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Incidence of lower limb amputation in the diabetic and nondiabetic population: A nationwide 5-year cohort study in Japan

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-048436
Article Type:	Original research
Date Submitted by the Author:	25-Dec-2020
Complete List of Authors:	Kamitani, Fumika; Nara Medical University Nishioka, Yuichi; Nara Medical University Noda, Tatsuya; Nara Medical University Myojin, Tomoya; Nara Medical University Kubo, Shinichiro; Nara Medical University Higashino, Tsuneyuki; Healthcare and Wellness Division, Mitsubishi Research Institute, Inc., Tokyo, 100-8141, Japan Okada, Sadanori; Nara Medical University Akai, Yasuhiro; Nara Medical University, Center for Postgraduate Training; Nara Medical University, Department of Nephrology Ishii, Hitoshi; Nara Medical University Takahashi, Yutaka; Nara Medical University Imamura, Tomoaki; Nara Medical University
Keywords:	Epidemiology < TROPICAL MEDICINE, ORTHOPAEDIC & TRAUMA SURGERY, DIABETES & ENDOCRINOLOGY

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11 **Incidence of lower limb amputation in the diabetic and nondiabetic population: A**
12 **nationwide 5-year cohort study in Japan**
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22 **Short Running Title:** Incidence of limb amputation in Japan
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29 **Word count:** 3113 words
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36 **Number of tables and figures:** 4 tables and 1 figure.
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Abstract

Introduction: This study was conducted to comprehensively investigate the incidence and risk of lower limb amputation (LLA) in the Japanese diabetic and nondiabetic population.

Research design and methods: This retrospective population-based cohort study was based on the national claims data in Japan, comprising a total population of 150 million. Data of all individuals who had LLA from April 2013 to March 2018 were obtained, and only the first major and minor amputation per individual during the 5-year period were counted. The sex- and age-adjusted incidence of LLA was calculated in the diabetic and nondiabetic population.

Results: In the 5-year period, 34,773 major and 24,904 minor LLAs were performed in Japan. The crude incidence of major and minor LLAs was 6.8 (diabetic, 49 vs. nondiabetic, 3.0) and 4.9 (diabetic, 38 vs. nondiabetic, 1.8), respectively, per 100,000 person-years. The sex- and age-adjusted incidence of major and minor LLAs was 20.3 and 27.1 times higher, respectively, in the diabetic population than in the nondiabetic population.

Conclusions: This is the first report of the national statistics of LLAs in Japan. The Japanese crude incidence of LLAs was lower than the incidence that was previously reported in other countries. The incidence of major and minor lower LLAs was 20 and 30

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5 times higher, respectively, in individuals with diabetes than in nondiabetic individuals.
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8 This information can help create an effective national healthcare strategy for preventing
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10 limb amputations, which affect the quality of life of patients with diabetes and add to the
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12 national healthcare expenditure.
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20 **Keywords:** amputation, cohort study, diabetes mellitus
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Strengths and limitations of this study

- This is the first report of the national statistics of lower limb amputations (LLAs) in the Japanese diabetic and nondiabetic population.
- This retrospective cohort study was based on the National Database (NDB) in Japan, comprising a total population of 150 million.
- Investigating the risk of LLA in diabetics can help create an effective national healthcare strategy for preventing limb amputations.
- The detailed medical information and parameters of each patient, including glycated hemoglobin, body weight, smoking history, and family history, could not be reviewed because of the nature of the database.
- However, NDB is a comprehensive survey and the likelihood of selection bias is relatively small, and we adjusted for sex and age when comparing the LLA rates of diabetic and nondiabetic patients.

INTRODUCTION

The objectives of diabetes management are to reduce the metabolic dysfunction that occurs because of hyperglycemia, to prevent the development or progression of diabetes-related complications and conditions associated with diabetes, and to enable the affected individuals to maintain their quality of life and life expectancy similar to that of healthy individuals.[1] Vascular and neurological complications of diabetes can considerably influence lower limb amputation (LLA).[2–4] Previous studies have shown that diabetes increases the risk of LLA, although there were considerable variations in the incidence of LLA in the diabetic population.[5] It is very important to understand the incidence rates of LLA in the diabetic and nondiabetic population to further improve the care of patients with diabetes and to avoid fatal outcomes, particularly with regard to decisions associated with health policy and the economy.[4,5]

In patients with diabetes, besides major LLAs (e.g., amputation through or proximal to the ankle joint), there may be many minor LLAs (e.g., toe amputation).[6] Major amputation represents a greater detrimental impact on physical integrity, but minor amputations should also be prevented. Given the increase in the diabetic population, not only major LLA but also minor LLA impose a burden on the healthcare system. With the significant aging of the population, the number of patients with diabetes in Japan continues to increase.[7] Therefore, it is important to grasp the prevalence associated with age and the total incidence of each major and minor LLA. However, no large-scale

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5 community-based surveys on the incidence of LLA and no comparison studies of LLA in
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8 the diabetic and nondiabetic population in Japan have been conducted. This study aimed
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11 to investigate the incidence of all LLA in Japan and to compare the age-adjusted incidence
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14 of LLA in the diabetic population with that in the nondiabetic population based on data
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17 obtained from the National Database of Health Insurance Claims in Japan. To the best of
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20 our knowledge, this study is the first to evaluate the LLA rate in Japan based on a
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23 nationwide dataset.

24 25 **METHODS**

26 27 28 **Study design and population**

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31 This population-based, retrospective cohort study was based on the National Database
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34 (NDB) dataset and was approved by the ethics committee of Nara Medical University
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37 (approval no. 1123-5). The use of NDB dataset was approved by the Ministry of Health,
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40 Labor and Welfare, and the need for informed consent was waived in view of the study
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43 design. All patient data were anonymized before analysis.

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46 The study cohort comprised individuals who are enrolled in the NDB; all patient
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49 data were anonymized. Japan has a universal public healthcare system, and the NDB
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52 includes almost all patients in Japan. The NDB data provided information on personal
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55 identifiers,[8] date, age group, sex, description of the medical procedures that were
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58 conducted, the World Health Organization International Classification of Diseases
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5 diagnosis codes, the medical care that was received, medical examinations that were
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8 conducted that did not include test results, and prescribed drugs, which were independent
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11 of the doctor's or patient's reports.[9] Drug information included the prescription amount,
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14 brand name, generic name, dosage, and the number of days for which the medicine was
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16 prescribed.
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19 We designed this cohort study to include all the data of LLA patients collected
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22 between April 2013 and March 2018 in the analysis. Japan has a population of
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25 approximately 127 million, although the total observable population of this study was
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28 approximately 150 million due to the inclusion of newborns within the 5-year observation
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31 period and the slight deficits in the linking of the NDB.
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33 34 **Criteria for diagnosing diabetes**

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37 We defined patients with diabetes as individuals who had any of the diagnosis codes
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40 associated with diabetes as well as those who were prescribed diabetes medication at least
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43 once in the past 5 years. The diagnosis and medicine codes for diabetes are the same as
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46 those reported in a previous study[9] and are presented in Supplementary Tables S1 and
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49 S2, respectively. We included all patients with any type of diabetes; however, patients on
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52 dietary or exercise management without antidiabetic medication were excluded.
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54 55 **Definition of LLA**

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58 The primary outcome was the first occurrence of each of the major or minor LLAs in the
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5 study period. The amputation codes are shown in Supplementary Table S3. We defined
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8 major LLAs by the use of six medical procedure codes through, or proximal to, the ankle
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10 joint, as follows: Limb amputation (thigh), Limb amputation (below legs), Limb
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12 amputation (foot), Limb joint dissection (crotch), Limb joint dissection (knee), and Limb
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14 joint dissection (foot) indicated by 150051610, 150051710, 150051810, 150052210,
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16 150052310, and 150052610 (in K084-00 and K085-00), respectively, which are Japanese
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18 original codes. In the Japanese medical code, finger and toe amputations are indicated by
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20 the same code, and it is impossible to distinguish between them. Therefore, we defined
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22 minor LLA as limb amputation (finger) and limb joint dissection (finger): 150051910 and
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24 150052710 (in K084-00 and K085-00).
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33 **Statistical analyses**

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36 We defined the duration between dates of the first occurrence of the medical treatment
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38 code or drug code and the last occurrence as the risk period. If the first major LLA
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40 occurred during the observation period, the major LLA observation was terminated at that
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42 time. Similarly, if the first minor LLA occurred during the observation period, the minor
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44 LLA observation was terminated at the time. Therefore, even when the major and minor
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46 LLA occurred many times in the same person during the 5-year study period, we counted
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48 only the first major and minor LLAs. Moreover, even if a minor LLA occurred, the major
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50 LLA observation continued such that the incidence of the major LLA was not
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52 underestimated. The age recorded in this study was the age at the time of the last treatment
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5 during the study period or the patient's age when the LLA was done. To calculate the rate
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8 of incidence of LLA, the denominator was extracted from the NDB dataset. Crude rates
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10 are presented as the number of amputations per 100,000 person-years. There were few
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13 LLAs in individuals younger than 44 years and in those aged 100 years or older during
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15 the study period; therefore, the crude rates were calculated for the diabetic and
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18 nondiabetic populations only in the age range of 45–100 years. Nonetheless, the sex- and
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21 age-adjusted LLA incidence rates were calculated for all age groups. To compare the
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24 LLA incidence rates between participants with and without diabetes, the incidence rates
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27 were evaluated, after adjusting for sex and age, at all ages, by using the direct method and
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30 the sex and age structure of the Japanese 1985 population model (A Virtual Population
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33 Model Based on population in 1985), which is commonly used in Japanese
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36 epidemiological studies (Supplementary Table S4).

37 38 **RESULTS**

39 40 41 **Population included in the NDB and the diabetic population**

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45 Of the 150,328,339 people (186,819,100,972 person-days) included in the NDB,
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48 9,962,459 had diabetes, which accounted for 6.6% of the total sample (Table 1). In the
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51 subgroups of men and women, the proportion of diabetic patients was higher in the elderly
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54 group (age ≥ 65 years).
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Table 1 Characteristics of the NDB study population categorized into diabetic and nondiabetic patients.

Age groups, years	Total	Diabetic, n (%)	Nondiabetic, n (%)
Total	150,328,339	9,962,459 (6.6)	140,365,880 (93.4)
Men, total	70,958,283	5,838,320 (8.2)	65,119,963 (91.8)
Men, age groups, years			
0–44	35,317,225	301,772 (0.9)	35,015,453 (99.1)
45–64	17,572,798	1,709,991 (9.7)	15,862,807 (90.3)
65–74	9,134,765	1,849,566 (20.2)	7,285,199 (79.8)
75–84	6,152,042	1,458,566 (23.7)	4,693,476 (76.3)
≥85	2,781,453	518,425 (18.6)	2,263,028 (81.4)

Women, total	79,370,056	4,124,139 (5.2)	75,245,917 (94.8)
Women, age groups, years			
0–44	37,492,073	212,476 (0.6)	37,279,597 (99.4)
45–64	18,906,831	792,993 (5.7)	18,113,838 (94.3)
65–74	9,860,220	1,154,454 (11.7)	8,705,766 (88.3)
75–84	7,538,821	1,191,531 (15.8)	6,347,290 (84.2)
≥85	5,572,111	772,685 (13.9)	4,799,426 (86.1)

Incidence of LLAs

Major LLAs occurred in 34,773 people, whereas minor LLAs occurred in 24,904 people in the 5-year period. In Japan, a new major and minor LLA occurred in approximately 7000 and 5000 individuals, respectively, per year. Table 2 shows the characteristics of LLA patients stratified into subgroups of diabetic and nondiabetic patients. Figures 1A and 1B show the sex and age composition of the patient population with major and minor LLA. In the overall study population, the incidence of LLA was higher in men than in women. Patients with diabetes accounted for 60% and 65% of the total major and the total minor LLAs, respectively; the highest number of LLAs in male patients occurred in the age group of 65–84 years, whereas, in female patients, the number was significantly associated with age. Therefore, most amputations occurred in the elderly population.

Table 2 Patients with lower limb amputations stratified into diabetic and nondiabetic groups by age group and type of amputation.

Age groups, years	Major LLA			Minor LLA		
	Total	Diabetic, n (%)	Nondiabetic, n (%)	Total	Diabetic, n (%)	Nondiabetic n (%)
Total	34,773	20,777 (59.8)	13,996 (40.2)	24,904	16,156 (64.9)	8748 (35.1)
Men, total	21149	14062 (66.5)	7087 (33.5)	16482	11,832 (71.8)	4650 (28.2)
Men, age groups, years						
0–44	655	325 (49.6)	330 (50.4)	602	374 (62.1)	228 (37.9)
45–64	4307	3515 (81.6)	792 (18.4)	4151	3448 (83.1)	7031 (16.9)

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	65–74	6102	4599 (75.4)	1503 (25.6)	4986	840 (77.0) 1146 (33.0)
	75–84	6486	4148 (64.0)	2338 (36.0)	4629	187 (68.8) 1442 (31.2)
	≥85	3599	1475 (41.0)	2124 (59.0)	2114	983 (46.5) 1131 (53.5)
	Women, total	13,624	6715 (49.3)	6909 (50.7)	8422	324 (51.3) 4098 (48.7)
	Women, age					
	groups, years					
	0–44	211	57 (27.0)	154 (73.0)	146	59 (40.4) 87 (59.6)
	45–64	1247	944 (75.7)	303 (24.3)	1023	756 (73.9) 267 (26.1)
	65–74	2203	1562 (70.9)	641 (29.1)	1649	136 (68.9) 513 (31.1)
	75–84	3840	2150 (56.0)	1690 (44.0)	2470	371 (55.5) 1099 (44.5)

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9 LLA, lower limb amputation.
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Crude incidence rate of LLA

Table 3 shows the crude incidence rate (per 100,000 person-years) of LLA in the diabetic and nondiabetic study population. Figures 1C and 1D show the crude incidence rates of major and minor LLA according to the sex and age of the patients. The crude incidence of major LLA per 100,000 person-years was 49.0 (95% confidence interval [CI] 48.7–50.0) in diabetic and 3.0 (95% CI 2.9–3.0) in nondiabetic subjects. The crude incidence of minor LLA per 100,000 person-years was 38 (95% CI 37.4–38.6) in diabetic and 1.8 (95% CI 1.8–1.9) in nondiabetic individuals, respectively. The incidence of LLA in the study subgroup with diabetes was higher than that in the nondiabetic group. The rate of LLA incidence in men was approximately 1.5 times higher than it was in women. The incidence of LLAs increased gradually with age, with regard to major and minor LLAs.

Table 3 Incidence rate (per 100,000 person-years) of lower limb amputations in diabetic and nondiabetic patients.

Men and women, age group, years	Major LLA				Minor LLA			
	Diabetic	95% CI	Nondiabetic	95% CI	Diabetic	95% CI	Nondiabetic	95% CI
All age groups	49.0	48.7-50.0	3.0	2.9-3.0	38	37.4-38.6	1.8	1.8-1.9
Men, age group, years								
45-64	50.3	48.7-52.0	1.5	1.4-1.6	48.9	47.2-50.5	1.3	1.2-1.4
65-74	58.1	56.4-59.8	5.5	5.2-5.8	48.0	46.5-49.5	4.1	3.9-4.4
75-84	66.2	64.2-68.2	12.2	11.7-12.7	50.4	48.6-52.1	7.4	7.1-7.8

85–99	71.0	67.4–74.6	24.9	23.8–25.9	46.8	43.9–49.8	13.1	12.3–13.9
All age groups	57.7	56.7–58.6	3.3	3.3–3.4	48.0	47.2–48.9	2.2	2.1–2.2
Women, age group,								
years								
45–64	28.6	26.7–30.4	0.5	0.4–0.5	22.7	21.0–24.3	0.4	0.4–0.5
65–74	30.5	29.0–32.0	1.8	1.7–2.0	22.0	20.7–23.2	1.5	1.3–1.6
75–84	40.7	39.0–42.4	6.2	5.9–6.5	25.7	24.3–27.1	4.0	3.8–4.2
85–99	63.3	60.5–66.0	21.5	20.8–22.2	31.3	29.3–33.2	11.0	10.5–11.5
All age groups	37.9	37.0–38.9	2.7	2.6–2.7	24.2	23.5–24.9	1.6	1.5–1.6

LLA, lower limb amputation; NDB, National Database.

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Age-adjusted incidence rate

To compare the differences in the incidence of LLA by age in individuals with and without diabetes, the age-adjusted incidence of LLA was calculated for all ages (Table 4). The age-adjusted incidence of major LLA in men and women was 16.7 and 21.7 times higher, respectively, in the population with diabetes than in the nondiabetic population. The age-adjusted incidence of minor LLA in men and women was 25.0 and 24.3 times higher, respectively, in patients with diabetes than in nondiabetic participants. After adjusting for sex and age, the incidence of major and minor LLA was 20.3 and 27.1 times higher, respectively, in the population with diabetes than in the nondiabetic population.

Table 4 Age-adjusted incidence rate (per 100,000 person-year) of LLA in the diabetic and nondiabetic general population.

Groups	Incidence of Major LLA			Incidence of Minor LLA		
	Diabetic	Nondiabetic	Diabetic/Nondiabetic	Diabetic	Nondiabetic	Diabetic/Nondiabetic
Men	25.0	1.5	16.7	25.0	1.0	25.0
Women	13.0	0.6	21.7	9.7	0.4	24.3
Total	20.3	1.0	20.3	19.0	0.7	27.1

LLA, lower limb amputation.

DISCUSSION

The NDB is a comprehensive database of health insurance claims that are covered by the Japanese National Health Insurance system. Japan has universal health coverage, with local governments providing healthcare payments for approximately 2% of the population who are on welfare; with the exception of accidents (which is covered by automobile liability insurance or worker's accident compensation in a previous health insurance plan); thus, the NDB is considered to be representative of almost all health claims in Japan.[8,9] By using the information from the Japanese NDB dataset, we conducted cohort studies that comprised almost all LLAs in Japan during the study period. This is the first report of LLAs across Japan.

