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RESEARCH ARTICLE

Effect of Body Mass Index and Intra-Abdominal Fat Measured by Computed Tomography on the Risk of Bowel Symptoms

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Abstract

Background

This study aims to investigate the association between body mass index (BMI) or intra-abdominal fat measured by computed tomography (CT) and bowel symptoms.

Method

A cohort of 958 Japanese adults who underwent colonoscopy and CT and completed questionnaires after excluding colorectal diseases was analyzed. Six symptoms (constipation, diarrhea, loose stools, hard stools, fecal urgency, and incomplete evacuation) using a 7-point Likert scale were evaluated between baseline and second questionnaire for test-retest reliability. Associations between BMI, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and symptom score were analyzed by a rank-ordered logistic model, adjusting for age, sex, smoking, and alcohol consumption, hypertension, diabetes mellitus, and dyslipidemia.

Results

Some bowel symptom scores were significantly ($p<0.05$) different between the age groups, sexes, smoking, and alcohol consumption. In multivariate analysis, constipation was associated with low BMI ($p<0.01$), low VAT area ($p = 0.01$), and low SAT area ($p<0.01$). Moreover, hard stools was associated with low BMI ($p<0.01$) and low SAT area ($p<0.01$). The remaining symptoms were not significantly associated with BMI or intra-abdominal fat. Test-retest reliability of bowel symptom scores with a mean duration of 7.5 months was good (mean kappa, 0.672).

Competing Interests: The authors have declared that no competing interests exist.

Conclusions

Both low BMI and low abdominal fat accumulation appears to be useful indicators of increased risk for constipation and hard stools. The long-term test-retest reliability of symptom score suggests that bowel symptoms relevant to BMI or visceral fat remain consistent over several months.

Introduction

Gastrointestinal (GI) symptoms are common in the general population, but studies on the role of GI symptoms in overweight individuals are limited.[1,2] Several studies have reported an increased risk of upper GI symptoms associated with high body mass index (BMI);[3–6] however, little information is available on the association between high BMI and functional bowel disorder.[4,6,7] Recent studies have shown that abdominal visceral fat as measured by computed tomography (CT) is a better predictor of the risk of upper GI disease (e.g., gastroesophageal reflux disease or Barrett's esophagus) than BMI.[8,9] However, the association between lower GI symptoms and CT-evaluated intra-abdominal fat has not been reported previously.

This study examined the relationship of BMI, CT-measured visceral adipose tissue (VAT), and CT-measured subcutaneous adipose tissue (SAT) with the risk of bowel symptoms. Bowel symptoms are caused by various colorectal diseases; however, previous population-based studies have not excluded colorectal diseases.[10–12] We therefore used colonoscopy to exclude the presence of colorectal diseases and applying the criteria of functional bowel disorder.[13]

Methods

Study Design, Setting, and Participants

We conducted a prospective, hospital-based, cross-sectional study of Japanese adults at the National Center for Global Health and Medicine (NCGM), Japan between September 2009 and June 2013. Participants who underwent elective colonoscopy and CT and completed a questionnaire were enrolled. The patient population and data collection procedure are described in detail in our previous report of a study with different research objectives from the present study [14]. We included patients > 18 years of age presenting with bowel symptoms or requiring colorectal cancer screening. Patients were excluded if their medication use was unknown, they were not independent in activities of daily living, or they were being followed after colonoscopy. Of the 11,222 eligible participants, 3798 Japanese patients completed the questionnaire (Fig 1), of which 1715 underwent multidetector computed tomography (MDCT) before colonoscopy. At our institution, MDCT is performed for individuals who request screening for non-colorectal cancer (e.g., stomach, pancreas, liver, biliary tract, lung, prostate, uterus, or ovarian cancer) or for the investigation of rectal bleeding, diarrhea, and abdominal pain in patients presenting to our institution's emergency outpatient department. The remaining 2083 participants who did not undergo MDCT (1393 men; mean age, 64.0 years) declined either because of anxiety due to radiation exposure or cost or because they had previously undergone CT at another institution. From the 1715 patients who underwent colonoscopy and MDCT, we excluded the following patients: (i) those with colorectal diseases identified by colonoscopy and CT (n = 212); (ii) those who did not fulfill the criteria for functional bowel disorder[13] (n = 512); and (iii) those who could not undergo total colonoscopy (n = 122). This left 958 patients for analysis in this study.

