ABSTRACT
The rising tide of diabetes in Asia has been preceded by high prevalence rates of diabetes among migrant Asian populations in the USA and elsewhere. A 1963 report from Hawaii showed that diabetes was much more prevalent in Japanese Americans than in Caucasians. The Japanese American Community Diabetes Study was begun in Seattle, Washington, to examine why this was the case, and explore the etiology and pathogenesis of type 2 diabetes among Japanese Americans who were Nisei (second generation) and Sansei (third generation) descendants of the original immigrants to the USA from Japan. This research was planned to be a metabolically-based longitudinal epidemiological study that assessed lifestyle factors, insulin sensitivity, insulin secretion and adiposity, including measurements of body fat distribution by anthropometry and computed tomography (CT). An important conclusion from this research was that visceral adiposity was a powerful risk factor for metabolic disease. Our observations suggested that among susceptible Japanese Americans lifestyle led to weight gain, especially in visceral fat depots, that in turn led to decreased insulin sensitivity that unmasked a reduced β-cell reserve, resulting in hyperglycemia and type 2 diabetes. This process can be prevented by dietary and exercise intervention. Thus, the Japanese American population has served as an early warning system for type 2 diabetes in Asians, just as caged canaries were used by coal miners as an early warning system for harmful gases in coal mines.

INTRODUCTION
Coal miners carried caged canaries with them down into mine tunnels in order to detect dangerous gases, such as methane or carbon monoxide (Figure 1). The gases would kill the canary before they could harm the miners, thus providing an early warning system. In retrospect, our study of Japanese Americans in Seattle has served as an early warning system for the diabetes tsunami that has swept through other Asian populations worldwide. My lecture reviewed how my research focus turned to the epidemiology of diabetes in Japanese Americans, and presented some of the history behind and the highlights from this research. An extensive review of this research has been previously published.

Diabetes rates are quite low in Japan when compared to your country. There are many Japanese people who were born and grew up in the United States. How do these Japanese Americans compare to our Japanese?

This was asked of me by a Japanese diabetologist at the annual scientific meeting of the American Diabetes Association in June 1971. Little did I know at that time that my later recollection of this conversation would lead to a major change in the direction of my research career which, at that time, was just beginning at the University of Washington and was entirely at the laboratory bench. Dr Robert Williams, who was head of the Division of Metabolism and Endocrinology, had given me the responsibility of establishing a cell culture laboratory in the Division, and my research was beginning to use cell cultures of islet cells, fibroblasts and adipocytes to examine some of the processes fundamental to an understanding of diabetes.
12. Being fully immersed in this research, I did not expect that within 10 years I would become deeply interested in studying culture of another type, lifestyle, in the development of diabetes in Japanese Americans. The lecture that I delivered at the 7th Annual Meeting of the Asian Association for the Study of Diabetes reviewed the history leading up to and some of the highlights from this metabolically-based epidemiological study into the etiology and pathogenesis of type 2 diabetes among Japanese Americans.

In 1963, Sloan published a report from Hawaii showing ethnic prevalence rates for diabetes. In 1958 and 1959, 38,103 ‘gainfully employed’ civilian residents of Oahu were studied. Screening glucose ≥130 mg/dL from finger blood samples obtained at 2–2.5 h after a meal containing at least 50 g of carbohydrate identified those who needed to be retested, and those identified as possibly diabetic were then referred to their physician for confirmation of diabetes. Although the diagnostic criteria for diabetes were quite different from those used today, nevertheless it was abundantly clear from that report that Asians in Hawaii had a much higher prevalence of diabetes than Caucasians (Table 1). Among those who were of single race, Japanese comprised by far the largest number (16,134). This might be the earliest report about ethnic differences in diabetes rates in the USA that included Asians, and suggested to me that Seattle Japanese Americans were likely to also have a high risk of diabetes.

**PILOT STUDY**

Because my laboratory research was well underway by 1978, to learn more about diabetes among Seattle Japanese Americans I successfully applied for funding from the Kroc Foundation and from the American Diabetes Association for a pilot study that would compare diabetic Japanese men in Seattle and Tokyo and diabetic Caucasian men in Seattle. I also took a sabbatical leave at the University of Tokyo in the Third Department of Medicine, which was directed by Professor Kinori Kosaka. Soon after arriving in Tokyo, I had my first meeting with Professor Kosaka, who discussed with me his thoughts about the differences in diabetes between Japan and the USA. The main points of this discussion were: (i) Japanese with diabetes have low blood insulin levels; (ii) Americans with diabetes have high blood insulin levels; (iii) diabetes develops in Japanese because their β-cells are ‘weak’; and (iv) diabetes develops in Americans because they are obese and insulin resistant.