In this study, we found that the crude incidence of LLAs was lower than the incidence that was previously reported from other countries.[4,5] Many studies of LLAs in diabetes have been published, but only few nationwide studies have investigated the "true" incidence of LLA with or without diabetes. We believe that the true incidence of LLA is ascertained by an assessment of whether an LLA occurs even once in life. Interestingly, studies that evaluated only the first amputation during the observation period, as with our study, are very few, and most of the studies which investigated the incidence of LLA have counted multiple LLAs in each patient. Therefore, those previous studies would surely have overestimated the incidence of LLA in patients with diabetes, because a patient with diabetes plus an LLA is at a higher risk of re-amputation in the

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5 future.[10–12] This study provides a more accurate incidence of LLA in the diabetic
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8 population and would be helpful for establishing a more effective healthcare strategy to
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10 prevent LLA, which could affect the quality of life of patients with diabetes.
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14 Compared with the few previous studies that evaluated only the first amputation to
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16 calculate the incidence LLA, the results of this study showed a much lower incidence of
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18 LLA. The crude incidence of major and minor LLA per 100,000 person-years for diabetes
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20 was 49 and 38, respectively, in this study. In a previous systematic review where only the
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22 first amputation was evaluated to calculate the incidence of LLA, the crude incidence of
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24 major LLA per 100,000 person-years was 78–455 in the diabetic population.[5] Two
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26 studies from Japan have investigated the incidence of LLA by including only the first
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28 amputation. One of the studies was conducted in the southern part of Japan and showed
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30 that the incidence of major LLAs was 50 per 100,000 person-years in participants with
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32 type 2 diabetes.[13] Another study that used data from disabled person certifications
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34 revealed that the incidence of major LLAs, regardless of diabetes, was 5.8 per 100,000
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36 person-years.[14] These results, in conjunction with the findings of this study,
37
38 demonstrate a lower incidence of LLA in the Japanese population. There are several
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40 explanations for the observed lower incidence of LLA in Japanese patients. First, the
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42 Japanese population has a lower obesity rate than the Western populations.[15,16] Second,
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44 the incidence of cardiovascular disease is much lower in Japan;[17] and this contributes
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46 to a lower risk for the progression of atherosclerosis, which is the most prevalent etiology
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5 of LLA. Third, many Japanese individuals tend to avoid amputations because of religious
6 beliefs,[18] and doctors' resort to limb-preservation measures (intravascular therapy,
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8 such as stenting) to preserve the legs and feet and to delay amputation.
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14 In this study, the incidence of major and minor LLA was approximately 20 and 30
15 times higher, respectively, in diabetic individuals compared to nondiabetic individuals.
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17 In Japan, foot care performed by trained nurses has been approved for medical insurance
18 coverage since 2008,[19,20] and bypass surgery and intravascular treatment have become
19 significantly advanced.[21,22] Despite these efforts, our data indicate that the risk of LLA
20 in diabetic individuals remained significantly higher than it was in nondiabetic
21 participants. This may be associated with the fact that despite the insurance coverage of
22 nurse-provided foot care, only few patients actually avail foot care services. The medical
23 expenses burden of LLA is large.[23] The LLA risk of diabetic patients is much higher
24 and, therefore, more diligent screening and management of the diabetic population are
25 important to reduce the burden of quality of life reduction and the national healthcare
26 expenditure associated with LLA.[24]
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47 A key strength of our study is that, by analyzing data from the nationwide NDB
48 that encompasses almost the entire Japanese population, this study is the first to evaluate
49 the true nationwide incidence of LLA in Japan. Nonetheless, this study has some
50 limitations. First, there is no generally accepted definition of major or minor
51 amputation.[5] We defined major LLA by the medical procedure codes that implied
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5 amputation through or proximal to the ankle joint. Second, in minor amputation, we could
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8 not distinguish between upper and lower limb amputation because of the coding system
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11 of the NDB. The incidence of each limb amputation in the 5-year period is shown in
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14 Supplementary Table S5, which demonstrates a considerably lower incidence of upper
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17 limb amputation. These results could justify our definition of minor LLA. Finally, the
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20 detailed medical information and parameters of each patient, including glycated
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23 hemoglobin, body weight, smoking history, and family history, could not be reviewed
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26 because of the nature of the database. However, with regard to the smoking rate, which
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29 can be an important confounding factor, a previous study in Japan reported that there was
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32 no difference between the diabetes group and the general population in terms of the
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35 current smoker rate in sex- and age-stratified analyses. Furthermore, NDB is a
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38 comprehensive survey and the likelihood of selection bias is relatively small; in addition,
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41 we adjusted for sex and age when comparing the LLA rates of diabetic and nondiabetic
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44 patients. Therefore, it is unlikely that the study results will be significantly affected even
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47 if the detailed medical information and parameters cannot be factored in.[25]

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50 In conclusion, this is the first report of nationwide LLAs in Japan, and we found
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53 that the Japanese crude incidence of LLAs was lower than the incidence reported in
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56 previous reports. The incidence of major and minor LLAs was 20 and 30 times higher,
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59 respectively, in diabetic individuals than in nondiabetic individuals. This important
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information could help create an effective national healthcare strategy for preventing

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5 lower limb amputations, which affects the quality of life of the patient with diabetes and
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8 confers an increased burden on the national healthcare expenditure.
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14 **Data availability statement** The research data are available from the corresponding
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17 authr on reasonable request.
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5 **Ethics approval** This study was approved by the ethics committee of Nara Medical
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8 University (approval no. 1123-5).
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14 **Acknowledgments** We would like to thank Editage (www.editage.com) for English
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17 language editing.
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24 **Funding.** This study was supported by the Research for Infrastructure Construction of
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27 Studies with the Next Generation NDB Data to Create New Evidence from the Japan
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29
30 Agency for Medical Research and Development. This study was supported by the Project
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33 for Accelerating Medical Research through Cross-regional ICT utilization from the Japan
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35
36 Agency for Medical Research and Development and Japan Society for the Promotion of
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38
39 Science KAKENHI (grant number: JP18K17390).
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45 **Competing interests** YN received consultant fees from Novo Nordisk. SO received
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47
48 speaker fees from Novo Nordisk, Mitsubishi Tanabe, Sumitomo Dainippon, Arkray,
49
50
51 Bayer, Eli Lilly, Boehringer Ingelheim, Ono, AstraZeneca, Sanofi, and Takeda, outside
52
53
54 of the submitted work. YA received lecture fees and consultant fees from MSD KK, Ono,
55
56
57 Otsuka, Sumitomo Dainippon, Daiichi Sankyo, Eli Lilly, Sanofi S.A., Chugai, Novo
58
59
60 Nordisk, Kissei, Nippon Boehringer Ingelheim, Astellas, Kyowa Hakko Kirin, Pfizer,

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5 Takeda, Mitsubishi Tanabe, Novartis, Janssen Pharmaceutical K.K, Japanese Red Cross
6
7
8 Society Nara Red Cross Blood Center, Sumitomo Dainippon, Ltd., Kissei. HI received
9
10 lecture fees and consultant fees from Takeda, Eli Lilly Japan, Sanofi, Merck & Co.,
11
12 Astellas, Mitsubishi Tanabe, Daiichi Sankyo, Ono, AstraZeneca, Taisho Toyama,
13
14 Shionogi, Kowa, Boehringer Ingelheim, Novo Nordisk, Sumitomo Dainippon, and
15
16 Kyowa Hakko Kirin. YT received consultant fees from Novo Nordisk, Otsuka, and
17
18 Recordati, and speaker fees from Novo Nordisk, Sumitomo Dainippon, Eli Lilly, Ono,
19
20 Novartis, Nippon Boehringer Ingelheim, AstraZeneca, and Kyowa Kirin. The other
21
22 authors declare that they have no conflict of interest.
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33 **Patient consent for publication** Not required.
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37 **Data availability statement** The research data are available from the corresponding author
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39 on reasonable request.
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5 **Data availability statement** The research data are available from the corresponding author
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13 **Supporting information**
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16 Table S1. Diagnosis codes for diabetes.
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20 Table S2. Medication codes for diabetes.
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23 Table S3. Amputation codes.
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27 Table S4. A standard Japanese population model (1985).
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30 Table S5. Incidence of each type of limb amputation during the study period.
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Figure legends

Figure 1. Results of sex- and age-stratified analyses: (A) number of major lower limb amputation (LLA); (B) number of minor LLA; (C) rates of incidence of major LLA; and (D) rates of incidence of minor LLA.

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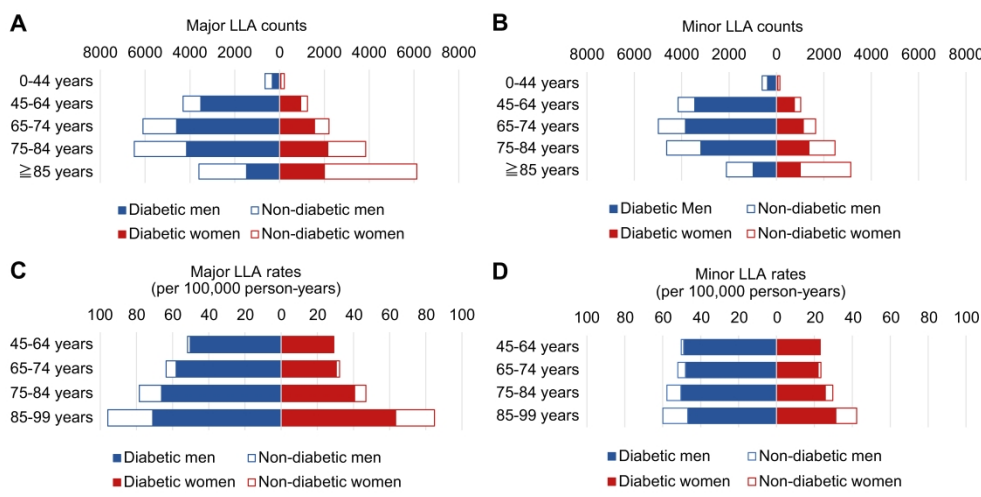


Figure 1. Results of sex- and age-stratified analyses: (A) number of major lower limb amputation (LLA); (B) number of minor LLA; (C) rates of incidence of major LLA; and (D) rates of incidence of minor LLA.

180x90mm (1200 x 1200 DPI)

Diagnosis in Japanese	Diagnosis in English	ICD-10 code	diagnosis code
1 型糖尿病	Type 1 diabetes mellitus	E10	2500014
不安定型糖尿病	Brittle diabetes	E10	2500027
緩徐進行 1 型糖尿病	SPIDDM - [Slowly progressive insulin-dependent diabetes mellitus]	E10	8844022
1 型糖尿病性昏睡	Type 1 diabetic coma	E10	8830030
1 型糖尿病・昏睡合併あり	Type 1 diabetes mellitus with coma	E10	8841679
緩徐進行 1 型糖尿病・昏睡合併あり	SPIDDM with coma - [Slowly progressive insulin-dependent diabetes mellitus]	E10	8844026
1 型糖尿病性低血糖性昏睡	Hypoglycemia in the context of type 1 diabetes mellitus	E10	8845065
1 型糖尿病性ケトアシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus	E10	8830028
1 型糖尿病・ケトアシドーシス合併あり	Type 1 diabetes mellitus with ketoacidosis	E10	8841680
緩徐進行 1 型糖尿病・ケトアシドーシス合併あり	SPIDDM with ketoacidosis - [Slowly progressive insulin-dependent diabetes mellitus]	E10	8844025
劇症 1 型糖尿病	Fulminant type 1 diabetes mellitus	E10	8844045
1 型糖尿病性アシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus	E10	8845044
1 型糖尿病性アセトン血症	Type 1 diabetic acetone hyperlipoproteinemia	E10	8845045
1 型糖尿病性腎症	Type 1 diabetic nephropathy	E10	8830031
1 型糖尿病・腎合併症あり	Type 1 diabetes mellitus with diabetic nephropathy	E10	8841681
1 型糖尿病性腎症第 1 期	Type 1 diabetic nephropathy phase 1	E10	8843983

Supplementary Table S1 Diagnostic codes of diabetes.

