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").

Pharmacoepidemiology and Drug Safety, 2013; **22**: 1134–1137
DOI: 10.1002/pds

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.

ACKNOWLEDGEMENTS

The study was supported by the Health and Labour Sciences Research Grant (H201 in fiscal years 2009–2011) from the Ministry of Health, Labour and Welfare (MHLW) (Principal Investigator: Professor Mayumi Mochizuki).

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)

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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.

Citation: Goto A, Goto M, Noda M, Tsugane S (2013) Incidence of Type 2 Diabetes in Japan: A Systematic Review and Meta-Analysis. PLoS ONE 8(9): e74699. doi:10.1371/journal.pone.0074699

Editor: Yu-Kang Tu, National Taiwan University, Taiwan

Received April 25, 2013; **Accepted** August 2, 2013; **Published** September 6, 2013

Funding: This work was based on the Program to Improve Preventive Medicine by Analysis of Cohort Data Linked to Medical Records supported by Funds for integrated promotion of social system reform and research and development, from the Ministry of Education, Culture, Sports, Science and Technology. This work was also funded by Health Sciences Research Grants (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus H22-019 and H25-016) from the Ministry of Health, Labour and Welfare of Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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

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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

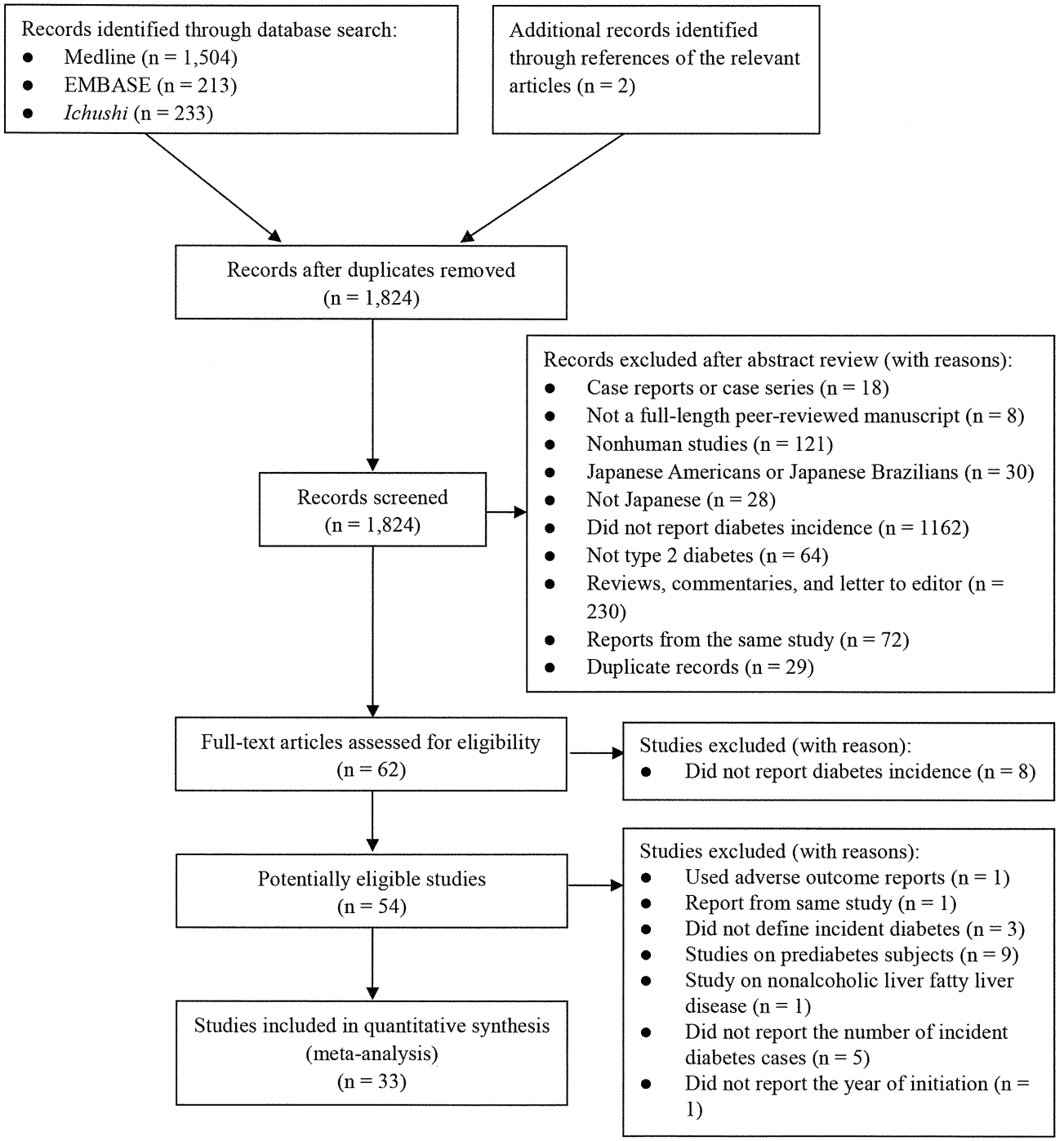

Figure 1. Literature search.

