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LETTER TO THE EDITOR

Temporal relationship between multiple drugs and multiple events in patient reports on adverse drug reactions: findings in a pilot study in Japan

To the Editor

Patient reporting of suspected adverse drug reactions (ADRs) has been accepted as an essential component of pharmacovigilance.[1,2] Important signals may be detected when combined with reports from health care professionals (HCPs)[3] but also from "patient-only" dataset.[4]

In January 2011, the Health and Labour Sciences Research Grant study ("HLSRG study") supported by the Ministry of Health, Labour and Welfare (MHLW) started a pilot study to determine whether the web-based patient reporting works in Japan. The online patient report form was linked from the main page of Pharmaceuticals and Medical Devices Agency (PMDA). To call for patient reports, a message was shown on the PMDA website and in 955 (1.7%) of about 55 000 community pharmacies, 1000 posters were displayed and 100 000 flyers were handed to patients. The study was approved by the Research Ethics Committee of Faculty of Pharmacy, Keio University.

In an interim analysis of the data collected during the first 2 months of the study, we found patients sometimes reported multiple drugs and multiple ADRs occurring at different occasions. It was often very difficult to specify the temporal relationship between the exposure to drugs and occurrence of ADRs. To improve the clarity of the temporal relationship, a revised form with multiple entry boxes for dates of ADR occurrence was used in the latter half of the study (see online Figure 1). At the end of the study, we conducted an ad hoc analysis to know whether the revised form worked as intended.

The drugs were classified by the anatomical therapeutic chemical (ATC) classification. ADRs were coded by Japanese translation of lowest level terms of the medical dictionary for regulatory activities (MedDRA) version 14.0J and converted to preferred terms (PTs) by two of authors (AH and KK) and then further checked independently by each of two psychiatric specialists (AI and TK) because many of reported ADRs were classified under the primary systemic organ class (SOC) "nervous" or "psychiatry". The temporal relationship was classified into "clear" (clear for all drug–event combinations), "clear/unclear" (clear for some but unclear for the other combinations) and "unclear" (unclear for all combinations) also by these two specialists. Any discrepancy between two specialists was resolved by discussion.

We also analyzed the spontaneous reports submitted by HCPs directly or through the drug company to the PMDA ("HCP reports") and reports submitted by the "consumer or other non-health professional" through the drug company ("indirect patient reports") during the same period using Japanese Adverse Drug Event Report database (http://www.info.pmda.go.jp/) and compared with "direct patient reports" in the HLSRG study.

Table 1 shows standardized differences[5] for demographic and other characteristics between a total of 214 direct patient reports with at least one identifiable drug and one identifiable ADR and 657 indirect patient reports as well as 34 843 HCP reports submitted to the PMDA between January and December 2011. In direct patient reports, median age of patients was 40 years old and much younger than "60's" in other two report types. There was a difference of ADRs and drugs frequently reported between three reporter types. The 214 reports were submitted by 166 (78%) patients and 48 (22%) family members, and 16 (7%) reports had one or more over-the-counter drugs.

As shown in Table 2, during the latter half of the study period where the revised form was used, two or more dates for ADR occurrence were often reported. The ratio of the odds of the clarity ("clear" vs. others ("clear/unclear" or "unclear")) in the latter half of the study period (51/3) to the odds in the first half (110/50) was 7.7 (95% CI:2.3–26.0). The logistic regression revealed that the "odds ratio" was 9.8 (95%CI:2.5–38.1) when adjusted for age and sex of reporters and other potentially relevant factors indicating that the revised form improved the clarity of the temporal relationship. The number of reports in the first to fourth quarter during the one-year study period was 108, 52, 30 and 24, respectively. This decrease was potentially because patients who used the internet regularly to avidly collect the information of ADRs tended to discover that the pilot study was in place and report ADRs they experienced early in the study period.

Table 1. Demographics, drugs and adverse drug reactions in spontaneous reports

Reporter type	Direct patient reports	Indirect patient reports	HCP reports	Standardized difference[†]
Period January 2011 – December 2011				
Number of reports	214	657	34,843	
Demographics of patients				
Sex, unknown (%)	0 (0)	29 (4.4)	719 (2.1)	−0.30, −0.21
Females (%)	111 (51.9)	340 (51.8)	16,997 (48.8)	0.002, 0.06
Age, unknown (%)	5 (2.3)	353 (53.7)	1,581 (4.5)	−1.40, −0.12
Median age (IQR)[‡]	40 (30, 55)	60s (40s, 70s)	60s (40s, 70s)	−0.81, −0.67
Median number per report				
ADRs (IQR)	3 (1, 5)	1 (1, 2)	1 (1, 2)	0.60, 0.63
Drugs (IQR)	2 (1, 5)	1 (1, 2)	4 (2, 8)	0.62, −0.39
Number of reports on ADR coded by a MedDRA PT with a specific primary SOC*				
Blood (%)	1 (0.5)	8 (1.2)	4,257 (12.2)	−0.08, −0.50
Eye (%)	24 (11.2)	51 (7.8)	632 (1.8)	0.12, 0.39
Gastrointestinal (%)	65 (30.4)	113 (17.2)	4,809 (13.8)	0.31, 0.41
General (%)	69 (32.2)	96 (14.6)	3,264 (9.4)	0.43, 0.59
Infections (%)	5 (2.3)	32 (4.9)	4,960 (14.2)	−0.14, −0.44
Investigations (%)	18 (8.4)	93 (14.2)	7,560 (21.7)	−0.18, −0.38
Musculoskeletal (%)	22 (10.3)	56 (8.5)	1,392 (4.0)	0.06, 0.25
Nervous (%)	91 (42.5)	212 (32.3)	5,545 (15.9)	0.21, 0.61
Psychiatric (%)	50 (23.4)	109 (16.6)	1,200 (3.4)	0.17, 0.61
Number of reports on suspect drug in a specific level-2 subgroup of ATC classification*				
Insulins (H04) (%)	0 (0)	33 (5.0)	83 (0.2)	−0.33, −0.07
Antibacterials (J01) (%)	8 (3.7)	27 (4.1)	3,075 (8.8)	−0.02,−0.21
Antivirals (J05) (%)	6 (2.8)	20 (3.0)	2,582 (7.4)	−0.01, −0.21
Vaccines (J07) (%)	4 (1.9)	33 (5.0)	1,478 (4.2)	−0.17, −0.14
Antineoplastic (L01) (%)	1 (0.5)	37 (5.6)	11,999 (34.4)	−0.30, −1.00
Psycholeptics (N05) (%)	41 (19.2)	87 (13.2)	1949 (5.6)	0.16, 0.42
Psychoanaleptics (N06) (%)	30 (14.0)	46 (7.0)	972 (2.8)	0.23, 0.41
Ophthalmologicals (S01) (%)	1 (0.5)	22 (3.3)	1982 (5.7)	−0.21, −0.31

IQR=interquartile range; ADR=adverse drug reaction; MedDRA=medical dictionary for regulatory activities; PT=preferred term; SOC=system organ class; ATC= anatomic therapeutic chemical.
*Data are shown when (i) proportion of reports >10% (SOCs) or >5% (ATC level-2 subgroups) in any reporter type and (ii) ratio of proportions >2 between any two of three reporter types.
[†]Standardized difference between direct and indirect patient reports (left) and that between direct patient and HCP reports (right).
[‡]When the information on age group was given (as for all the cases in indirect patient and HCP reports), middle point (e.g. 64 years for 60s) was used to calculate the standardized mean difference.

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Table 2. Before/after comparison of direct patient reports related to change of web-form design in early July 2011

Period	2011.01-06 (Single section for ADR *)			2011.07-12 (Single/multiple section for ADR †)		
	Psychotropic drug (N05/N06 ‡)			Psychotropic drug (N05/N06 ‡)		
	Yes	No	Total	Yes	No	Total
Number of reports	71 (44%)	89 (56%)	160 (100%)	21 (39%)	33 (61%)	54 (100%)
p-value§	Reference			0.53		
Median number of drugs per report						
All drugs (IQR)	4 (3, 7)	1 (1, 3)	2 (1, 5)	3 (2, 8)	2 (1, 4)	2 (1, 4)
p-value¶	Reference	Reference	Reference	0.48	0.50	0.76
p-value‖	<0.0001	Reference		0.023	Reference	
Psychotropic drug (N05/N06‡) (IQR)	3 (1, 5)	-	0 (0, 3)	2 (1, 4)	-	0 (0, 1.75)
p-value¶	Reference	-	Reference	0.26	-	0.32
Median number of ADRs per report						
All ADRs (IQR)	4 (2,7.5)	2 (1, 4)	3 (1,5)	4 (1, 5)	1 (1,3)	2 (1, 4)
p-value¶	Reference	Reference	Reference	0.29	0.05	0.03
p-value‖	<0.0001	Reference		0.054	Reference	
Psychiatric/Nervous ADRs						
ADRs (IQR)	2 (1, 4)	0 (0, 1)	1 (0, 2)	1 (0, 3)	0 (0, 0)	0 (0, 1)
p-value¶	Reference	Reference	Reference	0.07	0.07	0.01
Median number of dates of ADR occurrence per report						
Number (IQR)	1 (1, 1)	1 (1, 1)	1 (1, 1)	2 (1, 4)	1 (1, 2)	1 (1, 2)
p-value¶	Reference	Reference	Reference	<0.0001	<0.0001	<0.0001
Period from the first occurrence to reporting of ADRs						
Unknown (n)	5	6	11	2	1	3
Known (n)	66	83	149	19	32	51
Median months (IQR)	23 (9, 62)	6 (1, 14)	10 (2, 38)	15 (3, 19)	1 (1, 10)	4 (1, 17)
p-value¶	Reference	Reference	Reference	0.09	0.27	0.06
p-value‖	<0.0001	Reference		0.016	Reference	
Number of reports classified by the clarity of the temporal relationship between exposures to drugs and ADR occurrences						
"clear"††	37	73	110	20	31	51
"clear/unclear"††	21	11	32	0	2	2
"unclear"††	13	5	18	1	0	1
p-value**	Reference	Reference	Reference	0.0005	0.31	0.0003

ADR=adverse drug reaction; IQR=interquartile range.