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3	1 型糖尿病性腎症第 2 期	Type 1 diabetic nephropathy phase 2	E10436	8843984
4	1 型糖尿病性腎症第 3 期	Type 1 diabetic nephropathy phase 3	E10436	8843985
5	1 型糖尿病性腎症第 3 期 A	Type 1 diabetic nephropathy phase 3A	E10436	8843986
6	1 型糖尿病性腎症第 3 期 B	Type 1 diabetic nephropathy phase 3B	E10436	8843987
7	1 型糖尿病性腎症第 4 期	Type 1 diabetic nephropathy phase 4	E10436	8843988
8	1 型糖尿病性腎症第 5 期	Type 1 diabetic nephropathy phase 5	E10436	8843989
9	緩徐進行 1 型糖尿病・腎合併症あり	SPIDDM with nephropathy - [Slowly progressive insulin-dependent diabetes mellitus]	E10436	8844028
10	1 型糖尿病性腎硬化症	Type 1 diabetic nephrosclerosis	E10436	8845058
11	1 型糖尿病性腎不全	Type 1 diabetic kidney failure	E10436	8845059
12	1 型糖尿病性網膜症	Type 1 diabetic retinopathy	E10436	8830033
13	1 型糖尿病・眼合併症あり	Type 1 diabetes mellitus with eye complication	E10436	8841682
14	1 型糖尿病性黄斑浮腫	Type 1 diabetic macular edema	E10436	8843982
15	緩徐進行 1 型糖尿病・眼合併症あり	SPIDDM with eye complication - [Slowly progressive insulin-dependent diabetes mellitus]	E10436	8844024
16	1 型糖尿病性白内障	Type 1 diabetic cataracts	E10436	8844346
17	増殖性糖尿病性網膜症・1 型糖尿病	Proliferative diabetic retinopathy, type 1 diabetes	E10436	8844536
18	1 型糖尿病黄斑症	Type 1 diabetic macular disease	E10436	8845043
19	1 型糖尿病性眼筋麻痺	Type 1 diabetic eye muscle paralysis	E10436	8845049
20	1 型糖尿病性虹彩炎	Type 1 diabetic iritis	E10436	8845053
21	1 型糖尿病性中心性網膜症	Type 1 diabetic central retinopathy	E10436	8845064
22	1 型糖尿病性ニューロパチー	Type 1 diabetic neuropathy	E10436	8830032
23	1 型糖尿病・神経学的合併症あり	Type 1 diabetes mellitus with neurological	E10436	8841683
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5	緩徐進行 1 型糖尿病・神経学的合	SPIDDM with neurological complications - [Slowly	E10417	8844027
6	併症あり	progressive insulin-dependent diabetes mellitus]		
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8	1 型糖尿病性筋萎縮症	Type 1 diabetic muscular atrophy	E10418	8845050
9	1 型糖尿病性神経因性膀胱	Type 1 diabetic neuropathic bladder	E10419	8845055
10	1 型糖尿病性神経痛	Type 1 diabetic neuralgia	E10420	8845056
11	1 型糖尿病性自律神経ニューロパ	Type 1 diabetic autonomic neuropathy	E10421	8845057
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13	1 型糖尿病性多発ニューロパチー	Type 1 diabetic polyneuropathy	E10422	8845062
14	1 型糖尿病性単ニューロパチー	Type 1 diabetic mononeuropathy	E10423	8845063
15	1 型糖尿病性末梢神経障害	Type 1 diabetic peripheral neuropathy	E10424	8845071
16		Type 1 diabetes mellitus with peripheral circulation		
17	1 型糖尿病・末梢循環合併症あり	complications	E10425	8841684
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19	1 型糖尿病性壊疽	Type 1 diabetic gangrene	E10426	8843105
20		SPIDDM with peripheral circulation complications -		
21	緩徐進行 1 型糖尿病・末梢循環合	[Slowly progressive insulin-dependent diabetes	E10427	8844031
22	併症あり	mellitus]		
23				
24	1 型糖尿病性潰瘍	Type 1 diabetic ulcer	E10428	8845046
25	1 型糖尿病性血管障害	Type 1 diabetic vascular disease	E10429	8845051
26	1 型糖尿病性動脈硬化症	Type 1 diabetic atherosclerosis	E10430	8845066
27	1 型糖尿病性動脈閉塞症	Type 1 diabetic arterial occlusion	E10431	8845067
28	1 型糖尿病性末梢血管症	Type 1 diabetic peripheral vascular disease	E10432	8845069
29	1 型糖尿病性末梢血管障害	Type 1 diabetic peripheral vascular disease	E10433	8845070
30	1 型糖尿病・関節合併症あり	Type 1 diabetes mellitus with joint complications	E10434	8841685
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3	1 型糖尿病・糖尿病性合併症あり	Type 1 diabetes mellitus with diabetic complications	E10436	8841686
4	緩徐進行 1 型糖尿病・関節合併症	SPIDDM with joint complications - [Slowly	E10437	8844023
5	あり	progressive insulin-dependent diabetes mellitus]		
6	1 型糖尿病性水疱	Type 1 diabetic blister	E10438	8844626
7	1 型糖尿病性浮腫性硬化症	Type 1 diabetic edematous sclerosis	E10439	8844627
8	1 型糖尿病性肝障害	Type 1 diabetic liver injury	E10440	8845047
9	1 型糖尿病性関節症	Type 1 diabetic arthropathy	E10441	8845048
10	1 型糖尿病性高コレステロール血	Type 1 diabetic hypercholesterolemia	E10442	8845052
11	症			
12	1 型糖尿病性骨症	Type 1 diabetic osteopathy	E10443	8845054
13	1 型糖尿病性精神障害	Type 1 diabetic mental disorder	E10444	8845060
14	1 型糖尿病性そう痒症	Type 1 diabetic pruritus	E10445	8845061
15	1 型糖尿病性皮膚障害	Type 1 diabetic skin disorder	E10446	8845068
16	1 型糖尿病性胃腸症	Type 1 diabetic gastroenteritis	E10447	8845842
17	1 型糖尿病・多発糖尿病性合併症	Type 1 diabetes mellitus with multiple diabetic	E10448	8841687
18	あり	complications		
19	緩徐進行 1 型糖尿病・多発糖尿病	SPIDDM with multiple diabetic complications -	E10449	8844029
20	性合併症あり	[Slowly progressive insulin-dependent diabetes		
21		mellitus]		
22	1 型糖尿病・糖尿病性合併症なし	Type 1 diabetes mellitus without diabetic	E10450	8841688
23		complecations		
24	緩徐進行 1 型糖尿病・糖尿病性合	SPIDDM without diabetic complications - [Slowly	E10451	8844030
25	併症なし	progressive insulin-dependent diabetes mellitus]		
26	インスリン抵抗性糖尿病	Insulin resistant diabetes mellitus	E10452	2500001
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3	2 型糖尿病	Type 2 diabetes mellitus	E11	2500015
4	安定型糖尿病	Stable diabetes mellitus	E11	8830405
5	若年 2 型糖尿病	Juvenile type 2 diabetes	E11	8835244
6	2 型糖尿病性昏睡	Type 2 diabetic coma	E11	8830041
7	2 型糖尿病・昏睡合併あり	Type 2 diabetes mellitus with coma	E11	8841689
8	2 型糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of type 2 diabetes mellitus	E11	8845094
9	2 型糖尿病性ケトアシドーシス	Type 2 diabetic ketoacidosis	E11	8830040
10	2 型糖尿病・ケトアシドーシス合併あり	Type 2 diabetes mellitus with ketoacidosis	E11	8841690
11	2 型糖尿病性アシドーシス	Type 2 diabetic acidosis	E11	8845073
12	2 型糖尿病性アセトン血症	Type 2 diabetic acetone hyperlipoproteinemia	E11	8845074
13	2 型糖尿病性腎症	Type 2 diabetic nephropathy	E11	8830042
14	2 型糖尿病・腎合併症あり	Type 2 diabetes mellitus with diabetic nephropathy	E11	8841691
15	2 型糖尿病性腎症第 1 期	Type 2 diabetic nephropathy phase 1	E11	8843991
16	2 型糖尿病性腎症第 2 期	Type 2 diabetic nephropathy phase 2	E11	8843992
17	2 型糖尿病性腎症第 3 期	Type 2 diabetic nephropathy phase 3	E11	8843993
18	2 型糖尿病性腎症第 3 期 A	Type 2 diabetic nephropathy phase 3A	E11	8843994
19	2 型糖尿病性腎症第 3 期 B	Type 2 diabetic nephropathy phase 3B	E11	8843995
20	2 型糖尿病性腎症第 4 期	Type 2 diabetic nephropathy phase 4	E11	8843996
21	2 型糖尿病性腎症第 5 期	Type 2 diabetic nephropathy phase 5	E11	8843997
22	2 型糖尿病性腎硬化症	Type 2 diabetic nephrosclerosis	E11	8845087
23	2 型糖尿病性腎不全	Type 2 diabetic kidney failure	E11	8845088
24	2 型糖尿病性網膜症	Type 2 diabetic retinopathy	E11	8830045
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3	2 型糖尿病・眼合併症あり	Type 2 diabetes mellitus with eye complications	E11436	8841692
4	2 型糖尿病性黄斑浮腫	Type 2 diabetic macular edema	E11436	8843990
5	2 型糖尿病性白内障	Type 2 diabetic cataracts	E11436	8844347
6	増殖性糖尿病性網膜症・2 型糖尿病	Proliferative diabetic retinopathy, type 2 diabetes	E11436	8844537
7	病			
8	2 型糖尿病黄斑症	Type 2 diabetic macular disease	E11436	8845072
9	2 型糖尿病性眼筋麻痺	Type 2 diabetic eye muscle paralysis	E11436	8845078
10	2 型糖尿病性虹彩炎	Type 2 diabetic iritis	E11436	8845082
11	2 型糖尿病性中心性網膜症	Type 2 diabetic central retinopathy	E11436	8845093
12	2 型糖尿病性ニューロパチー	Type 2 diabetic neuropathy	E11436	8830043
13	2 型糖尿病性ミオパチー	Type 2 diabetic myopathy	E11436	8830044
14	2 型糖尿病・神経学的合併症あり	Type 2 diabetes mellitus with neurological complications	E11436	8841693
15	2 型糖尿病性筋萎縮症	Type 2 diabetic muscular atrophy	E11436	8845079
16	2 型糖尿病性神経因性膀胱	Type 2 diabetic neuropathic bladder	E11436	8845084
17	2 型糖尿病性神経痛	Type 2 diabetic neuralgia	E11436	8845085
18	2 型糖尿病性自律神経ニューロパチー	Type 2 diabetic autonomic neuropathy	E11436	8845086
19	病			
20	2 型糖尿病性多発ニューロパチー	Type 2 diabetic polyneuropathy	E11436	8845091
21	2 型糖尿病性単ニューロパチー	Type 2 diabetic mononeuropathy	E11436	8845092
22	2 型糖尿病性末梢神経障害	Type 2 diabetic peripheral neuropathy	E11436	8845100
23	2 型糖尿病・末梢循環合併症あり	Type 2 diabetes mellitus with peripheral circulation complications	E11436	8841694
24	2 型糖尿病性壊疽	Type 2 diabetic gangrene	E11436	8843106
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4	2 型糖尿病性潰瘍	Type 2 diabetic ulcer	E11436	8845075
5	2 型糖尿病性血管障害	Type 2 diabetic vascular disease	E11436	8845080
6	2 型糖尿病性動脈硬化症	Type 2 diabetic atherosclerosis	E11436	8845095
7	2 型糖尿病性動脈閉塞症	Type 2 diabetic arterial occlusion	E11436	8845096
8	2 型糖尿病性末梢血管症	Type 2 diabetic peripheral vascular disease	E11436	8845098
9	2 型糖尿病性末梢血管障害	Type 2 diabetic peripheral vascular disease	E11436	8845099
10	2 型糖尿病・関節合併症あり	Type 2 diabetes mellitus with joint complications	E11436	8841695
11	2 型糖尿病・糖尿病性合併症あり	Type 2 diabetes mellitus with diabetic complications	E11436	8841696
12	2 型糖尿病性水疱	Type 2 diabetic blister	E11436	8844628
13	2 型糖尿病性浮腫性硬化症	Type 2 diabetic edematous sclerosis	E11436	8844629
14	2 型糖尿病性肝障害	Type 2 diabetic liver injury	E11436	8845076
15	2 型糖尿病性関節症	Type 2 diabetic arthropathy	E11436	8845077
16	2 型糖尿病性高コレステロール血症	Type 2 diabetic hypercholesterolemia	E11436	8845081
17	2 型糖尿病性骨症	Type 2 diabetic osteopathy	E11436	8845083
18	2 型糖尿病性精神障害	Type 2 diabetic mental disorder	E11436	8845089
19	2 型糖尿病性そう痒症	Type 2 diabetic pruritus	E11436	8845090
20	2 型糖尿病性皮膚障害	Type 2 diabetic skin disorder	E11436	8845097
21	2 型糖尿病性胃腸症	Type 2 diabetic gastroenteritis	E11436	8848108
22	2 型糖尿病・多発糖尿病性合併症あり	Type 2 diabetes mellitus with multiple diabetic complications	E11436	8841697
23	2 型糖尿病・糖尿病性合併症なし	Type 2 diabetes mellitus without diabetic complications	E11436	8841698
24	栄養不良関連糖尿病	Malnutrition-related diabetes mellitus	E11436	2500037
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3	膵性糖尿病	Pancreatic diabetes mellitus	E1336	2500024
4	ステロイド糖尿病	Steroid diabetes mellitus	E1336	2509003
5	二次性糖尿病	Secondary diabetes mellitus	E1336	2509004
6	ウイルス性糖尿病	Viral diabetes mellitus	E1336	8830756
7	薬剤性糖尿病	Drug-induced diabetes mellitus	E1336	8840710
8	ウイルス性糖尿病・昏睡合併あり	Viral diabetes mellitus with coma	E1336	8843122
9	膵性糖尿病・昏睡合併あり	Pancreatic diabetes mellitus with coma	E1336	8843377
10	ステロイド糖尿病・昏睡合併あり	Steroid diabetes mellitus with coma	E1336	8843390
11	二次性糖尿病・昏睡合併あり	Secondary diabetes mellitus with coma	E1336	8843450
12	薬剤性糖尿病・昏睡合併あり	Drug-induced diabetes mellitus with coma	E1336	8843621
13	ウイルス性糖尿病・ケトアシドーシス合併あり	Viral diabetes mellitus with ketoacidosis	E1336	8843121
14	膵性糖尿病・ケトアシドーシス合併あり	Pancreatic diabetes mellitus with ketoacidosis	E1336	8843376
15	ステロイド糖尿病・ケトアシドーシス合併あり	Steroid diabetes mellitus with ketoacidosis	E1336	8843389
16	二次性糖尿病・ケトアシドーシス合併あり	Secondary diabetes mellitus with ketoacidosis	E1336	8843449
17	薬剤性糖尿病・ケトアシドーシス合併あり	Drug-induced diabetes mellitus with ketoacidosis	E1336	8843620
18	ウイルス性糖尿病・腎合併症あり	Viral diabetes mellitus with renal complications	E1336	8843124
19	膵性糖尿病・腎合併症あり	Pancreatic diabetes mellitus with renal complications	E1336	8843379
20	ステロイド糖尿病・腎合併症あり	Steroid diabetes mellitus with renal complications	E1336	8843392
21	二次性糖尿病・腎合併症あり	Secondary diabetes mellitus with renal complications	E1336	8843452
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4	薬剤性糖尿病・腎合併症あり	Drug-induced diabetes mellitus with renal complications	E1336	8843623
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6	ウイルス性糖尿病・眼合併症あり	Viral diabetes mellitus with eye complications	E1337	8843120
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8	膵性糖尿病・眼合併症あり	Pancreatic diabetes mellitus with eye complications	E1338	8843375
9				
10	ステロイド糖尿病・眼合併症あり	Steroid diabetes mellitus with eye complications	E1339	8843388
11	二次性糖尿病・眼合併症あり	Secondary diabetes mellitus with eye complications	E1340	8843448
12				
13	薬剤性糖尿病・眼合併症あり	Drug-induced diabetes mellitus with eye complications	E1341	8843619
14	ウイルス性糖尿病・神経学的合併症あり	Viral diabetes mellitus with neurological complications	E1342	8843123
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18	膵性糖尿病・神経学的合併症あり	Pancreatic diabetes mellitus with neurological complications	E1343	8843378
19				
20	ステロイド糖尿病・神経学的合併症あり	Steroid diabetes mellitus with neurological complications	E1344	8843391
21				
22	二次性糖尿病・神経学的合併症あり	Secondary diabetes mellitus with neurological complications	E1345	8843451
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26	薬剤性糖尿病・神経学的合併症あり	Drug-induced diabetes mellitus with neurological complications	E1346	8843622
27				
28	ウイルス性糖尿病・末梢循環合併症あり	Viral diabetes mellitus with peripheral circulatory complications	E1347	8843128
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32	膵性糖尿病・末梢循環合併症あり	Pancreatic diabetes mellitus with peripheral circulatory complications	E1348	8843383
33				
34	ステロイド糖尿病・末梢循環合併症あり	Steroid diabetes mellitus with peripheral circulatory complications	E1349	8843396
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38	二次性糖尿病・末梢循環合併症あり	Secondary diabetes mellitus with peripheral circulatory complications	E1350	8843456
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4	り	complications		
5	薬剤性糖尿病・末梢循環合併症あ	Drug-induced diabetes mellitus with peripheral	E13	8843627
6	り	circulatory complications		
7				
8	ウイルス性糖尿病・糖尿病性合併	Viral diabetes mellitus with diabetic complications	E13	8843126
9	症あり			
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11	膵性糖尿病・糖尿病性合併症あり	Pancreatic diabetes mellitus with diabetic	E13	8843381
12		complications		
13				
14	ステロイド糖尿病・糖尿病性合併	Steroid diabetes mellitus with diabetic complications	E13	8843394
15	症あり			
16				
17	二次性糖尿病・糖尿病性合併症あ	Secondary diabetes mellitus with diabetic	E13	8843454
18	り	complications		
19				
20	薬剤性糖尿病・糖尿病性合併症あ	Drug-induced diabetes mellitus with diabetic	E13	8843625
21	り	complications		
22				
23	ウイルス性糖尿病・多発糖尿病性	Viral diabetes mellitus with multiple diabetic	E13	8843125
24	合併症あり	complications		
25				
26	膵性糖尿病・多発糖尿病性合併症	Pancreatic diabetes mellitus with multiple diabetic	E13	8843380
27	あり	complications		
28				
29	ステロイド糖尿病・多発糖尿病性	Steroid diabetes mellitus with multiple diabetic	E13	8843393
30	合併症あり	complications		
31				
32	二次性糖尿病・多発糖尿病性合併	Secondary diabetes mellitus with multiple diabetic	E13	8843453
33	症あり	complications		
34				
35	薬剤性糖尿病・多発糖尿病性合併	Drug-induced diabetes mellitus with multiple diabetic	E13	8843624
36	症あり	complications		
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38	ウイルス性糖尿病・糖尿病性合併	Viral diabetes mellitus without diabetic complications	E13	8843127
39	症なし			
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4	膵性糖尿病・糖尿病性合併症なし	Pancreatic diabetes mellitus without diabetic complications	E13	8843382
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6	ステロイド糖尿病・糖尿病性合併症なし	Steroid diabetes mellitus without diabetic complications	E13	8843395
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8	二次性糖尿病・糖尿病性合併症なし	Secondary diabetes mellitus without diabetic complications	E13	8843455
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10	薬剤性糖尿病・糖尿病性合併症なし	Drug-induced diabetes mellitus without diabetic complications	E13	8843626
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12	糖尿病	Diabetes mellitus	E14	2500013
13	糖尿病合併症	Diabetic complications	E14	2507028
14	糖尿病性昏睡	Diabetic coma	E14	2502006
15	糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of diabetes mellitus	E14	8838076
16	糖尿病性アシドーシス	Diabetic acidosis	E14	2501002
17	糖尿病性アセトン血症	Diabetic acetonemia	E14	2501003
18	糖尿病性ケトアシドーシス	Diabetic ketoacidosis	E14	2501005
19	糖尿病性腎症	Diabetic nephropathy	E14	2503005
20	糖尿病性腎不全	Diabetic renal failure	E14	2503007
21	糖尿病性腎硬化症	Diabetic nephrosclerosis	E14	8838071
22	糖尿病性虹彩炎	Diabetic iritis	E14	2504004
23	糖尿病性中心性網膜症	Diabetic central retinopathy	E14	2504005
24	糖尿病性白内障	Diabetic cataract	E14	2504006
25	増殖性糖尿病性網膜症	Proliferative diabetic retinopathy	E14	2504010
26	糖尿病黄斑症	Diabetic maculopathy	E14	2504012
27	糖尿病網膜症	Diabetic retinopathy	E14	2504013
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3	糖尿病性眼筋麻痺	Diabetic ophthalmoplegia	E14436	8838065
4	糖尿病黄斑浮腫	Diabetic macular edema	E14436	8844089
5	糖尿病性神経痛	Diabetic neuralgia	E14436	2505011
6	糖尿病性末梢神経障害	Diabetic peripheral neuropathy	E14436	2505018
7	糖尿病性筋萎縮症	Diabetic muscular atrophy	E14436	2505021
8	糖尿病性神経因性膀胱	Diabetic neuropathic bladder	E14436	8838069
9	糖尿病性自律神経ニューロパチー	Diabetic autonomic neuropathy	E14436	8838070
10	糖尿病性多発ニューロパチー	Diabetic polyneuropathy	E14436	8838074
11	糖尿病性単ニューロパチー	Diabetic mononeuropathy	E14436	8838075
12	糖尿病性ニューロパチー	Diabetic neuropathy	E14436	8838078
13	糖尿病足病変	Diabetic foot lesion	E14436	8848634
14	糖尿病性神経障害性疼痛	Diabetic neuropathic pain	E14436	8848768
15	糖尿病性壊疽	Diabetic gangrene	E14436	2506006
16	糖尿病性動脈閉塞症	Diabetic arterial occlusion	E14436	2506011
17	糖尿病性潰瘍	Diabetic ulcer	E14436	8838063
18	糖尿病性血管障害	Diabetic angiopathy	E14436	8838066
19	糖尿病性動脈硬化症	Diabetic arteriosclerosis	E14436	8838077
20	糖尿病性末梢血管症	Diabetic peripheral vascular disease	E14436	8838079
21	糖尿病性末梢血管障害	Diabetic peripheral vascular disease	E14436	8838080
22	糖尿病足壊疽	Diabetic foot gangrene	E14436	8848632
23	糖尿病足潰瘍	Diabetic foot ulcer	E14436	8848633
24	糖尿病性関節症	Diabetic arthropathy	E14436	2507025
25	糖尿病性皮膚障害	Diabetic skin disorders	E14436	2507029
26	糖尿病性肝障害	Diabetic liver injury	E14436	8838064
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3	糖尿病性高コレステロール血症	Diabetic hypercholesterolemia	E14	8838067
4	糖尿病性骨症	Diabetic osteopathy	E14	8838068
5	糖尿病性精神障害	Diabetic mental disorder	E14	8838072
6	糖尿病性そう痒症	Diabetic pruritus	E14	8838073
7	糖尿病性水疱	Diabetic blister	E14	8844652
8	糖尿病性浮腫性硬化症	Diabetic edematous sclerosis	E14	8844653
9	高血糖高浸透圧症候群	Hyperglycemia hyperosmolarity syndrome	E14	8845128
10	糖尿病・糖尿病性合併症なし	Diabetes mellitus without diabetic complications	E14	8843439
11	非糖尿病性低血糖性昏睡	Hypoglycemic coma not in the context of diabetes mellitus	E15	8839324
12	果糖尿症	Levulosuria	E74	8831401
13	本態性果糖尿症	Essential levulosuria	E74	8840104
14	良性果糖尿症	Benign levulosuria	E74	8841021
15	腎性糖尿	Renal glycosuria	E74	2714002
16	青銅性糖尿病	Bronze diabetes mellitus	E83	8835941
17	膵全摘後二次性糖尿病	Secondary diabetes after pancreatectomy	E89	8835685
18	1型糖尿病合併妊娠	Pregnancy with type 1 diabetes	O24	8830029
19	2型糖尿病合併妊娠	with type 2 diabetes	O24	8830039
20	妊娠糖尿病	Pregnancy diabetes mellitus	O24	6489003
21	妊娠中の糖尿病	Overt diabetes in pregnancy	O24	8838621
22	妊娠中の耐糖能低下	Impaired glucose tolerance in pregnancy	O99	8838619
23	妊娠糖尿病母体児症候群	Gestational diabetes maternal syndrome	P70	8838633
24	糖尿病母体児	Diabetes maternal infant	P70	8838081
25	新生児一過性糖尿病	Neonatal transient diabetes mellitus	P70	7751001
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3	新生儿糖尿病	Neonatal diabetes mellitus	P70	7751002
4	新生儿一過性高血糖症	Neonatal transient hyperglycemia	P70	8844233
5	境界型糖尿病	Borderline type diabetes mellitus	R73	2500031
6	耐糖能異常	Impaired glucose tolerance	R73	2713009
7	化学的糖尿病	Chemical diabetes mellitus	R73	8831132
8	潜在性糖尿病	Latent diabetes mellitus	R73	8836104
9	前糖尿病	Pre-diabetes mellitus	R73	8836563
10	高血糖症	Hyperglycemia	R73	8833419
11	一過性糖尿	Transient diabetes mellitus	R81	7915002
12	五炭糖尿症	L-Xylulosemia	R81	7915003
13	高血糖性糖尿	Hypoglycemic glycosuria	R81	8833420
14	食事性糖尿	Dietary glycosuria	R81	8834843
15	情動性糖尿	Emotional glycosuria	R81	8835464
16	正常血糖性糖尿	Euglycemic glycosuria	R81	8835871
17	糖尿	Glycosuria	R81	8838062