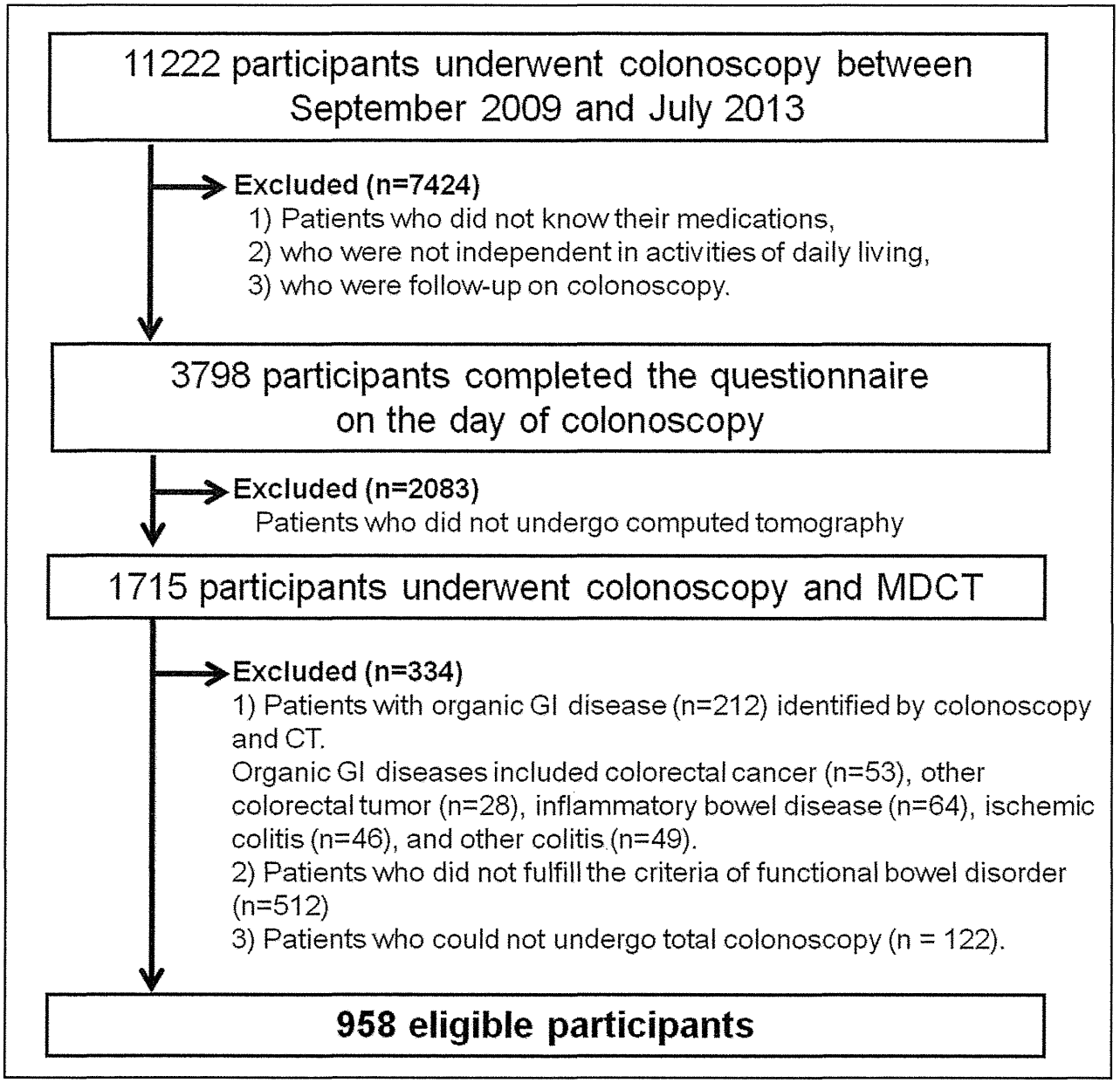

Fig 1. Study flow. Abbreviations: MDCT, multidetector computed tomography; GI, gastrointestinal.

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This study was approved by the ethics committee of the National Center for Global Health and Medicine Center (No. 1012) and was implemented in accordance with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to endoscopy and CT.

Evaluation of Bowel Symptoms

Diagnosis of functional bowel disorder requires the existence of certain characteristic bowel symptoms over the past 3 months, with an onset of more than 6 months before colonoscopy. [13] On day of pre-colonoscopy, bowel symptoms were evaluated using the GI symptom rating

scale (GSRS), which covered 6 bowel symptoms using a 7-point Likert scale (1, none at all; 2, minor; 3, mild; 4, moderate; 5, moderately severe; 6, severe; and 7, very severe).[15,16] The validity of GSRS has been well documented in conditions of functional bowel disorder.[17–19] The 6 bowel symptoms included constipation, diarrhea, loose stools, hard stools, fecal urgency, and incomplete evacuation.

To assess the test-retest reliability of bowel symptoms scores, we conducted a secondary questionnaire using the same GSRS among participants who visited our department over 1 week after the first interview.

Diagnosis of colorectal diseases

An electronic high-resolution video endoscope (model CFH260; Olympus Optical, Tokyo, Japan) with full preparation was used for diagnosis of colorectal diseases. Endoscopy was performed by well-trained staff who were blinded to the questionnaire results. When abnormalities were detected by colonoscopy, biopsy, polypectomy, or endoscopic mucosal resection was performed. All removed specimens were evaluated by expert pathologists, and final diagnoses of colorectal diseases were made.

Colorectal diseases included early and advanced colorectal cancer, other colorectal tumor, inflammatory bowel disease, ischemic colitis, and other colitis, as reported previously.[20] During the same period (within 1 week of colonoscopy), upper endoscopy was performed for 110 patients, none of whom were found to have cancerous or ulcerous lesions or severe gastritis.

Exposure Variables

A detailed questionnaire was completed at the endoscopy unit on the same day prior to colonoscopy.[14] Patients were asked about alcohol consumption and smoking status, and their medical history was recorded by well-trained medical researchers. Researchers also checked prescriptions and medical records in addition to the information provided by the patients to avoid inadvertences. Medical history included diseases such as hypertension, diabetes mellitus, and dyslipidemia, which were considered present in patients taking disease-specific drugs. Smoking status was classified as current (daily or occasionally) smoker, former smoker, or never smoker. BMI was calculated as weight divided by height squared (kg/m^2).

Measurement of the Abdominal Adipose Tissue Area by multidetector CT

The technique used for measuring the adipose tissue area on CT has been standardized and validated,[21] and shows only negligible inter-observer variation.[22] Participants were assessed in the supine position using a 320-row area detector CT scanner (Aquilion ONE, Toshiba Medical Systems, Japan). All CT examinations were performed with helical scanning using the following parameters: 64 × 0.5 mm collimation, 120 kVp; auto exposure control (AEC) beam pitch, 0.83 (table feed per gantry, 53 mm; collimation beam width, 64 mm); gantry rotation time, 0.5 s; matrix, 512 × 512; and field of view, 350–500 mm. All images were reconstructed using a standard reconstruction algorithm with a section thickness of 5 mm. The cross-sectional surface areas (cm^2) of different abdominal fat compartments were calculated at this slice using commercially available CT software (Aquilion ONE, Toshiba Medical Systems) to determine the adipose tissue area electronically by setting the attenuation values for a region of interest within the range of -150 to -30 Hounsfield units. The VAT area was defined as intra-abdominal fat bound by the parietal peritoneum or transversalis fascia, excluding the vertebral column and paraspinal muscles (**Fig 2**). The SAT area was defined as fat superficial to the abdominal and back muscles (**Fig 2**). A region of interest drawn around the external margin of