*A web-based report form with a single section for ADRs occurring on a single occasion was used.

†A web-based report form where the number of sections can be increased to report ADRs occurring on multiple occasions was used.

‡Reports with a drugs classified under N05 or N06 level-2 subgroups of ATC classification (defined as a psychotropic drug) was given in a report either as a suspect or concurrent drug.

§Comparison between first and latter halves of the pilot period (chi-square test).

¶Comparison between first and latter halves of the pilot period (Kruskal–Wallis test).

‖Comparison between reports with and those without a psychotropic drug as suspect or concurrent drug (Kruskal–Wallis test).

**Comparison between first and latter halves of the pilot study (Fisher's exact test).

††The temporal relationship between exposure to drug and event occurrence was clear for all the drug–event combinations ("clear"), clear for some but unclear for the other combinations ("clear/unclear") or unclear for all the combinations ("unclear").

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The pilot study has revealed a scheme of the web-based patient reports works in Japan and contributed to the nationwide online scheme started by the PMDA in March 2012. The postal form or telephone, known to be preferred by the elderly, [2] may be considered as an additional tool in Japan to encourage reports from elderly patients in the future.

CONFLICT OF INTEREST

This study is supported by the MHLW, and the manuscript was on patient reports in general but not on any specific products. Authors do not have any financial and personal relationship that might bias the work as given in the Conflict of Interest form prepared by each of all the co-authors. The study sponsor (MHLW) did not influence in any of the processes of the study design, collection, analysis and interpretation of data, writing of the report and the decision to submit the report.

KEY POINTS

- In Japan, the nationwide online scheme for patient reports was initiated in March 2012 following a pilot study.
- In the pilot study, patients often reported multiple drugs and multiple events occurring at different time points, and in the middle of the study, the report form was revised to inquire multiple dates of ADR occurrence.
- The median age of patients was young (40 years old) and the use of the postal form or telephone may be considered as an additional tool to encourage reports from the elderly in the future.

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SUPPORTING INFORMATION

Supporting information may be found in the online version of this paper:

Figure 1. Initial patient report form (Figure 1A) used in the first half and revised patient report form (Figure 1B) used in the latter half of the study period (translated into English). The number of entry boxes for dates of occurrence of adverse drug reaction (ADR) in Question 2 was increased from 1 in the initial patient report form (Figure 1A-c) to 5 or more in the revised patient report form (Figure 1B-c). Question 3 was also revised according to the change of Question 2 (see Figures 1A-d and 1B-d). Some alteration was also made for Question 4 in the revised patient report form (see Figures 1A-e and B-e)

REFERENCES

1. van Hunsel F, Talsma A, van Puijenbroek E, *et al.* The proportion of patient reports of suspected ADRs to signal detection in the Netherlands: case-control study. *Pharmacoepidemiol Drug Saf* 2011; **20**:286–291. DOI: 10.1002/pds.2092
2. McLernon DJ, Bond CM, Lee AJ *et al.* Patient views and experiences of making adverse drug reaction reports to the Yellow Card Scheme in the UK. *Pharmacoepidemiol Drug Saf* 2011; **20**: 523–531. DOI: 10.1002/pds.2117
3. Hammond IW, Rich DS, Gibbs TG. Effect of consumer reporting on signal detection: using disproportionality analysis. *Expert Opin Drug Saf* 2007; **6**: 705–712. DOI:10.1517/14740338.6.6.705
4. Avery AJ, Anderson C, Bond CM, *et al.* Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess* 2011; **15**: 1–234. DOI: 10.3310/hta15200
5. Austin PC, Mamdani M. A comparison of propensity score methods: A case-study estimating the effectiveness of post-AMI statin use. *Stats Med* 2006; **25**: 2084–2106. DOI: 10.1002/sim.2328

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Incidence of Type 2 Diabetes in Japan: A Systematic Review and Meta-Analysis

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Abstract

Background: The definition of incident type 2 diabetes varies across studies; hence, the actual incidence of type 2 diabetes in Japan is unclear. Here, we reviewed the various definitions of incident type 2 diabetes used in previous epidemiologic studies and estimated the diabetes incidence rate in Japan.

Methods: We searched for related literature in the MEDLINE, EMBASE, and *Ichushi* databases through September 2012. Two reviewers selected studies that evaluated incident type 2 diabetes in the Japanese population.

Results: From 1824 relevant articles, we included 33 studies with 386,803 participants. The follow-up period ranged from 2.3 to 14 years and the studies were initiated between 1980 and 2003. The random-effects model indicated that the pooled incidence rate of diabetes was 8.8 (95% confidence interval, 7.4–10.4) per 1000 person-years. We observed a high degree of heterogeneity in the results (I^2 = 99.2%; $p < 0.001$), with incidence rates ranging from 2.3 to 52.6 per 1000 person-years. Three studies based their definition of incident type 2 diabetes on self-reports only, 10 on laboratory data only, and 20 on self-reports and laboratory data. Compared with studies defining diabetes using laboratory data (n = 30; pooled incidence rate = 9.6; 95% confidence interval = 8.3–11.1), studies based on self-reports alone tended to show a lower incidence rate (n = 3; pooled incidence rate = 4.0; 95% confidence interval = 3.2–5.0; p for interaction < 0.001). However, stratified analyses could not entirely explain the heterogeneity in the results.

Conclusions: Our systematic review and meta-analysis indicated the presence of a high degree of heterogeneity, which suggests that there is a considerable amount of uncertainty regarding the incidence of type 2 diabetes in Japan. They also suggested that laboratory data may be important for the accurate estimation of the incidence of type 2 diabetes.

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Introduction

The prevalence of type 2 diabetes is increasing globally and the International Diabetes Federation has predicted that the number of people with diabetes will increase from 366 million to 552 million by 2030 [1]. Importantly, the prevalence of diabetes in Asia is rapidly increasing as 60% of the world's diabetic population are Asians [2]. In Japan, the estimated number of individuals with diabetes was approximately 6.9 million in 1997 [3], 7.4 million in 2002 [4], and 8.9 million in 2007 [5]. Although the estimates of the prevalence of diabetes have been computed from the National Health and Nutrition Survey of Japan, the incidence rate of type 2 diabetes in Japan has not been fully clarified. Furthermore, the definition of incident type 2 diabetes varies across studies. Changes in the diagnostic criteria for diabetes may account for these discrepancies [6–8]. The American Diabetes Association (ADA), World Health Organization (WHO), and Japan Diabetes Society (JDS) lowered the fasting plasma glucose (FPG) threshold from 140 to 126 mg/dL in 1997, 1998, and 1999, respectively [6,8,9]. In 2009, an International Expert Committee recommended the use of HbA1c level (with a threshold of ≥6.5% (48 mmol/mol) [10]) to diagnose diabetes, and the ADA, WHO, and JDS adopted this criterion in 2010, 2011, and 2010, respectively

[11–13]. However, in epidemiologic studies, measuring HbA1c or blood glucose is sometimes difficult for various reasons such as inconvenience or high costs. Therefore, several studies used self-reported diabetes as an outcome if laboratory findings were not available and self-administered questionnaires concerning diabetes history were [14,15]. However, the definition of diabetes diagnosis in epidemiologic studies remains controversial. Therefore, we conducted this systematic review and meta-analysis to estimate the incidence rate of type 2 diabetes in Japan and compile the various definitions of incident type 2 diabetes used in previous epidemiologic studies.

Methods

Search Strategy

This systematic review and meta-analysis did not have a registered review protocol, but was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Group [16]. We searched the MEDLINE, EMBASE, and *Ichushi* (*Japana Centra Revuo Medicina*) databases through September 2012. Two reviewers selected studies that evaluated newly diagnosed type 2 diabetes among the Japanese population. The MEDLINE search terms were ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "type 2 diabetes"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields] OR "incidence"[MeSH Terms] OR "incidence"[All Fields]) AND ("Japan"[MeSH Terms] OR "Japan"[All Fields]). Similar search terms were used for searching the EMBASE and *Ichushi* databases. We further searched the references of relevant studies.

