Lifestyle Modification and Prevention of Type 2 Diabetes in Overweight Japanese With Impaired Fasting Glucose Levels

A Randomized Controlled Trial

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Background: Previous studies demonstrated that intensive lifestyle modification can prevent type 2 diabetes mellitus among those with impaired glucose tolerance, but similar beneficial results have not been proved among those with impaired fasting glucose levels. We investigated the efficacy of lifestyle modification on type 2 diabetes incidence among those with impaired fasting glucose levels.

Methods: The present study was an unmasked, multicenter, randomized, controlled trial. A total of 641 overweight Japanese (aged 30-60 years) with impaired fasting glucose levels were recruited nationwide in Japan and randomly assigned to a frequent intervention group (n=311) or a control group (n=330). For 36 months after randomization, the frequent intervention group received individual instructions and follow-up support for lifestyle modification from the medical staff 9 times. The control group received similar individual instructions 4 times at 12-month intervals during the same period. The primary outcome was type 2 diabetes incidence in annual 75-g oral glucose tolerance tests, diagnosed according to World Health Organization criteria.

Results: There were no significant differences between the allocation groups in baseline characteristics and dropout rates. Estimated cumulative incidences of type 2 diabetes were 12.2% in the frequent intervention group and 16.6% in the control group. Overall, the adjusted hazard ratio in the frequent intervention group was 0.56 (95% confidence interval, 0.36-0.87). In the post hoc subgroup analyses, the hazard ratio reduced to 0.41 (95% confidence interval, 0.24-0.69) among participants with impaired glucose tolerance at baseline, and to 0.24 (0.12-0.48) among those with baseline hemoglobin A_{1c} levels of 5.6% or more (the Japan Diabetes Society method). Such risk reduction was not observed among those with isolated impaired fasting glucose findings or baseline hemoglobin A_{1c} levels of less than 5.6%.

Conclusions: Lifestyle modifications can prevent type 2 diabetes among overweight Japanese with impaired fasting glucose levels. In addition, identifying individuals with more deteriorated glycemic status by using 75-g oral glucose tolerance test findings or, especially, measurement of hemoglobin A_{1c} levels, could enhance the efficacy of lifestyle modifications.

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Group Information: A complete list of the members of the Zensharen Study for Prevention of Lifestyle Diseases Group is available in the eAppendix at http://www.archinternmed.com.

THERE IS MUCH CONCERN worldwide about the drastic increase in individuals with diabetes mellitus.[1-4] A recent report estimated that the prevalence of diabetes among adults would increase dramatically from 6.4% (135 million) in 2010 to 7.7% (439 million) by 2030 and that the increase would be particularly sharp in developing countries.[3,4] It is also anticipated that the drastic increase, mainly in type 2 diabetes mellitus, would lead to a large increment of microvascular and macrovascular complications of diabetes and become a serious burden on society in the near future.[5] Comprehensive public health approaches to type 2 diabetes prevention, including lifestyle modification, urgently need to be implemented in every country.

See Invited Commentary at end of article

Previous large-scale studies[6-10] demonstrated that intensive lifestyle modification among individuals with impaired glucose tolerance (IGT), who underwent screening with oral glucose tolerance tests (OGTTs), can prevent type 2 diabetes. On the other hand, similar beneficial results

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have not been proved sufficiently among those with impaired fasting glucose (IFG) levels who undergo screening only with fasting plasma glucose levels, although a large study in the United States[8] required that the subjects underwent IFG and IGT screening, and the other studies[6,7,9,10] partly included individuals with both IGT and IFG.

Levels of fasting plasma glucose are routinely measured in the usual clinical settings or health checkups rather than with OGTTs, and it is important to test whether lifestyle modification is effective for type 2 diabetes prevention among those with IFG findings. In the present study, we recruited individuals with fasting plasma glucose levels of 100 to 125 mg/dL (to convert glucose levels to millimoles per liter, multiply by 0.0555) at the initial screening and investigated the efficacy of lifestyle modification on type 2 diabetes incidence among overweight middle-aged Japanese.

METHODS

RECRUITMENT OF STUDY CENTERS

In 2002, the steering committee was established at the All Japan Federation of Social Insurance Associations (*Zensharen* in Japanese). The Zensharen is entrusted with administration of the Social Insurance Hospitals and Clinics, which have been established nationwide by the Japanese government. The steering committee sent the study protocol to 76 Social Insurance Hospitals and Clinics in 2003 and held a meeting to explain the study details and standardized intervention methods. Finally, the 38 hospitals and clinics were selected as local study centers in the Zensharen Study for Prevention of Lifestyle Diseases. (A complete list of the study group members is available in the eAppendix; http://www.archinternmed.com.)

RECRUITMENT OF STUDY PARTICIPANTS AND ELIGIBILITY

In Japan, the basic statutory health checkups are generally conducted by municipalities and companies. The first step of screening focused on those who visited the local study centers for such health checkups, and those who satisfied the inclusion criteria in their health checkups were invited to participate in the second step of screening. The inclusion criteria were age 30 to 60 years, fasting plasma glucose level of 100 to 125 mg/dL, and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of at least 24.0. Exclusion criteria were having received a diagnosis of diabetes or receiving treatment for diabetes; having a history of ischemic heart disease, stroke, chronic hepatitis, liver cirrhosis, chronic pancreatitis, chronic nephritis, pituitary disease, thyroid disease, adrenal gland disease, mental illness, gastrectomy, or advanced malignant tumor; receiving corticosteroid or thyroid hormone medication; and being judged by the responsible physician of the local study center as unfit to participate in the study (eg, persons with serious diseases not included in the other exclusion criteria).

