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ORIGINAL ARTICLE

Effect of diabetes and prediabetes on the development of disability and mortality among middle-aged Japanese adults: A 22-year follow up of NIPPON DATA90

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ABSTRACT

Aims/Introduction: To examine the association between diabetes and prediabetes at baseline, and disability, mortality over a 22-year period among middle-aged Japanese adults.

Materials and Methods: Participants consisted of 1,788 adults aged 45–64 years at baseline from the cohort study National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged 1990 (NIPPON DATA90). Disability, defined as having a decline in activities of daily living (ADL), was assessed by a modified Katz questionnaire at four time points. Disability and death without disability for 22-year follow up were used as outcomes to test the association with a diagnosis of diabetes or prediabetes at baseline, using multinomial logistic regression. Adjusted odds ratios (ORs) were obtained from four models that contained appropriate adjustment factors, such as age, sex, smoking status, drinking status, body mass index and cardiovascular risk factors (hypertension, hypercholesterolemia, triglycerides, low serum high-density lipoprotein), at baseline.

Results: In the present study, 334 participants (18.7%) reported at least one disability, and 350 (19.6%) were reported dead without observation of disability during follow up. Adjusting sex and other risk factors, participants with diabetes and prediabetes had a higher risk for disability (OR 1.43, 95% confidence interval [CI] 1.07–1.91 and OR 1.66, 95% CI 1.10–2.50, respectively) and for mortality (OR 1.56, 95% CI 1.16–2.08 and OR 1.77, 95% CI 1.18–2.65, respectively) than individuals with normal glucose tolerance.

Conclusions: In middle-aged Japanese adults, individuals with diabetes and prediabetes were more likely to be associated with disability and mortality. Our findings suggest that prediabetes and diabetes in middle-aged adults should be paid more attention, and requires more intervention to prevent disability and mortality in later life.

INTRODUCTION

Diabetes is a global public health issue, which is increasing rapidly in incidence and prevalence[1]. The rise of diabetes in Asia is surpassing earlier predictions, and poses huge social and

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economic problems to most nations in the region, and could impede national and global development. In Japan, diabetes is one of the major causes of death and disability, accounting for 11.2% nationwide[2]. Increases in the number of people with diabetes requiring dialysis might place a great burden on Japan's social security system[3].

Diabetes and its complications could lead to severe damage to the heart, eyes, kidneys and nervous system, which diminishes the patient's quality of life[4,5]. Disability, defined as a decline in activities of daily living (ADL), is considered as a long-term effect of diabetes on general health[6-8]. Wong *et al.*[9] reported that people with diabetes had 51–82% higher mobility disability and ADL decline than people without diabetes. A recent study in the USA found that middle-aged adults with diabetes experienced disability onset 6–7 years earlier than those without diabetes[10]. Prediabetes was associated with an increased risk of all-cause mortality, faster deterioration in chair stand performance, slower walking speed and disability than people with normal glucose tolerance[11,12]. However, most of the past studies were carried out on elderly populations with a cross-sectional design, self-reported diagnosis for diabetes, and only focused on the overall effect of diabetes and comorbidities on disability[13,14]. Thus, the association of prediabetes with disability and death without disability among middle-aged adults remains uncertain. If prediabetes among middle-aged adults is associated with future risk of disability and mortality, the findings would support the evidence to recommend early lifestyle modification in the prediabetes stage, which might be easier to control than in diabetes.

In the present study, we carried out a longitudinal analysis using a Japanese cohort study of national representatives to examine the association of diabetes and prediabetes among middle-aged Japanese adults at baseline in 1990 with two outcomes of interest in later life, including disability and death without disability at 22-year follow up.

MATERIALS AND METHODS

Study population

The National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged 1990 (NIPPON DATA90) was a cohort study. The baseline survey was carried out in 1990 as the National Survey on Circulatory Disorders. A total of 8,383 community residents (3,503 men, 4,880 women; aged ≥30 years) from 300 randomly selected areas participated in the survey, with a participation rate of 76.5% (8,383 of 10,956). NIPPON DATA90 also conducted a survey of ADL for participants aged 65 years and older in 1995[15-18]. The ethics committee of Shiga University of Medical Science approved this study. In the present study, we excluded those who met the following criteria: 4,690 participants who were aged <45 years and aged ≥65 years in 1990 (i.e., baseline), 47 participants who had a history of stroke in 1990, 272 participants with missing baseline data, and 1,586 participants who were lost to follow up or had no record of living status nor any ADL investigation in the 22-year follow up. Thus, 1,788 were eligible for the analysis (Figure 1).