Selection

Two independent reviewers read all the retrieved abstracts and titles. The predefined inclusion criteria were as follows: 1) new-onset of type 2 diabetes reported as a study outcome and 2) study on the Japanese population. The full text of studies meeting these criteria was retrieved and screened to determine eligibility, and studies on the same participant groups were excluded. Discrepancies between the reviewers' selection were resolved by discussion.

Data Extraction

The information extracted by 2 investigators (AG and MG) was as follows: study characteristics (authors, design, year of publication, year(s) when the studies were conducted, sample size, and duration of follow-up), participants' characteristics (age and gender), outcome assessment (definition of incident diabetes), analysis strategy, and validity studies (sensitivity, specificity, positive predictive value, and negative predictive value). HbA1c values are presented in percentage units as per the National Glycohemoglobin Standardization Program (NGSP) and in the units (mmol/mol) recommended by International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [17].

Data Synthesis

In studies with sufficient information on incident type 2 diabetes, we calculated the incidence rate per 1,000 person-years by dividing the number of incident diabetes cases by the duration of follow-up. When the mean follow-up duration was not available, the median was used. We used exact methods based on the Poisson distribution to compute the 95% confidence interval (CI) for each study [18]. The incidence rates of included studies were pooled on the log scale using inverse variance weighting and the random-effects model to calculate a pooled diabetes incidence rate and 95% CIs [19]. We assessed statistical heterogeneity of incidence rates across studies using the Cochrane's Q test [20] and I^2 statistic [21]. Potential publication bias was assessed using funnel plots, Begg's test [22], and Egger's test [23]. We also performed stratified analyses according to the definition of incident diabetes (self-report vs. laboratory data), source of subjects (population-based vs. others), areas (nonurban vs. others), mean or median follow-up period (≥ 5 vs. < 5 years), year of study initiation (before the year 2000 vs. in the year 2000 or later), and sample size (≥ 50,000 vs. < 50,000). We computed p values for comparisons between subgroups using the χ^2 test with one degree of freedom. To further explore potential sources of heterogeneity in the results, we conducted meta-regression analyses [24,25] with stratification according to year of study initiation (before the year 2000 vs. in the year 2000 or later). In the meta-regression analyses, we used the following characteristics as covariates: definition of incident diabetes (self-report vs. laboratory data), source of subjects (population-based vs. others), follow-up period (per 5-year increase), sample size (per 10,000 increase), and areas (provincial vs. others). All analyses were performed using Stata version 12.1 (StataCorp, College Station, TX).

Results

Literature Search

Initially, we identified 1824 related articles. Based on the titles and abstracts, 62 articles were considered potentially eligible, and the entire texts of these 62 articles were evaluated. After excluding 8 studies that did not report diabetes incidence, 54 relevant studies were further assessed for their eligibility (Figure 1). Of these 54 studies, 1 study based the ascertainment of incident type 2 diabetes on adverse outcome reports [26], 1 used an overlapping population [27], 3 did not define ascertainment of type 2 diabetes [28–30], 9 were studies on prediabetes populations [31–39], 1 was a study on nonalcoholic liver fatty liver disease patients (n = 1) [40], 2 did not report the follow-up period [41,42], 5 did not report the number of incident diabetes cases [41-45], and 1 did not report the year of study initiation [46]. All these studies were excluded, leaving 33 studies for the meta-analysis.

Study Characteristics

The number of participants, year, and the definition of diabetes diagnosis used in the selected studies are summarized in Table 1 [14,15,47–76]. The follow-up period was 1–15 years, and participants were followed monthly up to

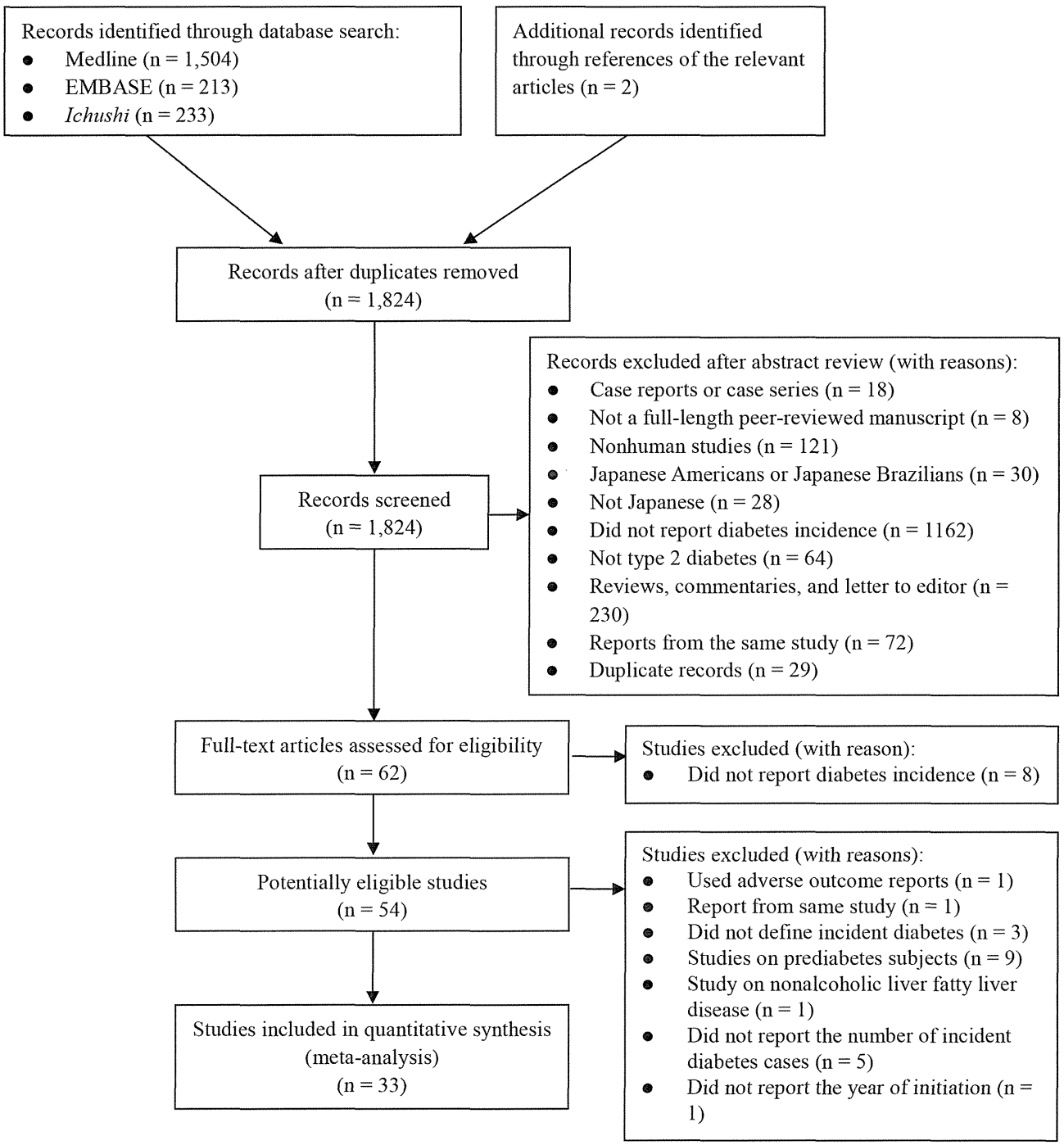

Figure 1. Literature search.
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10 years. Three studies based the definition of incident type 2 diabetes on self-reports only [14,47,48], 10 on laboratory data only (fasting glucose levels, casual glucose levels, 2-h post-load glucose levels after oral glucose tolerance tests, or HbA1c levels) [15,49-57], and 20 on self-reports and laboratory data [50,58–76]. Nine studies were population-based studies [14,47,49,51,53,64,68,69,77] with participation rates varying from 40.9% to 85.3%. Six studies [48,49,51,53,68,69] were performed in nonurban areas.

Table 1. Characteristics of the studies included in the systematic review.