doi: 10.1371/journal.pone.0074699.g001

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

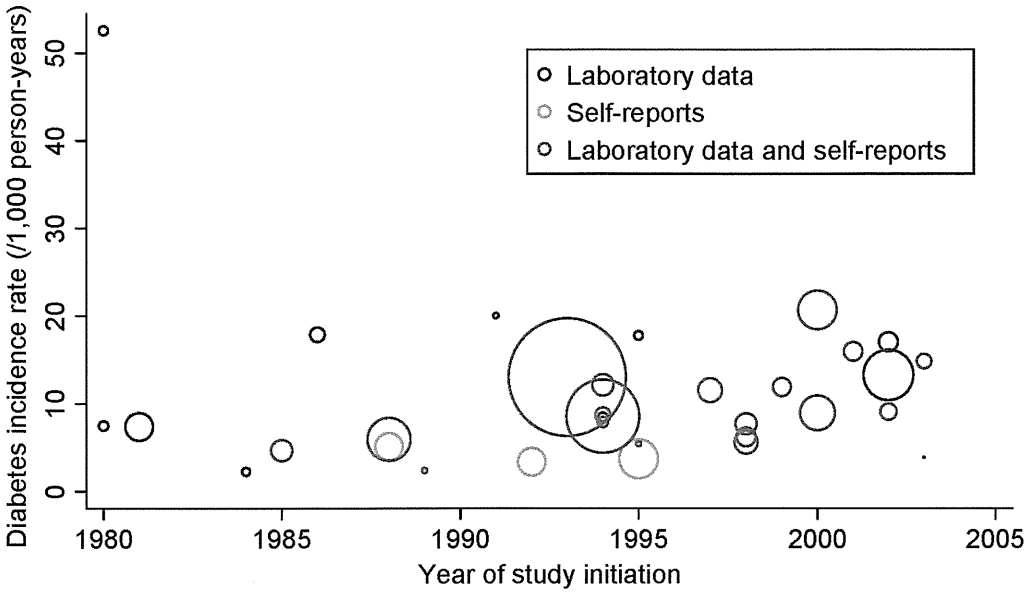

Figure 2. Forest plots of diabetes incidence rate. CI indicates confidence interval.Dots indicate diabetes incidence rates. Horizontal lines indicate 95% CIs for incidence rates. The diamonds represent the pooled incidence rate estimates with 95% CIs.
doi: 10.1371/journal.pone.0074699.g002