Baseline examination

The baseline survey that was carried out in 1990 included physical examinations, blood tests, and self-administered questionnaires on medical history and lifestyle. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Public health nurses obtained lifestyle data, including smoking and drinking habits, current health status, and medical history. A smoking habit was categorized into non-smoker, past smoker and current smoker. A drinking habit was categorized into non-drinker, past drinker and current drinker. Trained observers measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest.

The casual blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. The casual blood samples were categorized as fasting plasma glucose (≥4 h) and casual plasma glucose (<4 h)

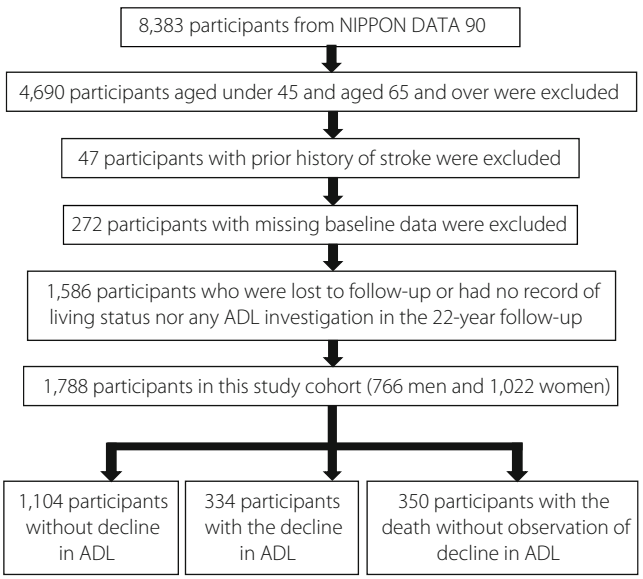

Figure 1 | Study cohort creation. A total of 8,383 community residents (3,503 men, 4,880 women; aged ≥30 years) from 300 randomly selected areas participated in the survey, with a participation rate of 76.5% (8,383 of 10,956). We excluded those who met the following criteria: 4,690 participants who were aged <45 years and aged ≥65 years in 1990 (i.e., baseline), 47 participants who had a history of stroke in 1990, 272 participants with missing baseline data and 1,586 participants who were lost to follow up or had no record of living status nor any activities of daily living (ADL) investigation in the 22-year follow up. Thus, 1,788 were eligible for the analysis. NIPPON DATA90, National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged 1990.

according to the following time intervals after meals: <0.5 h (5.8%); 0.5 to <1 h (5.7%); 1 to <2 h (10.0%); 2 to <3 h (20.9%), 3 to <4 h (18.9%); 4 to <6 h (30.2%); and 6 to <8 h (8.5%). Plasma samples were collected in siliconized tubes containing sodium fluoride and shipped to a laboratory (SRL, Tokyo, Japan) for blood measurements. Plasma glucose was measured enzymatically. Glycated hemoglobin (HbA1c; Japan Diabetes Society [JDS]) was measured by high-performance liquid chromatography. The coefficient of variation range of HbA1c measurement in this laboratory was 1.19–1.79% intra-assay and 0.24–0.45% interassay[19]. In the present study, HbA1c (JDS) values were converted to HbA1c (National Glycohemoglobin Standardization Program [NGSP]) values using the conversion formula provided by JDS: HbA1c NGSP value (%) = 1.02 × JDS value (%) + 0.25[16].

Serum triglycerides and total cholesterol were measured using enzymatic methods, and high-density lipoprotein cholesterol was measured after heparin–calcium precipitation[20]. Lipid measurements were standardized by the Centers for Disease Control/National Heart, Lung, and Blood Institute Lipids Standardization program. We defined cardiovascular risk factors as follows: hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) or on treatment for hypertension; hypercholesterolemia (total cholesterol ≥240 mg/dL) and/or medication for hypercholesterolemia; low serum high-density lipoprotein cholesterol (<40 mg/dL); and high serum triglyceride (>150 mg/dL) as serum total cholesterol ≥240 mg/dL.