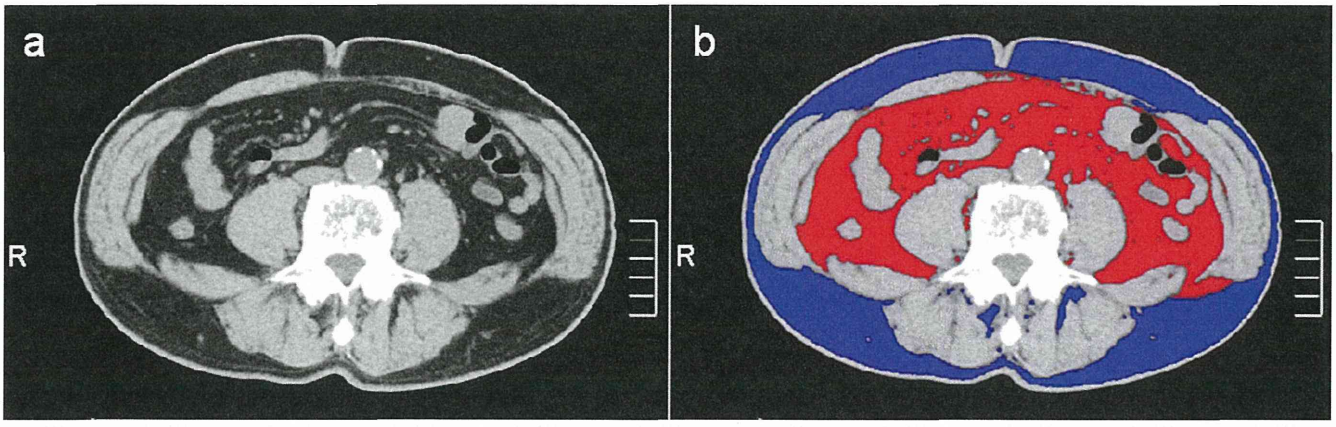

Fig 2. Measurement of intra-abdominal fat area by use of multidetector CT. A 61-year-old-male with a BMI of 24.8. (a) Initial CT images. (b) Intra-abdominal adipose tissue areas. Regions of red and blue color indicate visceral (107.3 cm^2) and subcutaneous (104.1 cm^2) adipose tissue, respectively.

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the dermis was used to calculate the total adipose tissue area. The SAT area was calculated by subtracting the VAT area from the total adipose tissue area.

Statistical Analysis

GSRS scores were compared using the Mann–Whitney U test. Rank-ordered logistic model [23] was used to determine the association between bowel symptoms and BMI, VAT area, or SAT area. Multivariate analysis was adjusted for age, sex,[20] alcohol consumption,[24] smoking status,[20,25] and diabetes mellitus,[26] all of which are known factors associated with functional bowel disorder.[13] Dyslipidemia and hypertension were potential confounders between obesity and bowel symptoms; we therefore also included these in the multivariate model. These associations were evaluated after excluding colorectal diseases on colonoscopy.

The test-retest reliability of the bowel symptom scores in the GSRS from the first and second questionnaires was analyzed using kappa statistics. Kappa values >0.80 denoted excellent agreement, >0.60–0.80 good,> 0.40–0.60 moderate, >0.20–0.40 fair, and ≤0.20 poor.[27] $P<0.05$ was considered significant. All statistical analysis was performed using Stata version 13 software (StataCorp, College Station, TX).

Results

Patient Characteristics

Baseline characteristics are shown in **Table 1**. Of the 958 patients who underwent colonoscopy plus CT and completed questionnaires, 441 (46%) were aged ≥65 years, and 647 (68%) were male. The mean BMI was 22.8 $kg/m^2$and 244 patients (26%) had a BMI of ≥25 kg/m^2.

Patient Characteristics and Bowel Symptoms

The association of patient characteristics and 6 bowel symptom scores is shown in **Table 2**. Among the age groups (age ≥65 and <65 years), patients aged <65 years had higher symptom scores for diarrhea, loose stools, fecal urgency, and incomplete evacuation than those aged ≥65 years. Among the 2 sexes, males had higher symptom scores for diarrhea and loose stools, whereas females had higher symptom scores for constipation and hard stools. Smokers had higher symptom scores for constipation, diarrhea, loose stools, and fecal urgency than non-smokers. Drinkers had lower symptom scores for constipation, diarrhea, loose stools, and fecal

Table 1. Characteristics of the 958 patients included in the study.

Age (years)	60.7 ± 14.5
Age ≥65 (years)	441 (46.0)
Male sex	647 (67.5)
Current smoker	232 (24.2)
Former smoker	269 (28.1)
Never smoker	457 (47.7)
Current drinker	516 (53.9)
Hypertension	340 (35.5)
Diabetes mellitus	158 (16.5)
Dyslipidemia	167 (17.4)
Height	163.2 ± 9.5
Weight	61.0 ± 12.8
Body mass index, kg/m^2	22.8 ± 3.8
< 18.5	107 (11.2)
18.5–24.9	607 (63.4)
25–29.9	206 (21.5)
30–34.9	32 (3.3)
35–39.9	5 (0.5)
≥ 40	1 (0.1)
Visceral adipose tissue area, cm^2	112.5 ± 82.6
Subcutaneous adipose tissue area, cm^2	124.8 ± 74.4
Visceral adipose tissue to subcutaneous adipose tissue ratio	1.02 ± 0.75
Total adipose tissue area, cm^2	234.8 ± 128.0
Bowel symptom scores (range)	
Constipation (1–7)	2.0 ± 1.5
Diarrhea (1–7)	2.1 ± 1.5
Loose stools (1–7)	1.9 ± 1.3
Hard stools (1–7)	1.9 ± 1.3
Fecal urgency (1–7)	2.1 ± 1.5
Incomplete evacuation (1–7)	2.3 ± 1.3

Values presented with plus/minus sign represent mean ± standard deviation.

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urgency than non-drinkers. Between patients with and without hypertension, no significant difference was noted in any of the 6 bowel symptoms. Patients with diabetes had higher symptom scores for hard stools than patients without diabetes.

Associations between Obesity Index and Bowel Symptoms

The association of BMI and intra-abdominal fat and bowel symptoms is shown in **Table 3**. Rank-ordered logistic model revealed that constipation was associated with low BMI ($p < 0.01$), low VAT area ($p = 0.01$), and low SAT area ($p < 0.01$), while hard stools was associated with low BMI ($p < 0.01$) and low SAT area ($p < 0.01$) in multivariate analysis. However, diarrhea, loose stools, fecal urgency, and incomplete evacuation were not associated with BMI or intra-abdominal fat.

Table 2. Association of patient characteristics and bowel symptom scores (n = 958).