	Study	Year of study initiation	Sample size (men, %)	Source of subjects	Participation rate (%)*	Mean Age (range)	Follow-up, years	Definition of incident diabetes
(i)	**Laboratory data only**							
	Maegawa et al. [53]	1980	1,338 (42)	Population-based (The Aito Study, Aito Town, Shiga)	79.3	50.0 (40–64)	5.6	FPG ≥ 140 mg/dL, 2-h PG ≥ 200 mg/dL
	Tanabe et al.(1) [56]	1980	230 (70)	Health checkups (Nishikawa town, Niigata)	–	55.9 (≥20)	4.3	FPG ≥ 126 mg/dL, 2-hPG ≥ 200 mg/dL
	Taniguchi et al. [15]	1981	6,356 (100)	Health checkups (The Osaka Health Survey, Work site, Osaka)	–	41.5 (35–60)	9.7	FPG ≥ 126 mg/dL, 2-hPG ≥ 200 mg/dL
	Kawakami et al. [52]	1984	2,380 (100)	Health checkups (Work site, Japan)	–	N.A. (18–53)	8	FPG ≥ 140 mg/dL, 2-h PG ≥ 200 mg/dL
	Yoshinaga et al. [57]	1986	1,604 (80)	Health checkups (Single center, Tokyo)	–	51.2 (20–81)	4.5	FPG ≥ 120 mg/dL more than twice
	Nakano et al. [55]	1991	435 (75)	Health checkups (Fukushima city, Fukushima)	–	51.9 (31–76)	2.3	FPG ≥ 140 mg/dL, 2-h PG ≥ 200 mg/dL
	Nakanishi et al. (1) [54]	1994	1,257 (100)	Health checkups (Work site, Osaka)	–	46.7 (35–59)	5	FPG ≥ 126 mg/dL
	Kameda et al. [51]	1995	940 (43)	Population-based (The Funagata Study, Funagata Town, Yamagata)	40.9	58.2 (N.A.)	5	FPG ≥ 140 mg/dL, 2-h PG ≥ 200 mg/dL
	Doi et al. [49]	2002	2,164 (40)	Population-based (The Hisayama Study, Hisayama Town, Fukuoka)	77.0	58.6 (40–79)	6	FPG ≥ 126 mg/dL, 2-h PG ≥ 200 mg/dL
	Fujita et al.(1) [50]	2002	27,760 (26)	Health checkups (Kashiwa City, Chiba)	–	61.8 (40–79)	4	FPG ≥ 126 mg/dL, HbA1c ≥ 6.9% (52 mmol/mol)
(ii)	**Laboratory data and self-reports of diagnosis/treatment**							
	Sawada et al. [74]	1985	4,187 (men)	Health checkups (Work site, Tokyo)	–	32.0 (22–40)	14	FPG ≥ 126 mg/dL, 2-h PG ≥ 200 mg/dL, diabetes treatment
	Nagaya et al. [65]	1988	25,196 (67)	Health checkups (Single center, Gifu)	–	43.8 (30–59)	7.3	Fasting serum glucose ≥ 126 mg/dL, diabetes treatment
	Okada et al. [69]	1989	717 (38)	Population-based (Yaeyama district, Okinawa)	58.9	55.0 (30–89)	10	FPG ≥ 126 mg/dL, 2-h PG ≥ 200 mg/dL, HbA1c ≥ 6.9% (52 mmol/mol), diabetes treatment
	Sairenchi et al. [70]	1993	128,141 (31)	Health checkups (Ibaraki)	–	N.A. (40–79)	4.8	FPG ≥ 126 mg/dL, casual PG ≥ 200 mg/dL, diabetes treatment
	Fujita et al.(2) [50]	1994	35,579 (21)	Health checkups (Chiba City, Chiba)	–	56.3 (40–79)	10.2	FPG ≥ 126 mg/dL, casual PG ≥ 200 mg/dL, self-reports of diagnosis
	Nakanishi et al. (2) [66]	1994	3,260 (100)	Health checkups (Work site, Japan)	–	N.A. (35–59)	7	FPG ≥ 126 mg/dL, diabetes treatment
	Ohnishi et al. [68]	1994	827 (40)	Population-based (The Tanno and Sobetsu Study, towns of Tanno and Sobetsu, Hokaido)	N.A.	N.A. (40–64)	10	FPG ≥ 126 mg/dL, diabetes treatment
	Sanada et al. [72]	1994	1,554 (62)	Health checkups (2 centers, Fukushima)	–	50.4 (23–80)	10	FPG ≥ 126 mg/dL, 2-h PG ≥ 200 mg/dL, diabetes treatment
	Inoue et al. [61]	1995	449 (76)	Health checkups (Work site, Japan)	–	45.6 (23–65)	7	FPG ≥ 126 mg/dL, diabetes treatment, self-reports of diagnosis
	Heianza et al. [60]	1997	6,241 (75)	Health checkups (The TOPICS, Single center, Tokyo)	–	49.9 (24–82)	4.7	FPG ≥ 126 mg/dL, HbA1c ≥ 6.5% (48 mmol/mol)
	Fukui et al. [58]	1998	4,153 (59)	Health checkups (Single center, Kyoto)	–	48.2 (N.A.)	8.2	FPG ≥ 126 mg/dL, diabetes treatment

Table 1 (continued).

	Study	Year of study initiation	Sample size (men, %)	Source of subjects	Participation rate (%)*	Mean Age (range)	Follow-up, years	Definition of incident diabetes
	Nomura et al. [67]	1998	9,322 (51)	Health checkups (Work site, Japan)	–	51.5 (19–69)	6	FPG ≥ 126 mg/dL, HbA1c ≥ 6.5%, diabetes treatment
	Tanabe et al.(2) [75]	1998	6,775 (32)	Health checkups (Tokachimachi City, Niigata)	–	62.0 (40–89)	5	FPG ≥126 mg/dL, casual PG ≥200 mg/dL, HbA1c ≥ 6.9% (52 mmol/mol), self-reports of diagnosis
	Hayashino et al. [59]	1999	4,975 (100)	Health checkups (The HIIPOP-OHP Study, Work site, Japan)	–	38.3 (19–69)	3.4	FPG ≥ 126 mg/dL, casual PG ≥ 200 mg/dL, diabetes treatment, self-reports of diagnosis
	Kato et al. [62]	2000	11,369 (29)	Health checkups (The Omiya MA Cohort Study, Omiya City, Saitama)	–	62 (55–68)	7	FPG ≥ 126 mg/dL, diabetes treatment, self-reports of diagnosis
	Sato et al. [73]	2000	10,631 (100)	Health checkups (The Kansai Healthcare Study, Work site, Kansai district)	–	47.9 (40–55)	4	FPG ≥ 126 mg/dL, diabetes treatment
	Muraki et al. [64]	2001	4,398 (36)	Population-based (The CIRCS, 5 areas, Japan)	N.A.	57.6 (40–69)	3	Fasting serum glucose ≥ 126 mg/dL, casual serum glucose ≥ 200 mg/dL, diabetes treatment
	Li et al. [63]	2002	3,008 (77)	Health checkups (Work site, Aichi)	–	47.3 (35–66)	6	Fasting glucose ≥ 126 mg/dL, self-reports of diagnosis
	Sakurai et al. [71]	2003	1,995 (100)	Health checkups (Work site, Toyama)	–	46.0 (35–55)	4.5	FPG ≥ 126 mg/dL, 2-h PG ≥ 200 mg/dL, diabetes treatment
	Totsuka et al. [76]	2003	172 (70)	Health checkups (Single center, Tsukuba City, Ibaraki)	–	49.4 (31–62)	3	FPG ≥ 126 mg/dL, 2-hPG ≥ 200 mg/dL, self-reports of diagnosis
(iii)	**Self-reports of diabetes diagnosis only**							
	Iso et al. [47]	1988	17,413 (39)	Population-based (The JACC Study, 45 areas, Japan)	83	53.2 (40–79)	5	Self-reports of diagnosis
	Kurotani et al. [14]	1995	48,437 (44)	Population-based (The JPHC Study, 11 areas, Japan)	81	50.7 (40–69)	5	Self-reports of diagnosis
	Oba et al. [48]	1992	13,540 (44)	Population-based (The Takayama Study, Takayama City, Gifu)	85.3	51.6 (≥35)	10	Self-reports of diagnosis

Abbreviations:

* Participation rates in population-based studies are shown.

Incidence Rate of Type 2 Diabetes

The 33 studies included 386,803 participants. The random-effects model indicated that the pooled incidence rate of diabetes was 8.8 (95% CI = 7.4–10.4) per 1,000 person-years (Figure 2). There was little evidence of publication bias. The funnel plot did not indicate asymmetry; Begg's p value was 0.45; and Egger's bias coefficient was -3.98 (95% CI, -9.72-1.77; p = 0.17) (not shown). We observed a high degree of heterogeneity (I^2 = 99.2%; p < 0.001), with incidence rates ranging from 2.3 to 52.6 per 1000 person-years. We also performed stratified analyses according to the definition of incident diabetes (self-reports vs. laboratory data), source of subjects (population-based vs. others), areas (nonurban vs. others), mean or median follow-up period (≥ 5 vs. < 5 years), year of study initiation (before the year 2000 vs. in the year 2000 or later 2000), and sample size (≥ 50,000 vs. < 50,000) (Table 2). The studies using self-reports of diabetes alone for diabetes diagnosis showed a lower diabetes incidence rate (N of studies = 3; pooled incidence rate = 4.0; 95% confidence interval = 3.2–5.0; p for interaction < 0.001) than did the studies using laboratory data (N of studies = 30; pooled incidence rate = 9.6; 95% CI = 8.3–11.1). The studies with longer follow-up periods (≥5 years) showed lower incidence rate estimates of diabetes (N of studies = 22; pooled incidence rate = 6.6; 95% CI = 5.5–8.0; p for interaction < 0.001) than did the studies with shorter follow-up periods (< 5 years; N of studies = 11; pooled incidence rate = 16.3, 95% CI = 14.0–18.9). The studies that initiated before the year 2000 (N of studies = 25) reported lower estimates of incidence rates (pooled incidence rate = 7.8; 95% CI = 6.2–9.5; p for interaction = 0.001) than did the studies that initiated in the year 2000 or later (N of studies= 8; pooled