Exposures: Diabetes categories

Diagnosis of prediabetes and diabetes was ascertained using a comprehensive method of medical treatment for diabetes, fasting plasma glucose (FPG; defined as no caloric intake for at least 4 h) and HbA1c (NGSP value), which was based on the Americans Diabetes Association's diagnostic criteria for diabetes in 2020[21]. The participants were categorized as follows: normoglycemia, both FPG <100 mg/dL (<5.6 mmol/L) and HbA1c <5.7% (39 mmol/mol), and no treatment for diabetes; prediabetes defined by FPG 100–125 mg/dL (5.6–6.9 mmol/L) or HbA1c 5.7%–6.4% (39–46 mmol/mol), or both, and no treatment for diabetes; and diabetes, FPG ≥126 mg/dL (≥7.0 mmol/L) or HbA1c ≥6.5% (47 mmol/mol), or both, or receiving treatment for diabetes regardless of FPG or HbA1c.

Outcomes: Disability and death without disability

As each participant visited a local public health center by themselves at the baseline in the 1990 examination, we assumed that they did not have any difficulties associated with ADL. In the pooled survey, over a 22-year follow up, participants aged ≥65 years who had reached age 65 years at four time points (1995, 2000, 2006, 2012) were eligible for the ADL survey. The ADL survey was carried out by face-to-face interviews at home, telephone interviews, a questionnaire sent by mail or other methods.

The modified questionnaire from Katz *et al.*[22] included six basic ADL items (eating and drinking, changing clothes, bathing, toileting, and walking indoors and outdoors), and participants were asked to answer either independently, with partial support or with full support for each item. Participants who required partial support or full support to carry out at least one of their six basic ADL items were considered to have a disability. According to their living status for the period of study, the participants who were still alive at the end of the study without observation of ADL decline were considered as "normal", and participants without observation of ADL decline who died before the next ADL survey were considered as "death without an observation of ADL decline" (death without disability). The participants who died after having observation of ADL decline were also considered as having disability (death with disability).

Vital statistics were obtained from the Management and Coordination Agency, Government of Japan, at the follow-up survey. Because an existence of a competing risk of disability and death was considered, death without observation of disability was assessed as an outcome separately.

Statistical analysis

Continuous data are presented as the mean ± standard deviation, and frequency data are presented as *n* (%). The χ^2-test and Student's *t*-test were used to test the differences in proportion and means, as appropriate, in the baseline characteristics categorized by baseline glucose tolerance status. Because it was difficult to establish the exact timing when participants experienced disability, and to avoid the competing risk of disability and death occurring, we used the multinomial logit model to estimate odds ratios (OR) and 95% confidence intervals (CI) for incident disability and death without having disability over 22 years of follow up among participants with prediabetes and diabetes compared with normoglycemia participants.

We carried out the analyses without any adjustment (crude) for the first step, then we used a series of multinomial logit models that were adjusted for the following baseline characteristics: demographics, cardiovascular risk factors to examine the association between baseline glucose tolerance status and disability, and death without disability at 22-year follow up. The multinomial logit models were adjusted as follows: model 1: age, sex, smoking status and alcohol drinking status; model 2: model 1 and cardiovascular risk factors (hypertension, hypercholesterolemia, triglycerides, low serum high-density lipoprotein); model 3: model 1 and BMI only; and model 4, the final fully adjusted model including all previous variables. ORs and 95% CIs were used, *P*-values <0.05 were significant. We also carried out the analysis stratified by sex, because the association might differ by sex.

All statistical analysis was carried out using Stata version 14.2 (StataCorp, College Station, TX, USA). Statistical significance was defined by a two-sided *P*-value <0.05.