The age distribution of Japanese Americans in Seattle is quite interesting and is explained by the immigration history of Japanese from Japan to the USA. Immigration began in the 1800s and continued until 1924 when immigration from Asia to the USA was blocked by the government. This resulted in the age distribution in 1980 shown in Figure 2. This age distribution pattern showed three peaks: the immigrant Issei (aged ≥75 years), their Nisei children (peak at approximately 55 years) and their Sansei grandchildren (peak at approximately 25 years). We chose to include Nisei men for the pilot study. From this pilot study, we observed that: (i) Nisei diabetic men in Seattle tended to be more overweight than Tokyo diabetic men, but not as overweight as Caucasian diabetic men; (ii) Nisei and Tokyo diabetic men consumed similar amounts of food, but less than Caucasian diabetic men; (iii) Nisei diabetic men consumed more total fat and less carbohydrates than Tokyo diabetic men; and (iv) Nisei diabetic men consumed proportionately as much fat (% of total calories as fat) as Caucasian diabetic men.

These early findings led to several conclusions and questions. For example, among those with diabetes, Japanese Americans were more overweight than native Japanese, but not as overweight as Caucasians, but Japanese Americans had higher diabetes rates than Caucasians. So was there anything else besides body size that was important? Also, we found that Japanese Americans had a dietary lifestyle that was more similar in

![Figure 1](http://onlinelibrary.wiley.com/journal/jdi)
BIRTH OF THE JAPANESE AMERICAN COMMUNITY DIABETES STUDY

We now had enough reason to proceed beyond the pilot study. The result of this was the Japanese American Community Diabetes Study (JACDS), an epidemiological study supported by funding from the National Institutes of Health that focused on the etiology and pathophysiology of type 2 diabetes. The hypothesis underlying the JACDS was that an interaction between nature; that is, an inherent propensity towards the development of type 2 diabetes in Japanese, and nurture; that is, an adverse lifestyle environment, caused pathophysiological changes that resulted in hyperglycemia and type 2 diabetes (Figure 3). In order to examine this hypothesis, we studied men and women who were of pure Japanese ethnicity, either Nisei or Sansei, who resided in King County, Washington, in which the Seattle metropolitan area was the biggest population center. Early findings from this research showed that the prevalence of diabetes was indeed higher in Seattle, approximately fourfold higher in Seattle Nisei men and women than had been previously reported for Tokyo men and women of similar age (Figure 4).

In addition, in a comparison of diabetic Nisei men and diabetic Japanese men in Tokyo, we observed that although mean glucose levels were very similar during a 3-h 75-g oral glucose tolerance test (OGTT) between these two groups, the corresponding insulin levels were much higher in Seattle. The relationship between the summed insulin and summed glucose plasma levels are shown in Figure 5; these showed that the Seattle men were very insulin resistant when compared with the native Japanese men. The mean ages were similar for both groups, but the Seattle Nisei men had a greater mean body mass index (BMI), although still not as high as commonly seen in other ethnic/racial populations of diabetic patients in the USA. We concluded that Japanese Americans were more resistant to insulin action than native Japanese, and
that this might be because of their higher BMI. Thus, the higher prevalence of diabetes in Japanese Americans than in native Japanese could be because of the presence of more insulin resistance in Japanese Americans. However, there was still an important question that remained from my earlier discussion with Professor Kosaka: could it be that this reduction in insulin sensitivity has been superimposed on an inherently lower β-cell reserve in Japanese? If this were the case, then the higher prevalence of diabetes in Japanese Americans might be attributable to a greater number of individuals with insulin resistance that would in turn make those with lesser degrees of β-cell dysfunction more vulnerable to the development of hyperglycemia.