Supplementary Table S2 Codes of antidiabetic medications

Types of antidiabetic medication	Medicine codes
Sulfonylureas	610412056, 610443002, 610443003, 613960002, 613960003, 613960008, 613960017, 613960026, 613960027, 613960028, 613960038, 613960039, 613960078, 620000048, 620002031, 620002032, 620003159, 620003160, 620003947, 620003948, 620006030, 620006890, 620009209, 620871601, 620872002, 620872003, 620872004, 620872009, 620872016, 620873202, 620873301, 620873402, 620873702, 621982701, 621997001, 621997101, 621998701, 621998801, 621998901, 621999001, 621999301, 621999401, 621999701, 621999801, 622000601, 622000701, 622001701, 622001801, 622004701, 622004801, 622005501, 622005601, 622005802, 622009802, 622009901, 622010001, 622011401, 622011501, 622011601, 622011701, 622013401, 622013501, 622013601, 622016001, 622016101, 622017301, 622017401, 622017501, 622017901, 622018001, 622018802, 622020903, 622021003, 622021801, 622021901, 622022001, 622022101, 622023501, 622023601, 622025201, 622025301, 622025801, 622025901, 622026501, 622026601, 622029901, 622030001, 622031401, 622031501, 622033001, 622033101, 622033201, 622033701, 622033801, 622035701, 622035801, 622036002, 622037901, 622038001, 622039901, 622048401, 622048501, 622058801, 622058901, 622059002, 622059102, 622075601, 622088301, 622088401, 622103201, 622114701, 622114801, 622118501, 622122201, 622122301, 622127301, 622127401, 622127501, 622128101, 622137701, 622141101, 622141302, 622143402, 622144001, 622159301, 622169102, 622169301, 622176301, 622177501, 622186201, 622187301, 622190001, 622190801,

	622193301, 622194901, 622198001, 622202201, 622202801, 622205101, 622205501, 622208901, 622211501, 622217701, 622219701, 622221001, 622222001, 622242001, 622246801, 622252501, 622254701, 622271101, 622271201, 622271301, 622313200, 622313300, 622338501, 622338601, 622338701
Meglitinides	622462501, 622462401, 620001908, 620001907, 622053601, 622040901, 622041001, 610432026, 610432027, 622196601, 622119301, 622230001, 622196701, 622119401, 622230101, 610432032, 610432033, 622518201, 622525401, 622515301, 622523401, 622521001, 622518101, 622525301, 622515201, 622523301, 622520901
α -glucosidase inhibitors	610406390, 620002841, 620002843, 620004045, 620004072, 620004071, 620008727, 620008726, 621665301, 621683401, 621673501, 621691201, 622090001, 621689303, 621689001, 621690402, 621690901, 621690203, 620002120, 620004069, 620005557, 620005558, 620005559, 620005560, 620005561, 620008071, 620008072, 620008073, 621953301, 621943301, 620009287, 621896502, 622008602, 620009286, 621896402, 622008502, 620009296, 620009294, 620009293, 622302301, 620009297, 621958801, 620005360, 621785002, 621942202, 620009295, 620009291, 620009289, 620009288, 622302201, 620009292, 621958701, 620005359, 621784902, 621942102, 620009290, 621937201, 621937101, 613960082, 613960081, 622053601, 622432501, 622426601, 622426701, 620003127, 620003128, 620003129, 620002121, 610406391, 621953401, 620004046, 620004070, 620005562, 620008074, 620005563, 620005564, 620005565, 620008075, 620005566, 621943401, 620008076, 620004073, 620002845, 621690303, 620008729, 620008728, 620004074, 621689403, 621689101, 621691001, 621691601, 621665401, 621683501, 620002847, 622090101, 621690502, 621673601
Biguanides	622517101, 622450401, 622450301, 620004480, 620004502, 620005979, 610463145, 621986401, 621986301, 610444147, 621974701, 622242501, 622070801, 621676001,

	620005570, 622427201, 622421901, 622424401, 622421101, 622412701, 622438401, 622417101, 622432601, 622436301, 622427301, 622422001, 622424501, 622421201, 622448601, 622438501, 622417201, 622432701, 622466601
Thiazolidinediones	621990901, 621991001, 610432040, 610432041, 622048501, 622048401, 622065301, 622061601, 622041402, 622155901, 622063201, 622156901, 622144601, 622167201, 622045401, 622159401, 622056001, 622147501, 622175601, 622071901, 622065401, 622061701, 622041502, 622156001, 622063301, 622157001, 622144701, 622167301, 622045501, 622159501, 622056101, 622147601, 622175701, 622072001, 622320800, 622320900, 622065101, 622042901, 622061401, 622166801, 622182401, 622041202, 622079101, 622155701, 622063001, 622066201, 622164301, 622062302, 622047701, 622049901, 622046801, 622163301, 622053101, 622081801, 622059201, 622045201, 622053801, 622055801, 622147301, 622078301, 622175401, 622071701, 622065201, 622043001, 622061501, 622166901, 622182501, 622041302, 622079201, 622155801, 622063101, 622066301, 622164401, 622062402, 622047801, 622050001, 622046901, 622163401, 622053201, 622081901, 622059301, 622045301, 622061001, 622055901, 622147401, 622078401, 622175501, 622071801, 621986401, 621986301, 622086101, 622086001
Dipeptidyl peptidase-4 inhibitors	621950901, 621951001, 621951101, 621970601, 621970701, 621970801, 621980701, 621986001, 621986101, 621986201, 622086001, 622086101, 622093501, 622182601, 622201701, 622245601, 622245701, 622277501, 622288401, 622415401, 622415501, 622448901, 622449001, 622450301, 622450401, 622517101
Sodium glucose cotransporter 2 inhibitor	622340101, 622360601, 622401201, 622401301, 622306601, 622306701, 622336801, 622342001, 622341901, 622335701, 622335801

Rapid-acting insulin	621911101, 621911301, 621911201, 620008895, 621926901, 622252701, 620008893, 620008894, 620008916, 640451027, 620007460
Short-acting insulin	620008897, 620000265, 620008909, 620008907, 622114401
Long-acting insulin	622440701, 620008945, 620008943, 620007536, 622198901, 622199001, 622410901, 622484801, 622411001, 621927001, 620008952, 620008953
Immediate-acting insulin	620000266, 620008912, 620008910, 622114501, 620002441, 620007459
Premixed insulin	620002439, 620007461, 620002440, 620007462, 620008915, 620008913, 622114601, 620000269, 620000448, 620008896, 621973201, 621973301, 640453023
Combination-acting insulin	622451001, 622450901
Glucagon-like peptide-1 receptor agonist	622038401, 622038301, 621974801, 622229001, 622406001, 622267001, 622442201

Supplementary Table S3 Amputation codes

	Category number (in Japan)	Medical procedure codes (in Japan)
Major LLA		
Limb amputation (thigh)	K084-00	150051610
Limb amputation (below-knee)	K084-00	150051710
Limb amputation (foot)	K084-00	150051810
Limb joint dissection (crotch)	K085-00	150052210
Limb joint dissection (knee)	K085-00	150052310
Limb joint dissection (foot)	K085-00	150052610
Minor LLA		
Limb amputation (finger)	K084-00	150051910
Limb joint dissection(finger)	K085-00	150052710
LLA, lower limb amputation.		

Supplementary Table S4 Standard Japanese Population Model (1985)

Age group, years	Standard population	Age group, years	Standard population	Age group, years	Standard population
0–4	8,180,000	35–39	9,289,000	70–74	3,476,000
5–9	8,338,000	40–44	9,400,000	75–79	2,441,000
10–14	8,497,000	45–49	8,651,000	80–84	1,406,000
15–19	8,655,000	50–54	7,616,000	≥85	784,000
20–24	8,814,000	55–59	6,581,000	Total	120,287,000
25–29	8,972,000	60–64	5,546,000		
30–34	9,120,000	65–69	4,511,000		

Supplementary Table S5 Incidence of each limb amputation during the observation period.

Amputation	Number of amputations
Limb amputation (upper arm)	450
Limb amputation (forearm)	318
Limb amputation (hand)	165
Limb amputation (thigh)	16,107
Limb amputation (below-knee)	15,211
Limb amputation (foot)	6,242
Limb amputation (finger)	23,184
Limb joint dissection (shoulder)	76
Limb joint dissection (crotch)	481
Limb joint dissection (knee)	318
Limb joint dissection (elbow)	12
Limb joint dissection (hand)	35
Limb joint dissection (foot)	456
Limb joint dissection (finger)	1,720

Contributorship statement

All authors contributed significantly. F.K. designed the study and wrote the manuscript. Y.N. contributed to the study design, data analysis, and discussion. T.N. provided advice on the study design and discussed the findings from an epidemiological perspective. T.M., S.K., and T.H. performed the initial NDB analysis and provided technical advice. S.O., Y.A., H.I., and Y.T. evaluated the results from a clinical perspective. T.I. provided advice on the study design and discussed the findings from the public health viewpoint.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9,10
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9,10
		(b) Describe any methods used to examine subgroups and interactions	9,10
		(c) Explain how missing data were addressed	9,10
		(d) If applicable, explain how loss to follow-up was addressed	9,10
		(e) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	No participants
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	13, Table2

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17, Table3
2			(b) Report category boundaries when continuous variables were categorized	17
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	20, Table4
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	25
13	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	24,25
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22-24
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	24
16				
17	Other information			
18	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Incidence of lower limb amputation in people with and without diabetes: A nationwide 5-year cohort study in Japan

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-048436.R1
Article Type:	Original research
Date Submitted by the Author:	23-May-2021
Complete List of Authors:	Kamitani, Fumika; Nara Medical University Nishioka, Yuichi; Nara Medical University Noda, Tatsuya; Nara Medical University Myojin, Tomoya; Nara Medical University Kubo, Shinichiro; Nara Medical University Higashino, Tsuneyuki; Healthcare and Wellness Division, Mitsubishi Research Institute, Inc., Tokyo, 100-8141, Japan Okada, Sadanori; Nara Medical University Akai, Yasuhiro; Nara Medical University, Center for Postgraduate Training; Nara Medical University, Department of Nephrology Ishii, Hitoshi; Nara Medical University Takahashi, Yutaka; Nara Medical University Imamura, Tomoaki; Nara Medical University
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Health services research, Surgery, Evidence based practice, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, ORTHOPAEDIC & TRAUMA SURGERY, DIABETES & ENDOCRINOLOGY

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10 **Manuscript category:** Original research
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16 **Incidence of lower limb amputation in people with and without diabetes: A nationwide 5-**
17 **year cohort study in Japan**
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33 **Short Running Title:** Incidence of limb amputation in Japan
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40 **Word count:** 3198 words
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46 **Number of tables and figures:** 4 tables and 2 figures.
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1 ABSTRACT

2 **Introduction:** This study was conducted to investigate the incidence and time trend of
3 lower limb amputation (LLA) among people with and without diabetes.

4 **Research design and methods:** This retrospective population-based cohort study was
5 based on the national claims data in Japan, comprising a total population of 150 million.
6 Data of all individuals who had LLA from April 2013 to March 2018 were obtained. We
7 analyzed the sex- and age-adjusted annual LLA rate (every fiscal year) in people with and
8 without diabetes for major and minor amputation. To test for time trend, Poisson
9 regression models were fitted.

10 **Results:** In the 5-year period, 30,187 major and 29,299 minor LLAs were performed in
11 Japan. The sex- and age-adjusted incidence of major and minor LLAs was 9.5 (people
12 with diabetes, 21.8 vs. people without diabetes, 2.3, per 100,000 person-years) and 14.9
13 (people with diabetes, 28.4 vs people without diabetes, 1.9, per 100,000 person-years)
14 times higher, respectively, in people with diabetes compared to those without. A
15 significant decline in the annual major amputation rate was observed ($p < 0.05$) and the
16 annual major amputation rate remained stable ($p = 0.63$) when sex, age, and people with
17 and without diabetes were included as dependent variables.

18 **Conclusions:** This is the first report of the national statistics of LLAs in Japan. The
19 incidence of major and minor LLAs was 10 and 15 times higher, respectively, in people
20 with diabetes compared to those without. A significant decline in the major amputation

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1 rate was observed, and the annual major amputation rate remained stable during
2 observation period. This information can help create an effective national healthcare
3 strategy for preventing limb amputations, which affect the quality of life of patients with
4 diabetes and add to the national healthcare expenditure.

5 **Keywords:** amputation, cohort study, diabetes mellitus

For peer review only

Strengths and limitations of this study

- This is the first report of the national statistics of lower limb amputations (LLAs) among people with and without diabetes.
- This retrospective cohort study was based on the National Database (NDB) in Japan, comprising almost all patients in Japan.
- Considering the definition of minor amputation, we could not distinguish between finger and toe amputations because of the coding system of the NDB.
- The detailed medical information and parameters of each patient, including glycated hemoglobin, body weight, smoking history, and family history, could not be reviewed because of the nature of the database.
- However, NDB is a comprehensive survey and the likelihood of selection bias is relatively small; we adjusted for sex and age when comparing the LLA rates of people with and without diabetes.

1 INTRODUCTION

2 The objectives of diabetes management are to reduce the metabolic dysfunction that
3 occurs because of hyperglycaemia, to prevent the development or progression of diabetes-
4 related complications and conditions, and to enable the affected individuals to maintain
5 their quality of life and life expectancy like healthy individuals [1]. Vascular and
6 neurological complications of diabetes can considerably influence lower limb amputation
7 (LLA) [2–4]. Previous studies have shown that diabetes increases the risk of LLA,
8 although there were considerable variations in its incidence among people with diabetes
9 [5]. It is important to understand the incidence rates of LLA in diabetic and nondiabetic
10 populations to further improve the care of patients with diabetes and to avoid fatal
11 outcomes, particularly regarding decisions associated with health policy and the economy
12 [4,5].

13 Among patients with diabetes, besides major LLAs (e.g., amputation proximal
14 to the ankle joint), there may be many minor LLAs (e.g., amputation through the ankle
15 joint and toe amputation) [6]. Major amputations have severe detrimental impact on
16 physical integrity, but minor amputations should also be prevented. Given the increasing
17 incidence of diabetes, not only major LLAs but also minor LLAs impose a burden on the
18 healthcare system. With significant ageing of the population, the number of patients with
19 diabetes in Japan continues to increase [7]. Therefore, it is important to understand the
20 association of age with the total incidence of each major and minor LLA. However, no
21 large-scale community-based surveys on the incidence of LLA among people with and
22 without diabetes in Japan have been conducted. We aimed to investigate the incidence of

1 LLAs in Japan and compare the age-adjusted incidence of LLA between people with and
2 without diabetes. We also analysed the time trend based on data obtained from the
3 National Database of Health Insurance Claims in Japan. To the best of our knowledge,
4 this study is the first to evaluate the LLA rate in Japan based on a nationwide dataset.

6 **METHODS**

7 **Study design and population**

8 This population-based, retrospective cohort study was based on the National Database
9 (NDB) dataset and was approved by the ethics committee of Nara Medical University
10 (approval no. 1123-5). The use of NDB dataset was approved by the Ministry of Health,
11 Labor and Welfare, and the need for informed consent was waived in view of the study
12 design. All patient data were anonymised before analysis.

13 The study cohort comprised individuals enrolled in the NDB; all patient data were
14 anonymised. Japan has a universal public healthcare system, and the NDB includes
15 almost all patients in Japan. However, people whose family names changed due to
16 marriage or divorce and people whose insurance changed due to social circumstances are
17 also counted as other individuals. Approximately 2% of the people on welfare were not
18 included in this study because they were not covered by the insurance programme. The
19 NDB data provided information on personal identifiers [8], date, age group, sex,
20 description of the medical procedures conducted, the World Health Organization
21 International Classification of Diseases diagnosis codes, medical care received, medical

1 examinations conducted (not including test results), and prescribed drugs, which were
2 independent of the doctor's or patient's reports [9]. Drug information included the
3 prescription amount, brand name, generic name, dosage, and the number of days for
4 which the medicine was prescribed. The age recorded in this study was age at the time of
5 the last treatment during the study period or the patient's age when LLA was performed.

6 We designed this cohort study to include all the data of LLA patients collected
7 between April 2013 and March 2018 in the analysis.

8 **Criteria for diagnosing diabetes**

9 We defined patients with diabetes as individuals who had any of the diagnosis codes
10 associated with diabetes and those who were prescribed diabetes medication at least once
11 in the past 5 years. The diagnosis and medicine codes for diabetes are the same as those
12 reported previously [9] and are presented in Supplementary Tables S1 and S2,
13 respectively. We included all patients with any type of diabetes. In Japan, the indication
14 for metformin is limited to type 2 diabetes patients, and prescriptions for obese people
15 and for women with polycystic ovary syndrome patients are not permitted. Patients on
16 dietary or exercise management without antidiabetic medication were excluded.

17 **Definition of LLA**

18 The medical procedure receipt codes (as LLA codes) are shown in Supplementary Table
19 S3. We defined major LLAs as the use four medical procedure receipt codes proximal to
20 the ankle joint, as follows: above-knee/transfemoral amputation, below-knee/transtibial
21 amputation, hindquarter amputation/ hip disarticulation, and through-knee amputation. In

1 the Japanese medical code, the amputation of fingers and toes is indicated by the same
2 code, and it is impossible to distinguish between them. Therefore, we defined minor LLA
3 as through-foot amputation, trans-metatarsal amputation and Lisfranc disarticulation,
4 finger and toe amputation, and finger and toe joint disarticulation. The primary outcome
5 was the first occurrence of each major or minor LLA in the study period. If the first major
6 LLA occurred during the observation period, its observation was terminated at that time.
7 Similarly, if the first minor LLA occurred during the observation period, its observation
8 was terminated at the time. Therefore, even when the major and minor LLAs occurred
9 many times in the same person during the 5-year study period, we counted only the first
10 major and minor LLAs. Moreover, even if a minor LLA occurred, the major LLA
11 observation was continued such that the incidence of the major LLA was not
12 underestimated.

13 **Statistical analyses**

14 We defined the duration between the first occurrence of the medical treatment code or
15 drug code and the last occurrence as the risk period. To calculate the incidence of LLA,
16 the denominator included all the observation populations of each group, extracted from
17 the NDB dataset. LLA rates are presented as the number of amputations per 100,000
18 person-years. To compare the LLA incidence rates between people with and without
19 diabetes, the incidence rates were evaluated after adjusting for sex and age using the direct
20 method, i.e., the sex and age structure of Japan's national census in 2015 (Supplementary
21 Table S4). We included age-adjusted standardised incidence of LLA for all ages.
22 Furthermore, the relative risk (RR) of LLA among people with diabetes was calculated

1 by dividing amputation rates among people with diabetes by amputation rates among
2 those without diabetes.