RESULTS

Baseline characteristics

In the present study, among 1,788 participants aged 45–64 years at baseline in 1990 who were included in longitudinal analysis, 565 (31.6%) were identified as having prediabetes and 215 (12.0%) as having diabetes at baseline in 1990 (Table 1). Men had a slightly higher proportion of diabetes than women (men 14.2% vs women 10.4%). In contrast, women had a higher proportion of prediabetes than men (women 32.1% vs men 30.9%). The mean ages of participants with prediabetes and diabetes were 58.2 and 58.6, respectively. The mean duration of follow up among participants ranged from 19.0 (±4.5) to 20.5 (±3.5) years. Participants with prediabetes and diabetes had a higher proportion of hypertension and lipidemia than individuals with normal glucose tolerance (63.6% and 68.5%, respectively). There was a significant difference in the distribution of all baseline characteristics, except drinking status, among diabetes categories. Details of other baseline characteristics of respondents are shown in Table 1.

Table 1 | General characteristics of the study population for 1,788 men and women aged 45–64 years according to blood glucose status at baseline in 1990, NIPPON DATA90

	Normal	Prediabetes	Diabetes	*P*-values
All participants (%)	1,008 (56.4)	565 (31.6)	215 (12.0)	
Men	420 (54.9)	237 (30.9)	109 (14.2)	0.046
Women	588 (57.5)	328 (32.1)	106(10.4)	
Mean age, years (SD)	56.9 (4.3)	58.2 (4.2)	58.6 (4.3)	<0.001
Men	57.1 (4.3)	58.1 (4.4)	58.7 (4.2)	<0.001
Women	56.8 (4.3)	58.0 (4.3)	58.4 (4.2)	<0.001
Mean BMI (SD)	23.2 (2.9)	23.5 (3.4)	23.8 (3.7)	<0.001
Hypertension, *n* (%)				
SBP ≥140 mmHg or DBP ≥90 mmHg	529 (52.5)	359 (63.6)	147 (68.7)	<0.001
Hypercholesterolemia, *n* (%)				
TCH ≥240 mg/dL	191 (18.9)	118 (20.9)	63 (29.3)	0.002
Low serum HDL				
HDL <40 mg/dL	158 (15.7)	99 (17.5)	55 (25.6)	0.003
Hypertriglyceridemia				
TG ≥150 mg/dL	300 (29.8)	199 (35.2)	100 (46.5)	<0.001
HbA1c% (mmol/mol) (*n* and %)				
<5.7 (<39)	1,008 (100)	410 (72.6)	83 (38.6)	<0.001
5.7 to <6.5 (39 to <48)	–	155 (27.4)	44 (20.5)	
≥6.5 (≥48)	–	–	88 (40.9)	
Smoking status, *n* (%)				
Never smoke	651 (64.6)	355 (62.8)	113 (52.6)	0.016
Ex-smoker	111 (11.0)	62 (11.0)	36 (16.7)	
Current smoker	246 (24.4)	148 (26.2)	66 (30.7)	
Alcohol drinking status, *n* (%)				
Never drink	681 (67.5)	382 (67.6)	132 (61.4)	0.183
Ex-drinker	22 (2.2)	14 (2.5)	10 (4.7)	
Current drinker	305 (30.3)	169 (29.9)	73 (33.9)	

Data are given as the mean (standard deviation) or as *n* (percentage). DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; TCH, total cholesterol; TG, triglycerides.

Proportions of disability and death without disability according to baseline glucose status

During the 22-year follow-up, 334 (18.6%) were reported as having disability and 350 (19.5%) as death without disability. Participants with prediabetes and diabetes reported a higher proportion of disability and death without an observation of disability than individuals with normal glucose tolerance (21.9% and 23.8%, and 23.2% and 27.4%, respectively). In general participants, women reported a higher proportion of disability than men (22% vs 14.2%), whereas men had a higher proportion of death without disability than women (28.5% vs 12.9%). Women with prediabetes reported a higher proportion of disability and death without disability than men with prediabetes (39.6% vs 32.1%, and 38.6% vs 36.7%, respectively). In contrast, men with diabetes reported a higher proportion of disability and death without disability than women with diabetes (16.5% vs 14.7%, and 17.4% vs 15.9%, respectively; Table 2).