	Age ≥65/ <65	p	Male/ female	p	Current smoking (yes/no)	p	Alcohol consumption (yes/no)	p	Hypertension (with/without)	p	Diabetes mellitus (with/ without)	p	Dyslipidemia (with/without)	p
Constipation	2.0 ± 1.4/ 2.0 ± 1.5	0.795	1.9 ± 1.4/ 2.2 ± 1.5	**<0.01**	2.2 ± 1.6/ 2.0 ± 1.4	**0.04**	2.0 ± 1.5/ 2.1 ± 1.5	**0.04**	2.0 ± 1.5/ 2.0 ± 1.5	0.35	2.2 ± 1.6/ 2.0 ± 1.4	0.48	2.0 ± 1.4/ 2.0 ± 1.5	0.81
Diarrhea	1.8 ± 1.3/ 2.3 ± 1.6	**<0.01**	2.1 ± 1.5 /1.9 ± 1.5	**<0.01**	2.3 ± 1.6/ 2.0 ± 1.5	**0.02**	2.0 ± 1.4/ 2.1 ± 1.6	**0.02**	2.0 ± 1.4/ 2.1 ± 1.6	0.40	2.0 ± 1.4/ 2.1 ± 1.5	0.92	1.9 ± 1.3/ 2.1 ± 1.5	0.07
Loose stools	1.7 ± 1.1/ 2.1 ± 1.4	**<0.01**	2.0 ± 1.3/ 1.8 ± 1.2	**<0.01**	2.1 ± 1.4/ 1.9 ± 1.3	**0.03**	1.9 ± 1.2/ 1.9 ± 1.3	**0.03**	1.8 ± 1.2/ 2.0 ± 1.4	0.16	1.9 ± 1.1/ 1.9 ± 1.3	0.67	1.9 ± 1.2/ 1.9 ± 1.3	0.91
Hard stools	1.9 ± 1.3/ 1.9 ± 1.3	0.579	1.8 ± 1.2/ 2.1 ± 1.4	**0.01**	1.9 ± 1.3/ 1.9 ± 1.3	0.85	1.9 ± 1.2/ 1.9 ± 1.3	0.85	1.9 ± 1.2/ 2.0 ± 1.3	0.20	2.2 ± 1.5/ 1.9 ± 1.2	**0.02**	2.0 ± 1.4/ 1.9 ± 1.3	0.28
Fecal urgency	1.9 ± 1.3/ 2.3 ± 1.6	**<0.01**	2.1 ± 1.5/ 2.0 ± 1.4	0.15	2.3 ± 1.6/ 2.0 ± 1.4	**<0.01**	2.1 ± 1.4/ 2.1 ± 1.5	**<0.01**	2.1 ± 1.5/ 2.1 ± 1.4	0.41	2.0 ± 1.4/ 2.1 ± 1.5	0.71	2.0 ± 1.4/ 2.1 ± 1.5	0.74
Incomplete evacuation	2.1 ± 1.3/ 2.4 ± 1.4	**<0.01**	2.3 ± 1.4/ 2.2 ± 1.3	0.26	2.4 ± 1.5/ 2.2 ± 1.3	0.63	2.2 ± 1.3/ 2.3 ± 1.4	0.63	2.1 ± 1.3/ 2.3 ± 1.4	0.06	2.3 ± 1.3/ 2.3 ± 1.3	0.40	2.2 ± 1.2/ 2.3 ± 1.4	0.63

Values presented with plus/minus sign represent mean ± standard deviation. Differences in symptom scores between 2 groups were analyzed using the Mann–Whitney U test. *p-values of <0.05 represent comparison of patients with and without the corresponding characteristics.

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Table 3. Effect of body mass index, visceral adipose tissue, and subcutaneous adipose tissue on the risk of bowel symptoms (n = 958).

	Univariate coefficient	p-value	Multivariate coefficient*	p-value
Constipation				
Body mass index	−0.0588	**<0.01**	−0.0537	**<0.01**
Visceral adipose tissue area	−0.0026	**<0.01**	−0.0024	**0.01**
Subcutaneous adipose tissue area	−0.0027	**<0.01**	−0.0032	**<0.01**
Diarrhea				
Body mass index	−0.0191	0.25	−0.0181	0.30
Visceral adipose tissue area	−0.0005	0.51	0.0001	0.90
Subcutaneous adipose tissue area	−0.0019	**0.03**	−0.0007	0.41
Loose stools				
Body mass index	−0.0167	0.31	−0.0236	0.18
Visceral adipose tissue area	−0.0015	0. 07	−0.0013	0.11
Subcutaneous adipose tissue area	−0.0014	0.09	−0.0008	0.39
Hard stools				
Body mass index	−0.0422	**0.01**	−0.0481	**<0.01**
Visceral adipose tissue area	−0.0009	0.26	−0.0006	0.47
Subcutaneous adipose tissue area	−0.0018	**0.04**	−0.0026	**<0.01**
Fecal urgency				
Body mass index	−0.0292	0.08	−0.0312	0.08
Visceral adipose tissue area	−0.0011	0.15	−0.0008	0.32
Subcutaneous adipose tissue area	−0.0015	0.07	−0.0010	0.28
Incomplete evacuation				
Body mass index	−0.0260	0.10	−0.0224	0.18
Visceral adipose tissue area	−0.0009	0.24	−0.0005	0.57
Subcutaneous adipose tissue area	−0.0014	0.08	−0.0009	0.31

*Adjusted for age, sex, current smoking, alcohol consumption, hypertension, diabetes mellitus, and dyslipidemia.

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Reliability of bowel symptom score

Among the 958 participants, 690 (72.0%) completed a secondary questionnaire of using the GSRS within a mean duration of 7.5±10.7 months. The test-retest reliability of the GSRS was good (mean Kappa values was 0.672; Table 4).

Discussion

To the best of our knowledge, this is the first study evaluating the relationship between functional bowel symptoms and BMI, VAT area, and SAT area as calculated by CT. After excluding colorectal diseases using colonoscopy and applying the criteria of functional bowel disorder, we found that constipation was associated with low BMI, low VAT area, and low SAT area, while hard stools was associated with low BMI and low SAT area. Finally we found that long-term test re-test reliability of GSRS was good.

Table 4. Test-retest reliability of bowel symptom score between 1st and 2nd questionnaire (n = 690).

	Agreement	Kappa	SE	P
Constipation	79.0%	0.686	0.022	<0.001
Diarrhea	80.1%	0.691	0.022	<0.001
Loose stools	79.1%	0.675	0.024	<0.001
Hard stools	78.1%	0.667	0.023	<0.001
Fecal urgency	76.7%	0.656	0.022	<0.001
Incomplete evacuation	74.9%	0.657	0.021	<0.001

Abbreviations: GI, Gastrointestinal: SE, standard error.

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In previous studies, the relationship between bowel symptoms and BMI has been controversial. For example, a cross-sectional study of 16,078 participants from China demonstrated that high BMI was associated with functional diarrhea.[28] A case-control study of 96 IBS patients from Sweden identified high BMI to be associated with the severity of bloating, gas, urgency, loose stools, and stool frequency.[29] In contrast, a well-designed birth cohort study of young adults in Australia showed that BMI was not associated with IBS, including bloating and constipation.[30] In a Korean study of 5,605 participants who took part in a health screening program, BMI and waist circumference were not risk factors of IBS after excluding organic disease.[20] Among 2,712 Japanese who underwent health check-ups, BMI was not associated with increased risk of any type of IBS.[25] In another study of 2,495 Japanese subjects who underwent health check-ups, BMI did not differ among groups of non-IBS, patients with constipation type-IBS, or patients with diarrhea type-IBD. Although different results were observed on account of the differences in study design, sample size, and ethics, diarrhea symptoms appear to be positively associated with obesity, particularly in Western countries. However, in Asian studies including the present study, no relationship between bowel symptoms and high BMI has been identified.