3 The statistics for this study were calculated directly using Microsoft SQL server, and we
4 used Excel to calculate the 95% confidence interval by multiplying it by a coefficient that
5 assumed Poisson distribution.

6 Annual standardized major and minor LLAs were analysed from 2013 to 2016 fiscal year.
7 2017 was excluded because the observation period in 2017 was shorter than other years,
8 and the denominator was smaller, which could overestimate the LLA rate. To test for time
9 trends, we fitted Poisson regression models for major or minor amputation rate using year
10 of outcome (difference from the first fiscal year 2013 as an ordinal variable), age and sex,
11 and the population with and without diabetes as independent variables. All models were
12 adjusted for over-dispersion using a dispersion parameter. All analyses were conducted
13 using the Statistical Analysis System (SPSS Advanced Statistics).

14 **Patient and Public Involvement.**

15 Patients and the public were not involved.

16 **RESULTS**

17 **Population included in the NDB and the diabetic population**

18 Of the 150,328,339 people (186,819,100,972 person-days) included in the NDB,
19 9,962,459 had diabetes, which accounted for 6.6% of the total sample (Table 1). In the
20 subgroups of men and women, the proportion of diabetic patients was higher in the elderly

1 group (age ≥ 65 years).

2

3 **Incidence of LLAs**

4 Major LLAs occurred in 30,187 people, whereas minor LLAs occurred in 29,299 people
5 in the 5-year period. In Japan, a new major and minor LLA occurred in approximately
6 6,000 individuals per year. Table 2 shows the characteristics of LLA patients stratified
7 into subgroups of people with and without diabetes. Figures 1A and 1B show the sex and
8 age composition of the patient population with major and minor LLAs. In the overall
9 study population, the incidence of LLA was higher among men than in women. Patients
10 with diabetes accounted for 58% and 66% of the total major and minor LLAs,
11 respectively; the highest number of LLAs in men were performed around 65–84 years of
12 age, whereas, in women, the number was significantly associated with age. Therefore,
13 most amputations occurred in the elderly population.

14

15 **Age-adjusted incidence rate**

16 Throughout the observation period, the major amputation risk was 9.5 times higher in
17 people with diabetes compared with people without diabetes (people with diabetes, 21.8
18 vs. people without diabetes, 2.3, per 100,000 person-years); the minor amputation risk
19 was also 14.9 times higher among people with diabetes (people with diabetes, 28.4 vs.
20 people without diabetes, 1.9, per 100,000 person-years) (Table 3). This difference was
21 particularly pronounced in minor amputations than major amputations. Additionally, the

1 RR was higher in men than in women.

2

3 **Time trend**

4 We observed a significant decrease in the major amputation rate in the general population,
5 from 5.5 per 100,000 person-years in 2013 to 4.4 in 2016 ($p < 0.05$, for time trend, Poisson
6 model). The major amputation rate decreased among people with (2013:22.8; 2016:20.0)
7 and without diabetes (2013:2.6; 2016: 2.1).

8 In contrast, the minor amputation rate remained stable in the general population, from
9 5.6 per 100,000 person-years in 2013 to 4.7 in 2016 ($p = 0.63$, for time trend, Poisson
10 model). The minor amputation rate remained stable among people with (2013:29.0;
11 2016:28.9) and without diabetes (2013 2.1; 2016: 1.7) (Table 4, Figure 2).

1 DISCUSSION

2 The NDB is a comprehensive database of health insurance claims that are covered by the
3 Japanese National Health Insurance system. Japan has universal health coverage, with
4 local governments providing healthcare payments for approximately 2% of the population
5 who are on welfare, with the exception of accidents (which is covered by automobile
6 liability insurance or worker's accident compensation in a previous health insurance
7 plan); thus, the NDB is considered to be the representative of almost all health claims in
8 Japan [8,9]. Using information from the Japanese NDB dataset, we conducted cohort
9 studies that comprised almost all LLAs in Japan during the study period. This is the first
10 report of LLAs across Japan.

11 Although several studies have analysed amputation risk in people with diabetes,
12 population-based and nationwide studies analysing amputation risk in populations with
13 and without diabetes are still limited. Additionally, study design such as definition and
14 counting LLA (counting all, counting only the first of the observation period, counting
15 only the first of each year), sex- and age- adjustment method (all ages or only specific
16 ages) were different significantly, so accurately comparing them is difficult. Considering
17 this, compared with the few previous studies that evaluated only the first amputation in
18 the observation period or each year to calculate the LLA incidence, LLA rates in the
19 general population of this study were much lower (e.g., 7.4–41.4 and 8.0–46.7 per
20 100,000 person-years in Europe and Australasia in 2010–2014, major and minor
21 amputation, respectively [10]; 7.8–13.2 per 100,000 person-years in OECD in 2000–2011,
22 major amputation [11]; in our study 4.8 and 5.0 per 100,000 person-years, major and

1 minor amputation, respectively). Herein, the LLA rates among people with diabetes were
2 much lower than those of previous studies (e.g., 78–704 per 100,000 person-years in a
3 systematic review in 1990–2010, major amputation [5]; 7.8–13.2 per 100,000 person-
4 years in OECD in 2000–2011, major amputation [11]; in our study 21.8 and 28.4 per
5 100,000 person-years, major and minor amputation, respectively). There are several
6 explanations for the observed lower incidence of LLA in Japanese patients. First, the
7 Japanese population has a lower obesity rate than the Western population [12,13]. Second,
8 the incidence of cardiovascular disease is much lower in Japan [14]; this contributes to
9 lower risk for the progression of atherosclerosis, which is the most prevalent aetiology of
10 LLA. Third, many Japanese individuals tend to avoid amputations because of religious
11 beliefs [15], and doctors resort to limb-preservation measures (endovascular therapy, such
12 as stenting) to preserve the legs and feet and to delay amputation.

13 In this study, the incidence of major and minor LLA was approximately 10 and 15
14 times higher, respectively, in people with diabetes compared to those without. Among
15 people with diabetes, both peripheral arterial disease and peripheral neuropathy can cause
16 foot ulceration and lower limb amputation. Strict chronic disease management (such as
17 plasma glucose, blood pressure, lipids, and renal failure control) is important to suppress
18 arteriosclerosis. Peripheral vascular disease is often not diagnosed in patients with
19 diabetes usually until the formation of a nonhealing ulcer. Therefore, identification of
20 patients with diabetes who are at high risk of ulceration is important and it can be achieved
21 through annual foot screening [2]. There is an emerging focus on lifestyle interventions
22 including weight loss and physical activity as well [16]. Further, in case of foot ulcer or

1 foot infection, many experts (diabetologists, vascular surgeons, orthopaedics,
2 interventional radiologists, infectious diseases specialists, specialised nurses, podiatrists,
3 and orthotic technicians) need to work together as a multidisciplinary team to prevent
4 LLA [17]. In Japan, foot care performed by trained nurses has been approved for medical
5 insurance coverage since 2008 [18,19], and bypass surgery and endovascular treatment
6 have become significantly advanced [20,21]. Despite these efforts, our data indicate that
7 the risk of LLA in people with diabetes remained significantly higher than in people
8 without diabetes. This may be associated with the fact that despite the insurance coverage
9 of nurse-provided foot care, only few patients actually availed foot care services. The
10 medical expenses burden of LLA is large [22]. The LLA risk among people with diabetes
11 is much higher and, therefore, more diligent screening and management of the people
12 with diabetes are important to reduce the burden of quality-of-life reduction and the
13 national healthcare expenditure associated with LLA [23]. The high risk of LLA in people
14 with diabetes clarified in this study will help to develop national medical strategies such
15 as more specialised diabetes treatments including insulin and foot care, expansion of team
16 medical care, and establishment of educational programmes and activities for patient
17 empowerment.

18 In this study, a significant decline in the annual major amputation rate was
19 observed in Japan and the annual major amputation rate remained stable. Our finding
20 concerning the time trend for major LLAs in people with and without diabetes is in line
21 with results from other international studies, which mainly demonstrated decreased
22 incidence of major LLAs. Major amputations decreased by 11.1% in 2005–2015 in the

1 general population of Germany [24]. A progressive decrease was observed for major
2 amputations among people with diabetes (-30.7%) and without diabetes (-12.5%) in
3 2001–2010 in Italy [25]. Minor amputations in people with and without diabetes had
4 different trends in each country. A significant but weaker decrease was observed for
5 minor amputations in 2009–2013 in Belgium (5% and 3%, people with and without
6 diabetes) [26]. A relative increase of +12.8% was observed for minor amputations in
7 2005–2011 in Germany [24]. Minor amputations may indicate better quality of care as
8 they maybe interventions to prevent major amputations and salvage the lower extremities.
9 A stable number of the total amputations, or even an increase, may actually hide a higher
10 number of minor vs. major amputations, which in turn would indicate better performance
11 [11].

12 A key strength of our study is that, by analysing data from the nationwide NDB
13 that encompasses almost the entire Japanese population, this study is the first to evaluate
14 the nationwide incidence of LLA in Japan. Nonetheless, this study has some limitations.
15 First, many similar studies investigated only the amputations related to peripheral arterial
16 disease or diabetes by excluding amputations due to trauma or malignancy using
17 diagnosis codes attached to the amputation episodes; it was technically impossible to
18 exclude amputations due to trauma or malignancy in this study. Second, in minor
19 amputation, we could not distinguish between finger and toe amputations because of the
20 coding system of the NDB. Although toe amputations are actually more than finger
21 amputations, it is possible that the number of minor amputations was overestimated. Third,
22 the total observable population of this study was approximately 150 million, although

1 Japan has a population of approximately 127 million. Even considering new births,
2 marriages, divorces, and changes in family names due to social circumstances, there could
3 be slight deficits in the linking of the NDB. However, this does not significantly change
4 the analysis of the results. Finally, the detailed medical information and parameters of
5 each patient, including glycated haemoglobin, body weight, smoking history, and family
6 history, could not be reviewed because of the nature of the database. However, regarding
7 smoking rate, which can be an important confounding factor, a previous study in Japan
8 reported no difference between the diabetes group and the general population in terms of
9 smoking status in sex- and age-stratified analyses. Furthermore, NDB is a comprehensive
10 survey and the likelihood of selection bias is relatively small; additionally, we adjusted
11 for sex and age while comparing LLA rates of people with and without diabetes.
12 Therefore, it is unlikely that the study results will be significantly affected even if detailed
13 medical information and parameters are considered [27].

14 In conclusion, this is the first report of nationwide LLAs in Japan, and we found
15 that the incidence of major and minor LLAs was 10 and 15 times higher, respectively, in
16 people with diabetes compared to those without diabetes. A significant decline in the
17 major amputation rate was observed and the annual major amputation rate remained
18 stable during the observation period. This information can help create an effective
19 national healthcare strategy for preventing limb amputations, which affect the quality of
20 life of patients with diabetes and add to the national healthcare expenditure.

21 **Data availability statement** The research data are available from the corresponding
22 author on reasonable request.

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1 **Ethics approval** This study was approved by the ethics committee of Nara Medical
2 University (approval no. 1123-5).

3
4 **Acknowledgments** We would like to thank Editage (www.editage.com) for English
5 language editing.

6
7 **Funding.** This study was supported by the Research for Infrastructure Construction of
8 Studies with the Next Generation NDB Data to Create New Evidence from the Japan
9 Agency for Medical Research and Development. This study was supported by the Project
10 for Accelerating Medical Research through Cross-regional ICT utilization from the Japan
11 Agency for Medical Research and Development and Japan Society for the Promotion of
12 Science KAKENHI (grant number: JP18K17390).

13
14 **Competing interests** YN received consultant fees from Novo Nordisk. SO received
15 speaker fees from Novo Nordisk, Mitsubishi Tanabe, Sumitomo Dainippon, Arkray,
16 Bayer, Eli Lilly, Boehringer Ingelheim, Ono, AstraZeneca, Sanofi, and Takeda, outside
17 of the submitted work. YA received lecture fees and consultant fees from MSD KK, Ono,
18 Otsuka, Sumitomo Dainippon, Daiichi Sankyo, Eli Lilly, Sanofi S.A., Chugai, Novo
19 Nordisk, Kissei, Nippon Boehringer Ingelheim, Astellas, Kyowa Hakko Kirin, Pfizer,
20 Takeda, Mitsubishi Tanabe, Novartis, Janssen Pharmaceutical K.K, Japanese Red Cross
21 Society Nara Red Cross Blood Center, Sumitomo Dainippon, Ltd., Kissei. HI received

1 lecture fees and consultant fees from Takeda, Eli Lilly Japan, Sanofi, Merck & Co.,
2 Astellas, Mitsubishi Tanabe, Daiichi Sankyo, Ono, AstraZeneca, Taisho Toyama,
3 Shionogi, Kowa, Boehringer Ingelheim, Novo Nordisk, Sumitomo Dainippon, and
4 Kyowa Hakko Kirin. YT received consultant fees from Novo Nordisk, Otsuka, and
5 Recordati, and speaker fees from Novo Nordisk, Sumitomo Dainippon, Eli Lilly, Ono,
6 Novartis, Nippon Boehringer Ingelheim, AstraZeneca, and Kyowa Kirin. The other
7 authors declare that they have no conflict of interest.

8 **Contributions**

9 FK designed the study, wrote the discussion section, and drafted the manuscript. YN
10 collected, analyzed and interpreted the data and critically revised the manuscript for
11 important intellectual content. TN provided advice on the Epidemiology/Health Services
12 Research study design and discussed the findings from the viewpoint of an epidemiologist.
13 SK, TM, and TH performed the initial NDB analysis and provided technical advice. SA,
14 YA, HI, and YT evaluated the results from the viewpoint of a clinician. TI provided advice
15 on the study design and discussed the findings from the viewpoint of public health.

16 **Patient consent for publication** Not required.

17 **Data availability statement** The research data are available from the corresponding
18 author on reasonable request.

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14 **Supporting information**

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17 Table S1. Diagnosis codes for diabetes.

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20 Table S2. Medication codes for diabetes.

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23 Table S3. Amputation codes.

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26 Table S4. The population of Japanese national census (2015).
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9 **Figure legends**

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12 **Figure 1.** Results of sex- and age-stratified analyses: (A) number of major lower limb
13 amputation (LLA); (B) number of minor LLA.
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17 **Figure 2.** Time trend of age- and sex- standardized amputation rate: (A) major amputation; (B)
18 minor amputation
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Table 1 Characteristics of the NDB study population categorized into people with and without diabetes.

Age groups, years	Total	People with diabetes, n (%)	People without diabetes, n (%)
Total	150,328,339	9,962,459 (6.6)	140,365,880 (93.4)
Men, total	70,958,283	5,838,320 (8.2)	65,119,963 (91.8)
Men, age groups, years			
0 – 44	35,317,225	301,772 (0.9)	35,015,453 (99.1)
45 – 64	17,572,798	1,709,991 (9.7)	15,862,807 (90.3)
65 – 74	9,134,765	1,849,566 (20.2)	7,285,199 (79.8)
75 – 84	6,152,042	1,458,566 (23.7)	4,693,476 (76.3)

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10	≥ 85	2,781,453	518,425 (18.6)	2,263,028 (81.4)
11				
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13	Women, total	79,370,056	4,124,139 (5.2)	75,245,917 (94.8)
14				
15				
16	Women, age groups, years			
17				
18				
19				
20	0 – 44	37,492,073	212,476 (0.6)	37,279,597 (99.4)
21				
22				
23	45 – 64	18,906,831	792,993 (5.7)	18,113,838 (94.3)
24				
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27	65 – 74	9,860,220	1,154,454 (11.7)	8,705,766 (88.3)
28				
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30	75 – 84	7,538,821	1,191,531 (15.8)	6,347,290 (84.2)
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33	≥ 85	5,572,111	772,685 (13.9)	4,799,426 (86.1)
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NDB, National Database.

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Table 2 Patients with lower limb amputations according to diagnosis of diabetes, sex, age.

Age groups, years	Major LLA			Minor LLA		
	Total	People with	People without	Total	People with	People without
		diabetes, n (%)	diabetes, n (%)		diabetes, n (%)	diabetes, n (%)
Total	30,187	17,390 (57.6)	12,797 (42.4)	29,299	19,331 (66.0)	9,968 (34.0)
Men, total	17,971	11,545 (64.2)	6,426 (35.8)	19,485	14,163 (72.7)	5,322(27.3)
Men, age groups, years						

29

0–44	515	218 (42.3)	297 (57.7)	736	468 (63.6)	268 (36.4)
45–64	3,376	2,699 (79.9)	677 (20.1)	4,989	4,173 (83.6)	816 (16.4)
65–74	5,077	3,748 (73.8)	1,329 (26.2)	5,934	4,621 (77.9)	1,313 (22.1)
75–84	5,710	3,568 (62.5)	2,142 (37.5)	5,404	3,761 (69.6)	1,643 (30.4)
≥85	3,293	1,312 (39.8)	1,981 (60.2)	2,422	1,140 (47.1)	1,282 (52.9)
Women, total	12,216	5845 (47.8)	6371 (52.2)	9,814	5,168 (52.7)	4646 (47.3)
Women, age groups, years						

10	0–44	183	44 (24.0)	139 (76.0)	177	72 (40.7)	105 (59.3)
14	45–64	1,011	747 (73.9)	264 (26.1)	1,243	946 (76.1)	297 (23.9)
18	65–74	1,900	1,335 (70.3)	565 (29.7)	1,945	1,361 (70.0)	584 (30.0)
21	75–84	3,429	1,894 (55.2)	1,535 (44.8)	2,854	1,606 (56.3)	1248 (43.7)
25	≥85	5,693	1,825 (32.1)	3,868 (67.9)	3,595	1,183 (32.9)	2412 (67.1)

LLA, lower limb amputation.

Table 3 Age-adjusted incidence rate (per 100,000 person-year) of LLA in people with and without diabetes.