The second step of screening consisted of a 75-g OGTT after overnight fasting. Individuals who satisfied neither of the following World Health Organization diagnostic criteria for diabetes were registered as eligible study participants: fasting plasma glucose level of at least 126 mg/dL and 2-hour plasma glucose level of at least 200 mg/dL.[11] Those who were diagnosed as having diabetes were not enrolled and were referred to a physician.

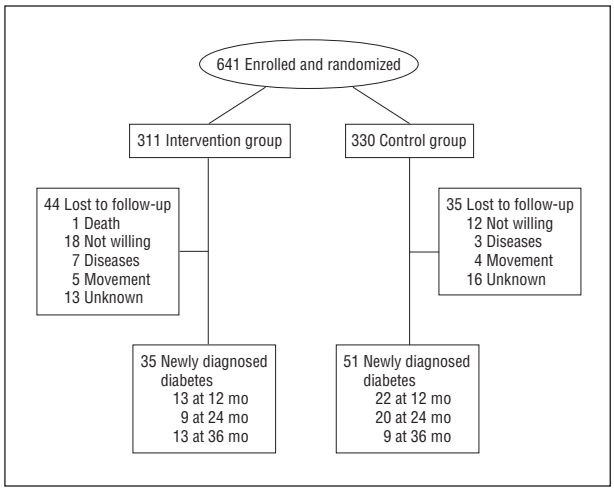

Figure 1. Flowchart of the study participants, May 1, 2004, through August 31, 2009, in the Zensharen Study for Prevention of Lifestyle Diseases.

RANDOMIZATION AND STUDY DESIGN

The responsible physicians in the local study centers obtained written informed consent individually from all the participants. The present study, an unmasked, multicenter, randomized controlled trial, adopted the central randomization method by telephone for allocation concealment. Allocation sequence, stratified by local study centers and sex, was generated with a computer by the collaborating epidemiologists of the Jichi Medical University who did not enroll the participants. The eligible 641 participants were randomly assigned, using the blocked randomization method with randomly selected block size (4 and 2) to the frequent intervention (FINT) group (n=311) or the control group (n=330).

For 36 months after randomization, each participant in the FINT and control groups received the intervention on different schedules. The FINT group received individual instructions and follow-up support for lifestyle modification from the medical staff at least 9 times (at baseline and 1, 3, 6, 12, 18, 24, 30, and 36 months; if necessary, 2 extra visits could be added at 9 and 15 months as an option). The control group received similar individual instructions 4 times only at 12-month intervals (at baseline and 12, 24, and 36 months) and continued to follow the instructions voluntarily without the follow-up support or the use of self-monitoring tools between each visit. At each visit after a 12-month interval, the responsible physician in the local study center checked whether each participant had any disease or treatment that was inappropriate for study participation or that clearly influenced glucose tolerance.

Assuming a 3-year cumulative incidence of 20% in the control and 45% reduction in the FINT groups, it was estimated that more than approximately 299 participants were required per group with a 2-sided α error of .05 and a power of 0.8, allowing for a dropout rate of 15%.

DATA COLLECTION

Baseline assessments consisted of anthropometric measurements, completion of self-report questionnaires, assessment of dietary intake, and blood sample tests. The same assessments were repeated annually (at 12, 24, and 36 months) in both groups.

Anthropometric measurements were conducted by well-trained medical staff. Height and weight were measured in light clothing without shoes. Waist circumference was measured at the umbilical level without clothes after exhaling in a relaxed

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Table 1. Baseline Characteristics of Study Participants by Assigned Groups: The Zensharen Study for Prevention of Lifestyle Diseases, 2004-2009[a]

Characteristic	FINT Group (n = 311)	Control Group (n = 330)	*P* Value
Male sex, %	72	71	.75
Age, median (IQR), y	50 (44-54)	48 (41-54)	.24
Age range, y, % of participants			
30-39	15	17	
40-49	34	39	.25
50-60	50	44	
Parental history of diabetes mellitus, % of participants	26	24	.54
Waist circumference, mean (SD), cm	92.1 (8.1)	91.9 (8.5)	.71
Weight, mean (SD), kg	74.1 (10.4)	74.8 (10.7)	.39
BMI, mean (SD)	26.9 (2.6)	27.1 (2.6)	.42
Plasma glucose level, mean (SD), mg/dL			
Fasting	108 (8)	107 (8)	.15
2 h after oral glucose load	135 (30)	133 (31)	.42
Glucose tolerance			
IGT, % of participants	42	40	.53
HbA_{1c}, level, mean (SD), %[b]	5.4 (0.4)	5.4 (0.4)	.42
Serum lipid levels, mg/dL			
Total cholesterol, mean (SD)	213 (35)	214 (35)	.86
Triglycerides, median (IQR)	127 (89-180)	124 (88-183)	.99
High-density lipoprotein cholesterol, mean (SD)	52 (12)	53 (14)	.24
Blood pressure, mean (SD), mm Hg			
Systolic	130 (16)	131 (16)	.31
Diastolic	81 (11)	81 (12)	.57
Current cigarette smokers, % of participants	25	28	.37
Nutrition			
Total energy intake, kcal/d	2055 (551)	2090 (572)	.44
Energy, mean (SD), % of intake			
Carbohydrate	58.3 (5.9)	58.2 (5.8)	.73
Fat	28.0 (5.1)	28.0 (4.9)	.95
Current alcohol consumption, % of participants	69	65	.22
Alcohol consumption in total energy intake in current drinkers, median (IQR), %	7.4 (2.5-12.2)	8.3 (3.2-11.6)	.97
Physical activity, median (IQR)			
Overall leisure time physical activity, min/mo	120 (0-540)	160 (0-600)	.35
Walking as leisure time physical activity, min/mo	0 (0-60)	0 (0-120)	.43

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FINT, frequent intervention; HbA_{1c}, hemoglobin A_{1c}; IGT, impaired glucose tolerance; IQR, interquartile range.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] Data were missing for 1 participant in the FINT group (waist circumference) and 3 in the control group (HbA_{1c} level in 2 and nutrition data in 1). Percentages have been rounded and may not total 100.