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

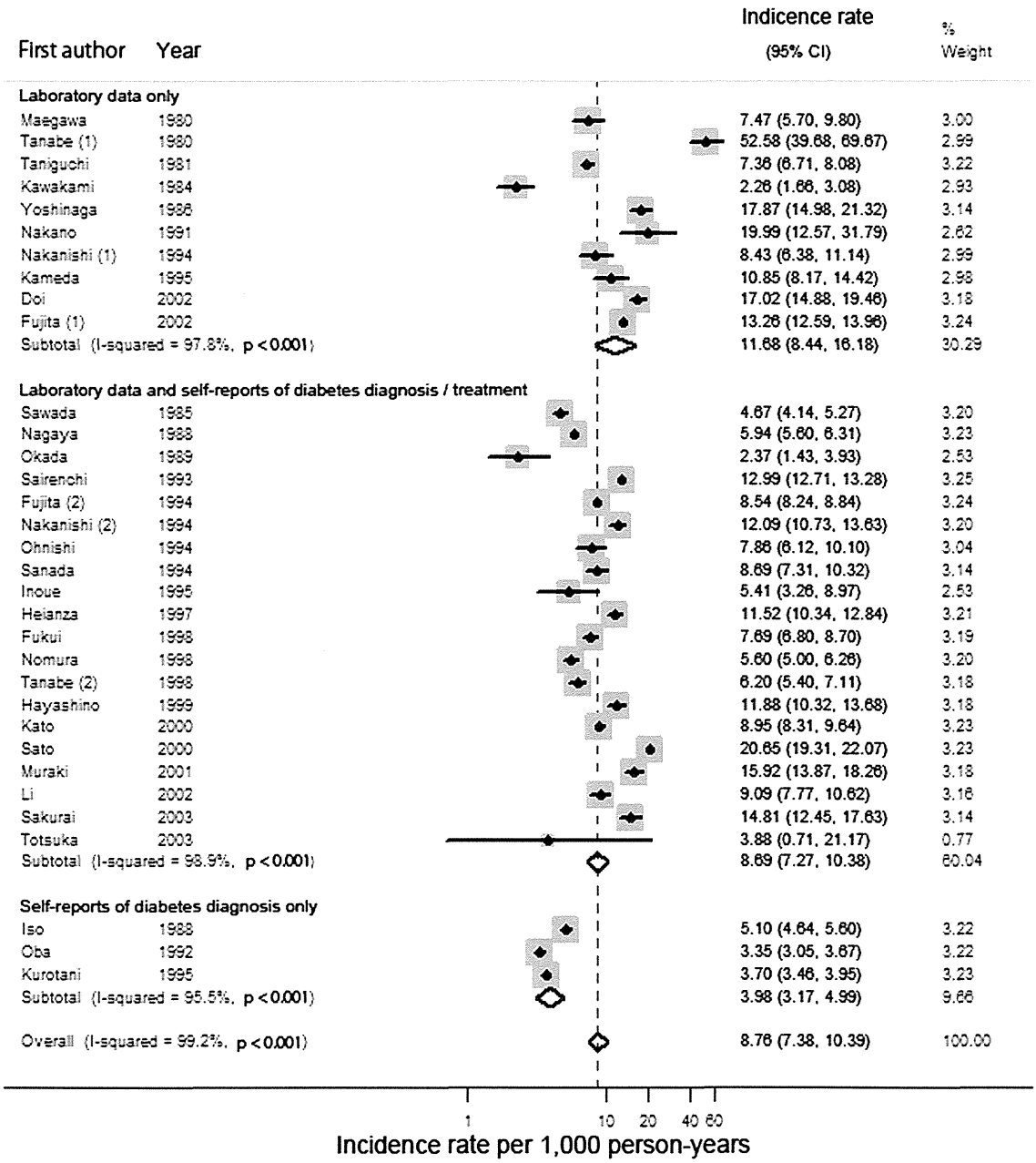

Figure 3. Bubble plots of diabetes incidence rate against the year of study initiation. A bubble shows a study, and the size of the bubble is proportional to the inverse of the variance of the log-transformed incidence rate. Diabetes incidence rate was calculated by dividing the number of new-onset diabetes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

doi: 10.1371/journal.pone.0074699.g003

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.

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.

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SHORT REPORT

Effect of calcium channel blockers on incidence of diabetes: a meta-analysis

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Aims: Insulin resistance and the progressive loss of β-cell function are components of the fundamental pathophysiology of type II diabetes. A recent experimental study suggested that calcium channel blockers (CCBs) might inhibit β-cell apoptosis, enhance β-cell function, and prevent diabetes. The present meta-analysis examined the clinical effect of CCBs on the incidence of diabetes.

Methods: MEDLINE, EMBASE, ISI Web of Science, the Cochrane Library, and ClinicalTrials.gov were each searched for relevant articles published up to March 11, 2013. Randomized controlled trials (RCTs) with a follow-up period of at least 1-year were included. Identified articles were systematically reviewed, and those with pertinent data were selected for inclusion in a meta-analysis.

Results: We included ten RCTs in a meta-analysis. Of the 108,118 people with hypertension and no pre-existing diabetes, 7,073 (6.5%) cases of type II diabetes were reported. CCBs were associated with a higher incidence of diabetes than angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs; pooled risk ratios [95% confidence intervals]: 1.23 [1.01–1.51] and 1.27 [1.14–1.42], respectively) and a lower incidence compared with β blockers or diuretics (0.83 [0.73–0.94] and 0.82 [0.69–0.98], respectively). The overall risk of diabetes among subjects taking CCBs was not significant (0.99 [0.85–1.15]).

Conclusion: The use of CCBs was not significantly associated with incident diabetes compared to other antihypertensive agents: the association with diabetes was lowest for ACEIs and ARBs, followed by CCBs, β blockers, and diuretics. Although CCBs can be safely used in hypertensive patients, it would be premature to advocate CCBs for the prevention or treatment of diabetes.

