Fig. 3E). This suggests that urban dietary habits with lower consumption of vegetables results in a reduction in colonic SCFA fermentation in Thai children.

These two cross-sectional studies may indicate a gut microbiota crisis in Asian children. Loss of SCFA fermentation in Bangkok children due to the shift away from traditional Thai foods suggests the advantage of Thai traditional foods and disadvantage of urban foods. Thailand is known as the "kitchen of the world", and traditional Thai foods may be representative of foods in Southeast Asia. The loss of benefits from this tradition and the impact of this on the gut microbiota of children may not be a problem only in Thailand but may also affect the whole area of Southeast Asia. The enterotype shift in children on Leyte island represents a strong impact of the introduction of Western foods to Asian people. The penetration of Western diets may drive the enterotype shift continuously throughout Southeast Asia. We should keep an eye on the impact of the enterotype shift on the health of Asian people.

Impact of the penetration of modern diets on gut microbiota in Asian people in developing areas

There is a clear difference in terms of dietary patterns between Western and Asian countries. Asian diets generally integrate several tastes, including sweet, sour, salty, spicy, and bitter tastes, and their main characteristics are known to be high fiber, vitamin, mineral, and antioxidant contents together with a high carbohydrate content but low concentrated and total fat contents [8]. Western diets, notably urban diets, tend to be short on fiber and to contain high-fat dairy products and excessive amounts of refined and processed foods, alcohol, salt, red meats, sugary drinks, snacks, eggs, and butter, meaning that they are enriched in terms of total fat, animal proteins, and refined sugars [8]. Noticeably, the Western diet is penetrating into traditional diets in developing areas as a part of urban lifestyles introduced in conjunction with ongoing economic growth.

Asian diets are basically considered to contain relatively beneficial foods, to protect against chronic metabolic disease, and to be helpful in promoting and inhibiting beneficial and non-beneficial gut bacteria, respectively. For example, studies have reported that a Japanese diet containing high levels of fiber promotes high numbers of *Bifidobacterium* but low numbers of gut pathogenic *Clostridium* spp. [10, 11]. Moreover, endosperm protein extracted from a Japanese rice cultivar, *Koshihikari*, alters the gut microbiota diversity and is associated with the suppression of high-fat diet (HFD)-induced obesity progression by suppressing the growth of endotoxin-related chronic inflammatory *Escherichia coli* in mice [9]. Another major component of the Asian diet is vegetables. The Thai diet is known

to be rich in vegetables (FAO, United Nations, http://www.fao.org/3/ac145e/ac145e02.htm). As mentioned above, the study of diets in relation to the gut microbiome and metabolome in the Thai cohort indicated that children who consume a traditional vegetable-based diet have a greater bacterial diversity with significantly higher levels of fecal SCFAs, mainly butyrate and propionate, compared with children who consume a modern high-fat diet (Fig. 3E) [17]. Another study investigating healthy Thai vegetarians indicated that their microbial communities are mainly driven by *Prevotella* but that they have a low abundance of potential pathogen varieties [12].

A Western diet with an urban lifestyle is generally considered to be harmful to health. One of the major characteristics of Western diets is that they are rich in total fat, so-called HFDs, and the consumption of a HFD has been linked to low-grade inflammation related to metabolic disease [46–48]. An animal study by Bortolin *et al.* found that a diet formulated based on a Western style generates excessive fat accumulation in mice and results in metabolic dysfunctions, as evaluated by significantly higher levels of several metabolic biomarkers associated with obesity-related diseases, mainly hepatic steatosis, inflammation, and insulin resistance, compared with a dietary control group [49]. Moreover, it alters the microbial community, resulting in gut dysbiosis [49]. In humans, a randomized crossover clinical trial was performed by Shin *et al.* to investigate the differences between a Korean diet (more plant-derived and fewer animal components) and two American diets (more animal and fewer plant-derived components) [7]. The results of four-week dietary interventions in overweight adults indicated that the Korean diet promotes gut microbial diversity and decreases the level of branched-chain amino acids, increased circulating levels of which are known to induce insulin resistance and aggravate glucose intolerance [50], which was the opposite of the American diets [7]. A cross-sectional study indicated that gut microbiota of European children, who ordinarily consume high-calorie diets,

harbor increased abundances of Proteobacteria and decreased abundances of *Prevotella* [6].