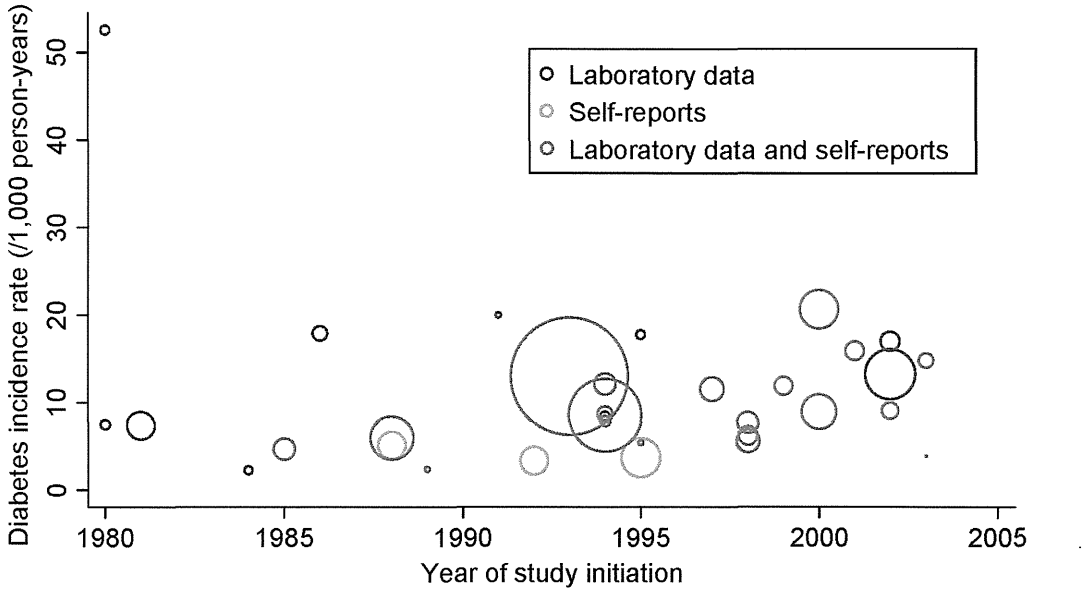

Figure 2. Forest plots of diabetes incidence rate. CI indicates confidence interval.Dots indicate diabetes incidence rates. Horizontal lines indicate 95% CIs for incidence rates. The diamonds represent the pooled incidence rate estimates with 95% CIs.
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incidence rate = 13.4; 95% CI = 10.4–17.1). Figure 3 shows a bubble plot of the diabetes incidence rate per 1,000 person-years as a function of the year of study initiation. The results indicated that more recent studies tended to show higher incidence rate estimates. However, stratification according to these characteristics could not entirely explain the heterogeneity in the results, with I^2 statistics being high within each stratum. We also conducted meta-regression analyses to further explore the sources of heterogeneity (Table 3). Meta-regression analyses indicated that a longer follow-up period was associated with lower incidence rates in studies before the year 2000; however, it explained only a small proportion of the heterogeneity (adjusted R^2 statistics = 22.1%; residual I^2 statistics = 99.1%). In addition, we estimated the pooled incidence rate of diabetes in the studies on prediabetes populations. The incidence rate among prediabetes populations (pooled incidence rate = 49.2 per 1,000 person-years; 95% CI = 31.5–76.8) (not shown) [31,32,34–39] was much higher than that among total populations (pooled incidence rate = 8.8 per 1,000 person-years).

Validity of Self-reported Diabetes

Among the studies that considered self-reports for the definition of diabetes diagnosis, 3 conducted validity studies among participants whose laboratory data were available [14,47,63]. In the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Study (JACC Study), self-reports were compared with laboratory data and treatment status in a subsample of study participants [47]. In the Japan Public Health Center-based prospective Study (JPHC Study) [14], self-reports were compared with medical records and laboratory data retrieved from health checkups [78,79]. In the study by Li et al [63], self-reports were compared with laboratory data and reports from the physicians of study participants [80]. Their positive predictive values, negative predictive values, sensitivity, and specificity were 95.7%-99.2%, 93.8%–96.3%, 70%-82.6%, and 95%–99.7%, respectively [47,78,80]. Because these validation studies were conducted among participants whose laboratory data were available, validity of self-reports among those who had not visited health checkups remains unclear.

Discussion

In the present systematic review and meta-analysis of studies that evaluated new-onset type 2 diabetes in the Japanese population, we found that there was a high degree of heterogeneity in the incidence of diabetes in Japan and an increasing number recent studies tended to show higher incidence rate estimates. Our study also indicated that studies that used self-reported diagnosed diabetes tended to show a lower incidence rate than studies that used laboratory data, suggesting that laboratory data are important for the accurate estimation of the incidence rate of diabetes. In addition, the studies with longer follow-up durations tended to show lower incidence rates. In the cohorts with longer follow-up durations, individuals who did not develop diabetes at earlier stages of study period were likely less predisposed toward diabetes and would have had a lower likelihood of developing diabetes later in the study, which might have led to the lower overall incidence rates in the studies with follow-up durations that were longer than those of the others. Although we observed a high degree of heterogeneity between studies, stratified analyses or

Table 2. Stratified analysis of the incidence rate of diabetes.

Group	Number of studies	Incidence rate* (95% CI)	p value (heterogeneity†)	I^2 (%)	p value (interaction‡)
Total	33	8.8 (7.4–10.4)	< 0.001	99.2	
Definition of incident diabetes					< 0.001
Laboratory data	30	9.6 (8.3–11.1)	< 0.001	97.6	
Self-reports only	3	4.0 (3.2–5.0)	< 0.001	95.5	
Source of subjects					0.13
Population-based	9	6.7 (4.3–10.4)	< 0.001	99.0	
Others	24	9.7 (8.2–11.4)	< 0.001	98.9	
Area					0.40
Nonurban	6	6.7 (3.3–13.7)	< 0.001	98.8	
Others	27	9.2 (7.7–11.1)	< 0.001	99.2	
Follow-up period					< 0.001
≥5 years	22	6.6 (5.5–8.0)	< 0.001	98.3	
<5 years	11	16.3 (14.0–18.9)	< 0.001	96.5	
Year of study initiation					0.001
≥ 2000	8	13.4 (10.4–17.1)	< 0.001	97.8	
< 2000	25	7.8 (6.3–9.5)	< 0.001	99.2	
Sample size					0.39
≥ 10,000	9	7.8 (5.6–10.8)	< 0.001	99.7	
< 10,000	24	9.2 (7.5–11.3)	< 0.001	97.2	

Abbreviation:

* Incidence rate estimates were obtained using a random-effects model.

† p values for heterogeneity across studies were computed using Cochrane's Q test.

‡ p values for comparisons between subgroups were computed using the χ^2 test with one degree of freedom.

meta-regression analyses did not identify major sources of the heterogeneity.

The overall incidence rate of diabetes in Japan was found to be 9.0 per 1,000 person-years. This estimate is slightly higher than the self-report-based [81,82] or administrative database-based [83] estimates from the U.S. [81], U.K. [83], and China [82]. The U.S. National Health Interview Survey reported that the incidence rate of medically diagnosed diabetes was 8.4 per 1,000 person-years among men and 8.1 per 1,000 person-years among women in 2008 [81]. Using a primary care medical records database in the U.K, the incidence rate of diabetes in the U.K. was reported to be 4.4 per 1,000 person-years in 2005 [83]. In addition, the Shanghai Diabetes Study reported that diabetes incidence rate identified by self-reports was 6.0 per 1,000 person-years among Chinese women in Shanghai [82]. However, because estimates based on self-reports or administrative databases would have overlooked undiagnosed or untreated diabetes, these studies may have underestimated the incidence rate. Indeed, our overall estimate of diabetes incidence in Japan was mainly driven by the incidence rates from studies using laboratory data. The overall rate (9.0 per 1,000 person-years) was close to that observed in the study among Australians, in which diabetes was defined by fasting plasma glucose levels ≥126 mg/dL and/or diabetes diagnosed by physicians [84]. In the Blue Mountains Eye Study, the incidence rate of type 2 diabetes was 9.3 per 1,000 person-years among non-Aboriginal Australians [84]. Further studies that standardize the definition of incident diabetes are required to compare the incidence rate of diabetes between countries.

Diabetes is often defined exclusively on the basis of self-reports [85,86]. In the present review, we found that studies based on self-reports alone tended to show a lower incidence rate compared with studies based on laboratory data, suggesting that laboratory data are important to estimate the incidence rate of diabetes correctly. Three studies conducted validation studies among participants whose laboratory data were available; the range for the specificity of self-reports as obtained in this review (95–99.7%) was relatively high. In studies based on self-reports, diabetes incidence may have been underestimated probably because the sensitivity was not sufficiently high. Moreover, the validity of self-reports among those who had not visited health checkups is unclear. In particular, the sensitivity of self-reports among participants who had not been screened for diabetes may be much lower than the range (70%–82.6%) obtained in this review. Of note, laboratory data were not available in any of the large-scale population-based studies [14,47,77]. This seems to indicate that multiple sources of evidence including self-reports, claim-based data, hospital admission data, and mortality data should be considered in such situations.