A few studies have investigated the relationship between low BMI and bowel symptoms. Kubo et al.[25] reported that low BMI (OR: 0.95) was significantly associated with IBS in multivariate analysis. Farzaneh et al.[31] identified low BMI (OR: 0.94) as an independent risk factor associated with IBS in Iran. These 2 Asian studies support our findings.

Reproducible relates to the interpretation of scores from psychometric instruments (eg, symptom scales, questionnaires, and observer ratings) used in clinical practice. In this study, we confirmed a good long-term test-retest reliability (mean kappa, 0.66), which is above the kappa value of 0.6 usually considered to be good.[32] Our results imply that patients with specific GI symptoms and the severity of these symptoms remain consistent over several months.

This study has several strengths. First, colonoscopy enables the exclusion of colorectal diseases. Second, we were able to confirm the long-term reliability of the bowel symptom scores. Third, the sample size was relatively large, facilitating adjustment for confounding factors. However, this study also has limitations. First, although, our subjects met the definition of functional bowel disorder, we could not classify functional bowel disorder into IBS, functional bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder because we did not assess stool condition, such as improvement with defecation, onset associated with a change in stool frequency, or onset associated with a change in stool form.[13] Second, although we collected data on smoking and alcohol consumption habits and metabolic factors while interviewing patients in the pre-colonoscopy setting in the endoscopy room, we did not obtain information on educational level or somatic disorders that may be associated with functional bowel disorder.[13] In particular, somatic disorders, which are characterized

by somatic symptoms (e.g., pain, GI distress, and sexual problems) and pseudoneurological symptoms (e.g., amnesia and breathing difficulties), tend to be accompanied by high levels of worry, anxiety, and increased reactions in response to physical symptoms[33] and to show a positive association with bowel symptoms.[34] Thus, the lack of assessment of somatic disorder in this study is a major limitation. Third, we did not evaluate the composition of feces (bacteria, fat, or pH), conduct lactose intolerance tests, or perform breath tests to rule out small intestinal bacterial overgrowth in this study, which are all useful examinations for diagnosing functional bowel disorder.[35–37] Fourth, both bowel symptoms and BMI or intra-abdominal fat was associated with dietary intake or dietary pattern[38], but we could not the diet information. In the pre-colonoscopy setting in the endoscopic room, we could gather information only on lifestyle habits, medication use, comorbidities, and bowel symptoms scores.

In conclusion, both low BMI and low abdominal fat accumulation increased risk of constipation and hard stools. The long-term test-retest reliability of symptom score suggests that bowel symptoms relevant to BMI or visceral fat remain consistent over several months.

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Author Contributions

Conceived and designed the experiments: NN NU MN. Performed the experiments: K. Sakamoto TA MS. Analyzed the data: T. Shimbo NN. Wrote the paper: NN NI. Collected clinical information and performed endoscopy: RN K. Sekine HO KW T. Sakurai CY MY JA.

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ORIGINAL ARTICLE

Impact of population aging on trends in diabetes prevalence: A meta-regression analysis of 160,000 Japanese adults

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ABSTRACT

Aims/Introduction: To provide age- and sex-specific trends, age-standardized trends, and projections of diabetes prevalence through the year 2030 in the Japanese adult population.

Materials and Methods: In the present meta-regression analysis, we included 161,087 adults from six studies and nine national health surveys carried out between 1988 and 2011 in Japan. We assessed the prevalence of diabetes using a recorded history of diabetes or, for the population of individuals without known diabetes, either a glycated hemoglobin level of ≥6.5% (48 mmol/mol) or the 1999 World Health Organization criteria (i.e., a fasting plasma glucose level of ≥126 mg/dL and/or 2-h glucose level of ≥200 mg/dL in the 75-g oral glucose tolerance test).

Results: For both sexes, prevalence appeared to remain unchanged over the years in all age categories except for men aged 70 years or older, in whom a significant increase in prevalence with time was observed. Age-standardized diabetes prevalence estimates based on the Japanese population of the corresponding year showed marked increasing trends: diabetes prevalence was 6.1% among women (95% confidence interval [CI] 5.5–6.7), 9.9% (95% CI 9.2–10.6) among men, and 7.9% (95% CI 7.5–8.4) among the total population in 2010, and was expected to rise by 2030 to 6.7% (95% CI 5.2–9.2), 13.1% (95% CI 10.9–16.7) and 9.8% (95% CI 8.5–12.0), respectively. In contrast, the age-standardized diabetes prevalence using a fixed population appeared to remain unchanged.

Conclusions: This large-scale meta-regression analysis shows that a substantial increase in diabetes prevalence is expected in Japan during the next few decades, mainly as a result of the aging of the adult population.

INTRODUCTION

Japan's aging rate is currently the highest in the world[1]. Population aging is a major public health concern globally because of the substantial burden that aging-associated diseases place on society. Diabetes mellitus is one of the most common aging-associated diseases affecting the adult population worldwide. Its repercussions on health are numerous: macrovascular and microvascular complications, liver disease, cognitive decline, increased susceptibility to infection, reduced life expectancy, as well as impaired quality of life, among others[2]. A growing body of evidence suggests that diabetes might also be associated with the development of various types of cancer[3–5]. Furthermore, a recent report from the International Diabetes Federation shows

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that approximately 4.5 million deaths in 2011 could be attributed to diabetes, representing more than 8% of global all-cause mortality[6]. Type 2 diabetes, which accounts for most cases of diabetes, is highly dependent on modifiable risk factors, such as unhealthy eating habits, obesity and lack of physical activity. A large proportion of diabetes cases are therefore considered preventable, and controlled trials have confirmed this in Japan and elsewhere[7–9].

The availability of trends data in diabetes prevalence is thus critical to helping policy makers and healthcare providers both measure the extent of the problem and implement appropriate measures to halt its spread[10]. Although global estimates are valuable in alerting the international community to the ongoing diabetes epidemic, they might fail to provide accurate information at the specific country level. Indeed, estimates of the prevalence of diabetes in the Japanese population in recent international studies differ quite substantially[11–14]. This discrepancy could be partly attributed to the diversity of methods and data used to produce them. In 2009, an International Expert Committee recommended the use of glycated hemoglobin (HbA1c) with a threshold of ≥6.5% (48 mmol/mol) to diagnose diabetes[15]. The American Diabetes Association, World Health Organization and Japan Diabetes Society (JDS) used this criterion in 2010, 2011 and 2010, respectively[16–18]. Nevertheless, relatively few studies have reported estimates of diabetes prevalence using this new criterion at a national level[19,20].