As mentioned in the previous subsection regarding the changes in the gut microbiotas of Asian children with a change in their dietary lifestyle, regional comparative studies of Asian children suggested that their gut microbiotas are recently being affected by the modernization of their diets. This leads to the question of how adults are affected. To discuss this point, we present here a dataset we obtained through the Asian Microbiome Project (http://www.agr.kyushu-u.ac.jp/lab/microbt/AMP/). A principal component analysis (PCA) was performed by using gut microbial compositions at the genus level of adults from six Asian countries, including Japan, China, South Korea, Mongolia, Indonesia, and Thailand (Fig. 4A). As shown in Fig. 4B, three enterotype-like clusters, namely a *Ruminococcus* type (R type) in addition to the P and BB types, were observed, although the border between the clusters was rather unclear. Differences in the distribution of enterotypes were present among the Asian countries; for example, Japanese samples were mostly typed as the BB type, and Mongolian and Indonesian samples were highly classified as the P type (Fig. 4C). Although it is known that the P type favorably colonizes the intestines of people who favor plant-based diets, Mongolian people have dietary habits that mainly consist of the consumption of meats and dairy products, with less consumption of vegetables [51]. However, it is known that Mongolian people consume high amounts of whole-wheat products [52], which contain high contents of arabinoxylan, which is known to promote the colonization of *Prevotella* in the intestine [53]. Korean, Chinese (Beijing), and especially Thai samples were highly localized in the R-type cluster, namely the *Ruminococcus*-rich microbiome cluster (Fig. 4C), probably as a result of the fiber-rich diets in these countries [54].

To address the relationships between consumed foods and gut microbiota more directly, we performed cross-sectional studies in two countries, Mongolia [55] and the Philippines [56, 57].
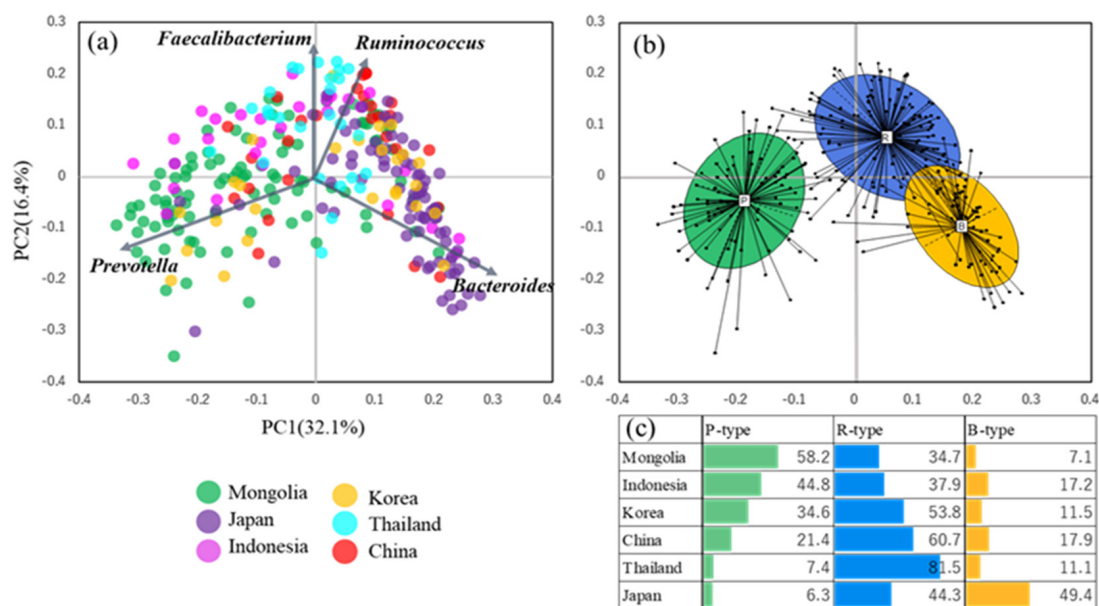
Fig. 4. Enterotype clustering of the gut microbiomes of adults from six Asian countries. (A) Principal component analysis (PCA) of fecal samples of adults from six countries using their genus-level composition data. (B) Enterotype clustering based on the PCA plots in A. (C) Percentages of samples classified into each enterotype in each country. Figures are reproduced from Shinoda *et al.* [57] with permission from the publisher.

In each country, we collected food consumption data as well as gut microbiome data in urban and rural sites. In Mongolia, we collected samples in the capital city, Ulaanbaatar, and a rural city, Bulgan. The food consumption data showed contrasting dietary habits: people in Bulgan mainly consumed a traditional Mongolian diet, whereas people in Ulaanbaatar consumed far fewer traditional foods (Fig. 5A). In the Philippines study, we collected samples in the capital city, Manila, and a rural area, Albay. The food consumption data indicated that people in Manila consumed a high ratio of fat, while people in Albay consumed a high ratio of carbohydrates (Fig. 5A). The microbiome data for these two countries similarly showed the tradeoff of *Prevotella* and *Bacteroides* between urban and rural areas in association with the penetration of urban diets (Fig. 5B). Figure 5B also shows Japanese data indicating that *Prevotella* is no longer present in most people. Japan has undergone drastic development that began in the second half of the twentieth century, and people in cities now live completely urban lifestyles. Taken together, the results of these studies suggest that dietary urbanization has been a strong driving force for the shift in enterotype from the P to BB type in Asian people.