Our study also indicated that the incidence of type 2 diabetes in Japan may be increasing. The FPG threshold was lowered from ≥140 to ≥126 mg/dl by the ADA, WHO, and JDS in 1997, 1998, and 1999, respectively [6,8,9]; this may have reflected the change in the diagnoses and incidence rates of diabetes. The increase in obesity prevalence [87], decline in physical

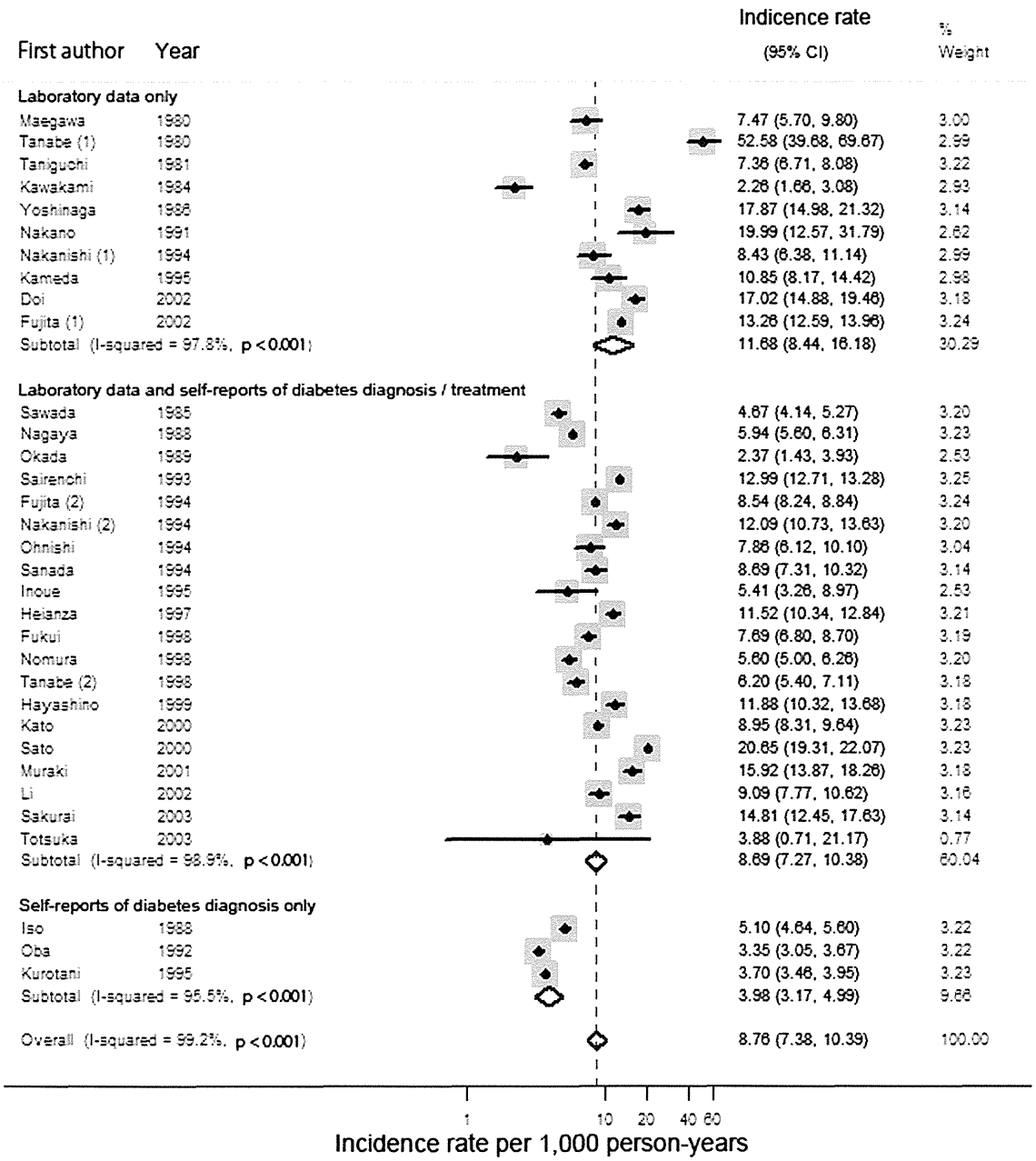

Figure 3. Bubble plots of diabetes incidence rate against the year of study initiation. A bubble shows a study, and the size of the bubble is proportional to the inverse of the variance of the log-transformed incidence rate. Diabetes incidence rate was calculated by dividing the number of new-onset diabetes cases by the duration of follow-up. When the mean follow-up duration was not available, the median was used.

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activity [5], and population aging [88] may also explain possible trend toward an increasing rate of diabetes incidence in Japan.

Table 3. Meta-regression analyses of the incidence rate of diabetes with stratification according to year of study initiation (before the year 2000 vs. in the year 2000 or later).

Study characteristic	Ratio of incidence rate* (95% CI)	p value	Adjusted R^2	Residual I^2 (%)
Studies before the year 2000 (N = 25)				
Self-reports only	0.47 (0.21–1.04)	0.06	12.4	98.6
Population-based	0.57 (0.32–1.03)	0.06	11.3	98.7
Nonurban areas	0.66 (0.33–1.33)	0.24	1.7	99.2
5-year increase in follow-up period	0.55 (0.35–0.86)	0.01	22.1	99.1
5-year increase in year of study initiation	0.96 (0.75–1.23)	0.73	-4.1	99.3
10,000 increase in sample size	1.00 (0.90–1.12)	0.94	-4.8	98.7
Studies in the year 2000 or later (N = 8)				
Population-based	1.33 (0.67–2.64)	0.35	-1.4	98.0
Nonurban areas	1.32 (0.52–3.34)	0.49	-9.5	98.1
5-year increase in follow-up period	0.54 (0.19–1.51)	0.19	31.1	96.3
5-year increase in year of study initiation	0.82 (0.17–3.96)	0.76	-21.4	98.1
10,000 increase in sample size	1.00 (0.68–1.49)	0.98	-21.4	98.1

Abbreviation:

* Incidence rate with characteristic divided by incidence rate without characteristic. Ratios < 1 correspond to a smaller incidence rate for studies with the characteristic.

Future studies using the standardized definition of incident type 2 diabetes are warranted to clarify the trend in the incidence of diabetes in Japan.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 94: 311-321. doi:10.1016/j.diabres.2011.10.029. PubMed: 22079683.
2. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS et al. (2009) Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 301: 2129-2140. doi:10.1001/jama.2009.726. PubMed: 19470990.
3. Ministry of Health (1997) National Diabetes Survey. Available: http://www.mhlw.go.jp/toukei/kouhyo/indexkk_4_1.html. Accessed 23 August 2012.
4. Ministry of Health, Labour and Welfare (2002) National Diabetes Survey. Available: http://www.mhlw.go.jp/shingi/2004/03/s0318-15.html#tyosa. Accessed 23 August 2012.
5. Ministry of Health, Labour and Welfare (2007) National Health and Nutrition Survey. Available: http://www.mhlw.go.jp/bunya/kenkou/eiyou09/01.html. Accessed 23 August 2012.
6. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15: 539-553. doi:10.1002/(SICI)1096-9136(199807)15:7. PubMed: 9686693.
7. American Diabetes Association (2013) Diagnosis and classification of diabetes mellitus. Diabetes Care 36 Suppl 1: S67-S74. doi:10.2337/dc13-S067. PubMed: 23264425.
8. Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y et al. (1999) Report of the committee of Japan Diabetes Society on the classification and diagnostic criteria of diabetes mellitus. J Japan Diab Soc 42: 385-404
9. American Diabetes Association (1997) Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 20: 1183-1197. PubMed: 9203460.
10. International Expert C (2009) International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32 (1327-1334)
11. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33 Suppl 1: S62-S69. doi:10.2337/dc10-S062. PubMed: 20042775.
12. World Health Organization (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. Geneva: WHO. pp. 1-25.
13. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A et al. (2010) Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Invest 1: 212-228. doi:10.1111/j.2040-1124.2010.00074.x.
14. Kurotani K, Nanri A, Goto A, Mizoue T, Noda M et al. (2013) Vegetable and fruit intake and risk of type 2 diabetes: Japan Public Health Center-based Prospective Study. Br J Nutr 109: 709-717. doi:10.1017/S0007114512001705. PubMed: 22571826.

The strengths of this study include its large sample size and comprehensive assessment of definitions used to identify incident type 2 diabetes. Several limitations also exist. First, we limited our search to the Japanese population, which limits the generalizability our findings. Second, we did not have individual participant data or age- and gender-specific estimates of type 2 diabetes incidence. Therefore, we were not able to compute age-standardized incidence rates. Third, although we searched 3 large electronic databases (MEDLINE, EMBASE, and *Ichushi* [the largest database for medical literature in Japan]), we may have missed some related studies. Finally, large regional differences in diabetes incidence may exist, but we were unable to establish a region-specific estimate.