Another nagging question regarded BMI. ‘Fatness’ is important, but was there something else, for example body shape, that contributed (Figure 6)? The importance of body shape was reported by Jean Vague in a seminal paper published in 1956

Figure 5 | Relationship between summed insulin and summed glucose during a 3-h 75-g oral glucose tolerance test in Seattle Nisei (●) and Tokyo Japanese (○) men.

in which he described the android body habitus as predisposing to several conditions including diabetes. Body shape, the extremes of which have been called android and gynoid, had been traditionally assessed by anthropometric means, such as skinfold thicknesses and body circumferences. The novel addition to our research was the use of CT to assess subcutaneous and intra-abdominal or visceral fat in all participants. These CT scans were obtained by single slices in the chest, abdomen and thigh. Shown in Figure 7 are two computed tomography scans through the abdomen at the level of the umbilicus from two Nisei men, one of whom has diabetes (Figure 7a) and another who does not (Figure 7b). Tissue with the radiographic density of fat has been painted white in these scans. Clearly, the diabetic individual has much more intra-abdominal fat. Thus, very early on we became aware that those Nisei men with diabetes tended to have a larger intra-abdominal fat area at the level of the umbilicus as shown by this frequency distribution of intra-abdominal fat areas in normal and diabetic Nisei men (Figure 8). Subsequently, we found the same to be true for Nisei women as well as for Sansei men and women.

Figure 6 | Body shape patterns: gynoid and android. BMI, body mass index.

Figure 7 | Two computed tomography scans at the level of the umbilicus, (a) one of a Nisei man with diabetes and (b) the other of a Nisei man without diabetes. Tissue with the radiographic density of fat is shown in white.
In 1989, based on what we were finding, we wrote in a review paper: “The Japanese are a population with an inherent risk for developing diabetes. Among Japanese Americans in the United States, changes brought about through westernization in environmental variables such as nutrition, health habits, acting in conjunction with aging, weight gain, and central (visceral) adiposity, have furthered the development of insulin resistance, manifested as hyperinsulinemia, and glucose intolerance, either impaired glucose tolerance or diabetes.”

**VISCE RAL ADIPOSITY: AN INDEPENDENT RISK FACTOR FOR OBESITY-RELATED CONDITIONS**

We have now reported visceral adiposity to be a powerful independent risk factor for several obesity-related conditions in Japanese Americans: coronary heart disease, impaired glucose tolerance, type 2 diabetes, hypertension, metabolic syndrome and insulin resistance. The relationship of visceral adiposity to the development of insulin resistance is especially important, linking how insulin resistance might develop despite BMI levels that were not very high and thereby predispose Japanese Americans to diabetes.

In a prospective cohort analysis of future insulin resistance, we studied 407 Japanese American men and women not taking either oral hypoglycemic medications or insulin at baseline and at follow up. Among the metabolic assessments were: (i) insulin resistance (homeostasis model assessment for insulin resistance [HOMA-IR] and fasting plasma insulin level); (ii) glycemia (fasting plasma glucose and 2-h plasma glucose); and (iii) β-cell function (incremental insulin response over glucose between fasting and 30-min of the OGTT). Measurements of adiposity were BMI, waist circumference and fat distribution by CT: (i) intra-abdominal fat area at the level of the umbilicus; (ii) subcutaneous fat area at the chest, at the abdomen and at the right thigh; (iii) total subcutaneous fat area calculated as the sum of the chest, abdomen and two times the right thigh subcutaneous fat areas; and (iv) total fat area calculated as the sum of the total subcutaneous and intra-abdominal fat areas.

Multiple linear regression analysis was used to model future insulin resistance as a function of other variables while adjusting for the baseline value of the same insulin resistance measure. For example, in model 1 intra-abdominal fat area at baseline was significantly associated with increased future HOMA-IR after adjusting for abdominal subcutaneous fat, HOMA-IR, incremental insulin response, 2-h glucose, age and sex at baseline (Table 2). The results were similar when fasting insulin was substituted for HOMA-IR. In additional models – models 2, 3, 4 and 5 – another adiposity measurement was substituted for abdominal subcutaneous fat: model 2, total subcutaneous fat area; model 3, total fat area; model 4, BMI; and model 5, waist circumference. In all of these, the results were similar to that seen with Model 1; that is, only intra-abdominal fat was associated with increased future insulin resistance.

Hence visceral adiposity, measured as intra-abdominal fat area, was associated with higher future insulin resistance, measured as either HOMA-IR or fasting plasma insulin, at follow up. This relationship was independent of baseline HOMA-IR or fasting plasma insulin, other measurements of adiposity, age, sex, 2-h plasma glucose level and incremental insulin response. Importantly, no other measurement of baseline regional or total adiposity was significantly correlated with future HOMA-IR or fasting plasma insulin in models that contained intra-abdominal fat. This provides a possible pathway for the link between adiposity and development of insulin resistance among Japanese Americans who are not as heavy as other racial populations in the USA.