Impact of tradeoff between Prevotella *and* Bacteroides *on the health of Asians*

Wu *et al.* investigated the links of long-term dietary patterns with enterotypes [5]. They found that *Bacteroides* was associated with protein and animal fat diets, whereas *Prevotella* was associated with plant-based carbohydrate diets. Similar results were revealed in the Asian cohort studies presented in the previous subsection regarding the impact of the penetration of modern diets on gut microbiota in Asian people in developing areas, suggesting that tradeoff between *Prevotella*-type and *Bacteroides*-type microbiomes is ongoing due to the penetration of modern Western-type diets [16, 45]. Recently, the *Bacteroides* enterotype was reported to be associated with a high prevalence of T2D. A study conducted by Wang *et al.* indicated a high prevalence of T2D in Chinese subjects with *Bacteroides*-type microbiomes and elevated levels of blood lipopolysaccharide (LPS), diamine oxidase (DAO), and tumor necrosis factor-alpha [58]. Their study suggests that these T2D patients suffer from endotoxemia and low-

grade inflammation, causing impaired insulin sensitivity [58]. On the other hand, beneficial effects of *Prevotella* colonization have been reported in some studies. The response to a barley kernel diet with improved glucose tolerance is dependent on a high ratio of *Prevotella* to *Bacteroides* in the human intestine [59]. Mice administered *Prevotella copri* by gavage showed improved glucose tolerance and an increase in hepatic glycogen storage via the modulation of intestinal gluconeogenesis and systemic energy homeostasis, with succinate serving as a source of intestinal glucose [60]. Furthermore, a subsequent study indicated that subjects with a high *Prevotella* level displayed an overall lower insulin response, lower IL-6 concentrations, and hunger sensations compared with a low *Prevotella* group, suggesting the benefit of a higher *Prevotella*/*Bacteroides* ratio in host metabolic regulation [61]. However, it should be noted that the opposite results have also been reported, with mice administered *P. copri* by gavage having significantly higher serum glucose levels after a three-week challenge compared with controls administered a sham gavage and the fecal *P. copri* abundance being positively correlated with homeostasis model assessment-insulin resistance (HOMA-IR) at two weeks post bacterial challenge [62].