Keywords: diabetes, calcium channel blockers, hypertension, meta-analysis

Introduction

A growing body of evidence has suggested that the effects of different classes of antihypertensive medications on the incidence of diabetes vary, with the lowest association reported for angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) followed by calcium channel blockers (CCBs), β blockers, and diuretics.[1] The progressive loss of pancreatic β-cell mass/function is a key component in the pathogenesis of both type I and type II diabetes and also underlies insulin resistance in type II diabetes. A recent study using human islet cells and murine models for type I and type II diabetes demonstrated that verapamil, a CCB, might inhibit the expression of the proapoptotic β-cell thioredoxin-interacting protein (TXNIP) in INS-1 cells and human islets, thereby enhancing β-cell survival and function and preventing diabetes in BTBR ob/ob mice.[2]

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http://dx.doi.org/10.2147/DMSO.S49767

In light of the worldwide epidemics of diabetes and hypertension, explorations of the effect of antihypertensive drugs on the incidence of diabetes are of clinical importance. Moreover, they are crucial in the areas of public health, since a modest increase in the risk of diabetes translates into a substantial social burden. These circumstances prompted us to investigate, with greater precision, the effects of CCBs on diabetes prevention by scrutinizing pertinent up-to-date original reports and combining their data in an attempt to obtain meaningful clues for an evaluation of the potential benefits of CCBs.

Methods

Searches of MEDLINE, EMBASE, ISI Web of Science, the Cochrane Library, and ClinicalTrials.gov from their inception until March 11, 2013, were performed. Studies evaluating the incidence of diabetes among subjects taking CCBs, compared to those taking other antihypertensive medications, were identified using a combination of the following keywords: "calcium channel blocker" and "diabetes mellitus". The reference lists of the pertinent articles were also inspected. We assessed all the identified studies with regard to the effects of CCBs on the incidence of diabetes based on original data analyses to determine their eligibility for inclusion in a qualitative analysis. The inclusion criteria for the meta-analysis were as follows: a published full-text report, the use of a randomized controlled trial (RCT) with a follow-up period of at least 1-year, and the reporting of event numbers. To ascertain the validity of the eligible studies, the quality of each report was appraised in reference to the CONSORT statement[3] and the QUOROM statement.[4] We then reviewed each full-text report to determine its eligibility and extracted and tabulated all the relevant data independently. The extracted data included the characteristics of the subjects (including age, sex, and region), published year, follow-up period, outcomes, and the methods used for risk estimation. Any disagreement was resolved by a consensus among the investigators. If more than one study was published for the same subjects with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

In the meta-analysis, the relative risks with CCBs compared with each comparator were combined and the pooled risk ratio (RR) with the 95% confidence interval (CI) was calculated using the Mantel–Haenszel random-effects model. Heterogeneity among the studies was evaluated using the I^2 statistics. A subgroup analysis and a meta-regression analysis[5] were also conducted, as appropriate. The equality of the risk ratios between subgroups was assessed using the z-statistic test. RevMan (version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for these calculations. All the procedures were performed in accordance with the PRISMA statement.[6]

Results

A total of 1,146 articles were identified during our search; of these, 12[7–18] were assessed with respect to their eligibility for inclusion in our review, which was aimed at determining the influence of CCBs on the incidence of diabetes. Out of these 12 articles, one study[10] in which CCBs were compared with a placebo and another[18] in which there was no event excluded; consequently, ten RCTs were included in the meta-analysis (Figure 1). The selected articles were moderately heterogeneous in terms of the population demographics. Most of the included studies were conducted in the United States and European countries, and their follow-up durations (range: 2.7–5.5 years) were sufficiently long for the outcomes to occur.

Of the total of 108,118 people with hypertension and no pre-existing diabetes, 7,073 (6.5%) cases of type II diabetes were reported. The RRs against each comparator and the overall RR are depicted in Figure 2. CCBs were associated with a higher incidence of diabetes, compared to ACEIs (n = 3)[7,8,14] or ARBs (n = 2; pooled RR [95% CI], 1.23 [1.01–1.51] and I^2 = 27%, 1.27 [1.14–1.42] and I^2 = 2%, respectively),[15,16] and a lower incidence compared with β blockers (n = 5)[7,9,12–14] or diuretics (n = 3; pooled RR, 0.83 [0.73–0.94] and I^2 = 61%, 0.82 [0.69–0.98] and I^2 = 19%, respectively).[8,11,17] As described in Table 1, the RRs against newer modalities (ACEIs and ARBs) were significantly higher than those against traditional agents (β blockers and diuretics). Only two reports investigated the risk associated with non-dihydropyridines against β blockers,[12,13] which was not statistically different from the risk associated with dihydropyridines against β blockers (n = 3).[7,9,14] The overall risk of diabetes among those with CCBs was nonsignificant (pooled RR, 0.99 [0.85–1.15] and I^2 = 87%). The heterogeneity among the reports in each medication category and for the overall analysis was generally high. The risk was consistent despite differences in age, the proportion of men, the risk of cardiovascular disease, and blood pressure between the randomized groups (Table 1).