In the present study, we aimed to estimate age- and sex-specific trends, and projections of diabetes prevalence through the year 2030 using the most recently adopted diagnostic criteria, and to examine the impact of population aging on trends in diabetes prevalence in Japan, the most rapidly aging society in the world. To accomplish these objectives, we carried out a meta-regression analysis of the results of studies conducted during the past two decades in Japan.

METHODS

Criteria for the Definition of Diabetes

To estimate the frequency of diabetes, the JDS recommends the use of either HbA1c of ≥6.5%[21] (48 mmol/mol[22]) or 2-h plasma glucose of ≥200 mg/dL in a 75-g oral glucose tolerance test (OGTT)[18]. The use of either of these is particularly important in the Japanese population, because screening for a fasting plasma glucose (FPG) level of ≥126 mg/dL alone could miss a substantial proportion of previously undiagnosed cases of diabetes[23]. We therefore included studies that used any of the following standard diagnostic criteria: (i) HbA1c level of ≥6.5% (48 mmol/mol); or (ii) the 1999 World Health Organization criteria (i.e., FPG level of ≥126 mg/dL and/or OGTT 2-h glucose level of ≥200 mg/dL)[24]. Consistent with the JDS recommendations[18], studies that reported a FPG level ≥126 mg/dL, casual glucose level, or self-report of diabetes diagnosis or treatment were also included, provided they also reported the standard HbA1c or 2-h glucose diagnostic criterion. HbA1c values are presented as percentage units, in accordance with the National Glycohemoglobin Standardization Program, and in mmol/mol, as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine[22].

Study Population and Data Collection

We searched the MEDLINE, EMBASE and *Ichushi* (*Japana Centra Revuo Medicina*) databases through March 2013[25]. Two investigators (AG and MG) selected studies that were carried out in the Japanese population, and that evaluated the prevalence of diabetes using either of the aforementioned diagnostic criteria. The MEDLINE search terms were 'Prevalence' (MeSH terms) AND ('diabetes mellitus' [MeSH:noExp] OR 'diabetes mellitus, type 2'[MeSH terms]) AND ('Japan' [MeSH terms] OR 'Japan' [all fields]). Similar search terms were used to search the EMBASE and *Ichushi* databases. The search was limited to studies on adult human subjects with no restriction on language. A manual search was also carried out to identify pertinent data sources from the references of the identified studies. When data necessary for estimating sex- and age-specific (10-year groups) diabetes prevalence estimates were missing, authors were contacted and asked if they could provide the missing information.

Initially, we identified 613 relevant articles. On the basis of the titles and abstracts, 51 articles were considered potentially eligible, and the entire texts of these 51 articles were reviewed. We excluded 20 studies that did not use the standard diagnostic criteria, nine duplicate studies, seven studies that did not report diabetes prevalence and five reviews, editorials or letters to the editor. We further excluded four studies in which sex- and age-specific diabetes prevalence was not available[26–29]. SX (investigator) of the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Asia study[30] coordinated by TN, QQ and JT provided information from three studies (Hisayama Study[31], Funagata Study[32] and Ojika Study[33]). One article[34] provided prevalence estimates for a subset of the study population of the Japan Public Health Center-based Prospective Study Diabetes Study (JPHC Diabetes Study)[35]; MN and ST (investigators) of the JPHC Diabetes Study provided information on the total population for the present study. YH, YA and HS (investigators) of the Toranomon Hospital Health Management Center Study[36], and Machiko Inoue (investigator) of the Yuport Medical Checkup Center Study provided information for the present study[37]. One article[38] provided results from the National Survey on Circulatory Disorders in 1990[39]. Furthermore, we retrieved an additional eight national health surveys[20,40–46]. The study identification process is summarized in Figure S1 of the supplementary material.

For each selected study, we extracted the year of publication, year(s) when data were collected, central year of data collection, definition of diabetes, and the total number of participants and cases of diabetes by 10-year age group and sex. The central year was estimated as the mean between the starting and ending years of data collection. This sometimes resulted in non-integer years, but this did not constitute a problem, as year was

considered a continuous variable in the meta-regression analysis.

Statistical Analysis

In the first step, the sex- and 10-year age-specific diabetes prevalence was estimated by meta-analysis. Prevalence estimates from each study were transformed on the logistic link function (or logit) scale and the corresponding variances were obtained by the Delta method[47]. A random effect meta-analysis was then carried out[48]. The impact of heterogeneity was measured by means of the I^2 statistic, which describes the proportion of total variation in estimates that is as a result of heterogeneity between studies[49]. In the second step, trends in diabetes prevalence were assessed through linear random effect meta-regression[50] of the transformed prevalence estimates using year of assessment as the independent variable. Predicted prevalence estimates for a particular year were obtained on the logit scale by using the estimated parameters of the linear regression model and then transforming back to the prevalence scale using the inverse logistic link (or expit) function. Corresponding variance estimates were computed from the covariance matrix of the model using the Delta method. A sensitivity analysis was carried out by repeating the meta-analysis and meta-regression steps with the exclusion of: (i) studies using both HbA1c and OGTT for diabetes diagnosis; and (ii) studies carried out in a single center.

Sex-specific age-standardized estimates of the prevalence of diabetes in the adult Japanese population (age 20 years or older) for a given year were obtained using the direct standardization method. We estimated the age-standardized estimates using the Japanese population distribution of the corresponding year, year 2010[51,52] and year 2030[53], and the world population distribution of the corresponding year, year 2010 and year 2030[54] as standardization populations. We computed the sum of the 10-year age-specific prevalence estimates weighted by the proportion of the population in the corresponding age category. Confidence intervals of the predicted age-standardized prevalence estimates were obtained by simulation. More precisely, we constructed an empirical diabetes prevalence distribution for each year of interest by sampling 20,000 times from the distribution of the model parameters and calculating the corresponding age-standardized prevalence estimates. Confidence intervals were then obtained by taking the 2.5 and 97.5 percentiles of the resulting empirical diabetes prevalence distribution. The estimated number of cases of diabetes was obtained by multiplying the age-standardized prevalence values by the adult Japanese population estimates.

Projections of the sex- and age-specific prevalence of diabetes until 2030 were calculated using population distribution projections[53,54] under the assumption that the trends in prevalence identified in the meta-regression would remain the same in the next decades. The aforementioned procedure was used to compute projected sex-specific age-standardized diabetes prevalence as well as the corresponding confidence intervals. It should be noted that these confidence intervals do not take into account the uncertainty in projected population estimates.