We summarized the action of the enterotype shift from the *Prevotella* type to the *Bacteroides* type in Fig. 6A. It seems that *Bacteroides* appears to be a new player related to the promotion of T2D. A study by Sun *et al.* found that over-representation of *Bacteroides fragilis* in Chinese patients is associated with T2D via bile acid biotransformation [63]. Bile acids (BAs) are the end products of cholesterol catabolism and are synthesized only in the liver [64]. Produced BAs are pooled in the gallbladder, and after a meal, they are secreted into the ileum. Most BAs are reabsorbed and recycled via the enterohepatic circulation, and the remaining BAs enter the colon, are therein metabolized by a certain group of gut bacteria, and are eventually voided in feces [64]. BAs regulate metabolism and pathophysiology in the liver as signaling molecules that activate several nuclear receptors. Among the receptors, farnesoid X receptor (FXR) plays an important role in the metabolic regulation related to obesity and diabetes [64]. Inhibition of intestinal FXR is suggested to have beneficial effects on glucose homeostasis [65–67]. Sun *et al.* elucidated that *B. fragilis* is involved in T2D through its bile salt hydrolase (BSH)
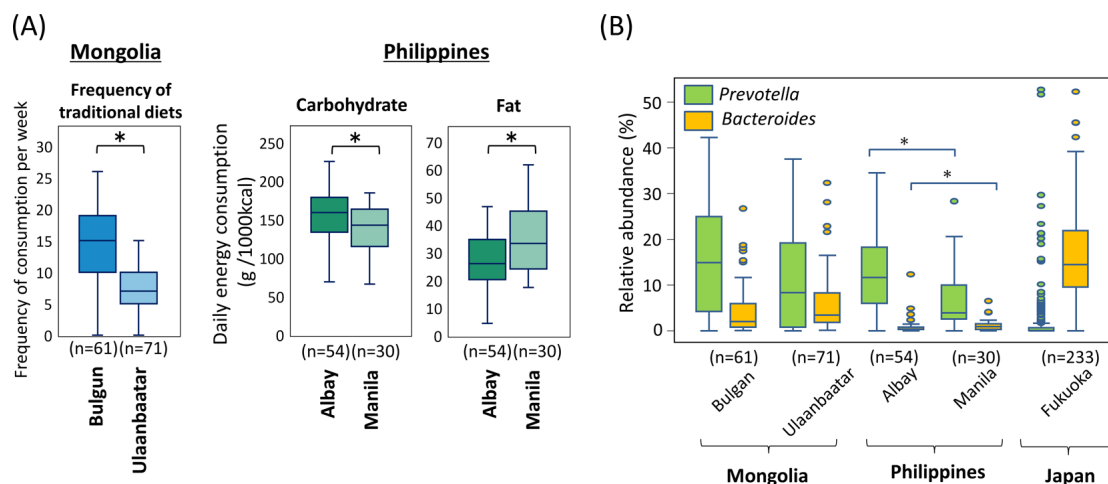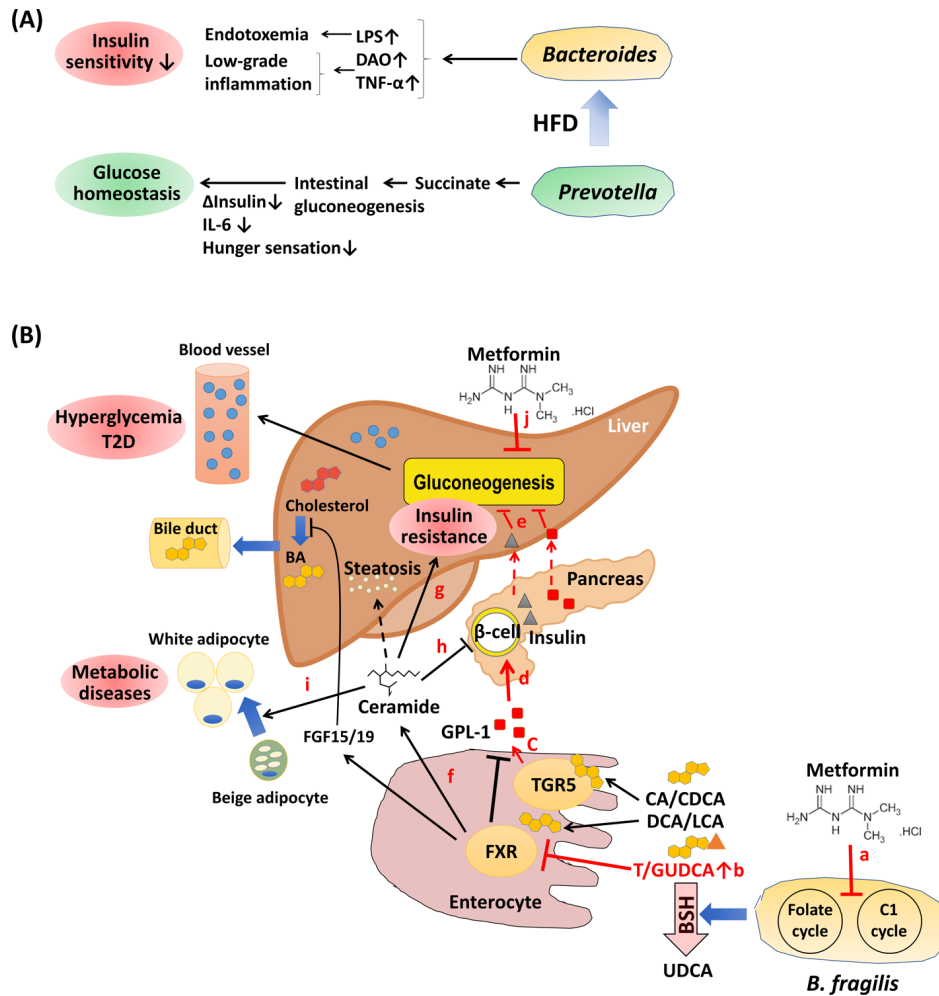

Fig. 5. Dietary habits (A) and *Prevotella*/*Bacteroides* abundance (B) in urban and rural cites in Mongolia and the Philippines. Figures are reproduced from Shinoda *et al.* [57] with permission from the publisher.