Associations of baseline glucose status and disability

In multinomial logistic regression analysis, the risk of disability was higher in participants with diabetes and prediabetes than participants with normal glucose tolerance, this observation was seen in all models. After we adjusted for all variables in the final model (model 4), the associations of baseline glucose status and disability were still statistically significant, participants with prediabetes and diabetes reported a 43% (OR 1.43, 95% CI 1.07–1.91) and 66% (OR 1.66, 95% CI 1.10–2.50) higher risk

Table 2 | Functional ability with living status according to baseline glucose tolerance status at 22-year follow up for 1,788 men and women aged 45–64 years at baseline

	Normal	Prediabetes	Diabetes	*P*-values
Functional ability status				
Total study population				
Without disability	689 (68.3)	310 (54.9)	105 (48.8)	<0.001
Disability	159 (15.8)	124 (21.9)	51 (23.8)	
Death without disability	160 (15.9)	131 (23.2)	59 (27.4)	
Men				
Without disability	264 (60.1)	122 (27.8)	53 (12.1)	0.012
Disability	56 (51.4)	35 (32.1)	18 (16.5)	
Death without disability	100 (45.9)	80 (36.7)	38 (17.4)	
Women				
Without disability	425 (63.9)	188 (28.3)	52 (7.8)	<0.001
Disability	103 (45.7)	89 (39.6)	33 (14.7)	
Death without disability	60 (45.5)	51 (38.6)	21 (15.9)	

Data are given as *n* (percentage).

Table 3 | Association between baseline glucose tolerance status and activities of daily living status at 22-year follow up

	Normal	Prediabetes		Diabetes	
		Adjusted OR (95% CI)	*P*-values	Adjusted OR (95% CI)	*P*-values
Disability					
Model 1	1.00 (Reference)	1.47 (1.10–1.95)	0.008	1.73 (1.16–2.59)	0.007
Model 2	1.00 (Reference)	1.45 (1.09–1.92)	0.011	1.69 (1.12–2.54)	0.011
Model 3	1.00 (Reference)	1.44 (1.08–1.93)	0.011	1.68 (1.12–2.52)	0.011
Model 4	1.00 (Reference)	1.43 (1.07–1.91)	0.014	1.66 (1.10–2.50)	0.014
Death without disability					
Model 1	1.00 (Reference)	1.59 (1.19–2.13)	0.002	1.80 (1.20–2.68)	0.004
Model 2	1.00 (Reference)	1.55 (1.16–2.08)	0.003	1.75 (1.17–2.63)	0.007
Model 3	1.00 (Reference)	1.59 (1.19–2.12)	0.002	1.80 (1.21–2.69)	0.004
Model 4	1.00 (Reference)	1.56 (1.16–2.08)	0.003	1.77 (1.18–2.65)	0.006

Data are odds ratios (95% confidence intervals). Model 1: adjusted for age, sex, smoking status and drinking status. Model 2: adjustments in model 1 plus cardiovascular risk factors (hypertension, hypertriglyceridemia and low high-density lipoprotein, hypercholesterolemia). Model 3: adjustments in model 1 plus body mass index. Model 4 was adjusted for all variables.

of disability than participants with normal glucose tolerance, respectively (Table 3).

Associations of baseline glucose status and death without disability

We evaluated the association between the risk of all-cause mortality without disability according to baseline glucose status. We found an increased risk of death without disability in participants with diabetes and prediabetes, as they reported a 59% (OR 1.59, 95% CI 1.19–2.13) and 80% (OR 1.80, 95% CI 1.20–2.68) higher risk of death without disability than participants with normal glucose tolerance (model 1), respectively (Table 3). In the final model (model 4), odds ratios slightly decreased in the participants with prediabetes and diabetes (1.56 [OR 1.56, 95% CI 1.16–2.08] and 1.77 [OR 1.77, 95% CI 1.18–2.65], respectively; Table 3).

Associations of disability and death without disability according to baseline glucose status, stratified by sex

Although we did not find an interaction between sex and diabetes status, we carried out a stratified analysis by sex to clarify the effect of baseline glucose status on disability and death without disability within sex groups (Table 4). Among women participants, after full adjustment for all variables in the final model (model 4), women with prediabetes and diabetes had 1.57-fold (OR 1.57, 95% CI 1.10–2.24) and 2.20-fold (OR 2.20, 95% CI 1.29–3.76) higher ORs of disability than others, respectively (Table 4). The same observation was reported among those who were reported as death without disability, women with prediabetes and diabetes also reported higher odds ratios of mortality than participants with normal glucose tolerance (OR 1.61, 95% CI 1.05–2.49; OR, 2.35 95% CI 1.26–4.39, respectively) (Table 4). In contrast, the statistically significant association was not found among men with diabetes and prediabetes after adjustment for all variables.