[b] A value of 5.4% was based on the Japan Diabetes Society method, corresponding to 39.3 mmol/mol using the International Federation of Clinical Chemistry and Laboratory Medicine method and 5.8% using the National Glycohemoglobin Standardization Program method.

standing position. Blood pressure was measured at each visit after a sufficient rest.

Self-report questionnaires were composed of a family history of diabetes, cigarette smoking, leisure time physical activity, motivation for lifestyle modifications, and daily habits regarding diet and exercise. The questionnaire inquired about the type and frequency of and the time spent on leisure time physical activity, and the total time spent on leisure time physical activity and walking per month was calculated.

Blood sample tests included a 75-g OGTT, measurement of hemoglobin A_{1c} (HbA_{1c}) levels in whole blood, and lipid profiles in serum (total and high-density lipoprotein cholesterol and triglyceride levels), which were measured by autoanalyzers at the in-house laboratory of each local study center. All in-house laboratories participated in the external quality control programs for blood sample tests of the Japan Medical Association, the Zensharen, or both. The HbA_{1c} values were based on the Japan Diabetes Society method. The formulas for converting the HbA_{1c} values from the Japan Diabetes Society method to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method and from the IFCC method to the National Glycohemoglobin Standardization Program method were as follows[12]:

IFCC Value (in millimoles per mole) = [10.39 × Japan Diabetes Society Value (in percentages)] − 16.8

National Glycohemoglobin Standardization Program Value (in percentages) = [0.0981 × IFCC Value (in millimoles per mole)] + 1.95

For the assessment of dietary intake, a validated self-report food frequency questionnaire based on food groups and the designated computer software for calculating nutrients from this food frequency questionnaire were purchased and provided to each local center.[13,14]

INTERVENTION

Irrespective of the assigned groups, all the participants were individually instructed to reduce total energy intake and increase physical activity, aiming at a 5% reduction in body weight, through

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the help of nurses, dieticians, physical therapists, and physicians. We used existing human and material resources of each local study center as much as possible. Nurses and dieticians were mainly involved in the intervention at most local study centers, although it depended on the personnel situation at each center. The participants were given pedometers and pamphlets providing general information on diabetes and lifestyle modifications. The participants in both groups determined their own lifestyle goals, based on the results of the assessments and their motivation. Participants in the FINT group were invited to a series of follow-up visits and worked toward their goals by using self-monitoring sheets for recording body weight, pedometer counts, and how close they came to attaining their goals. If necessary, they altered their goals or added new goals.

The dietary intervention aimed at reducing total energy intake mainly by restricting excess intake of fat or carbohydrates, taking into consideration the Japan Diabetes Society recommendation for diabetic patients, and by controlling fat intake at 20% to 25% of total energy intake and carbohydrate intake at 55% to 60% of total energy intake. Where necessary, additional intake of dietary fiber, appropriate alcohol consumption (≤23 g/d), and corrective measures for undesirable dietary habits were also set as goals. Practical and feasible goals were proposed to the participants, such as "reducing the frequency of eating sweet foods between meals to less than 3 times per week."

Participants who hoped to do any leisure time physical activity were advised on how to gradually increase their physical activity to 200 kcal/d (837.2 kJ/d) (mainly by walking more and walking faster). Sedentary or busy participants were encouraged to increase daily life physical activity by, for example, "getting off the bus at 1 bus stop prior to the destination in order to walk the rest of the way." Such modifications were easier to do and incorporate than was periodic leisure time physical activity (eg, engaging in sports). A common goal for total counts of pedometer steps was set at 70 000 steps per week (10 000 per day).

OUTCOMES

The primary outcome was incidence of type 2 diabetes mellitus, defined by either of the following World Health Organization diagnostic criteria: fasting plasma glucose level of at least 126 mg/dL, or 2-hour plasma glucose level of at least 200 mg/dL determined in annual 75-g OGTT results without the confirmatory testing.[11] The participants who began treatment for diabetes, such as receiving medication, were also diagnosed as having clinical diabetes and included in the primary outcome.

STATISTICAL ANALYSIS

Baseline characteristics were compared between the assigned groups. Means and standard deviations were calculated for continuous variables with *P* values using unpaired *t* tests for the between-group comparison and paired *t* tests for the within-group comparison between baseline and the 12-month visit. If normal distribution was not assumed, the median and interquartile range were reported with *P* values calculated using the Wilcoxon rank sum test for the between-group comparison and the Wilcoxon signed rank sum test for the within-group comparison. Proportions were compared between groups using the χ^2 test.