Fig. 6. Mechanism of *Bacteroides*-related predisposition to type 2 diabetes mellitus. (A) Predisposition to insulin sensitivity caused by an enterotype shift from the *Prevotella* type to *Bacteroides* type. (B) Tentative overview of T2D alleviation via *B. fragilis* inhibition with metformin.

function, which causes the loss of conjugated BAs, notably glycoursodeoxycholic acid (GUDCA) and tauroursodeoxycholic acid (TUDCA), functioning as an intestinal FXR antagonist and improving glucose homeostasis [63]. Moreover, the administration of an antidiabetic drug, metformin, in T2D patients has been suggested to suppress *B. fragilis*, causing a decrease in BSH activity with a consequent increase in GUDCA and TUDCA levels. Eventually, the recovered levels of these conjugated BAs improve the blood glucose level. A similar phenomenon was found in Indonesian T2D patients. A study by Therdtatha *et al.* found that a T2D group of subjects harboring a high abundance of *B. fragilis* showed low levels of conjugated BAs, especially TUDCA, the level of which was restored by the administration of metformin [18].

It can be inferred that the key mechanism of the abovementioned T2D promotion is BSH activity, the inhibition of which leads to the accumulation of conjugated BAs, which have an FXR antagonistic effect. BSH, which is widely present in gut bacteria, hydrolyzes and deconjugates glycine or taurine from the sterol core of the primary BAs, and this activity has been known to have effects on various aspects of health [68]. A number of studies have suggested that BSH activity is commonly found in strains of gram-positive probiotic candidates, such as *Lactobacillus* spp.

and *Bifidobacterium* spp., and other gram-positive genera, such as *Clostridium* and *Enterococcus* [69, 70]. In contrast, the activity of Gram-negative bacteria has been largely unexplored, and the characterization of BSH related to the members of Bacteroidetes has started [71]. Further underlying modes of action in the microbiota-BSH axis involved in T2D and some other metabolic diseases require more investigation.

Finally, we show a model of T2D promotion by *B. fragilis* in Fig. 6B. *B. fragilis* synthesizes folate, which mediates a broader set of biotransformations known as one-carbon (C1) metabolism that serve as biosynthetic processes for amino acids, including glycine, serine, and methionine, required for bacterial growth and survival. Metformin is known to suppress folate and methionine production in gut bacteria (Fig. 6B (a)) [72]. Collectively, this indicates that metformin inhibits the growth of *B. fragilis* via the modification of folate and methionine metabolism, resulting in a decrease in BSH activity and subsequently increasing in the levels of TUDCA and GUDCA, which are intestinal FXR antagonists (Fig. 6B (b)) [63]. Inhibition of intestinal FXR is suggested to have beneficial effects on glucose homeostasis via the induction of glucagon-like peptide-1 (GLP-1) production (Fig. 6(c)) [65] Induction of GLP-1 production is controlled by Takeda-G-protein-receptor-5 (TGR5) [73, 74], whereas FXR

activation has found suppressing the transcription and secretion of GLP-1 [66]. Subsequently, GLP-1 induces insulin secretion in β-cells (Fig. 6(d)) and downregulates hepatic gluconeogenesis (Fig. 6(e)) [66]. It is also known that intestinal FXR inhibition attenuates hepatic gluconeogenesis due to suppression of the expression of genes involved in ceramide synthesis in the intestine (Fig. 6(f)) [67]. Ceramides are lipid molecules that are known to disturb glucose homeostasis via inhibition of the insulin signaling leading to insulin resistance (Fig. 6(g)) [75]. Moreover, they induce pancreatic β-cell apoptosis that impairs insulin production (Fig. 6(h)) [76]. Ceramides also impair adipose function through increased endoplasmic reticulum stress, resulting in a decrease in the ratio of beige to white adipocytes leading to obesity, and possibly also inflammation and insulin resistance (Fig. 6(i)) [77]. It should also be noted that metformin controls the blood glucose level via the inhibition of gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase (Fig. 6(j)) [78].

CONCLUDING REMARKS

The rates of metabolic diseases have been increasing in Asia over the past few decades in conjunction with rapid socioeconomic growth and in association with lifestyle-related diseases of Asian people and their specific phenotypes. A shift in dietary habits from Asian traditional to modern styles distorts the gut microbiota and metabolome, resulting in a worsening of health. Particularly in Asian developing countries, where diets have gradually modernized in urban areas, the enterotypes show a clear trend of change from the P type to BB type. Diabetes is a metabolic disease that has recently become a serious problem among Asian people. In terms of gut microbiota-related diabetes, the *Bacteroides* enterotype can be a marker for a high risk of T2D in people in developing countries in Asia. In particular, Indonesian study has indicated that *B. fragilis* together with BSH activity shows a strong association with T2D. Collectively, this review warns of the common risk of modernization of dietary habits with regard to the health of Asian people.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest relevant to this article.

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