Discussion

Our meta-analyses of worldwide RCTs suggested that the metabolic effect of CCBs was neutral, compared to other

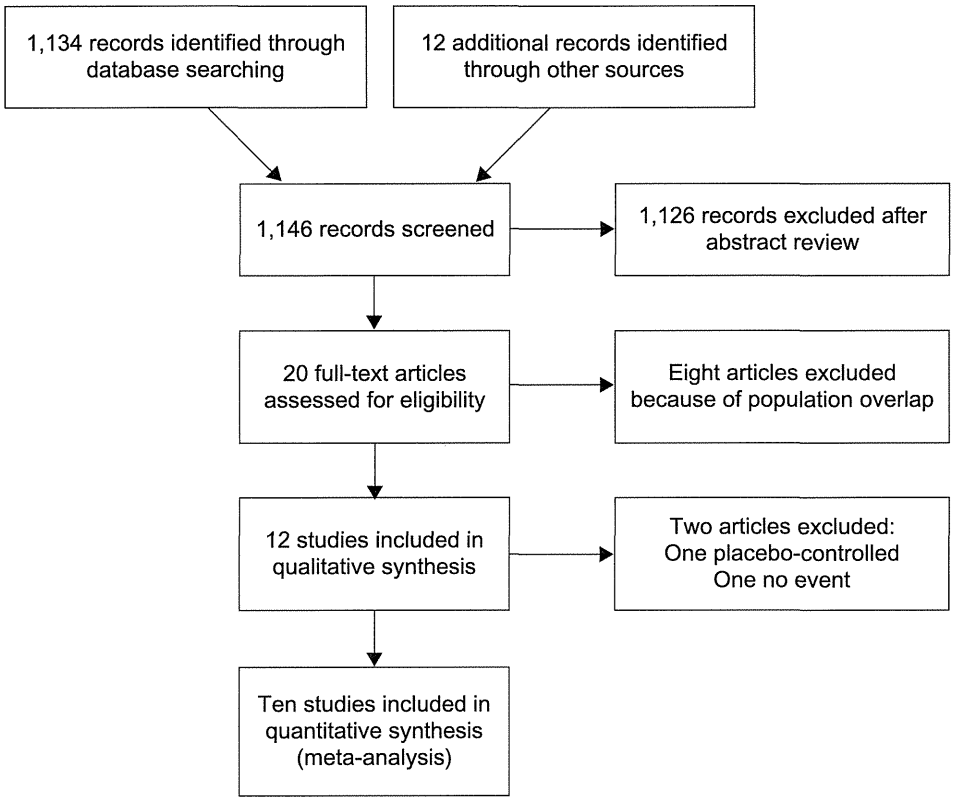

Figure 1 Flow diagram of study selection.

antihypertensive drugs, which did not support the notion that CCBs might prevent diabetes[2] or refute the current guidelines for compelling indications.[19,20] For those with overt diabetes and hypertension, ACEIs and ARBs are generally preferred in light of the lower risk of diabetes progression, as suggested by our analysis and the nephroprotective effects of these agents.

The strength of our present study is that the analysis was solely based on long-term, large-scale RCTs originating from multiple nations and was thus more comprehensive than previous articles.[1,21] The included data were good quality, apparently had sufficient power to detect differences in the risk of the outcome, and were biologically plausible. The temporal sequence of the events was appropriate. The outcome ascertainment tools were valid, and there were few, if any, missed confounders. The heterogeneity of the results within each comparator group was low except for β blockers: this low heterogeneity suggests that each of the results was consistent and that most of the variation was attributable to chance alone. The large I^2 values in some analyses indicated that the range of the plausible risk estimates was wide, generally because of the diversity of the study design, population backgrounds, and ethnicities. The heterogeneity of the overall analysis was quite high, probably because of the variety of drug classes that were confounded by indication. The extent of blood pressure change was possibly another source of heterogeneity, but this hypothesis cannot be statistically tested in light of the scarcity of data. A subgroup analysis and a meta-regression, which suggested a consistent risk regardless of the CCB subclass, age, sex, cardiovascular risk, or difference in achieved blood pressure, support the safety and the clinical generalizability of CCBs.

Verapamil was recently reported to inhibit TXNIP expression in INS-1 cells and human islets, and orally administered verapamil reduced TXNIP expression and β-cell apoptosis, enhanced endogenous insulin levels, and rescued mice from streptozotocin-induced diabetes.[2] Verapamil also reportedly promoted β-cell survival and improved glucose homeostasis and insulin sensitivity in BTBR ob/ob mice.[2] Despite these facts, our study did not find a metabolic benefit. Thus, the magnitude of the protective effect may be too small to have an effect on type II diabetes in clinical settings, and trials in patients with type I diabetes may provide some insights. Further studies to scrutinize the effect of CCBs on glycemic control in diabetic patients are also pending.