For the post hoc subgroup analyses, the participants were dichotomized into the IFG + IGT and isolated IFG groups by baseline glucose tolerance. For the IFG + IGT group, criteria consisted of a fasting plasma glucose level of less than 126 mg/dL and a 2-hour plasma glucose level of at least 140 mg/dL and less than 200 mg/dL. For the isolated IFG group, criteria consisted of a fasting plasma glucose level of less than 126 mg/dL and a 2-hour plasma glucose level of less than 140 mg/dL. The Cox propor-

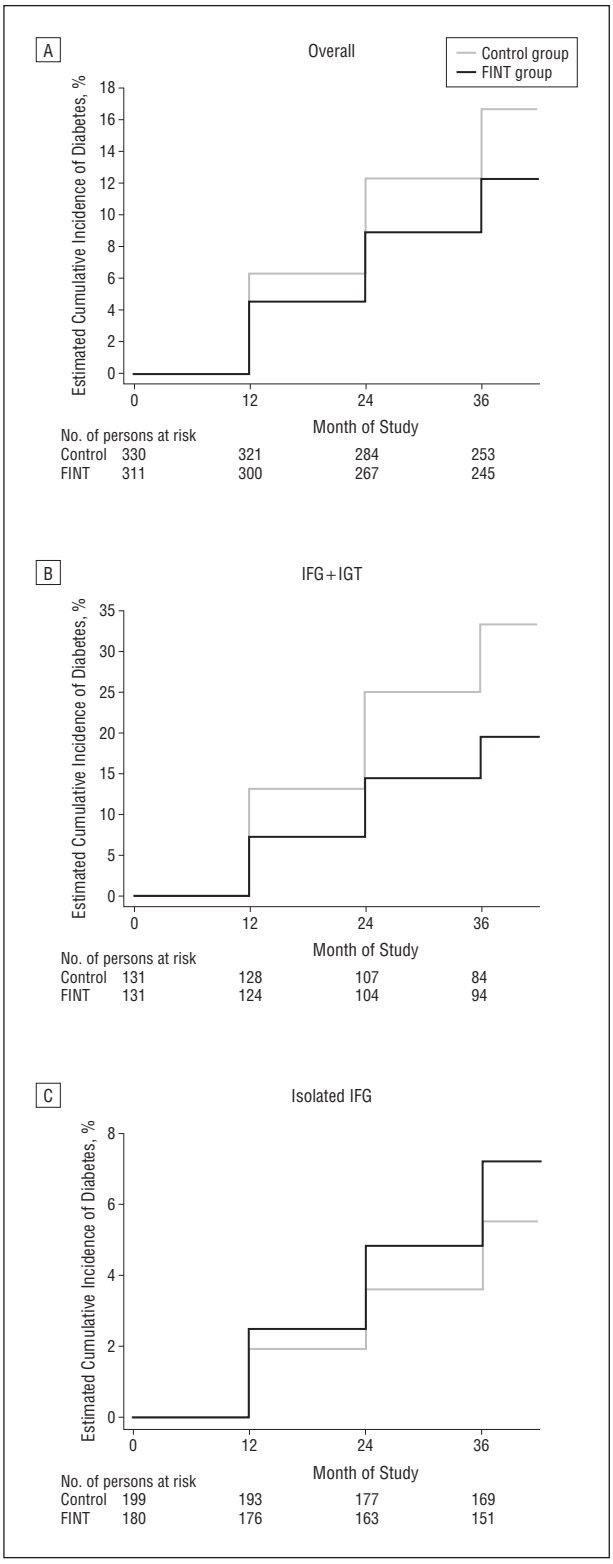

Figure 2. Estimated cumulative incidence of diabetes by baseline glucose tolerance and assigned groups, May 1, 2004, through August 31, 2009, in the Zensharen Study for Prevention of Lifestyle Diseases. A, Overall findings for the control and frequent intervention (FINT) groups. B, The group with impaired fasting glucose levels and impaired glucose tolerance (IFG + IGT) was defined by the baseline 75-g oral glucose tolerance test as follows: fasting plasma glucose level of less than 126 mg/dL and 2-hour plasma glucose level of at least 140 mg/dL and less than 200 mg/dL (IFG + IGT). C, The group with isolated IFG was defined by the baseline 75-g oral glucose tolerance test as follows: fasting plasma glucose level of less than 126 mg/dL and 2-hour plasma glucose level of less than 140 mg/dL.

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Table 2. HRs for Incidence of Type 2 Diabetes Mellitus According to Baseline Glycemic Status: The Zensharen Study for Prevention of Lifestyle Diseases, 2004-2009

	No. of Participants	No. of Events	Incidence Rates per 100 Person-years	Adjusted HR (95% CI)[a]
Overall				
Control group	330	51	5.8	1 [Reference]
FINT group	311	35	4.2	0.56 (0.36-0.87)
IFG + IGT[b]				
Control group	131	41	12.6	1 [Reference]
FINT group	131	23	6.8	0.41 (0.24-0.69)
Isolated IFG[c]				
Control group	199	10	1.8	1 [Reference]
FINT group	180	12	2.4	1.17 (0.50-2.74)
Fasting plasma glucose level ≥110 mg/dL				
Control group	120	35	11.8	1 [Reference]
FINT group	133	26	7.4	0.50 (0.29-0.84)
Fasting plasma glucose level <110 mg/dL				
Control group	210	16	2.8	1 [Reference]
FINT group	178	9	1.9	0.67 (0.29-1.53)
HbA_{1c} level ≥5.6%[d]				
Control group	97	36	15.3	1 [Reference]
FINT group	86	13	5.7	0.24 (0.12-0.48)
HbA_{1c} level <5.6%[d]				
Control group	233	15	2.3	1 [Reference]
FINT group	225	22	3.6	1.37 (0.70-2.66)

Abbreviations: CI, confidence interval; FINT, frequent intervention; HbA_{1c}, hemoglobin A_{1c}; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

[a] Hazard ratios were adjusted for age, sex, body mass index, fasting plasma glucose level, 2-hour plasma glucose level, and parental history of diabetes at baseline.