Conclusions

Our systematic review and meta-analysis indicated the presence of a high degree of heterogeneity, which suggests that there is a considerable amount of uncertainty regarding the incidence of type 2 diabetes in Japan. They also suggested that laboratory data may be important to identify undiagnosed diabetes. Future studies should aim to standardize the definition of incident diabetes in order to compare the incidence rate of type 2 diabetes between countries

Supporting Information

Checklist S1. (DOCX)

Author Contributions

Conceived and designed the experiments: AG MG MN ST. Performed the experiments: AG MG. Analyzed the data: AG MG. Contributed reagents/materials/analysis tools: AG MG MN ST. Wrote the manuscript: AG MG. Critical revision of the manuscript for important intellectual contents: MN ST.

15. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S et al. (2001) Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens 19: 1209-1215. doi:10.1097/00004872-200107000-00005. PubMed: 11446710.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Med 6: e1000097
17. Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR et al. (2004) IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 50: 166-174. doi:10.1373/clinchem.2003.024802. PubMed: 14709644.
18. Ulm K (1990) A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 131: 373-375. PubMed: 2296988.
19. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177-188. doi:10.1016/0197-2456(86)90046-2. PubMed: 3802833.
20. Cochran W (1954) The combination of estimates from different experiments. Biometrics 10: 101-129. doi:10.2307/3001666.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557-560. doi:10.1136/bmj.327.7414.557. PubMed: 12958120.
22. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088-1101. doi:10.2307/2533446. PubMed: 7786990.
23. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634. doi:10.1136/bmj.315.7109.629. PubMed: 9310563.
24. Thompson SG (2008) Why and how Sources of Heterogeneity Should be Investigated. Systematic Reviews in Health Care. BMJ Publishing Publishing House Group. pp. 157-175.
25. Harbord RM, Higgins JPT (2008) Meta-regression in Stata. STATA J 8: 493-519.
26. Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K et al. (2008) Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. Hypertension 51: 393-398. doi:10.1161/HYPERTENSIONAHA.107.098475. PubMed: 18172059.
27. Noda M, Kato M, Takahashi Y, Matsushita Y, Mizoue T et al. (2010) Fasting plasma glucose and 5-year incidence of diabetes in the JPHC diabetes study - suggestion for the threshold for impaired fasting glucose among Japanese. Endocr J 57: 629-637. doi:10.1507/endocrj.K10E-010. PubMed: 20508383.
28. Fukagawa K (1998) The background behind the incidence of diabetes in patient with obesity in the Oita Prefecture. J Japan Soc Study Obesity 4: 38-43
29. Takahashi K, Uchiyama H, Yanagisawa S, Kamae I (2006) The logistic regression and ROC analysis of group-based screening for predicting diabetes incidence in four years. Kobe J Med Sci 52: 171-180. PubMed: 17329955.
30. Akiyama T, Kanda K, Yoshikawa H, Hirohata Y, Kihara Y et al. (2002) α-Glucosidase inhibitor prevents the development of impaired glucose tolerance in type 2 diabetes. J Japan Diab Soc 45: 791-795 (in Japanese)
31. Ishida S, Ito C, Murakami F, Horikawa C, Gennai N et al. (2004) Prevention of type 2 diabetes mellitus by changing lifestyle among high risk persons: The Diabetes Prevention Program of Hiroshima (DPPH) - *Design and one-year interm report on feasibility*. J *Japan Diab Soc* 47: 707-713 (in Japanese)
32. Kadowaki T, Miyake Y, Hagura R, Akanuma Y, Kajinuma H et al. (1984) Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. Diabetologia 26: 44-49. PubMed: 6368299.
33. Kawahara T, Takahashi K, Inazu T, Arao T, Kawahara C et al. (2008) Reduced progression to type 2 diabetes from impaired glucose tolerance after a 2-day in-hospital diabetes educational program: the Joetsu Diabetes Prevention Trial. Diabetes Care 31: 1949-1954. doi:10.2337/dc07-2272. PubMed: 18591401.
34. Kosaka K, Noda M, Kuzuya T (2005) Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract 67: 152-162. doi:10.1016/j.diabres.2004.06.010. PubMed: 15649575.
35. Matsumoto K, Ozaki M, Fujita N, Miyake S (2005) Insulin resistance and metabolic syndrome contribute significantly to the transition of borderline glucose tolerance to type 2 diabetes mellitus. J Japan Diab Soc 48: 849-854 (in Japanese)
36. Saito T, Watanabe M, Nishida J, Izumi T, Omura M et al. (2011) Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med 171: 1352-1360. doi:10.1001/archinternmed.2011.275. PubMed: 21824948.
37. Sakane N, Sato J, Tsushita K, Tsujii S, Kotani K et al. (2011) Prevention of type 2 diabetes in a primary healthcare setting: three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance. BMC Public Health 11: 40. doi:10.1186/1471-2458-11-40. PubMed: 21235825.
38. Satoh M, Orisaka M (2006) A retrospective study on the development of diabetes mellitus in the individuals with impaired fasting glucose for four years. J Prevent Med 419: 48-50 (in Japanese)
39. Toshihiro M, Saito K, Takikawa S, Takebe N, Onoda T et al. (2008) Psychosocial factors are independent risk factors for the development of Type 2 diabetes in Japanese workers with impaired fasting glucose and/or impaired glucose tolerance. Diabet Med 25: 1211-1217. doi:10.1111/j.1464-5491.2008.02566.x. PubMed: 19046200.
40. Arase Y, Suzuki F, Ikeda K, Kumada H, Tsuji H et al. (2009) Multivariate analysis of risk factors for the development of type 2 diabetes in nonalcoholic fatty liver disease. J Gastroenterol 44: 1064-1070. doi:10.1007/s00535-009-0091-1. PubMed: 19533014.
41. Ito C, Maeda R, Nakamura K, Sasaki H (1996) *Prediction of diabetes* mellitus (NIDDM). Diabetes Res Clin Pract 34 Suppl: S7-11. doi:10.1016/S0168-8227(96)01298-3. PubMed: 9015664.
42. Kawazu S (1998) Incidence of type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus) by the levels of fasting plasma glucose, 2 hour plasma glucose and insulin response to glucose during 75g OGTT. J Japan Diab Soc Supplement 2: A53-56 (in Japanese)
43. Seki A, Takigawa T, Ito T, Fukuoka E, Takahashi K et al. (2002) Obesity and the risk of diabetes mellitus in middle-aged Japanese men. Acta Med Okayama 56: 255-260. PubMed: 12530509.
44. Sohma M, Mutoh E, Kohgo Y (2007) Effects of exercise on the blood sugar, blood lipid profile, risk of diabetes and risk of cerebral infarction: The Higashikagura study. J Japan Diab Soc 50: 297-301 (in Japanese)
45. Takahashi M, Kaji K, Togashi A, Ogino Y, Shibosawa T et al. (2001) Usefulness of paired estimation of fating plasma glucose and HbA1c: A long-term follow-up study of screened nondiabetic subjects. J Japan Diab Soc 44: 745-750 (in Japanese)
46. Takashina S (1996) The investigation of diabetes prevention. Nouson no Kenkou Hukushi series 65: 11-19 (in Japanese)
47. Iso H, Date C, Wakai K, Fukui M, Tamakoshi A et al. (2006) The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med 144: 554-562. doi:10.7326/0003-4819-144-8-200604180-00005. PubMed: 16618952.
48. Oba S, Nagata C, Nakamura K, Fujii K, Kawachi T et al. (2010) Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to risk of diabetes in Japanese men and women. Br J Nutr 103: 453-459. doi:10.1017/S0007114509991966. PubMed: 19818197.
49. Doi Y, Ninomiya T, Hirakawa Y, Takahashi O, Mukai N et al. (2013) Angiopoietin-like protein 2 and risk of type 2 diabetes in a general Japanese population: the hisayama study. Diabetes Care 36: 98-100. doi:10.2337/dc12-0166. PubMed: 22966088.
50. Fujita M, Ueno K, Hata A (2009) Effect of obesity on incidence of type 2 diabetes declines with age among Japanese women. Exp Biol Med (Maywood) 234: 750-757. doi:10.3181/0810-RM-292. PubMed: 19429850.
51. Kameda W, Daimon M, Oizumi T, Jimbu Y, Kimura M et al. (2005) Association of decrease in serum dehydroepiandrosterone sulfate levels with the progression to type 2 diabetes in men of a Japanese population: the Funagata Study. Metabolism 54: 669-676. doi:10.1016/j.metabol.2004.12.011. PubMed: 15877298.
52. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H (1999) Depressive symptoms and occurrence of type 2 diabetes among Japanese men. Diabetes Care 22: 1071-1076. doi:10.2337/diacare.22.7.1071. PubMed: 10388970.
53. Maegawa H, Hidaka H, Okayama A, Kikkawa R, Kobayashi M et al. (1992) Risk factors for non-insulin dependent diabetes mellitus in a rural Japanese population - Incidence and risk factors-. J Japan Diab Soc 35: 241-248 (in Japanese)
54. Nakanishi N (2000) The effect of cigarette smoking on the incidence of *diabetes: an investigation among late middle age male workers*. J Health Welfare Stat 47: 28-33 (in Japanese)
55. Nakano A (1996) The epidemiological study of risk factors for noninsulin-dependent diabetes mellitus. Fukushima J Med Sci 46: 39-46 (in Japanese)
56. Tanabe N, Saito K, Yamada Y, Takasawa T, Seki N et al. (2009) Risk assessment by post-challenge plasma glucose, insulin response ratio, and other indices of insulin resistance and/or secretion for predicting