**DIET AND EXERCISE FOR ELIMINATING NIKKEI DIABETES STUDY**

Diet and Exercise for Eliminating Nikkei Diabetes was a lifestyle modification randomized clinical trial developed as a proof-of-concept study. The hypothesis was that aerobic exercise...
training and reduction of dietary animal fat in Japanese Americans with impaired glucose tolerance would ameliorate risk factors associated with progression to type 2 diabetes. Both men and women who had impaired glucose tolerance on two 75-g OGTT were randomly assigned to either of two groups and followed for 24 months: (i) a treatment group that received instruction in an isocaloric American Heart Association Step 2 diet (30% of calories as fat, 7% as animal fat and 55% as carbohydrate) and aerobic exercise training to 70% of heart rate reserve; and (ii) a control group that received instruction in an isocaloric American Heart Association Step 1 diet (30% of calories as fat, 10% as animal fat and 50% as carbohydrate) and stretching exercise. A total of 29 participants completed the treatment arm and 30 completed the control arm. OGTTs were carried out at 0, 6, 12 and 24 months, and at 0, 6 and 24 months we carried out an intravenous glucose tolerance test (to calculate insulin sensitivity as SI and β-cell function as AIG), anthropometric measurements, CT (body fat distribution), underwater weighing (percent body fat) and treadmill test (VO₂max).

The treatment group showed significantly lower body weight, percent body fat and intra-abdominal fat at 6 months, and for all of these plus waist circumference at 24 months when compared with the control group (Figure 9). In addition, the treatment group showed significantly greater insulin sensitivity (SI) at 6 and 24 months, but β-cell function (AIG) did not differ between the two groups (Figure 10). OGTTs were carried out at 6, 12 and 24 months, and 67% of the treatment group showed normal glucose tolerance at least once, significantly more often than the control group (30%). However, at 24 months the prevalence of normal glucose tolerance, although higher in the treatment group (40%), was not significantly different from the control group (30%).

We concluded from this proof-of-concept study that lifestyle modification consisting of dietary saturated fat restriction and prescription of aerobic exercise might be an effective approach to preventing type 2 diabetes in Japanese Americans by changing body composition and reducing insulin resistance.

**INSULIN RESISTANCE VERSUS β-CELL DYSFUNCTION**

Simply stated, when insulin resistance is great enough to offset the β-cells’ ability to compensate, glucose levels increase (Figure 11). This is the issue that I had discussed with Professor Kosaka when we covered some of the difference between Japan and the USA regarding diabetes rates and risk factors. We were able to examine this in greater detail in a subanalysis of data from the Genetics of Non-Insulin Dependent Diabetes Study36.

From the Genetics of Non-Insulin Dependent Diabetes cohort, we identified 531 individuals who had no prior history of diabetes, but on doing an OGTT, just 240 had normal glucose tolerance whereas the remainder had prediabetes (n = 191, impaired fasting glucose and/or impaired glucose tolerance) or diabetes (n = 100). The self-described ethnic/racial composition of these individuals was Caucasian (n = 217), Hispanic (n = 193), Asian (n = 66) or black (n = 55). Many of the Asians were from the JACDS. Both β-cell function, assessed as 30-min incremental insulin over 30-min incremental glucose derived from the OGTT, and insulin resistance, assessed as

![Figure 9](http://onlinelibrary.wiley.com/journal/jdi Japanese American Diabetes Study)

**Figure 9** | Effect of lifestyle intervention on adiposity measurements at baseline and at 6 and 24 months in the Diet and Exercise for Eliminating Nikkei Diabetes study: (a) body weight, (b) percent body fat, (c) intra-abdominal fat area (IAF) and (d) waist circumference.
HOMA-IR, were examined by glucose metabolic status (normal, prediabetes, diabetes) for each racial/ethnic group. Caucasians were the reference group. As glucose tolerance deteriorated from normal to prediabetes to diabetes, β-cell function fell in all ethnic/racial groups (Figure 12). Asians had the lowest β-cell function, significantly so in the normal glucose tolerance and prediabetes categories. In the diabetic category, however, all of the groups were similarly impaired. As glucose tolerance deteriorated, insulin resistance increased in all groups (Figure 13). Asians had the lowest insulin resistance, significantly so in the normal and prediabetes categories. In the diabetic category, Asians had the same degree of insulin resistance as Caucasians. These findings suggested that increasing insulin resistance was unmasking the ‘weak’ β-cells that had been proposed by Professor Kosaka to be present in Japanese.