[b] Defined by the baseline 75-g oral glucose tolerance test results as a fasting plasma glucose level of less than 126 mg/dL and a 2-hour plasma glucose level of at least 140 mg/dL and less than 200 mg/dL.

[c] Defined by the baseline 75-g oral glucose tolerance test results as a fasting plasma glucose level of less than 126 mg/dL and a 2-hour plasma glucose level of less than 140 mg/dL.

[d] Value of 5.6% was based on the Japan Diabetes Society method, corresponding to 41.4 mmol/mol using the International Federation of Clinical Chemistry and Laboratory Medicine method and 6.0% using the National Glycohemoglobin Standardization Program method.

tional hazard model was adopted to estimate the incidence of type 2 diabetes overall and in the IFG + IGT group and the isolated IFG group. The model was also used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) in the FINT group as a reference for the control group, which was adjusted for age, sex, BMI, fasting and 2-hour plasma glucose levels, and parental history of diabetes at baseline. Furthermore, as post hoc analyses, HRs were similarly estimated by the subgroups of baseline glycemic status (for the IFG + IGT group vs the isolated IFG group, an HbA_{1c} level ≥5.6% vs <5.6% and a fasting plasma glucose level ≥110 vs <110 mg/dL), in which the cutoffs were set nonarbitrarily on the basis of existing diagnostic criteria for diabetes.[11,15] We conducted statistical testing by adding the interaction term to the model to examine whether HRs (intervention effects) differed between the IFG + IGT and isolated IFG groups. Proportionality assumption was checked by adding the interaction term between time and each variable to the models, and no violation to assumption was observed in all analyses. The number needed to treat (NNT) was calculated overall and, for the IFG + IGT group, those with an HbA_{1c} level of at least 5.6% and a fasting plasma glucose level of at least 110 mg/dL.[16] Baseline characteristics were also compared between the IFG + IGT and isolated IFG groups. In addition, we conducted sensitivity analyses to estimate the effect of waist circumferences, by replacing BMI with waist circumferences in the models and by adding waist circumferences to the models.

All analyses for the outcomes were conducted on the basis of the intention-to-treat analysis principle. All P values were 2 tailed, and $P < .05$ was considered statistically significant. All analyses were conducted using commercially available software (SAS, version 8.2; SAS Institute, Cary, North Carolina).

The study protocol was approved by the institutional review board of the Zensharen for ethical issues.

RESULTS

A flowchart of the study participants is shown in **Figure 1**. In total, 641 individuals were randomly assigned to the FINT group (n=311) or the control group (n=330) from May 1, 2004, through May 30, 2006. The proportions lost to or unavailable for follow-up were similar between groups, at 14.1% in the FINT group and 10.6% in the control group (P=.17). Overall participation rate in 9 scheduled visits in the FINT group was 92.4%. The mean follow-up duration was 32.1 months. There was no serious adverse event reported from any local study center.

No significant differences in baseline characteristics were observed between the groups (**Table 1**). Prevalence of fasting plasma glucose levels of 100 to 125 mg/dL with 2-hour plasma glucose levels of less than 140 mg/dL was also similar between the groups (FINT group, 48.2%; control group, 48.8%). Proportions of BMI categories (≤24.9, 25.0-29.9, and ≥30.0) did not differ between the groups (FINT, 22.0%, 68.0%, and 10.0%, respectively; control, 21.0%, 66.2%, and 12.8%, respectively; P=.54).

During the 36-month study, 86 participants (13.4%), including 1 case of clinical diabetes diagnosed immedi-

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Table 3. Changes in Anthropometry and Clinical Variables During the First 12 Months: The Zensharen Study for Prevention of Lifestyle Diseases, 2004-2009[a]

	FINT Group	Control Group	*P* Value
	Intention-to-Treat Analysis		
No. of participants	311	330	
Weight reduction ≥5%, % of participants	32	15	<.001
	Per-Protocol Analysis[b]		
No. of participants[c]	300	321	
Waist circumference, cm	−3.1 (4.3)[d]	−1.3 (4.7)[d]	<.001
Weight, kg	−2.5 (3.2)[d]	−1.1 (3.2)[d]	<.001
BMI	−0.9 (1.2)[d]	−0.4 (1.2)[d]	<.001
Plasma glucose level, median (IQR) , mg/dL			
Fasting	−3 (−7 to 3)[d]	−1 (−7 to 4)	.02
2 h after oral glucose load	−6 (−26 to 16)[d]	2 (−18 to 21)	.001
HbA_{1c} level, %	0.0 (0.2)	0.0 (0.4)	.18
Blood pressure, mm Hg			
Systolic	−4 (14)[d]	−3 (13)[d]	.31
Diastolic	−2 (10)[d]	−1 (10)[d]	.15
Serum lipid levels, mg/dL			
Total cholesterol	−3 (26)[d]	1 (26)	.03
Triglycerides, median (IQR)	−8 (−40 to 22)[d]	−3 (−32 to 23)	.30
High-density lipoprotein cholesterol	3 (8)[d]	2 (8)[d]	.22

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FINT, frequent intervention; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] Unless otherwise indicated, data are expressed as mean (SD). Mean and median values indicate change.

[b] Excludes participants without the 12-month visit.