Although the quality of the included studies was high, our analysis should be interpreted in the context of the following limitations. The number of available studies for each

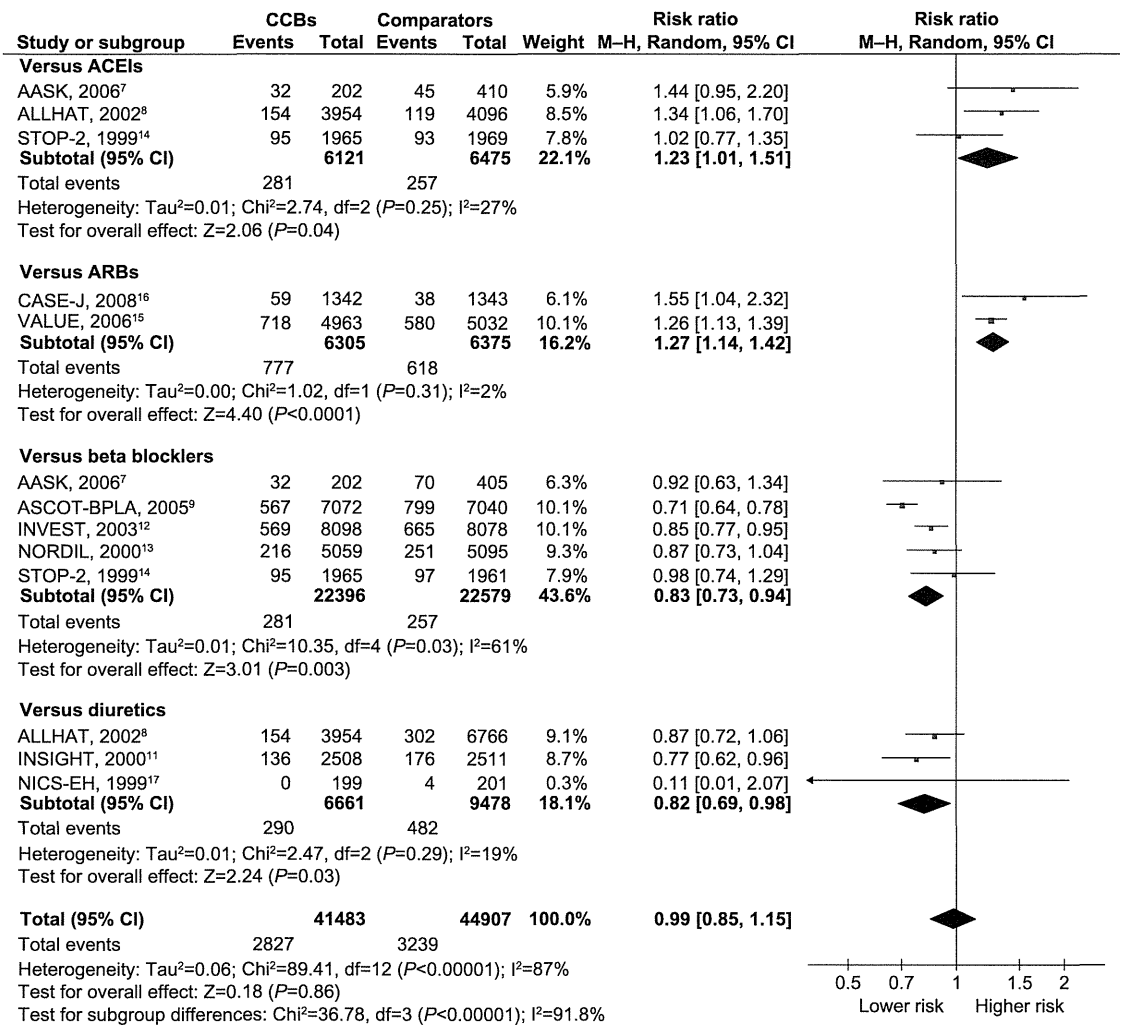

Figure 2 Risk ratios for diabetes associated with CCBs, compared to other antihypertensive drugs.

Notes: Boxes, estimated risk ratios (RRs); bars, 95% CI. Diamonds, fixed-effects model RRs; width of diamonds, pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis.

Abbreviations: AASK, African American Study of Kidney diseases and hypertension; ACEI, Angiotensin-Converting Enzyme Inhibitor; ALLHAT, Antihypertensive and Lipid Lowering to prevent Heart Attack Trial; ARB, angiotensin-receptor blocker; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; CASE-J, Candesartan Antihypertensive Survival Evaluation in Japan; CCB, calcium channel blocker; INSIGHT, International Nifedipine; GITS Study, Intervention as a Goal in Hypertension Treatment Study; INVEST, International Verapamil-Trandolapril Study; NICS-EH, National Intervention Cooperative Study in Elderly Hypertensives; NORDIL, Nordic Diltiazem study; M-H, Mantel–Haenszel; STOP-2, Second Swedish Trial in Older Patients with hypertension-2; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

medication subclass was relatively small and the studies were moderately heterogeneous, especially for β blockers. Thus, a publication bias may exist, although we cannot assess this hypothesis. Regarding the external validity of the results, it is also important to realize that the participants of the studies may not represent general populations. The incident of diabetes was not the primary endpoint in the majority of the included trials and thus diagnostic ascertainment may not have been valid.