Thus, although many Asians are not obese by standards established in mainly white populations, if standards more appropriate to Asian populations are used, it is clear that body fat and especially the central (visceral) distribution of body fat are very important risk factors for type 2 diabetes in Asians. Similarly, insulin resistance contributes importantly to the development of type 2 diabetes in Asians, and may play an important role in unmasking an underlying less robust β-cell reserve in Asians.

**BODYWEIGHT AND DIABETES RISK IN ASIANS**

In the JACDS, we recognized early on that the definition of ‘obesity’ was likely to be different in Japanese Americans than in other populations: ‘...some ethnic groups are prone to gain weight with urbanization and westernization, and weight gain
is a powerful risk factor for diseases such as NIDDM, CHD, and hypertension. Asians constitute an ethnic group that seems to be especially at risk. The weight gain, however, need not lead to obesity as defined in predominantly Caucasian populations.

The discrepancy between obesity rates and diabetes rates in Asians was illustrated very nicely in a paper appearing in Nature Medicine in 2004. Shown in a figure from that paper was the prevalence of overweight and obesity in the USA, India, China, Japan and Singapore, and in a second graph, the prevalence of diabetes in these same countries. The definition of overweight was BMI 25 to <30 and for obesity, BMI ≥30 kg/m². Although the prevalence of overweight and obesity in all of the Asian nations was much lower than in the USA, the prevalence of diabetes in these nations was higher (Singapore) or nearly the same (Japan and India) as in the USA. For Japan, as an example, the prevalence of diabetes was nearly as high as in the USA, but the prevalence of overweight and obesity in Japan were a fraction of what it was in the USA (overweight approximately one-third and obesity approximately one-eighth). Professor Yutaka Seino is quoted in that article: 'If the Japanese had the same BMI distribution as the US, 80% of the population would have diabetes.' The message to be learned from these data is that Asians are at risk for diabetes at bodyweight levels much lower than in non-Asians.

Very recently, we carried out a careful review of published data collected in Asian Americans, looking at the relationship between BMI and risk for diabetes. In previous versions of their annual ‘Standards of Medical Care in Diabetes,’ the American Diabetes Association has recommended that testing for diabetes or prediabetes in asymptomatic adults should be considered in all who are overweight (BMI ≥25 kg/m²). Based on our review, we published a position statement and a research paper in which we recommended that screening for diabetes in Asian Americans should be carried out at BMI ≥23 kg/m². This recommendation was incorporated into the 2015 ‘Standards of Medical Care in Diabetes’.

**CANARY IN THE COAL MINE**

In 1992, as we were beginning to understand what was happening in Japanese Americans, I wrote the following in a review: ‘Because of the rapidity with which western influences can now be introduced, the prevalence of NIDDM in many non-migrant, native Asian populations may be expected to increase and reach those levels already seen in migrant Asians unless measures are taken to reduce this risk. This is a significant public health issue because the large populations in many Asian countries will assure that if this prediction is correct, NIDDM will become a major health problem in Asia in the near future.’ In other words, what we were finding in Japanese Americans was a harbinger or warning of future deterioration of health, such as developing type 2 diabetes, among native Japanese and other persons of Asian origin. Unfortunately, this is being found to be correct. For example, the global estimates of the prevalence of diabetes for 2011 and 2030 published by Whiting et al. in 2011 showed that there were 205 million cases of diabetes in 2011 in those countries that fall within Asia, approximately 56% of all cases worldwide, while in 2030, the projection was 319 million cases in Asia, or 58% of all cases worldwide. Japanese Americans have been figurative ‘canaries in the coal mine.’

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culture studies; (iv) Dr Tomoshige Hayashi joined the group in 2001 from Japan to work with Dr Boyko for 3 years, and has been instrumental in continuing a very productive analysis of data from this research even after returning to Japan; and (v) Dr Marguerite McNeely was an epidemiologist who joined our research group relatively late in 1997 when we were looking for additional epidemiological expertise and who promptly took up much of the analysis of our data, but a promising career ended prematurely when she succumbed to an aggressive brain tumor in 2014. I also gratefully acknowledge the support and assistance provided by Dr Kinori Kosaka, Dr Yasuo Akanuma and Dr Yasunori Kanazawa at the University of Tokyo, and Dr Nobusada Kuzuya at the Asahi Institute in Tokyo during the pilot study and the early years of the JACDS, and the many skilled staff members at the University of Washington, especially Pamela Asberry, Jane Shofer, Christine Tsumehara, Pamela Yang and the staff of the General Clinical Research Center. I am particularly grateful for the unswerving support and cooperation of the King County Japanese American community and our Community Advisory Board, without which it would not have been possible to carry out the research.