[c] Data were missing for 2 participants in the FINT group (waist circumference, 1; 2-hour plasma glucose level, 1) and 4 in the control group (waist circumference, 1; BMI, 1; weight, 1; and blood pressure, 1).

[d] Significant difference ($P<.05$) between baseline and 12 months was observed.

ately before the 24-month visit, were newly diagnosed as having type 2 diabetes: 35 in the FINT and 51 in the control groups. Estimated cumulative incidences of type 2 diabetes at 36 months by assigned groups and baseline glucose tolerance were 12.2% (95% CI, 8.5%-15.9%) in the FINT group and 16.6% (12.5%-20.6%) in the control group in the overall analysis; 19.6% (12.5%-26.2%) and 33.4% (25.1%-40.8%), respectively, in the IFG + IGT group; and 7.2% (3.2%-11.0%) and 5.5% (2.1%-8.7%), respectively, in the isolated IFG group (**Figure 2**). The NNTs were 22.7 in the overall analysis, 7.2 in the IFG + IGT group, 9.1 in those with fasting plasma glucose levels of 110 mg/dL or more, and 4.4 in those with HbA_{1c} levels of 5.6% or more.

In the overall analysis, the adjusted HR for type 2 diabetes in the FINT group was 0.56 (95% CI, 0.36-0.87), whereas it was 0.41 (0.24-0.69) in the IFG + IGT group (**Table 2**). On the other hand, it was 1.17 (95% CI, 0.50-2.74) in the isolated IFG group. The HRs (intervention effects) differed between the IFG + IGT and isolated IFG groups with statistical significance ($P=.03$). The adjusted HR further decreased to 0.24 (95% CI, 0.12-0.48) when restricted to participants with HbA_{1c} levels of 5.6% or more (corresponding to 41.4 mmol/mol using the IFCC method and 6.0% using the National Glycohemoglobin Standardization Program method). In the sensitivity analyses, replacing BMI with waist circumference in the models and simply adding waist circumference to the models hardly altered any result.

The proportion of participants who achieved weight reduction of 5% or more was significantly higher in the FINT group during the first 12 months on the intention-to-treat analysis ($P<.001$) (**Table 3**), and almost similar results were observed at 24 and 36 months (FINT group, 33% and 32%, respectively; control group, 19% and 18%, respectively [$P<.001$ for both]). Mean weight reduction was 2.5 kg in the FINT group and 1.1 kg in the control group, with a statistically significant difference between the groups ($P<.001$). The fasting plasma glucose level or the 2-hour plasma glucose level also significantly decreased more in the FINT than in the control groups.

The proportions of participants achieving reduction in total energy intake of 5% or more and an increase in walking time of at least 60 min/mo were significantly higher in the FINT group during the first 12 months ($P=.04$ and $P=.01$, respectively) (**Table 4**). In the FINT group, the decrease in women's total energy intake was significant ($P=.02$), and the decrease in the percentage of alcohol intake in total energy intake was also significant ($P=.02$). Walking time significantly increased in the FINT group ($P=.046$).

The significant or borderline significant differences were observed between the isolated IFG and IFG + IGT groups for glycemic status, waist circumferences, and high-density lipoprotein cholesterol and triglyceride levels (**Table 5**).

The estimated essential cost for the intervention itself was approximately $476 000 (US $1 = ¥100 [Japanese yen]) in total, which included the expenses for laboratory tests and instruction or management of the participants. The estimated cost per capita was approximately $800 in the FINT group and $650 in the control group.

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Table 4. Changes in Nutrition and Physical Activity During the First 12 Months: The Zensharen Study for Prevention of Lifestyle Diseases, 2004-2009[a]

	FINT Group	Control Group	*P* Value
	Intention-to-Treat Analysis		
No. of participants	311	330	
Changes, % of participants			
Reduction in total energy intake ≥5%	57	49	.04
Increase in leisure time physical activity ≥60 min/mo	48	40	.08
Increase in walking ≥60 min/mo	37	28	.01
	Per-Protocol Analysis[b]		
Nutrition			
No. of participants[c]	299	319	
Total energy intake, kcal/d	−153 (−390 to 113)[d]	−82 (−389 to 147)[d]	.28
Men	−126 (−380 to 128)[d]	−84 (−446 to 151)[d]	.93
Women	−193 (−410 to 69)[d]	−66 (−294 to 143)	.02
Energy, % of intake			
Carbohydrates	0.1 (−3.7 to 3.8)	0.0 (−3.3 to 3.6)	.82
Men	−0.1 (−3.8 to 3.8)	0.1 (−3.3 to 3.6)	.81
Women	0.3 (−3.1 to 3.9)	0.0 (−3.5 to 4.0)	.92
Fat	−0.7 (−4.1 to 2.4)[d]	−0.5 (−3.1 to 2.2)[d]	.48
Men	−0.5 (−4.1 to 2.5)[d]	−0.5 (−2.9 to 2.1)	.70
Women	−1.5 (−3.6 to 1.8)[d]	−0.5 (−3.8 to 2.5)	.53
Alcohol consumption in current drinkers[e]	−0.4 (−2.5 to 1.3)[d]	0.0 (−1.7 to 2.1)	.02
Men	−0.3 (−3.3 to 1.4)[d]	0.3 (−1.7 to 2.3)	.01
Women	−0.5 (−1.4 to 0.8)	−0.4 (−1.4 to 1.2)	.83
Physical activity			
No. of participants[f]	229	234	
Leisure time physical activity, min/mo	160 (−80 to 490)[d]	120 (−240 to 460)[d]	.11
Men	120 (−80 to 480)[d]	120 (−240 to 450)[d]	.26
Women	255 (50 to 660)[d]	100 (−160 to 500)[d]	.07
No. of participants[g]	160	151	
Walking, min/mo	209 (35 to 600)[d]	120 (−120 to 480)[d]	.046
Men	180 (10 to 600)[d]	150 (−120 to 600)[d]	.14
Women	240 (60 to 425)[d]	85 (−100 to 400)[d]	.01