Incidence of Major LLA							
Groups	Total	95%CI	With diabetes	95% CI	Without diabetes	95% CI	Relative risk (With / Without)
Men	6.2	5.9 - 6.5	26.4	23.4 - 29.5	2.6	2.3 - 2.8	10.2
Women	3.5	3.3 - 3.7	17.3	14.5 - 20.1	2.0	1.8 - 2.2	8.7
Total	4.8	4.5 - 5.1	21.8	18.9 - 24.7	2.3	2.1 - 2.5	9.5
Incidence of Minor LLA							
Groups	Total	95% CI	With	95% CI	Without	95% CI	Relative risk

	diabetes		diabetes		(With / Without)		
Men	7.1	6.7 - 7.5	39.3	35.7 - 43.0	2.2	2.0 - 2.5	17.9
Women	3.0	2.7 - 3.2	18.0	15.4 - 20.5	1.5	1.3 - 1.7	12.0
Total	5.0	4.7 - 5.3	28.4	25.3 - 31.4	1.9	1.7 - 2.1	14.9

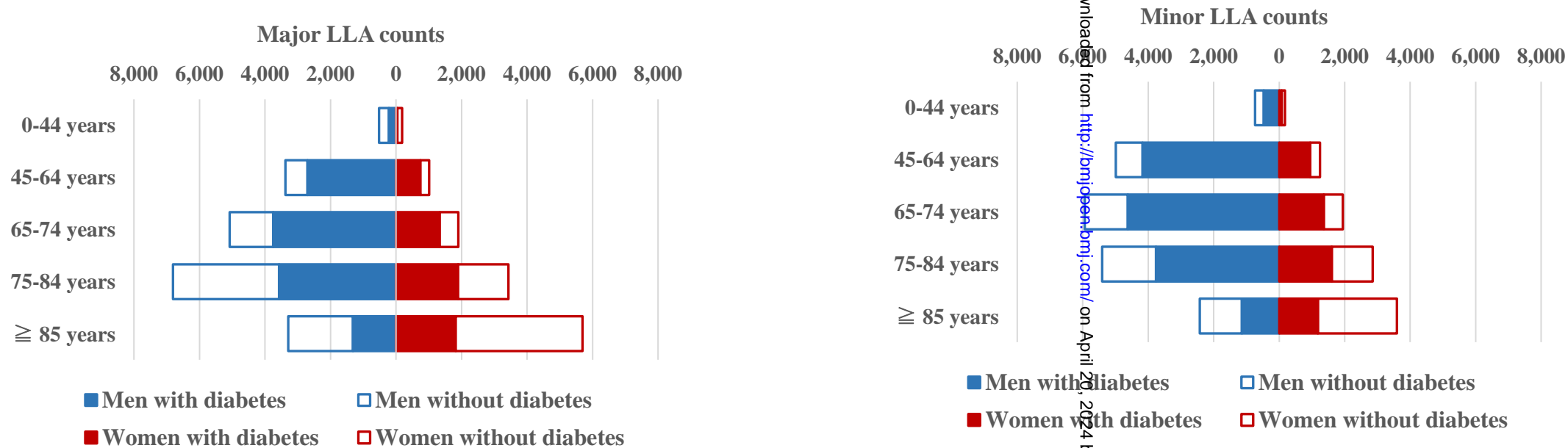
LLA, Lower limb amputation; CI, confidence interval.

Table 4 Time trend of age- and sex- standardized amputation rates (/100,000 person-years, annual fiscal year)

Fiscal year	2013		2014		2015		2016	
	rate	95% CI	rate	95% CI	rate	95% CI	rate	95% CI
Major amputation								
Men and women with diabetes	22.8	17.3 - 28.3	20.9	15.6 - 26.1	20.0	14.9 - 26.1	20.0	14.7 - 25.4
Men with diabetes	26.8	22.2 - 31.4	25.0	19.0 - 31.0	22.9	17.7 - 28.2	25.7	19.1 - 32.3
Women with diabetes	19.1	12.8 - 25.4	17.0	12.4 - 21.6	17.2	12.4 - 24.1	14.7	10.6 - 18.8
Men and women without diabetes	2.6	2.0 - 3.1	2.2	1.7 - 2.6	2.1	1.7 - 2.5	2.1	1.7 - 2.6
Men without diabetes	3.1	2.4 - 3.7	2.5	2.0 - 3.0	2.3	1.8 - 2.8	2.4	1.8 - 2.9
Women without diabetes	2.1	1.7 - 2.5	1.9	1.5 - 2.3	1.9	1.5 - 2.2	1.9	1.5 - 2.3
Minor amputation								

Men and women with diabetes	29.0	21.7 - 36.4	25.5	19.4 - 31.6	25.7	21.7 - 31.7	28.9	22.0 - 35.8
Men with diabetes	39.6	30.9 - 48.4	35.9	28.1 - 43.6	34.9	27.8 - 42.0	39.8	31.7 - 47.9
Women with diabetes	19.0	13.1 - 25.0	15.6	11.1 - 20.2	17.0	12.0 - 22.0	18.6	12.8 - 24.4
Men and women without diabetes	2.1	1.6 - 2.6	1.7	1.3 - 2.1	1.9	1.2 - 2.7	1.7	1.3 - 2.1
Men without diabetes	2.7	2.1 - 3.3	2.1	1.6 - 2.6	2.1	1.6 - 2.5	1.9	1.5 - 2.4
Women without diabetes	1.6	1.2 - 2.0	1.4	1.0 - 1.7	1.8	0.7 - 2.8	1.4	1.1 - 1.8

Figure 1. Results of sex- and age-stratified analyses:
(A) number of major lower limb amputation (LLA); (B) number of minor LLA.



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Figure 2. Time trend of age- and sex- standardized amputation rate:
 (A) major amputation; (B) minor amputation

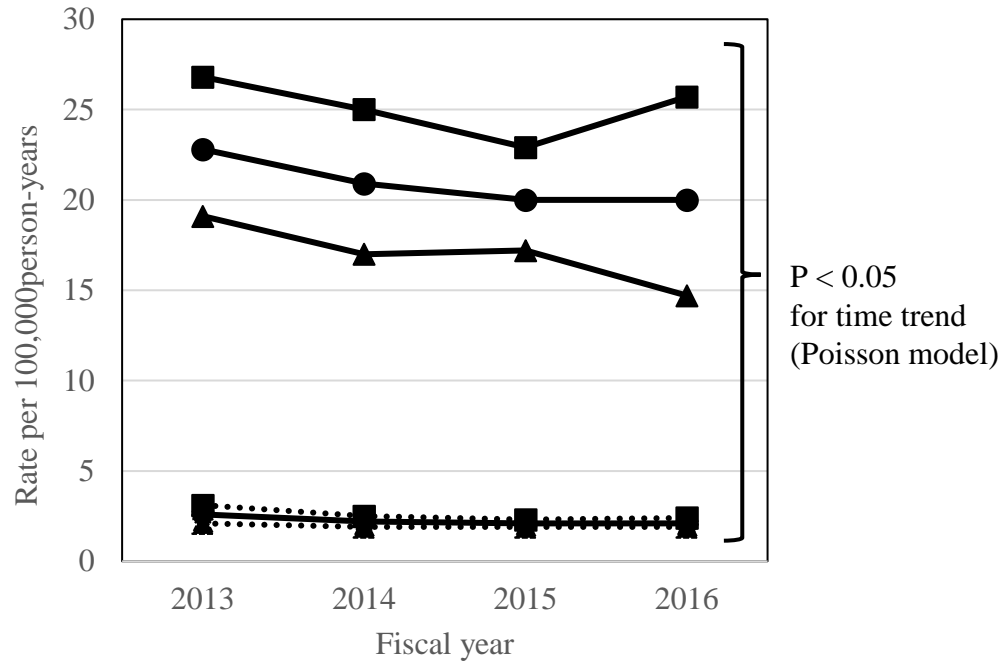


Fig.2-A Time trend of age- and sex- standardized major amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

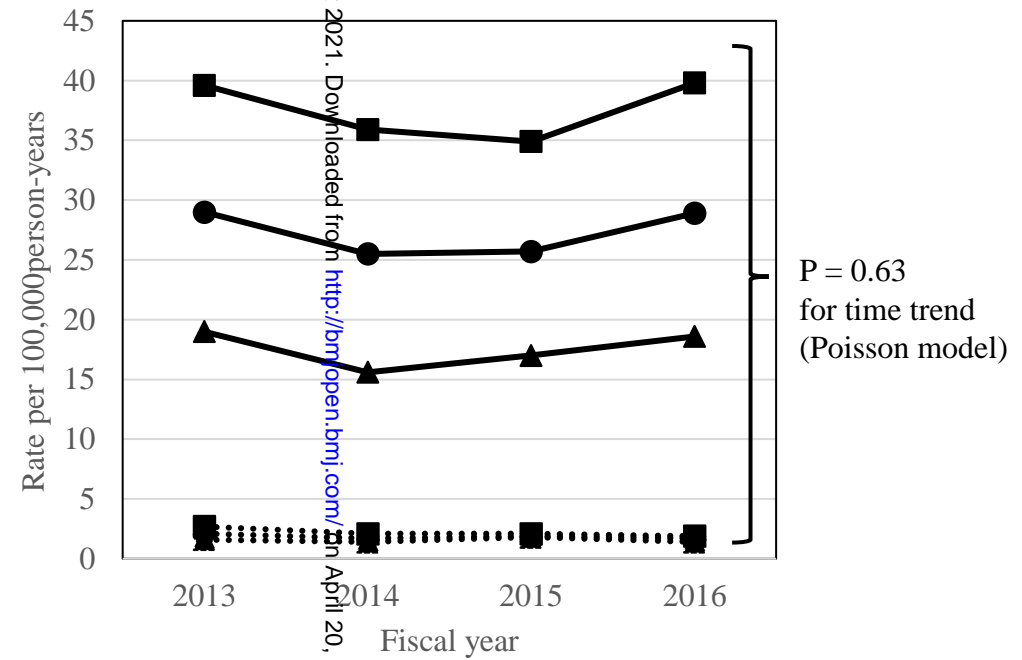


Fig.2-B Time trend of age- and sex- standardized minor amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

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Supplementary Table S1 Diagnostic codes of diabetes.

For peer review only

Diagnosis in Japanese	Diagnosis in English	BMJ Open	ICD-10 code	diagnosis code
1 型糖尿病	Type 1 diabetes mellitus		E10	2500014
不安定型糖尿病	Brittle diabetes		E10	2500027
緩徐進行 1 型糖尿病	SPIDDM - [Slowly progressive insulin-dependent diabetes mellitus]		E10	8844022
1 型糖尿病性昏睡	Type 1 diabetic coma		E10	8830030
1 型糖尿病・昏睡合併あり	Type 1 diabetes mellitus with coma		E10	8841679
緩徐進行 1 型糖尿病・昏睡合併あり	SPIDDM with coma - [Slowly progressive insulin-dependent diabetes mellitus]		E10	8844026
1 型糖尿病性低血糖性昏睡	Hypoglycemia in the context of type 1 diabetes mellitus		E10	8845065
1 型糖尿病性ケトアシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus		E10	8830028
1 型糖尿病・ケトアシドーシス合併あり	Type 1 diabetes mellitus with ketoacidosis		E10	8841680
緩徐進行 1 型糖尿病・ケトアシドーシス合併あり	SPIDDM with ketoacidosis - [Slowly progressive insulin-dependent diabetes mellitus]		E10	8844025
劇症 1 型糖尿病	Fulminant type 1 diabetes mellitus		E10	8844045
1 型糖尿病性アシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus		E10	8845044
1 型糖尿病性アセトン血症	Type 1 diabetic acetone hyperlipoproteinemia		E10	8845045
1 型糖尿病性腎症	Type 1 diabetic nephropathy		E10	8830031
1 型糖尿病・腎合併症あり	Type 1 diabetes mellitus with diabetic nephropathy		E10	8841681
1 型糖尿病性腎症第 1 期	Type 1 diabetic nephropathy phase 1		E10	8843983
1 型糖尿病性腎症第 2 期	Type 1 diabetic nephropathy phase 2		E10	8843984
1 型糖尿病性腎症第 3 期	Type 1 diabetic nephropathy phase 3		E10	8843985
1 型糖尿病性腎症第 3 期 A	Type 1 diabetic nephropathy phase 3A		E10	8843986
1 型糖尿病性腎症第 3 期 B	Type 1 diabetic nephropathy phase 3B		E10	8843987
1 型糖尿病性腎症第 4 期	Type 1 diabetic nephropathy phase 4		E10	8843988
1 型糖尿病性腎症第 5 期	Type 1 diabetic nephropathy phase 5		E10	8843989