DISCLOSURE
The author declares no conflict of interest.

REFERENCES
1. Nanditha A, Ma RCW, Ramachandran A, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. Diabetes Care 2016; 39: 472–485.
2. Fujimoto WY, Boyko EJ, Hayashi T, et al. Risk factors for type 2 diabetes: lessons learned from Japanese Americans in Seattle. J Diabetes Investig 2012; 3: 212–224.
3. Fujimoto WY, Williams RH. Insulin release from cultured fetal human pancreas. Endocrinology 1972; 91: 1133–1136.
4. Fujimoto WY, Williams RH. Insulin action on the cultured human fibroblast: glucose uptake, protein synthesis, RNA synthesis. Diabetes 1974; 23: 443–448.
5. Fujimoto WY. Somatostatin inhibition of glucose-, tolbutamid-, theophylline-, cytochalasin B-, and calcium-stimulated insulin release in monolayer cultures of rat endocrine pancreas. Endocrinology 1975; 97: 1494–1500.
6. Fujimoto WY, Ensinck JW. Somatostatin inhibition of insulin and glucagon secretion in rat islet culture: reversal by ionophore A23187. Endocrinology 1976; 98: 259–262.
7. Fujimoto WY, Ensinck JW, Merchant FW, et al. Stimulation by gastric inhibitory polypeptide of insulin and glucagon secretion by rat islet cultures. Proc Soc Exp Bio Med 1978; 157: 89–93.
8. Eckel RH, Fujimoto WY, Brunzell JD. Gastric inhibitory polypeptide-enhanced lipoprotein lipase activity in cultured preadipocytes. Diabetes 1979; 28: 1141–1142.
9. Metz SA, Robertson RP, Fujimoto WY. Inhibition of prostaglandin E synthesis augments glucose-induced insulin secretion in cultured pancreas. Diabetes 1981; 30: 551–557.
10. Fujimoto WY, Metz SA. Phasic glucose-stimulated insulin secretion by neonatal rat pancreatic islet cells: enhancement by sodium salicylate. Diabetes 1984; 33: 872–878.
11. Cook DL, Ikeuchi M, Fujimoto W. Lowering of pH, inhibits Ca2+-activated K+ channels in pancreatic B-cells. Nature 1984; 311: 269–271.
12. Kahn SE, Verchere CB, D’Alessio DA, et al. Evidence for selective release of rodent islet amyloid polypeptide through the constitutive secretory pathway. Diabetesologia 1993; 36: 570–573.
13. Sloan NR. Ethnic distribution of diabetes mellitus in Hawaii. JAMA 1963; 183: 419–424.
14. Fujimoto WY, Hershon K, Kinyoun J, et al. Type II diabetes mellitus in Seattle and Tokyo. Tohoku J Exp Med 1983; 141 (suppl): 133–139.
15. Fujimoto WY, Hershon KS, Kinyoun JL, et al. Maturity-onset diabetes in second generation Japanese-American (Nisei) and Caucasian males in Seattle, Washington: a pilot study. In: Melish JS, Hanna J, Baba S (eds). Genetic Environmental Interaction in Diabetes Mellitus. Excerpta Medica, Amsterdam, 1982; 101–106.
16. Fujimoto WY, Leonetti DL, Kinyoun JL, et al. Prevalence of diabetes mellitus and impaired glucose tolerance among second-generation Japanese-American men. Diabetes 1987; 36: 721–729.
17. Fujimoto WY, Leonetti DL, Bergstrom RW, et al. Glucose intolerance and diabetic complication among Japanese-American women. Diabetes Res Clin Pract 1991; 13: 119–130.
18. Fujimoto WY, Bergstrom RW, Leonetti DL, et al. Metabolic and adipose risk factors for NIDDM and coronary disease in third-generation Japanese-American men and women with impaired glucose tolerance. Diabetologia 1994; 37: 524–532.
19. Fujimoto WY, Bergstrom RW, Boyko EJ, et al. Diabetes and diabetes risk factors in second- and third-generation Japanese Americans in Seattle, Washington. Diabetes Res Clin Pract 1994; 24(Suppl): S43–S52.
20. Fujimoto WY, Akanuma Y, Kanazawa Y, et al. Plasma insulin levels in Japanese and Japanese-American men with type 2 diabetes may be related to the occurrence of cardiovascular disease. Diabetes Res Clin Pract 1989; 6: 121–127.
21. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculus disease. Am J Clin Nutr 1956; 4: 20–34.
22. Borkan GA, Gerzof SG, Robbins AH, et al. Assessment of abdominal fat content by computed tomography. Am J Clin Nutr 1982; 36: 172–177.
23. Borkan GA, Hults DE, Gerzof SG, et al. Relationships between computed tomography tissue areas, thickness and total body composition. Ann Hum Biol 1983; 10: 537–546.
24. Tokunaga K, Matsuzawa Y, Ishikawa K, et al. A novel technique for the determination of body fat by computed tomography. *Int J Obes* 1983; 7: 437–445.