Although CCBs might inhibit proapoptotic β-cell TXNIP expression, thereby enhancing β-cell survival and function, we found that the use of CCBs was not significantly associated with incident diabetes compared to other antihypertensive agents. Further studies on the complex interactions between CCBs and TXNIP are warranted before CCBs can be advocated as a measure for diabetes prevention or treatment.

Acknowledgments

All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conceived and designed the experiments: HN, MN. Performed the experiments: HN, AG, TT. Analyzed the data: HN, AG, TT. Contributed reagents/materials/analysis tools: HN, AG, TT. Wrote the paper: HN. Reviewed/edited the manuscript: AG, TT, MN.

This study was supported by a Health Sciences Research Grant (Comprehensive Research on Diabetes/Cardiovascular and Life-Style Related Diseases H22-019) from the Ministry of Health, Labor and Welfare of Japan. The funders had no role in the study design, data collection and analysis, decision to publish, or the preparation of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2013 December;68(12):1482–1492
doi:10.1093/gerona/glt041

Advance Access publication May 8, 2013

Royal Jelly Prevents the Progression of Sarcopenia in Aged Mice In Vivo and In Vitro

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Sarcopenia is characterized by the age-related loss of muscle mass and strength. One of the mechanisms of sarcopenia is the loss in the function and number of muscle satellite cells. Royal jelly (RJ) is a health food used worldwide. To obtain better digestion and absorption than RJ, protease-treated RJ (pRJ) has been developed. RJ and pRJ have been suggested to have potential pharmacological benefits such as prolonging the life span and reducing fatigue. Because these effects may improve sarcopenia and the functions of satellite cells, we examined the effects of RJ or pRJ treatment on the skeletal muscles in an animal model using aged mice. In vivo, RJ/pRJ treatment attenuated the decrease in the muscle weight and grip strength and increased the regenerating capacity of injured muscles and the serum insulin-like growth factor-1 levels compared with controls. In vitro, using isolated satellite cells from aged mice, pRJ treatment increased the cell proliferation rate, promoted cell differentiation, and activated Akt intracellular signaling pathway compared with controls. These findings suggest that RJ/pRJ treatment had a beneficial effect on age-related sarcopenia.

Key Words: Aged mice—Sarcopenia—Satellite cells—Royal jelly—Insulin-like growth factor-1—Akt signaling.

Received September 3, 2012; Accepted March 1, 2013

Decision Editor: Rafael de Cabo, PhD

THE population of people aged 60 and older is currently growing at the rate of 2.6% per year, which is more than twice the rate of growth of the total population in the world (1). In general, aging is accompanied by frailty, functional limitations, and disabilities that interfere with the activities of daily life. These factors reduce the quality of life of the elderly patients and eventually cause their loss of autonomy in daily life. Sarcopenia is the age-related loss of the muscle mass and strength, which causes frailty, functional limitations in daily living, disabilities, and, finally, a higher mortality rate in the elderly patients (2).

Satellite cells are resident myogenic progenitors in the skeletal muscles. They play a central role in the growth and regeneration of the skeletal muscles (3). In response to stimulation, satellite cells form myoblasts, fuse together, and generate new fibers (4). The age-related functional disability and decrease in the number of satellite cells contribute to the development of sarcopenia (5). Thus, maintaining the functions of satellite cells and their numbers may reduce sarcopenia and, furthermore, may improve the regenerating capacity of the skeletal muscles in the elderly patients. However, to isolate satellite cells, specific cell surface markers were not available until recently (6).

Among the factors that stimulate satellite cells, insulin-like growth factor-1 (IGF-1) plays a central role. IGF-1 stimulates satellite cell proliferation, their differentiation into myoblasts, and, finally, their differentiation into myotubes (4). IGF-1 is the most important mediator of muscle growth and repair (7). Furthermore, a recent study suggested the potential of IGF-1 to improve sarcopenia in the elderly patients (7).

Worker honeybees produce royal jelly (RJ) in their hypopharyngeal and mandibular glands (8). RJ has been used worldwide for many years as commercially available medical products and health foods and has been considered beneficial to health. These days, a modified RJ product, protease-treated RJ (pRJ), has been developed to improve digestion and absorption compared with regular RJ. Accumulating evidence suggests that RJ is rich in a wide variety of nutrients, including vitamins, minerals, and more than 20 amino acids (9). RJ also has numerous potential pharmacological capacities, such as prolonging the life span (in mice and nematodes) (10,11) and reducing fatigue (12), hypertension (13), and hypercholesterolemia, as well as antioxidant and anti-inflammatory effects (8,14–16).