DISCUSSION

The present longitudinal cohort study was the first study to be carried out in Asia that used longitudinal analysis and repeated measurements in middle-aged adults, with a focus on the relative association between prediabetes in middle-aged population with disability and mortality in later life. Our findings support the conceptual framework that middle-aged adults with prediabetes have higher risks of disability and death without disability than individuals with normal glucose tolerance. Middle-aged women with blood glucose tolerance disorder were more likely to be associated with disability and mortality at 22-year follow up than others. Furthermore, the present results support the hypothesis that middle-aged participants with diabetes have higher ORs of disability and mortality.

In NIPPON DATA90, the study population was randomly selected from 300 community areas in Japan. In the present study, the prevalence of diabetes among middle-aged Japanese adults was close to another survey on the trends of diabetes in Japan[23]. Furthermore, the proportion of middle-aged adults with prediabetes was similar to a study carried out among a working-age population[20]. The present study found that middle-aged adults with blood glucose tolerance disorder had higher risks of disability and mortality than people without these conditions at later life.

Disability among participants with prediabetes and diabetes were 1.43- and 1.66-fold higher, respectively, than participants with normal glucose tolerance in the present study. Our results are comparable with other studies that were carried out in different populations with various age groups, although the disability definitions were slightly different[6]. In a cross-sectional study for diabetes carried out in Canadian people aged ≥45 years, which used the OARS (Older Americans Resources and Services) Multidimensional Functional Assessment Questionnaire (OMFAQ) scale to measure functional disability in

Table 4 | Association between baseline glucose tolerance status and activities of daily living status at 22-year follow up, stratified by sex

	Men				Women			
	Prediabetes		Diabetes		Prediabetes		Diabetes	
	Adjusted OR (95% CI)	*P*-values	Adjusted OR (95% CI)	*P*-values	Adjusted OR (95% CI)	*P*-values	Adjusted OR (95% CI)	*P*-values
Disability								
Model 1	1.18 (0.72–1.94)	0.499	1.24 (0.66–2.35)	0.505	1.62 (1.14–2.31)	0.007	2.21 (1.31–3.73)	0.003
Model 2	1.17 (0.71–1.92)	0.527	1.23 (0.64–2.37)	0.518	1.59 (1.12–2.27)	0.010	2.23 (1.30–3.79)	0.003
Model 3	1.18 (0.72–1.94)	0.500	1.22 (0.64–2.33)	0.540	1.58 (1.12–2.26)	0.010	2.15 (1.27–3.64)	0.004
Model 4	1.17 (0.71–1.93)	0.524	1.22 (0.63–2.35)	0.547	1.57 (1.10–2.24)	0.012	2.20 (1.29–3.76)	0.004
Death without disability								
Model 1	1.51 (1.01–2.25)	0.042	1.44 (0.86–2.25)	0.166	1.67 (1.08–2.56)	0.020	2.31 (1.25–4.25)	0.007
Model 2	1.47 (0.99–2.20)	0.057	1.42 (0.83–2.43)	0.197	1.63 (1.05–2.51)	0.028	2.36 (1.26–4.41)	0.007
Model 3	1.53 (1.02–2.27)	0.038	1.48 (0.87–2.52)	0.141	1.65 (1.06–2.54)	0.024	2.27 (1.23–4.19)	0.009
Model 4	1.49 (0.99–2.25)	0.052	1.45 (0.85–2.48)	0.170	1.61 (1.05–2.49)	0.030	2.35 (1.26–4.39)	0.007

Data are odds ratios (95% confidence intervals). Model 1: adjusted for age, smoking status, and drinking status. Model 2: adjustments in model 1 plus cardiovascular risk factors (hypertension, hypertriglyceridemia and low high-density lipoprotein, hypercholesterolemia). Model 3: adjustments in model 1 plus body mass index. Model 4 was adjusted for all variables.