25. Shuman WP, Newell-Morris LL, Leonetti DL, et al. Abnormal body fat distribution detected by computed tomography in diabetic men. *Invest Radiol* 1986; 21: 483–487.

26. Newell-Morris LL, Treder RP, Shuman WP, et al. Fatness, fat distribution, and glucose tolerance in second-generation Japanese-American (Nisei) men. *Am J Clin Nutr* 1989; 50: 9–18.

27. Fujimoto WY, Bergstrom RW, Newell-Morris L, et al. Nature and nurture in the etiology of type 2 diabetes mellitus in Japanese Americans. *Diab Metab Rev* 1989; 5: 607–625.

28. Fujimoto WY, Bergstrom RW, Boyko EJ, et al. Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. *Diabetes Care* 1999; 22: 1808–1812.

29. Hayashi T, Boyko EJ, Leonetti DL, et al. Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. *Ann Intern Med* 2004; 140: 992–1000.

30. Hayashi T, Boyko EJ, Leonetti DL, et al. Visceral adiposity and the risk of impaired glucose tolerance: A prospective study among Japanese Americans. *Diabetes Care* 2003; 26: 650–655.

31. Boyko EJ, Fujimoto WY, Leonetti DL, et al. Visceral adiposity and risk of type 2 diabetes. A prospective study among Japanese Americans. *Diabetes Care* 2000; 23: 465–471.

32. Tong J, Boyko EJ, Utschneider KM, et al. Intra-abdominal fat accumulation predicts the development of the metabolic syndrome in non-diabetic Japanese Americans. *Diabetologia* 2007; 50: 1156–1160.

33. Hayashi T, Boyko EJ, McNeeley MJ, et al. Visceral adiposity, not abdominal subcutaneous fat area, is associated with an increase in future insulin resistance in Japanese Americans. *Diabetes* 2008; 57: 1269–1275.

34. Liao D, Asberry PJ, Shofer JB, et al. Improvement of BMI, body composition, and body fat distribution with lifestyle modification in Japanese Americans with impaired glucose tolerance. *Diabetes Care* 2002; 25: 1504–1510.

35. Carr DB, Utschneider KM, Boyko EJ, et al. A reduced-fat diet and aerobic exercise in Japanese Americans with impaired glucose tolerance decreases intra-abdominal fat and improves insulin sensitivity but not β-cell function. *Diabetes* 2005; 54: 340–347.

36. Jensen CC, Cron M, Hull RL, et al. β-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. *Diabetes* 2002; 51: 2170–2178.

37. Fujimoto WY, Bergstrom RW, Boyko EJ, et al. Susceptibility to development of central adiposity among populations. *Obesity Res* 1995; 3(suppl 2): 179s–186s.

38. Mandavilla A, Cyranoski D. News feature: Asia’s big problem. *Nature Med* 2004; 10: 325–327.

39. Hsu WC, Araneta MRG, Kanaya AM, et al. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care* 2015; 38: 814–820.

40. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care* 2015; 38(Suppl 1): S8–S16.

41. Fujimoto WY. The growing prevalence of non-insulin-dependent diabetes in migrant Asian populations and its implication for Asia. *Diabetes Res Clin Pract* 1992; 15: 167–184.

42. Whiting DR, Guariguata L, Weil C, et al. IDF Diabetes Atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; 94: 311–321.