Because these effects of RJ might have a potential to improve sarcopenia and the functions of satellite cells (17–21), we hypothesized that RJ might have a beneficial effect on the prevention of sarcopenia. Furthermore, we hypothesized that this effect might involve IGF-1. To the best of our knowledge, few studies have examined the effects of RJ on muscles in elderly patients or aged animals or the relationship between RJ and IGF-1. Thus, in this study, we examined the effects of the RJ/pRJ on muscle weight, muscle strength, satellite cell functions, the regenerating capacity of the skeletal muscles in vivo and in vitro, and the involvement of IGF-1 in an animal model using aged mice.

Methods

Culture Conditions of Satellite Cells and Cell Proliferation Assay

Sorted satellite cells from untreated, aged mice were cultured in growth medium containing high-glucose Dulbecco's modified Eagle's medium with 20% fetal bovine serum (MP Biomedicals, Morgan Irvine, CA), 2.5 ng/mL basic fibroblast growth factor (Invitrogen, Eugene, OR), 100 U/mL penicillin, and 100 μg/mL streptomycin (Sigma, St. Louis, MO). Satellite cells under eight passages were used in this study. Differentiation was induced as previously shown with some modifications in differentiation medium containing high-glucose Dulbecco's modified Eagle's medium, 5% horse serum (Sigma), penicillin, and streptomycin for several days (22). RJ and pRJ were dissolved in water, sterilized by a filter, and then added to the culture medium at the following concentrations: 100, 200, 500, or 1000 μg/mL. Some cells were serum starved for overnight and then stimulated with 10 nM insulin (Sigma), which is a potent activator of Akt, for 5 minutes. The cells were cultured for 24, 48, or 72 hours, and the number of cells was determined by water-soluble tetrazolium-8 (WST-8, DOJINDO, Tokyo, Japan) assay using a cell-counting kit (23,24).

Mice and Dietary Treatment

Male C57BL/6 mice were obtained from Clea Japan (Tokyo, Japan) and maintained under specific pathogen-free conditions with unrestricted access to food and water. Experiments were carried out in accordance with guidelines established by the Tohoku University Committee on Animal Research. At the age of 21 months, mice were divided into five groups according to the diets provided for each group and maintained for the next 3 months, with 10 mice in each group. The five groups of diets were normal diet (controls), diet mixed with 1% weight RJ (1% RJ), diet mixed with 5% weight RJ (5% RJ), diet mixed with 1% weight pRJ (1% pRJ), and diet mixed with 5% pRJ (5% pRJ). All diets were manufactured by Oriental Yeast Co., Ltd. (Chiba, Japan), stored at 4°C, and sealed in plastic bags in vacuo until use to avoid oxidation. The base diet was composed of 20% milk casein, 0.3% cystine, 39.7% starch, 13.2% a-starch, 10% sucrose, 0.0014% cellulose, 1% vitamins, 3.5% mineral mixture, 0.25% choline bitartrate, and 0.5% *tert*-butylhydroquinone. The amounts of milk casein and starch were adjusted to equalize total proteins and calories between the groups in accordance with the amounts of added RJ/pRJ. Therefore, total energy and protein levels per weight were the same in all the diet groups. However, the amino acid contents were different among the groups. Dried RJ and pRJ powder was supplied by Institute for Bee Products & Health Science (Okayama, Japan). The vitamin and mineral components of RJ and pRJ were analyzed by Japan Food Research Laboratories (Tokyo, Japan) and are shown in Table 1. The mice had unrestricted access to food and water. After 3 months of the diet treatment, the grip strength was measured. Then, 25 mice (five mice from each group) were anesthetized and sacrificed, their sera were collected, and skeletal muscle samples were isolated. The other 19 (≥ 3 mice from each group) mice were sacrificed for evaluation of the regenerating capacity of injured skeletal muscles at 5 days after the injury.

Wire Hang Test

A wire mesh grid (10 × 10 cm) was used to assess the muscle strength. The mouse was placed on the wire mesh, then the mesh was inverted, and the mouse was forced to hang on the wire using its four limbs. The longest hanging time was recorded as the duration. The previously mentioned measuring process was repeated until the mouse could not hang on the wire mesh after the inversion. The number of repeated times is shown as the number of times (25).

Muscle Injury Model

After 3 months of the diet treatment, mice were anesthetized, and cardiotoxin from *Naja mossambica mossambica* (Sigma) dissolved in 100 μL phosphate-buffered saline (PBS) (10 μM) was injected into the tibialis anterior (TA) muscle. Five days later, the mice were sacrificed; and the