ADL, Griffith *et al.*[24] reported that diabetes made the largest contribution to ADL-related functional disability in middle-aged adults and older people. In a 1997–1999 National Health Interview Survey study in a USA population, activities limitations (as measured by nine physical tasks) were nearly twofold more common in USA adults with diabetes than in those without diabetes[25]. In addition, a longitudinal study carried out by Koye *et al.*[7] also found that people with diabetes aged >47 years at baseline were more likely to report more limitations (using Katz ADL questionnaire 6 items) than participants with normal glucose tolerance after 12 years. However, their study found no significant association between a diagnosis of prediabetes at baseline and disability. Another study among middle-aged adults (aged >53 years) in a USA population found that people with prediabetes were 1.48-fold more likely to report physical functional limitations (using the Katz ADL scale 5 items)[26]. The present findings that middle-aged participants with prediabetes had a higher risk of disability than participants with normal glucose tolerance are consistent with these other studies.

Furthermore, the present study supports the hypothesis that people with diabetes have a higher risk of mortality than individuals with normal glucose tolerance. Moreover, we found that a diagnosis of prediabetes in middle-aged adults significantly increased the risk of mortality in their later life. Meanwhile, other studies reported non-significant relationships of prediabetes and mortality in elderly populations using cross-sectional designs[27,28]. The differences of population age and study design might lead to different results.

In the present study, we found that women with prediabetes were significantly more likely to be associated with disability and mortality than participants with normal glucose tolerance. A similar finding was found in women with diabetes. However, we did not find significant findings among men. The present findings are consistent with other studies that reported a similar pattern within sex subgroups. Women with diabetes had greater comorbidity, and were more likely to be taking medications that increase the risk of falling and decrease bone mineral density. Compared with men, women have a longer duration of life with disability, in part due to the higher prevalence of non-fatal chronic conditions; constitutional factors, such as lower muscle strength and lower bone density; and higher rates of lifestyle factors, such as sedentary behavior and obesity[29,30]. Japanese women spend their lifetime with more disability than men. The higher prevalence of fragility fractures and dementia, along with higher life expectancy that was reported in other studies among Japanese women, could extend the understanding for this finding[31-33]. The association between men with prediabetes and death without disability is inconsistent after adjusted for all variables, and the association among men with prediabetes with death without disability was significant adjusted for BMI only. A previous study suggested that men with initial BMI <21.7 at age 20 years was associated with twofold increased risk of coronary heart disease, but not in men with initial BMI ≥21.7[34]. In

addition to their finding, men with prediabetes reported a higher proportion of BMI <21.7 than men with diabetes in our study.

Disability is considered a long-term effect for people with diabetes. People with diabetes and prediabetes spend their lifetime with poor quality of life[35-37]. The relationship between diabetes and disability is multifactorial, has modifiable factors, and varies between men and women. An appropriate prevention program that focuses on middle-aged adults with prediabetes might slow the progression to diabetes, reduce the incidence of functional limitations and mortality in later life, improve quality of life, reduce the cost of healthcare visits, and lessen the burden on their spouse and society.

The present study had several strengths. First, the sampling collection was randomly carried out around Japan; thus, the results are generally representative among Japanese people, and can be applied for middle-aged adults in other similar communities. Second, we used a comprehensive method with three diagnostic criteria to categorize the baseline blood glucose tolerance status, which lessened the underreporting diabetes rate and reduced recall bias; thus, overcoming the main limitations reported in previous studies. Third, our longitudinal design with repeated measures provides more precise estimates for the outcome of interest than the previous cross-sectional studies. Our study was limited by the lack of a baseline ADL survey in 1990. We also underestimated the development of baseline blood glucose tolerance status over the 22-year follow up. In addition, we were unable to establish the exact time of disability due to the discrete time point of the survey; thus, the development of disability along with blood glucose status could not be clarified. Due to the sample sizes, we could not analyze by 5-year interval age groups, although the age groups had different number of chances for the ADL survey due to the study design. We could not assess the type of diabetes mellitus due to lack of detailed information.

In summary, prediabetes in middle-aged adults is a predictor for disability and increases the risk of mortality in later life, especially in women. Early screening and intervention might decrease the progression of diabetes and its complications. Other prominent factors need to be considered to explore the causal relationship between prediabetes and disability in further studies.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: R2005-021 (The ethics committee of Shiga University of Medical Science).
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Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | Aknowledgements and the member list of NIPPON DATA80/90 Research Group.