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3	緩徐進行 1 型糖尿病・腎合併症あり	SPIDDM with nephropathy - [Slowly progressive insulin-dependent diabetes mellitus]	E10369	8844028
4				
5				
6	1 型糖尿病性腎硬化症	Type 1 diabetic nephrosclerosis	E10370	8845058
7				
8	1 型糖尿病性腎不全	Type 1 diabetic kidney failure	E10371	8845059
9				
10	1 型糖尿病性網膜症	Type 1 diabetic retinopathy	E10372	8830033
11	1 型糖尿病・眼合併症あり	Type 1 diabetes mellitus with eye complication	E10373	8841682
12				
13	1 型糖尿病性黄斑浮腫	Type 1 diabetic macular edema	E10374	8843982
14	緩徐進行 1 型糖尿病・眼合併症あり	SPIDDM with eye complication - [Slowly progressive insulin-dependent diabetes mellitus]	E10375	8844024
15				
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17	1 型糖尿病性白内障	Type 1 diabetic cataracts	E10376	8844346
18				
19	増殖性糖尿病性網膜症・1 型糖尿病	Proliferative diabetic retinopathy, type 1 diabetes	E10377	8844536
20				
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22	1 型糖尿病黄斑症	Type 1 diabetic macular disease	E10378	8845043
23				
24	1 型糖尿病性眼筋麻痺	Type 1 diabetic eye muscle paralysis	E10379	8845049
25				
26	1 型糖尿病性虹彩炎	Type 1 diabetic iritis	E10380	8845053
27				
28	1 型糖尿病性中心性網膜症	Type 1 diabetic central retinopathy	E10381	8845064
29				
30	1 型糖尿病性ニューロパチー	Type 1 diabetic neuropathy	E10382	8830032
31				
32	1 型糖尿病・神経学的合併症あり	Type 1 diabetes mellitus with neurological complications	E10383	8841683
33				
34	緩徐進行 1 型糖尿病・神経学的合併症あり	SPIDDM with neurological complications - [Slowly progressive insulin-dependent diabetes mellitus]	E10384	8844027
35				
36	1 型糖尿病性筋萎縮症	Type 1 diabetic muscular atrophy	E10385	8845050
37				
38	1 型糖尿病性神経因性膀胱	Type 1 diabetic neuropathic bladder	E10386	8845055
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40	1 型糖尿病性神経痛	Type 1 diabetic neuralgia	E10387	8845056
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4	1 型糖尿病性自律神経ニューロパ	Type 1 diabetic autonomic neuropathy	E10436	8845057
5	チー			
6	1 型糖尿病性多発ニューロパチー	Type 1 diabetic polyneuropathy	E10437	8845062
7				
8	1 型糖尿病性単ニューロパチー	Type 1 diabetic mononeuropathy	E10438	8845063
9				
10	1 型糖尿病性末梢神経障害	Type 1 diabetic peripheral neuropathy	E10439	8845071
11				
12	1 型糖尿病・末梢循環合併症あり	Type 1 diabetes mellitus with peripheral circulation complications	E10440	8841684
13				
14	1 型糖尿病性壊疽	Type 1 diabetic gangrene	E10441	8843105
15				
16	緩徐進行 1 型糖尿病・末梢循環合	SPIDDM with peripheral circulation complications -		
17	併症あり	[Slowly progressive insulin-dependent diabetes mellitus]	E10442	8844031
18				
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20	1 型糖尿病性潰瘍	Type 1 diabetic ulcer	E10443	8845046
21				
22	1 型糖尿病性血管障害	Type 1 diabetic vascular disease	E10444	8845051
23				
24	1 型糖尿病性動脈硬化症	Type 1 diabetic atherosclerosis	E10445	8845066
25				
26	1 型糖尿病性動脈閉塞症	Type 1 diabetic arterial occlusion	E10446	8845067
27				
28	1 型糖尿病性末梢血管症	Type 1 diabetic peripheral vascular disease	E10447	8845069
29				
30	1 型糖尿病性末梢血管障害	Type 1 diabetic peripheral vascular disease	E10448	8845070
31				
32	1 型糖尿病・関節合併症あり	Type 1 diabetes mellitus with joint complications	E10449	8841685
33				
34	1 型糖尿病・糖尿病性合併症あり	Type 1 diabetes mellitus with diabetic complications	E10450	8841686
35				
36	緩徐進行 1 型糖尿病・関節合併症	SPIDDM with joint complications - [Slowly		
37	あり	progressive insulin-dependent diabetes mellitus]	E10451	8844023
38				
39	1 型糖尿病性水疱	Type 1 diabetic blister	E10452	8844626
40				
41	1 型糖尿病性浮腫性硬化症	Type 1 diabetic edematous sclerosis	E10453	8844627
42				
43	1 型糖尿病性肝障害	Type 1 diabetic liver injury	E10454	8845047
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3	1 型糖尿病性関節症	Type 1 diabetic arthropathy	E10436	8845048
4	1 型糖尿病性高コレステロール血	Type 1 diabetic hypercholesterolemia	E10437	8845052
5	症			
6	1 型糖尿病性骨症	Type 1 diabetic osteopathy	E10438	8845054
7	1 型糖尿病性精神障害	Type 1 diabetic mental disorder	E10439	8845060
8	1 型糖尿病性そう痒症	Type 1 diabetic pruritus	E10440	8845061
9	1 型糖尿病性皮膚障害	Type 1 diabetic skin disorder	E10441	8845068
10	1 型糖尿病性胃腸症	Type 1 diabetic gastroenteritis	E10442	8845842
11	1 型糖尿病・多発糖尿病性合併症	Type 1 diabetes mellitus with multiple diabetic	E10443	8841687
12	あり	complications		
13	緩徐進行 1 型糖尿病・多発糖尿病	SPIDDM with multiple diabetic complications -		
14	性合併症あり	[Slowly progressive insulin-dependent diabetes	E10444	8844029
15		mellitus]		
16	1 型糖尿病・糖尿病性合併症なし	Type 1 diabetes mellitus without diabetic	E10445	8841688
17		complications		
18	緩徐進行 1 型糖尿病・糖尿病性合	SPIDDM without diabetic complications - [Slowly	E10446	8844030
19	併症なし	progressive insulin-dependent diabetes mellitus]		
20	インスリン抵抗性糖尿病	Insulin resistant diabetes mellitus	E11447	2500001
21	2 型糖尿病	Type 2 diabetes mellitus	E11448	2500015
22	安定型糖尿病	Stable diabetes mellitus	E11449	8830405
23	若年 2 型糖尿病	Juvenile type 2 diabetes	E11450	8835244
24	2 型糖尿病性昏睡	Type 2 diabetic coma	E11451	8830041
25	2 型糖尿病・昏睡合併あり	Type 2 diabetes mellitus with coma	E11452	8841689
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4	2 型糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of type 2 diabetes mellitus	E1116	8845094
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6	2 型糖尿病性ケトアシドーシス	Type 2 diabetic ketoacidosis	E1117	8830040
7				
8	2 型糖尿病・ケトアシドーシス合併あり	Type 2 diabetes mellitus with ketoacidosis	E1118	8841690
9				
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11	2 型糖尿病性アシドーシス	Type 2 diabetic acidosis	E1119	8845073
12				
13	2 型糖尿病性アセトン血症	Type 2 diabetic acetone hyperlipoproteinemia	E1120	8845074
14				
15	2 型糖尿病性腎症	Type 2 diabetic nephropathy	E1121	8830042
16				
17	2 型糖尿病・腎合併症あり	Type 2 diabetes mellitus with diabetic nephropathy	E1122	8841691
18				
19	2 型糖尿病性腎症第 1 期	Type 2 diabetic nephropathy phase 1	E1123	8843991
20				
21	2 型糖尿病性腎症第 2 期	Type 2 diabetic nephropathy phase 2	E1124	8843992
22				
23	2 型糖尿病性腎症第 3 期	Type 2 diabetic nephropathy phase 3	E1125	8843993
24				
25	2 型糖尿病性腎症第 3 期 A	Type 2 diabetic nephropathy phase 3A	E1126	8843994
26				
27	2 型糖尿病性腎症第 3 期 B	Type 2 diabetic nephropathy phase 3B	E1127	8843995
28				
29	2 型糖尿病性腎症第 4 期	Type 2 diabetic nephropathy phase 4	E1128	8843996
30				
31	2 型糖尿病性腎症第 5 期	Type 2 diabetic nephropathy phase 5	E1129	8843997
32				
33	2 型糖尿病性腎硬化症	Type 2 diabetic nephrosclerosis	E1130	8845087
34				
35	2 型糖尿病性腎不全	Type 2 diabetic kidney failure	E1131	8845088
36				
37	2 型糖尿病性網膜症	Type 2 diabetic retinopathy	E1132	8830045
38				
39	2 型糖尿病・眼合併症あり	Type 2 diabetes mellitus with eye complications	E1133	8841692
40				
41	2 型糖尿病性黄斑浮腫	Type 2 diabetic macular edema	E1134	8843990
42				
43	2 型糖尿病性白内障	Type 2 diabetic cataracts	E1135	8844347
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45	増殖性糖尿病性網膜症・2 型糖尿病	Proliferative diabetic retinopathy, type 2 diabetes	E1136	8844537
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3	2 型糖尿病黄斑症	Type 2 diabetic macular disease	E11436	8845072
4	2 型糖尿病性眼筋麻痺	Type 2 diabetic eye muscle paralysis	E11437	8845078
5	2 型糖尿病性虹彩炎	Type 2 diabetic iritis	E11438	8845082
6	2 型糖尿病性中心性網膜症	Type 2 diabetic central retinopathy	E11439	8845093
7	2 型糖尿病性ニューロパチー	Type 2 diabetic neuropathy	E11440	8830043
8	2 型糖尿病性ミオパチー	Type 2 diabetic myopathy	E11441	8830044
9	2 型糖尿病・神経学的合併症あり	Type 2 diabetes mellitus with neurological complications	E11442	8841693
10	2 型糖尿病性筋萎縮症	Type 2 diabetic muscular atrophy	E11443	8845079
11	2 型糖尿病性神経因性膀胱	Type 2 diabetic neuropathic bladder	E11444	8845084
12	2 型糖尿病性神経痛	Type 2 diabetic neuralgia	E11445	8845085
13	2 型糖尿病性自律神経ニューロパチー	Type 2 diabetic autonomic neuropathy	E11446	8845086
14	2 型糖尿病性多発ニューロパチー	Type 2 diabetic polyneuropathy	E11447	8845091
15	2 型糖尿病性単ニューロパチー	Type 2 diabetic mononeuropathy	E11448	8845092
16	2 型糖尿病性末梢神経障害	Type 2 diabetic peripheral neuropathy	E11449	8845100
17	2 型糖尿病・末梢循環合併症あり	Type 2 diabetes mellitus with peripheral circulation complications	E11450	8841694
18	2 型糖尿病性壊疽	Type 2 diabetic gangrene	E11451	8843106
19	2 型糖尿病性潰瘍	Type 2 diabetic ulcer	E11452	8845075
20	2 型糖尿病性血管障害	Type 2 diabetic vascular disease	E11453	8845080
21	2 型糖尿病性動脈硬化症	Type 2 diabetic atherosclerosis	E11454	8845095
22	2 型糖尿病性動脈閉塞症	Type 2 diabetic arterial occlusion	E11455	8845096
23	2 型糖尿病性末梢血管症	Type 2 diabetic peripheral vascular disease	E11456	8845098
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3	2 型糖尿病性末梢血管障害	Type 2 diabetic peripheral vascular disease	E11436	8845099
4	2 型糖尿病・関節合併症あり	Type 2 diabetes mellitus with joint complications	E11436	8841695
5	2 型糖尿病・糖尿病性合併症あり	Type 2 diabetes mellitus with diabetic complications	E11436	8841696
6	2 型糖尿病性水疱	Type 2 diabetic blister	E11436	8844628
7	2 型糖尿病性浮腫性硬化症	Type 2 diabetic edematous sclerosis	E11436	8844629
8	2 型糖尿病性肝障害	Type 2 diabetic liver injury	E11436	8845076
9	2 型糖尿病性関節症	Type 2 diabetic arthropathy	E11436	8845077
10	2 型糖尿病性高コレステロール血症	Type 2 diabetic hypercholesterolemia	E11436	8845081
11	2 型糖尿病性骨症	Type 2 diabetic osteopathy	E11436	8845083
12	2 型糖尿病性精神障害	Type 2 diabetic mental disorder	E11436	8845089
13	2 型糖尿病性そう痒症	Type 2 diabetic pruritus	E11436	8845090
14	2 型糖尿病性皮膚障害	Type 2 diabetic skin disorder	E11436	8845097
15	2 型糖尿病性胃腸症	Type 2 diabetic gastroenteritis	E11436	8848108
16	2 型糖尿病・多発糖尿病性合併症あり	Type 2 diabetes mellitus with multiple diabetic complications	E11436	8841697
17	2 型糖尿病・糖尿病性合併症なし	Type 2 diabetes mellitus without diabetic complications	E11436	8841698
18	栄養不良関連糖尿病	Malnutrition-related diabetes mellitus	E12436	2500037
19	膵性糖尿病	Pancreatic diabetes mellitus	E13436	2500024
20	ステロイド糖尿病	Steroid diabetes mellitus	E13436	2509003
21	二次性糖尿病	Secondary diabetes mellitus	E13436	2509004
22	ウイルス性糖尿病	Viral diabetes mellitus	E13436	8830756
23	薬剤性糖尿病	Drug-induced diabetes mellitus	E13436	8840710
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3	ウイルス性糖尿病・昏睡合併あり	Viral diabetes mellitus with coma	E13	8843122
4	膵性糖尿病・昏睡合併あり	Pancreatic diabetes mellitus with coma	E13	8843377
5	ステロイド糖尿病・昏睡合併あり	Steroid diabetes mellitus with coma	E13	8843390
6	二次性糖尿病・昏睡合併あり	Secondary diabetes mellitus with coma	E13	8843450
7	薬剤性糖尿病・昏睡合併あり	Drug-induced diabetes mellitus with coma	E13	8843621
8	ウイルス性糖尿病・ケトアシドーシス合併あり	Viral diabetes mellitus with ketoacidosis	E13	8843121
9	膵性糖尿病・ケトアシドーシス合併あり	Pancreatic diabetes mellitus with ketoacidosis	E13	8843376
10	ステロイド糖尿病・ケトアシドーシス合併あり	Steroid diabetes mellitus with ketoacidosis	E13	8843389
11	二次性糖尿病・ケトアシドーシス合併あり	Secondary diabetes mellitus with ketoacidosis	E13	8843449
12	薬剤性糖尿病・ケトアシドーシス合併あり	Drug-induced diabetes mellitus with ketoacidosis	E13	8843620
13	ウイルス性糖尿病・腎合併症あり	Viral diabetes mellitus with renal complications	E13	8843124
14	膵性糖尿病・腎合併症あり	Pancreatic diabetes mellitus with renal complications	E13	8843379
15	ステロイド糖尿病・腎合併症あり	Steroid diabetes mellitus with renal complications	E13	8843392
16	二次性糖尿病・腎合併症あり	Secondary diabetes mellitus with renal complications	E13	8843452
17	薬剤性糖尿病・腎合併症あり	Drug-induced diabetes mellitus with renal complications	E13	8843623
18	ウイルス性糖尿病・眼合併症あり	Viral diabetes mellitus with eye complications	E13	8843120
19	膵性糖尿病・眼合併症あり	Pancreatic diabetes mellitus with eye complications	E13	8843375
20	ステロイド糖尿病・眼合併症あり	Steroid diabetes mellitus with eye complications	E13	8843388
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3	二次性糖尿病・眼合併症あり	Secondary diabetes mellitus with eye complications	E13436	8843448
4	薬剤性糖尿病・眼合併症あり	Drug-induced diabetes mellitus with eye complications	E13436	8843619
5	ウイルス性糖尿病・神経学的合併症あり	Viral diabetes mellitus with neurological complications	E13436	8843123
6				
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8				
9	膵性糖尿病・神経学的合併症あり	Pancreatic diabetes mellitus with neurological complications	E13436	8843378
10				
11	ステロイド糖尿病・神経学的合併症あり	Steroid diabetes mellitus with neurological complications	E13436	8843391
12				
13	二次性糖尿病・神経学的合併症あり	Secondary diabetes mellitus with neurological complications	E13436	8843451
14				
15	薬剤性糖尿病・神経学的合併症あり	Drug-induced diabetes mellitus with neurological complications	E13436	8843622
16				
17	ウイルス性糖尿病・末梢循環合併症あり	Viral diabetes mellitus with peripheral circulatory complications	E13436	8843128
18				
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20	膵性糖尿病・末梢循環合併症あり	Pancreatic diabetes mellitus with peripheral circulatory complications	E13436	8843383
21				
22	ステロイド糖尿病・末梢循環合併症あり	Steroid diabetes mellitus with peripheral circulatory complications	E13436	8843396
23				
24	二次性糖尿病・末梢循環合併症あり	Secondary diabetes mellitus with peripheral circulatory complications	E13436	8843456
25				
26	薬剤性糖尿病・末梢循環合併症あり	Drug-induced diabetes mellitus with peripheral circulatory complications	E13436	8843627
27				
28	ウイルス性糖尿病・糖尿病性合併症あり	Viral diabetes mellitus with diabetic complications	E13436	8843126
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4	膵性糖尿病・糖尿病性合併症あり	Pancreatic diabetes mellitus with diabetic complications	E136	8843381
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6	ステロイド糖尿病・糖尿病性合併症あり	Steroid diabetes mellitus with diabetic complications	E136	8843394
7				
8	二次性糖尿病・糖尿病性合併症あり	Secondary diabetes mellitus with diabetic complications	E136	8843454
9				
10	薬剤性糖尿病・糖尿病性合併症あり	Drug-induced diabetes mellitus with diabetic complications	E136	8843625
11				
12	ウイルス性糖尿病・多発糖尿病性合併症あり	Viral diabetes mellitus with multiple diabetic complications	E136	8843125
13				
14	膵性糖尿病・多発糖尿病性合併症あり	Pancreatic diabetes mellitus with multiple diabetic complications	E136	8843380
15				
16	ステロイド糖尿病・多発糖尿病性合併症あり	Steroid diabetes mellitus with multiple diabetic complications	E136	8843393
17				
18	二次性糖尿病・多発糖尿病性合併症あり	Secondary diabetes mellitus with multiple diabetic complications	E136	8843453
19				
20	薬剤性糖尿病・多発糖尿病性合併症あり	Drug-induced diabetes mellitus with multiple diabetic complications	E136	8843624
21				
22	ウイルス性糖尿病・糖尿病性合併症なし	Viral diabetes mellitus without diabetic complications	E136	8843127
23				
24	膵性糖尿病・糖尿病性合併症なし	Pancreatic diabetes mellitus without diabetic complications	E136	8843382
25				
26	ステロイド糖尿病・糖尿病性合併症なし	Steroid diabetes mellitus without diabetic complications	E136	8843395
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3	二次性糖尿病・糖尿病性合併症な	Secondary diabetes mellitus without diabetic		
4	し	complications	E136	8843455
5	薬剤性糖尿病・糖尿病性合併症な	Drug-induced diabetes mellitus without diabetic		
6	し	complications	E136	8843626
7	糖尿病	Diabetes mellitus	E14	2500013
8	糖尿病合併症	Diabetic complications	E14	2507028
9	糖尿病性昏睡	Diabetic coma	E14	2502006
10	糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of diabetes mellitus	E14	8838076
11	糖尿病性アシドーシス	Diabetic acidosis	E14	2501002
12	糖尿病性アセトン血症	Diabetic acetonemia	E14	2501003
13	糖尿病性ケトアシドーシス	Diabetic ketoacidosis	E14	2501005
14	糖尿病性腎症	Diabetic nephropathy	E14	2503005
15	糖尿病性腎不全	Diabetic renal failure	E14	2503007
16	糖尿病性腎硬化症	Diabetic nephrosclerosis	E14	8838071
17	糖尿病性虹彩炎	Diabetic iritis	E14	2504004
18	糖尿病性中心性網膜症	Diabetic central retinopathy	E14	2504005
19	糖尿病性白内障	Diabetic cataract	E14	2504006
20	増殖性糖尿病性網膜症	Proliferative diabetic retinopathy	E14	2504010
21	糖尿病黄斑症	Diabetic maculopathy	E14	2504012
22	糖尿病網膜症	Diabetic retinopathy	E14	2504013
23	糖尿病性眼筋麻痺	Diabetic ophthalmoplegia	E14	8838065
24	糖尿病黄斑浮腫	Diabetic macular edema	E14	8844089
25	糖尿病性神経痛	Diabetic neuralgia	E14	2505011
26	糖尿病性末梢神経障害	Diabetic peripheral neuropathy	E14	2505018
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3	糖尿病性筋萎縮症	Diabetic muscular atrophy	E14436	2505021
4	糖尿病性神経因性膀胱	Diabetic neuropathic bladder	E14436	8838069
5	糖尿病性自律神経ニューロパチー	Diabetic autonomic neuropathy	E14436	8838070
6	糖尿病性多発ニューロパチー	Diabetic polyneuropathy	E14436	8838074
7	糖尿病性単ニューロパチー	Diabetic mononeuropathy	E14436	8838075
8	糖尿病性ニューロパチー	Diabetic neuropathy	E14436	8838078
9	糖尿病足病変	Diabetic foot lesion	E14436	8848634
10	糖尿病性神経障害性疼痛	Diabetic neuropathic pain	E14436	8848768
11	糖尿病性壊疽	Diabetic gangrene	E14436	2506006
12	糖尿病性動脈閉塞症	Diabetic arterial occlusion	E14436	2506011
13	糖尿病性潰瘍	Diabetic ulcer	E14436	8838063
14	糖尿病性血管障害	Diabetic angiopathy	E14436	8838066
15	糖尿病性動脈硬化症	Diabetic arteriosclerosis	E14436	8838077
16	糖尿病性末梢血管症	Diabetic peripheral vascular disease	E14436	8838079
17	糖尿病性末梢血管障害	Diabetic peripheral vascular disease	E14436	8838080
18	糖尿病足壊疽	Diabetic foot gangrene	E14436	8848632
19	糖尿病足潰瘍	Diabetic foot ulcer	E14436	8848633
20	糖尿病性関節症	Diabetic arthropathy	E14436	2507025
21	糖尿病性皮膚障害	Diabetic skin disorders	E14436	2507029
22	糖尿病性肝障害	Diabetic liver injury	E14436	8838064
23	糖尿病性高コレステロール血症	Diabetic hypercholesterolemia	E14436	8838067
24	糖尿病性骨症	Diabetic osteopathy	E14436	8838068
25	糖尿病性精神障害	Diabetic mental disorder	E14436	8838072
26	糖尿病性そう痒症	Diabetic pruritus	E14436	8838073
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3	糖尿病性水疱	Diabetic blister	E14	8844652
4	糖尿病性浮腫性硬化症	Diabetic edematous sclerosis	E14	8844653
5	高血糖高浸透圧症候群	Hyperglycemia hyperosmolarity syndrome	E14	8845128
6	糖尿病・糖尿病性合併症なし	Diabetes mellitus without diabetic complications	E14	8843439
7				
8	非糖尿病性低血糖性昏睡	Hypoglycemic coma not in the context of diabetes mellitus	E15	8839324
9				
10	果糖尿症	Levulosuria	E74	8831401
11	本態性果糖尿症	Essential levulosuria	E74	8840104
12	良性果糖尿症	Benign levulosuria	E74	8841021
13	腎性糖尿	Renal glycosuria	E74	2714002
14	青銅性糖尿病	Bronze diabetes mellitus	E83	8835941
15	膵全摘後二次性糖尿病	Secondary diabetes after pancreatectomy	E89	8835685
16	1 型糖尿病合併妊娠	Pregnancy with type 1 diabetes	O24	8830029
17	2 型糖尿病合併妊娠	Pregnancy with type 2 diabetes	O24	8830039
18	妊娠糖尿病	Pregnancy diabetes mellitus	O24	6489003
19	妊娠中の糖尿病	Overt diabetes in pregnancy	O24	8838621
20	妊娠中の耐糖能低下	Impaired glucose tolerance in pregnancy	O99	8838619
21	妊娠糖尿病母体児症候群	Gestational diabetes maternal syndrome	P70	8838633
22	糖尿病母体児	Diabetes maternal infant	P70	8838081
23	新生児一過性糖尿病	Neonatal transient diabetes mellitus	P70	7751001
24	新生児糖尿病	Neonatal diabetes mellitus	P70	7751002
25	新生児一過性高血糖症	Neonatal transient hyperglycemia	P70	8844233
26	境界型糖尿病	Borderline type diabetes mellitus	R73	2500031
27	耐糖能異常	Impaired glucose tolerance	R73	2713009
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3	化学的糖尿病	Chemical diabetes mellitus	R734.36	8831132
4	潜在性糖尿病	Latent diabetes mellitus	R734.00	8836104
5	前糖尿病	Pre-diabetes mellitus	R734.1	8836563
6	高血糖症	Hyperglycemia	R734.99	8833419
7	一過性糖尿	Transient diabetes mellitus	R81.21	7915002
8	五炭糖尿症	L-Xylulosemia	R81.22	7915003
9	高血糖性糖尿	Hypoglycemic glycosuria	R81.23	8833420
10	食事性糖尿	Dietary glycosuria	R81.24	8834843
11	情動性糖尿	Emotional glycosuria	R81.25	8835464
12	正常血糖性糖尿	Euglycemic glycosuria	R81.26	8835871
13	糖尿	Glycosuria	R81.27	8838062
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Supplementary Table S2 Codes of antidiabetic medications