All analyses were carried out with R statistical software version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria)[55].

RESULTS

In the present analysis, we included a total of six studies and nine national health surveys providing diabetes prevalence estimates for 161,087 individuals (75,250 men and 85,837 women) from 1988 to 2011. Four studies were population-based[31–33,35], two were carried out at single centers[36,37] and nine were national health surveys[20,39–46]. Three studies defined diabetes using OGTT[31–33], whereas 12 used HbA1c[20,35–37,39–46]. Ignoring the effect of age and year of assessment, the overall observed prevalence was 11.5% (8,681 cases) for men and 6.9% (5,925 cases) for women. Details of the studies' characteristics are summarized in Table 1.

Age- and sex-specific estimates showed that the prevalence of diabetes increased with age for both sexes and was higher among men than women in all age categories between 1990 and 2010 (Table 2, Figure S2–S3). For both sexes, the prevalence of diabetes appeared to remain unchanged over the years in all age categories, except for men aged 70 years or older, in whom a significantly increasing trend in diabetes prevalence over time was observed (Tables 2 and S1). Trends in the age-standardized prevalence using the Japanese population of the corresponding year as a standardization population showed an increase among both sexes, which was slightly greater among men (22%) than women (14%), from 1990 to 2010. Diabetes prevalence was 8.1% among men, 5.3% among women and 6.6% among the total population in 1990, and rose to 9.9, 6.1 and 7.9% in 2010, respectively (Table 3). In contrast, the age-standardized prevalence using a fixed population (2010 Japanese, 2010 world, 2030 Japanese or 2030 world population) appeared to remain unchanged over the years, suggesting that population aging is the main factor influencing trends in diabetes prevalence in the Japanese adult population. The age-standardized diabetes prevalence using the 2010 Japanese population as a standardization population was 9.3% among men, 6.6% among women and 7.9% among the total population in 1990, and 9.9, 6.1 and 7.9% in 2010, respectively (Table 3).

Projected age- and sex-specific estimates showed that the prevalence of diabetes might increase with age among men and women, and should be higher among men than women in all age categories between 2015 and 2030 (Table 4). In both sexes, there appeared to be slight decreasing trends in the projected age- and sex-specific diabetes prevalence for individuals in the first four younger age categories (Table 4); however, these decreasing trends were not statistically significant (Table S1). For men aged 70 years or older, it is projected that there should be a significant increasing trend in diabetes prevalence with time (Table 4, Table S1). A further increase in the age-

Table 1 | Characteristics of studies included in the analysis

Study	Year(s) carried out	Source of participants	Definition of diabetes	Men		Women		Age range (years)
				Total *n*	No. cases	Total *n*	No. cases	
Hisayama Study[31]	1988	Population-based, Hisayama Town, Fukuoka	FPG ≥126 mg/dL and/or OGTT 2-h glucose ≥200 mg/dL and/or self-reported diagnosis	1,073	196	1,407	149	≥40
Funagata Study[32]	1990–1992	Population-based, Funagata Town, Yamagata	FPG ≥126 mg/dL and/or OGTT 2-h glucose ≥200 mg/dL and/or self-reported diagnosis	1,160	109	1,485	157	≥40
Ojika Study[33]	1991	Population-based, Ojika Town, Nagasaki	FPG ≥126 mg/dL and/or OGTT 2-h glucose ≥200 mg/dL and/or self-reported diagnosis	554	51	817	48	≥30
JPHC[35]	1998–1999	Population-based, 10 areas in Japan	HbA1c ≥6.5% (48 mmol/mol) and/or FPG ≥126 mg/dL and/or casual glucose ≥200 mg/dL and/or self-reported diagnosis	4,947	654	8,884	640	≥40
	2000			5,338	778	9,095	693	≥50
	2003–2004			4,219	748	6,773	720	≥50
	2005			3,460	539	5,855	599	≥50
Yuport Medical Checkup Center Study[37]	1998–2006	Single center, Tokyo	HbA1c ≥6.5% (48 mmol/mol) and/or FPG ≥126 mg/dL and/or self-reported diagnosis	17,100	1,620	17,200	735	≥20
TOPICS[36]	2002–2007	Single center, Tokyo	HbA1c ≥6.5% (48 mmol/mol) and/or FPG ≥126 mg/dL and/or self-reported diagnosis	19,506	1,682	8,374	292	≥20
National Survey on Circulatory Disorders[39]	1990	Randomly selected from the overall Japanese population	HbA1c ≥6.5% (48 mmol/mol) and/or casual glucose ≥200 mg/dL and/or self-reported diagnosis	3,403	404	4,660	292	≥30
National Diabetes Survey[40]	1997	Randomly selected from the overall Japanese population	HbA1c ≥6.5% (48 mmol/mol) and/or self-reported diabetes treatment	2,403	237	3,656	260	≥20
National Diabetes Survey[41]	2002			2,150	275	3,196	207	20+
NHNS-J[42]	2006	Randomly selected from the overall Japanese population	HbA1c ≥6.5% (48 mmol/mol) and/or self-reported diabetes treatment	1,744	214	2,552	209	≥20
[43]	2007			1,619	247	2,384	173	≥20
[44]	2008			1,813	211	2,621	168	≥20
[45]	2009			1,730	226	2,543	217	≥20
[46]	2010			1,589	264	2,268	208	≥20
[20]	2011			1,442	226	2,067	158	≥20
Total				75,250	8,681	85,837	5,925	

2-h post-load glucose level after oral glucose tolerance test; FPG, fasting plasma glucose level; HbA1c, glycated hemoglobin; JPHC, Japan Public Health Center-based Prospective Study; NHNS-J, National Health and Nutrition Survey in Japan; OGTT 2-hour glucose; TOPICS, the Toranomon Hospital Health Management Center Study; Japan National Diabetes Survey.