the development of type 2 diabetes. Intern Med 48: 401-409. doi: 10.2169/internalmedicine.48.1325. PubMed: 19293537.
57. Yoshinaga H, Kosaka K (1999) Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulin-dependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. Diabetes Res Clin Pract 44: 129-136. doi: 10.1016/S0168-8227(99)00019-4. PubMed: 10414932.
58. Fukui M, Tanaka M, Toda H, Senmaru T, Sakabe K et al. (2011) Risk factors for development of diabetes mellitus, hypertension and dyslipidemia. Diabetes Res Clin Pract 94: e15-e18. doi:10.1016/j.diabres.2011.07.006. PubMed: 21802759.
59. Hayashino Y, Fukuhara S, Okamura T, Tanaka T, Ueshima H et al. (2011) High oolong tea consumption predicts future risk of diabetes among Japanese male workers: a prospective cohort study. Diabet Med 28: 805-810. doi:10.1111/j.1464-5491.2011.03239.x. PubMed: 21244473.
60. Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K et al. (2011) HbA1c 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet 378: 147-155. doi:10.1016/S0140-6736(11)60472-8. PubMed: 21705064.
61. Inoue K, Matsumoto M, Kobayashi Y (2007) The combination of fasting plasma glucose and glycosylated hemoglobin predicts type 2 diabetes in Japanese workers. Diabetes Res Clin Pract 77: 451-458. doi: 10.1016/j.diabres.2007.01.024. PubMed: 17346846.
62. Kato M, Noda M, Suga H, Matsumoto M, Kanazawa Y (2009) Fasting plasma glucose and incidence of diabetes - implication for the threshold for impaired fasting glucose: results from the population-based Omiya MA cohort study. J Atheroscler Thromb 16: 857-861. PubMed: 20032586.
63. Li Y, Yatsuya H, Iso H, Toyoshima H, Tamakoshi K (2012) Inverse relationship of serum adiponectin concentration with type 2 diabetes mellitus incidence in middle-aged Japanese workers: six-year follow-up. Diabetes/Metab Res Rev 28: 349-356. doi:10.1002/dmrr.2277. PubMed: 22228701.
64. Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T et al. (2010) Nocturnal intermittent hypoxia and the development of type 2 diabetes: the Circulatory Risk in Communities Study (CIRCS). Diabetologia 53: 481-488. doi:10.1007/s00125-009-1616-0. PubMed: 19946661.
65. Nagaya T, Yoshida H, Takahashi H, Kawai M (2010) Resting heart rate and blood pressure, independent of each other, proportionally raise the risk for type-2 diabetes mellitus. Int J Epidemiol 39: 215-222. doi: 10.1093/ije/dyp229. PubMed: 19564246.
66. Nakanishi N, Suzuki K, Tatara K (2004) Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care 27: 1427-1432. doi:10.2337/diacare.27.6.1427. PubMed: 15161799.
67. Nomura K, Inoue K, Akimoto K (2012) A two-step screening, measurement of HbA1c in association with FPG, may be useful in predicting diabetes. PLOS ONE 7: e36309. doi:10.1371/journal.pone.0036309. PubMed: 22558430.
68. Ohnishi H, Saitohi S, Takagii S, Katohi N, Chibai Y et al. (2006) Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: the Tanno and Sobetssu study: response to Oda. Diabetes Care 29: 1989. doi:10.2337/dc06-0874. PubMed: 16873828.
69. Okada K, Furusyo N, Sawayama Y, Kanamoto Y, Murata M et al. (2010) Prevalence and risk factors for diabetes: a ten year follow-up study of the Yaeyama district of Okinawa. Fukuoka Igaku Zasshi 101: 215-224. PubMed: 21375144.
70. Sairenchi T, Iso H, Nishimura A, Hosoda T, Irie F et al. (2004) Cigarette smoking and risk of type 2 diabetes mellitus among middle-aged and elderly Japanese men and women. Am J Epidemiol 160: 158-162. doi: 10.1093/aje/kwh183. PubMed: 15234937.
71. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K et al. (2012) Dietary glycemic index and risk of type 2 diabetes mellitus in middle-aged Japanese men. Metabolism 61: 47-55. doi:10.1016/j.metabol.2011.05.015. PubMed: 21803381.
72. Sanada H, Yokokawa H, Yoneda M, Yatabe J, Sasaki Yatabe M et al. (2012) High body mass index is an important risk factor for the development of type 2 diabetes. Intern Med 51: 1821-1826. doi: 10.2169/internalmedicine.51.7410. PubMed: 22821094.
73. Sato KK, Hayashi T, Harita N, Koh H, Maeda I et al. (2012) Relationship between drinking patterns and the risk of type 2 diabetes: the Kansai Healthcare Study. J Epidemiol Community Health 66: 507-511. doi:10.1136/jech.2010.109777. PubMed: 21131305.
74. Sawada SS, Lee IM, Naito H, Noguchi J, Tsukamoto K et al. (2010) Long-term trends in cardiorespiratory fitness and the incidence of type 2 diabetes. Diabetes Care 33: 1353-1357. doi:10.2337/dc09-1654. PubMed: 20215460.
75. Tanabe N, Seki N, Aizawa Y, Suzuki H (2009) Association of diagnostic components of metabolic syndrome with risk of developing diabetes mellitus: Is obesity necessary for prediction? JPN J Cardiovasc Dis Prev 44: 152-160 (in Japanese)
76. Totsuka K, Maeno T, Saito K, Kodama S, Asumi M et al. (2011) Self-reported fast eating is a potent predictor of development of impaired glucose tolerance in Japanese men and women: Tsukuba Medical Center Study. Diabetes Res Clin Pract 94: e72-e74. doi:10.1016/j.diabres.2011.08.015. PubMed: 21908066.
77. Oba S, Noda M, Waki K, Nanri A, Kato M et al. (2012) Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. PLOS ONE 7: e17061. doi:10.1371/journal.pone.0017061. PubMed: 22879858.
78. Kato M, Noda M, Inoue M, Kadowaki T, Tsugane S et al. (2009) Psychological factors, coffee and risk of diabetes mellitus among middle-aged Japanese: a population-based prospective study in the JPHC study cohort. Endocr J 56: 459-468. doi:10.1507/endocrj.K09E-003. PubMed: 19270421.
79. Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y et al. (2005) Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I. Diabet Med 22: 323-331. doi:10.1111/j.1464-5491.2004.01403.x. PubMed: 15717882.
80. Wada K, Yatsuya H, Ouyang P, Otsuka R, Mitsuhashi H et al. (2009) Self-reported medical history was generally accurate among Japanese workplace population. J Clin Epidemiol 62: 306-313. doi:10.1016/j.jclinepi.2008.04.006. PubMed: 18774692.
81. Beckles GL, Zhu J, Moonesinghe R, Centers for Disease C (2011) Prevention. Diabetes - United States, 2004, and 2008 MMWR Surveill Summ 60 Suppl: 90-93
82. Villegas R, Shu X-O, Li H, Yang G, Matthews CE et al. (2006) Physical activity and the incidence of type 2 diabetes in the Shanghai women's health study. Int J Epidemiol 35: 1553-1562. doi:10.1093/ije/dyl209. PubMed: 16984936.
83. González EL, Johansson S, Wallander MA, Rodríguez LA (2009) Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health 63: 332-336. doi:10.1136/jech.2008.080382. PubMed: 19240084.
84. Cugati S, Wang JJ, Rochtchina E, Mitchell P (2007) Ten-year incidence of diabetes in older Australians: the Blue Mountains Eye Study. Med J Aust 186: 131-135. PubMed: 17309402.
85. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC (1995) Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 310: 555-559. doi:10.1136/bmj.310.6979.555. PubMed: 7888928.
86. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE et al. (2000) Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 160: 2117-2128. doi:10.1001/archinte.160.14.2117. PubMed: 10904454.
87. Yatsuya H, Yamagishi K, Iso H (2011) Adiposity and risk of cardiovascular diseases in Japan: secular trend, individual level associations and causal pathway - implications for the prevention of cardiovascular diseases in societies with rapid economic development. EPMA J 2: 65-73. doi:10.1007/s13167-011-0071-4. PubMed: 23199128.
88. Ministry of Health, Labour and Welfare (2012) The second. Health Japan 21 project. Available: http://www.mhlw.go.jp/bunya/kenkou/dl/kenkounippon21_02.pdf. Accessed 27 June 2013