Abbreviation: FINT, frequent intervention.
SI conversion factor: To convert energy intake to kilojoules, multiply by 4.186.
[a] Unless otherwise indicated, data are expressed as median (interquartile range).
[b] Excludes participants without the 12-month visit.
[c] Numbers of participants by sex were 216 men and 83 women in the FINT group and 227 men and 92 women in the control group.
[d] Significant difference of medians between baseline and 12 months was observed ($P < .05$).
[e] Indicates among those consuming alcohol at baseline or 12 months. Includes 188 men and 35 women in the FINT group and 182 men and 49 women in the control group.
[f] Indicates participants who did any physical activity at baseline or 12 months. Includes 171 men and 58 women in the FINT group and 168 men and 66 women in the control group.
[g] Indicates participants who did any walking at baseline or 12 months. Includes 116 men and 44 women in the FINT group and 101 men and 50 women in the control group.

COMMENT

The present study demonstrated that lifestyle modification can prevent type 2 diabetes mellitus among middle-aged overweight Japanese with fasting plasma glucose levels of 100 to 125 mg/dL at the initial screening. Weight reduction of 5% or more was also attained by almost twice as many participants in the FINT group throughout the study period than those in the control group. It can be inferred that reduction of total energy intake, increase in physical activity, and subsequent weight reduction observed in the FINT group could lead to improvement in glucose tolerance.

The mean weight reduction in the FINT group was about 2.5 kg at 12 months. Although it was not as large as weight reductions in previous studies performed in Western countries,[7,8] it is considered reasonable because the intervention in the present study was probably milder and the participants had considerably lower baseline BMIs (approximately 90% had a BMI <30.0). This suggests that even relatively modest weight reduction (approximately 3.5%) was beneficial enough for type 2 diabetes prevention in overweight or mildly obese Japanese.

Subgroup analyses demonstrated that lifestyle modifications in the IFG + IGT group were remarkably effective, but not in the isolated IFG group. This finding could not be examined by the previous studies in which all subjects had IGT.[6-10] In addition, insulin resistance–related factors at baseline, such as waist circumferences and triglycerides levels, differed between the IFG + IGT and isolated IFG groups. This indirectly suggests that the difference in the efficacy of lifestyle modification on diabetes prevention might be related to the presence or absence of insulin resistance.

The NNT in the overall analysis was much larger than those of previous studies among IGT subjects.[7-9] When

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restricted to individuals with IGT, the NNT decreased to about one-third of the overall analysis, the result of which was similar with those of the previous studies.[7-9] These findings suggest that further selection of the subjects with more deteriorated glucose tolerance would be necessary in practical settings with limited human, material, or funding resources.

In a recent report by an international expert committee, which proposed diagnosis of diabetes by means of HbA_{1c} levels, the committee recommended that those with HbA_{1c} levels of 6.0% to 6.4% should receive effective preventive interventions.[15] The present study indicated that selection of the subjects with a similar HbA_{1c} cutoff level could substantially reduce relative risk and NNT more than 75-g OGTTs could. In addition, because HbA_{1c} level is not much affected by fasting status in blood sampling, measurement of HbA_{1c} levels would be more feasible except in those with anemia or hemoglobinopathy affecting HbA_{1c} levels.[15,17] Therefore, HbA_{1c} level could be an excellent risk marker in screening for lifestyle modification.

The overall relative risk reduction (44.1%) of type 2 diabetes incidence was smaller than those of studies in the United States and Finland (58% in both),[7,8] but similar to those of studies in China (42%) and India (38%).[6,9] In the IFG + IGT subgroup, relative risk reduction (59%) was similar to those of the Western studies[7,8] but larger than those of the Asian studies.[6,9] Our results are likely to indicate that lifestyle modification for individuals with IGT could be effective in various races, although comparison of the intervention effects with those of the Western studies is not always simple because of different genetic backgrounds. Even compared with the Asian studies of participants with relatively similar backgrounds, incidence rates in our study were lower.[6,9] In the Indian study, weight reduction by lifestyle interventions was not observed, but the lifestyle intervention was effective for type 2 diabetes prevention.[9] These findings suggest the possibility that relatively large differences in background factors might exist among the Asian populations, such as genetic factors, lifestyles, and socioeconomic statuses. Accordingly, the generalizability of the present results to other populations would be limited. Our findings should be further investigated among various populations, races, and geographical areas.