Table 2 | Estimated age- and sex-specific diabetes prevalence (%) in the Japanese population 1990–2010

Sex	Year	Age category (years)					
		20–29	30–39	40–49	50–59	60–69	≥70
Men	1990	0.99 (0.15–6.23)	2.87 (1.98–4.14)	7.71 (6.19–9.57)	14.17 (11.84–16.87)	14.62 (12.46–17.09)	14.52 (12.11–17.31)
	1995	0.93 (0.27–3.15)	2.52 (1.97–3.23)	7.11 (6.08–8.30)	13.60 (12.00–15.37)	15.37 (13.77–17.13)	15.79 (13.94–17.84)
	2000	0.87 (0.44–1.71)	2.21 (1.89–2.60)	6.55 (5.77–7.42)	13.05 (11.90–14.29)	16.15 (14.93–17.45)	17.15 (15.74–18.63)
	2005	0.81 (0.46–1.45)	1.94 (1.63–2.32)	6.04 (5.18–7.01)	12.51 (11.27–13.88)	16.96 (15.59–18.42)	18.59 (17.10–20.19)
	2010	0.76 (0.26–2.17)	1.71 (1.29–2.26)	5.56 (4.48–6.87)	12.00 (10.29–13.95)	17.81 (15.79–20.03)	20.13 (17.87–22.60)
Women	1990	0.79 (0.18–3.43)	1.45 (0.63–3.29)	3.51 (2.17–5.62)	7.05 (5.40–9.18)	10.25 (8.14–12.86)	12.30 (10.10–14.91)
	1995	0.74 (0.27–1.98)	1.24 (0.69–2.24)	3.19 (2.26–4.49)	6.64 (5.50–8.01)	10.35 (8.79–12.14)	12.26 (10.67–14.04)
	2000	0.69 (0.37–1.26)	1.06 (0.69–1.63)	2.91 (2.20–3.82)	6.26 (5.43–7.20)	10.45 (9.27–11.77)	12.21 (11.07–13.45)
	2005	0.64 (0.37–1.11)	0.91 (0.59–1.40)	2.64 (1.92–3.62)	5.90 (5.02–6.92)	10.55 (9.26–12.04)	12.17 (10.98–13.46)
	2010	0.59 (0.24–1.46)	0.78 (0.43–1.41)	2.40 (1.55–3.72)	5.56 (4.41–6.98)	10.65 (8.84–12.79)	12.12 (10.46–14.00)

Data are point estimates (95% confidence intervals) of prevalence.

Table 3 | Estimated age-standardized diabetes prevalence in the Japanese population 1990–2010

Sex	Year	Standardization population						
		Japanese population of the corresponding year		World population of the corresponding year	2010 Japanese population	2010 world population	2030 Japanese population	2030 world population
			No. cases (×1,000)					
Men	1990	8.06 (7.38–9.31)	3,546	6.25 (5.65–7.96)	9.30 (8.57–10.43)	6.84 (6.22–8.36)	10.32 (9.46–11.50)	7.78 (7.13–9.09)
	1995	8.22 (7.73–8.90)	3,858	6.16 (5.75–6.93)	9.39 (8.85–10.06)	6.69 (6.26–7.42)	10.52 (9.89–11.28)	7.71 (7.25–8.38)
	2000	8.65 (8.29–9.08)	4,222	6.19 (5.90–6.56)	9.51 (9.11–9.95)	6.57 (6.27–6.95)	10.76 (10.29–11.29)	7.66 (7.33–8.05)
	2005	9.21 (8.79–9.67)	4,599	6.31 (6.00–6.68)	9.67 (9.23–10.15)	6.49 (6.17–6.87)	11.05 (10.53–11.61)	7.65 (7.29–8.05)
	2010	9.86 (9.24–10.60)	4,988	6.43 (5.99–7.04)	9.86 (9.24–10.60)	6.43 (5.99–7.04)	11.38 (10.63–12.24)	7.67 (7.17–8.30)
Women	1990	5.31 (4.72–6.26)	2,498	4.05 (3.55–5.09)	6.57 (5.86–7.56)	4.32 (3.80-5.32)	7.53 (6.68–8.65)	5.08 (4.51–6.04)
	1995	5.40 (4.96–5.97)	2,701	3.89 (3.54–4.45)	6.42 (5.91–7.06)	4.15 (3.78–4.70)	7.39 (6.78–8.13)	4.92 (4.51–5.47)
	2000	5.59 (5.25–5.98)	2,913	3.80 (3.55–4.14)	6.29 (5.91–6.73)	3.99 (3.72–4.33)	7.27 (6.82–7.77)	4.76 (4.47–5.13)
	2005	5.81 (5.44–6.24)	3,116	3.75 (3.48–4.08)	6.17 (5.77–6.63)	3.84 (3.57–4.19)	7.15 (6.68–7.69)	4.62 (4.32–5.00)
	2010	6.06 (5.53–6.72)	3,307	3.71 (3.36–4.21)	6.06 (5.53–6.72)	3.71 (3.36–4.21)	7.04 (6.40–7.82)	4.50 (4.09–5.04)
Total	1990	6.64 (6.21–7.45)	6,044	5.14 (4.77–6.17)	7.88 (7.39–8.66)	5.57 (5.19–6.51)	8.86 (8.28–9.70)	6.43 (6.02–7.27)
	1995	6.76 (6.45–7.22)	6,558	5.02 (4.76–5.50)	7.85 (7.49–8.32)	5.41 (5.14–5.88)	8.88 (8.45–9.42)	6.31 (6.01–6.76)
	2000	7.07 (6.83–7.36)	7,135	4.99 (4.80–5.24)	7.84 (7.57–8.15)	5.27 (5.08–5.53)	8.93 (8.61–9.30)	6.21 (5.99–6.48)
	2005	7.45 (7.17–7.77)	7,715	5.02 (4.82–5.27)	7.85 (7.56–8.19)	5.16 (4.95–5.42)	9.01 (8.66–9.40)	6.13 (5.90–6.41)
	2010	7.89 (7.49–8.39)	8,295	5.06 (4.80–5.47)	7.89 (7.49–8.39)	5.06 (4.79–5.47)	9.11 (8.62–9.69)	6.08 (5.76–6.50)

Data are point estimates (95% confidence intervals) of prevalence.

standardized prevalence using the Japanese population of the corresponding year is projected during 2010 to 2030, if the trend observed remains similar, namely an increase of 33% for men and 10% for women (Table 5). In women, it is probable that this trend is mainly a result of the aging of the population, because age-specific prevalence estimates remained constant: the proportion of women aged 70 years or older is expected to increase from 23% in 2010 to 33% in 2030, whereas the proportion of women aged less than 40 years is expected to decrease from 29% in 2010 to 22% in 2030. For men, it appears that the increasing trend in diabetes prevalence is a result of the combined effect of the aging of the population (17% of men aged 70 or older in 2010 vs 26% in 2030) and the increase in the age-specific diabetes prevalence in the older age categories. The overall prevalence of diabetes in the Japanese adult population is expected to rise from 7.9% (representing about 8.3 million people with diabetes) in 2010 to 9.8% (9.7 million people with diabetes) in 2030. In contrast, the projected age-standardized diabetes prevalence using a fixed population (2010 Japanese, 2010 world, 2030 Japanese or 2030 world population) as a standardization population appeared to remain stable between 2015 and 2030 (Table 5).