The present study had several limitations other than generalizability. First, misclassification in the diagnosis of type 2 diabetes might occur because type 2 diabetes was diagnosed only with a single 75-g OGTT conducted annually. Such misclassification is usually a random error, which might weaken the actual relation toward null and result in underestimation. Second, the present study did not have information on medication other than that included in the exclusion criteria. Previous studies have indicated that insulin sensitivity or type 2 diabetes incidence might be influenced by antihypertensive drugs.[18] The influence of such medications could not be ruled out completely. Third, because the study subjects voluntarily participated in this trial, they were likely to have relatively higher motivation. Accordingly, the present findings might not be applied to less motivated individuals. Fourth, the subgroup analyses by baseline glycemic sta-

Table 5. Baseline Characteristics by Baseline Glucose Tolerance: The Zensharen Study for Prevention of Lifestyle Diseases, 2004-2009[a]

Characteristic	Isolated IFG[b]	IFG + IGT[c]	*P* Value
No. of participants[d]	379	262	
Male sex, %	71	73	.62
Age, y, %			
30-39	17	14	.22
40-49	39	35	
50-60	44	51	
Parental history of diabetes mellitus, %	22	28	.12
Waist circumference, cm	91.4 (8.0)	92.8 (8.8)	.03
Weight, kg	74.0 (10.6)	75.1 (10.5)	.21
BMI	26.9 (2.5)	27.2 (2.7)	.27
Plasma glucose level, mg/dL			
Fasting	106 (8)	110 (8)	<.001
2 h after oral glucose load	113 (18)	164 (17)	<.001
HbA_{1c} level, %[e]	5.3 (0.4)	5.5 (0.4)	<.001
Serum lipid, mg/dL			
Total cholesterol	213 (35)	215 (35)	.37
Triglycerides, median (IQR)	116 (86-167)	131 (95-196)	.004
High-density lipoprotein cholesterol	53 (13)	52 (13)	.07
Blood pressure, mm Hg			
Systolic	130 (16)	132 (16)	.11
Diastolic	80 (12)	81 (11)	.28
Current cigarette smokers, %	28	25	.37
Nutrition			
Total energy intake, kcal/d	2074 (558)	2071 (569)	.94
Energy, % of intake			
Carbohydrate	58.2 (5.7)	58.4 (6.1)	.76
Fat	28.1 (4.9)	27.8 (5.2)	.57
Current alcohol consumption, %	67	68	.83
Alcohol consumption in total energy intake in current drinkers, median (IQR), %	7.5 (2.7-12.0)	8.3 (2.9-11.5)	.76
Physical activity, median (IQR)			
Overall leisure time physical activity, min/mo	120 (0-600)	120 (0-600)	.41
Walking as leisure time physical activity, min/mo	0 (0-40)	0 (0-120)	.08

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA_{1c}, hemoglobin A_{1c}; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] Unless otherwise indicated, data are expressed as mean (SD).

[b] Defined by the baseline 75-g oral glucose tolerance test results as a fasting plasma glucose level of less than 126 mg/dL and a 2-hour plasma glucose level of less than 140 mg/dL.

[c] Defined by the baseline 75-g oral glucose tolerance test results as a fasting plasma glucose level of less than 126 mg/dL and a 2-hour plasma glucose level of at least 140 mg/dL and less than 200 mg/dL.

[d] Data were missing in 3 participants in the isolated IFG group (waist circumference in 1 and HbA_{1c} level in 2) and 2 in the IFG + IGT group (nutrition).

[e] Values of 5.3% and 5.5% were based on the Japan Diabetes Society method, corresponding to 38.3 and 40.3 mmol/mol, respectively, using the International Federation of Clinical Chemistry and Laboratory Medicine method, and 5.7% and 5.9%, respectively, using the National Glycohemoglobin Standardization Program method.

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tus were post hoc analyses in which randomization was not guaranteed, and the statistical power might not have been great enough. Accordingly, we cannot completely rule out the possibility that the results are confounded by the unadjusted prognostic factors or the possibility that the actual relation is underestimated.

In conclusion, the present study demonstrated that 3-year individual-based lifestyle intervention could prevent type 2 diabetes mellitus among overweight Japanese who meet the fasting plasma glucose screening criterion of 100 to 125 mg/dL. In addition, identifying individuals with more deteriorated glycemic status by using findings of 75-g OGTTs or, especially, measurement of HbA_{1c} levels, could enhance the efficacy of lifestyle modifications.

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REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21(9):1414-1431.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-1053.
3. Yang W, Lu J, Weng J, et al; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. *N Engl J Med*. 2010;362(12):1090-1101.
4. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87(1):4-14.
5. Zhang P, Zhang X, Brown J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87(3):293-301.
6. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20(4):537-544.
7. Tuomilehto J, Lindström J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344(18):1343-1350.
8. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
9. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*. 2006;49(2):289-297.
10. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res Clin Pract*. 2005;67(2):152-162.
11. World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, Switzerland: World Health Organization; 1999.
12. Committee on Diabetes Mellitus Indices, Japan Society of Clinical Chemistry. Japanese guideline for reporting HbA_{1c} results reported in IFCC units and JDS units [in Japanese]. *Rinsho Kagaku*. 2008;37(4):393-409.
13. Takahashi K, Yoshimura Y, Kaimoto T, Kunii D, Komatsu T, Yamamoto S. Validation of a food frequency questionnaire based on food groups for estimating individual nutrient intake [in Japanese]. *Jpn J Nutr*. 2001;59(5):221-232.
14. Yoshimura Y, Takahashi K. *Ekuseru-eiyoukun, version 3.0*. Tokyo, Japan: Kenpakusha Inc; 2001.
15. International Expert Committee. International Expert Committee report on the role of the A_{1C} assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32(7):1327-1334.
16. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ*. 1999;319(7223):1492-1495.
17. Kilpatrick ES, Bloomgarden ZT, Zimmet PZ. Is haemoglobin A_{1c} a step forward for diagnosing diabetes? *BMJ*. 2009;339:b4432. doi:10.1136/bmj.b4432.
18. Sarafidis PA, McFarlane SI, Bakris GL. Antihypertensive agents, insulin sensitivity, and new-onset diabetes. *Curr Diab Rep*. 2007;7(3):191-199.

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