Types of antidiabetic medication	Medicine codes
Sulfonylureas	610412056, 610443002, 610443003, 613960002, 613960003, 613960008, 613960017, 613960026, 613960027, 613960028, 613960038, 613960039, 613960078, 620000048, 620002031, 620002032, 620003159, 620003160, 620003947, 620003948, 620006030, 620006890, 620009209, 620871601, 620872002, 620872003, 620872004, 620872009, 620872016, 620873202, 620873301, 620873402, 620873702, 621982701, 621997001, 621997101, 621998701, 621998801, 621998901, 621999001, 621999301, 621999401, 621999701, 621999801, 622000601, 622000701, 622001701, 622001801, 622004701, 622004801, 622005501, 622005601, 622005802, 622009802, 622009901, 622010001, 622011401, 622011501, 622011601, 622011701, 622013401, 622013501, 622013601, 622016001, 622016101, 622017301, 622017401, 622017501, 622017901, 622018001, 622018802, 622020903, 622021003, 622021801, 622021901, 622022001, 622022101, 622023501, 622023601, 622025201, 622025301, 622025801, 622025901, 622026501, 622026601, 622029901, 622030001, 622031401, 622031501, 622033001, 622033101, 622033201, 622033701, 622033801, 622035701, 622035801, 622036002, 622037901, 622038001, 622039901, 622048401, 622048501, 622058801, 622058901, 622059002, 622059102, 622075601, 622088301, 622088401, 622103201, 622114701, 622114801, 622118501, 622122201, 622122301, 622127301, 622127401, 622127501, 622128101, 622137701, 622141101, 622141302, 622143402, 622144001, 622159301, 622169102, 622169301, 622176301, 622177501, 622186201, 622187301, 622190001, 622190801,

	622193301, 622194901, 622198001, 622202201, 622202801, 622205101, 622205501, 622208901, 622211501, 622217701, 622219701, 622221001, 622222001, 622242001, 622246801, 622252501, 622254701, 622271101, 622271201, 622271301, 622313200, 622313300, 622338501, 622338601, 622338701
Meglitinides	622462501, 622462401, 620001908, 620001907, 622053601, 622040901, 622041001, 610432026, 610432027, 622196601, 622119301, 622230001, 622196701, 622119401, 622230101, 610432032, 610432033, 622518201, 622525401, 622515301, 622523401, 622521001, 622518101, 622525301, 622515201, 622523301, 622520901
α -glucosidase inhibitors	610406390, 620002841, 620002843, 620004045, 620004072, 620004071, 620008727, 620008726, 621665301, 621683401, 621673501, 621691201, 622090001, 621689303, 621689001, 621690402, 621690901, 621690203, 620002120, 620004069, 620005557, 620005558, 620005559, 620005560, 620005561, 620008071, 620008072, 620008073, 621953301, 621943301, 620009287, 621896502, 622008602, 620009286, 621896402, 622008502, 620009296, 620009294, 620009293, 622302301, 620009297, 621958801, 620005360, 621785002, 621942202, 620009295, 620009291, 620009289, 620009288, 622302201, 620009292, 621958701, 620005359, 621784902, 621942102, 620009290, 621937201, 621937101, 613960082, 613960081, 622053601, 622432501, 622426601, 622426701, 620003127, 620003128, 620003129, 620002121, 610406391, 621953401, 620004046, 620004070, 620005562, 620008074, 620005563, 620005564, 620005565, 620008075, 620005566, 621943401, 620008076, 620004073, 620002845, 621690303, 620008729, 620008728, 620004074, 621689403, 621689101, 621691001, 621691601, 621665401, 621683501, 620002847, 622090101, 621690502, 621673601
Biguanides	622517101, 622450401, 622450301, 620004480, 620004502, 620005979, 610463145, 621986401, 621986301, 610444147, 621974701, 622242501, 622070801, 621676001,

	620005570, 622427201, 622421901, 622424401, 622421101, 622412701, 622438401, 622417101, 622432601, 622436301, 622427301, 622422001, 622424501, 622421201, 622448601, 622438501, 622417201, 622432701, 622466601
Thiazolidinediones	621990901, 621991001, 610432040, 610432041, 622048501, 622048401, 622065301, 622061601, 622041402, 622155901, 622063201, 622156901, 622144601, 622167201, 622045401, 622159401, 622056001, 622147501, 622175601, 622071901, 622065401, 622061701, 622041502, 622156001, 622063301, 622157001, 622144701, 622167301, 622045501, 622159501, 622056101, 622147601, 622175701, 622072001, 622320800, 622320900, 622065101, 622042901, 622061401, 622166801, 622182401, 622041202, 622079101, 622155701, 622063001, 622066201, 622164301, 622062302, 622047701, 622049901, 622046801, 622163301, 622053101, 622081801, 622059201, 622045201, 622053801, 622055801, 622147301, 622078301, 622175401, 622071701, 622065201, 622043001, 622061501, 622166901, 622182501, 622041302, 622079201, 622155801, 622063101, 622066301, 622164401, 622062402, 622047801, 622050001, 622046901, 622163401, 622053201, 622081901, 622059301, 622045301, 622061001, 622055901, 622147401, 622078401, 622175501, 622071801, 621986401, 621986301, 622086101, 622086001
Dipeptidyl peptidase-4 inhibitors	621950901, 621951001, 621951101, 621970601, 621970701, 621970801, 621980701, 621986001, 621986101, 621986201, 622086001, 622086101, 622093501, 622182601, 622201701, 622245601, 622245701, 622277501, 622288401, 622415401, 622415501, 622448901, 622449001, 622450301, 622450401, 622517101
Sodium glucose cotransporter 2 inhibitor	622340101, 622360601, 622401201, 622401301, 622306601, 622306701, 622336801, 622342001, 622341901, 622335701, 622335801

Rapid-acting insulin	621911101, 621911301, 621911201, 620008895, 621926901, 622252701, 620008893, 620008894, 620008916, 640451027, 620007460
Short-acting insulin	620008897, 620000265, 620008909, 620008907, 622114401
Long-acting insulin	622440701, 620008945, 620008943, 620007536, 622198901, 622199001, 622410901, 622484801, 622411001, 621927001, 620008952, 620008953
Immediate-acting insulin	620000266, 620008912, 620008910, 622114501, 620002441, 620007459
Premixed insulin	620002439, 620007461, 620002440, 620007462, 620008915, 620008913, 622114601, 620000269, 620000448, 620008896, 621973201, 621973301, 640453023
Combination-acting insulin	622451001, 622450901
Glucagon-like peptide-1 receptor agonist	622038401, 622038301, 621974801, 622229001, 622406001, 622267001, 622442201

Supplementary Table S3 Amputation codes

	Medical procedure receipt codes (in Japan)
Major LLA	
above-knee/transfemoral amputation	150051610
below-knee/transtibial amputation	150051710
Hindquarter amputation/ Hip disarticulation	150052210
through-knee amputation	150052310
Minor LLA	
Foot amputation, trans-metatarsal amputation, Lisfranc disarticulation	150051810
Foot joint disarticulation	150052610
Finger and toe amputation	150051910
Finger and toe joint disarticulation	150052710

Supplementary Table S4 The population of Japanese national census (2015)

Age group, years	total	men	women	Age group, years	total	men	women	Age group, years	total	men	women
0-4	4,987,706	2,550,921	2,436,785	35-39	8,316,157	4,204,202	4,111,955	70-74	6,695,811	3,582,440	4,113,371
5-9	5,299,787	2,714,591	2,585,196	40-44	9,732,218	4,914,018	4,818,200	75-79	5,276,856	2,787,417	3,489,439
10-14	5,599,317	2,868,024	2,731,293	45-49	8,662,804	4,354,877	4,307,927	80-84	4,961,420	1,994,326	2,967,094
15-19	6,008,388	3,085,416	2,922,972	50-54	7,930,296	3,968,311	3,961,985	≥85	4,887,487	1,461,624	3,425,863
20-24	5,968,127	3,046,392	2,921,735	55-59	7,515,246	3,729,523	3,785,723	Total	127,094,745	61,841,738	65,253,007
25-29	6,409,612	3,255,717	3,153,895	60-64	8,455,010	4,151,119	4,303,891				
30-34	7,290,878	3,684,747		60-65	9,643,867	4,659,662	4,984,205				

Contributorship statement

All authors contributed significantly. F.K. designed the study and wrote the manuscript. Y.N. contributed to the study design, data analysis, and discussion. T.N. provided advice on the study design and discussed the findings from an epidemiological perspective. T.M., S.K., and T.H. performed the initial NDB analysis and provided technical advice. S.O., Y.A., H.I., and Y.T. evaluated the results from a clinical perspective. T.I. provided advice on the study design and discussed the findings from the public health viewpoint.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9,10
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9,10
		(b) Describe any methods used to examine subgroups and interactions	9,10
		(c) Explain how missing data were addressed	9,10
		(d) If applicable, explain how loss to follow-up was addressed	9,10
		(e) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	No participants
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	13, Table2

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17, Table3
2			(b) Report category boundaries when continuous variables were categorized	17
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	20, Table4
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	25
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	24,25
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22-24
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	24
10	Other information			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Incidence of lower limb amputation in people with and without diabetes: A nationwide 5-year cohort study in Japan

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-048436.R2
Article Type:	Original research
Date Submitted by the Author:	24-Jun-2021
Complete List of Authors:	Kamitani, Fumika; Nara Medical University Nishioka, Yuichi; Nara Medical University Noda, Tatsuya; Nara Medical University Myojin, Tomoya; Nara Medical University Kubo, Shinichiro; Nara Medical University Higashino, Tsuneyuki; Healthcare and Wellness Division, Mitsubishi Research Institute, Inc., Tokyo, 100-8141, Japan Okada, Sadanori; Nara Medical University Akai, Yasuhiro; Nara Medical University, Center for Postgraduate Training; Nara Medical University, Department of Nephrology Ishii, Hitoshi; Nara Medical University Takahashi, Yutaka; Nara Medical University Imamura, Tomoaki; Nara Medical University
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Health services research, Surgery, Evidence based practice, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, ORTHOPAEDIC & TRAUMA SURGERY, DIABETES & ENDOCRINOLOGY

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7 **Manuscript category:** Original research
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14 **Incidence of lower limb amputation in people with and without diabetes: A nationwide 5-**
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16 **year cohort study in Japan**
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27 **Short Running Title:** Incidence of limb amputation in Japan
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34 **Word count:** 3352 words
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41 **Number of tables and figures:** 4 tables and 2 figures.
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1 ABSTRACT

2 **Introduction:** This study was conducted to investigate the incidence and time trend of
3 lower limb amputation (LLA) among people with and without diabetes.

4 **Research design and methods:** This retrospective population-based cohort study was
5 based on the national claims data in Japan, comprising a total population of 150 million.
6 Data of all individuals who had LLA from April 2013 to March 2018 were obtained. We
7 analyzed the sex- and age-adjusted annual LLA rate (every fiscal year) in people with and
8 without diabetes for major and minor amputation. To test for time trend, Poisson
9 regression models were fitted.

10 **Results:** In the 5-year period, 30,187 major and 29,299 minor LLAs were performed in
11 Japan. The sex- and age-adjusted incidence of major and minor LLAs was 9.5 (people
12 with diabetes, 21.8 vs. people without diabetes, 2.3, per 100,000 person-years) and 14.9
13 (people with diabetes, 28.4 vs people without diabetes, 1.9, per 100,000 person-years)
14 times higher, respectively, in people with diabetes compared to those without. A
15 significant decline in the annual major amputation rate was observed ($p < 0.05$) and the
16 annual minor amputation rate remained stable ($p = 0.63$) when sex, age, and people with
17 and without diabetes were included as dependent variables.

18 **Conclusions:** This is the first report of the national statistics of LLAs in Japan. The
19 incidence of major and minor LLAs was 10 and 15 times higher, respectively, in people
20 with diabetes compared to those without. A significant decline in the major amputation
21 rate was observed, and the annual minor amputation rate remained stable during
22 observation period. This information can help create an effective national healthcare

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1 strategy for preventing limb amputations, which affect the quality of life of patients with
2 diabetes and add to the national healthcare expenditure.

3 **Keywords:** amputation, cohort study, diabetes mellitus

For peer review only

Strengths and limitations of this study

- This is the first report of the national statistics of lower limb amputations (LLAs) among people with and without diabetes.
- This retrospective cohort study was based on the National Database (NDB) in Japan, comprising almost all patients in Japan.
- Considering the definition of minor amputation, we could not distinguish between finger and toe amputations because of the coding system of the NDB.
- The detailed medical information and parameters of each patient, including glycated hemoglobin, body weight, smoking history, and family history, could not be reviewed because of the nature of the database.
- However, NDB is a comprehensive survey and the likelihood of selection bias is relatively small; we adjusted for sex and age when comparing the LLA rates of people with and without diabetes.

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1 INTRODUCTION

2 The objectives of diabetes management are to reduce the metabolic dysfunction that
3 occurs because of hyperglycaemia, to prevent the development or progression of diabetes-
4 related complications and conditions, and to enable the affected individuals to maintain
5 their quality of life and life expectancy like healthy individuals [1]. Vascular and
6 neurological complications of diabetes can considerably influence lower limb amputation
7 (LLA) [2–4]. Previous studies have shown that diabetes increases the risk of LLA,
8 although there were considerable variations in its incidence among people with diabetes
9 [5]. It is important to understand the incidence rates of LLA in diabetic and nondiabetic
10 populations to further improve the care of patients with diabetes and to avoid fatal
11 outcomes, particularly regarding decisions associated with health policy and the economy
12 [4,5].

13 Among patients with diabetes, besides major LLAs (e.g., amputation proximal
14 to the ankle joint), there may be many minor LLAs (e.g., amputation through the ankle
15 joint and toe amputation) [6]. Major amputations have severe detrimental impact on
16 physical integrity, but minor amputations should also be prevented. Given the increasing
17 incidence of diabetes, not only major LLAs but also minor LLAs impose a burden on the
18 healthcare system. With significant ageing of the population, the number of patients with
19 diabetes in Japan continues to increase [7]. Therefore, it is important to understand the
20 association of age with the total incidence of each major and minor LLA. However, no
21 large-scale community-based surveys on the incidence of LLA among people with and
22 without diabetes in Japan have been conducted. We aimed to investigate the incidence of
23 LLAs in Japan and compare the age-adjusted incidence of LLA between people with and

1 without diabetes. We also analysed the time trend based on data obtained from the
2 National Database of Health Insurance Claims in Japan. To the best of our knowledge,
3 this study is the first to evaluate the LLA rate in Japan based on a nationwide dataset.

4 5 **METHODS**

6 **Study design and population**

7 This population-based, retrospective cohort study was based on the National Database
8 (NDB) dataset and was approved by the ethics committee of Nara Medical University
9 (approval no. 1123-5). The use of NDB dataset was approved by the Ministry of Health,
10 Labor and Welfare, and the need for informed consent was waived in view of the study
11 design. In this study, not only patients with LLA, but also the general public are included.
12 All civilian and patient data were anonymised before analysis.

13 The study cohort comprised individuals enrolled in the NDB; all civilian and
14 patient data were anonymised. Japan has a universal public healthcare system, and the
15 NDB includes almost all patients in Japan. However, people whose family names changed
16 due to marriage or divorce and people whose insurance changed due to social
17 circumstances are also counted as other individuals. Approximately 2% of the people on
18 welfare were not included in this study because they were not covered by the insurance
19 programme. The NDB data provided information on personal identifiers [8], date, age
20 group, sex, description of the medical procedures conducted, the World Health
21 Organization International Classification of Diseases diagnosis codes, medical care
22 received, medical examinations conducted (not including test results), and prescribed

1 drugs, which were independent of the doctor's or patient's reports [9]. Drug information
2 included the prescription amount, brand name, generic name, dosage, and the number of
3 days for which the medicine was prescribed. The age recorded in this study was age at
4 the time of the last treatment during the study period or the patient's age when LLA was
5 performed.

6 We designed this cohort study to include all the data of LLA patients collected
7 between April 2013 and March 2018 in the analysis.

8 **Criteria for diagnosing diabetes**

9 We defined patients with diabetes as individuals who had any of the diagnosis codes
10 associated with diabetes and those who were prescribed diabetes medication at least once
11 in the past 5 years. The diagnosis and medicine codes for diabetes are the same as those
12 reported previously [9] and are presented in Supplementary Tables S1 and S2,
13 respectively. We included all patients with any type of diabetes. In Japan, the indication
14 for metformin is limited to type 2 diabetes patients, and prescriptions for obese people
15 and for women with polycystic ovary syndrome patients are not permitted. Patients on
16 dietary or exercise management without antidiabetic medication were excluded.

17 **Definition of LLA**

18 The medical procedure receipt codes (as LLA codes) are shown in Supplementary Table
19 S3. We defined major LLAs as the use four medical procedure receipt codes proximal to
20 the ankle joint, as follows: above-knee/transfemoral amputation, below-knee/transtibial
21 amputation, hindquarter amputation/ hip disarticulation, and through-knee amputation. In
22 the Japanese medical code, the amputation of fingers and toes is indicated by the same

1 code, and it is impossible to distinguish between them. Therefore, we defined minor LLA
2 as through-foot amputation, trans-metatarsal amputation and Lisfranc disarticulation,
3 finger and toe amputation, and finger and toe joint disarticulation. The primary outcome
4 was the first occurrence of each major or minor LLA in the study period. If the first major
5 LLA occurred during the observation period, its observation was terminated at that time.
6 Similarly, if the first minor LLA occurred during the observation period, its observation
7 was terminated at the time. Therefore, even when the major and minor LLAs occurred
8 many times in the same person during the 5-year study period, we counted only the first
9 major and minor LLAs. Moreover, even if a minor LLA occurred, the major LLA
10 observation was continued such that the incidence of the major LLA was not
11 underestimated.

12 **Statistical analyses**

13 We defined the duration between the first occurrence of the medical treatment code or
14 drug code and the last occurrence as the risk period. To calculate the incidence of LLA,
15 the denominator included all the observation populations of each group, extracted from
16 the NDB dataset. LLA rates are presented as the number of amputations per 100,000
17 person-years. To compare the LLA incidence rates between people with and without
18 diabetes, the incidence rates were evaluated after adjusting for sex and age using the direct
19 method, i.e., the sex and age structure of Japan's national census in 2015 (Supplementary
20 Table S4). We included age-adjusted standardised incidence of LLA for all ages.
21 Furthermore, the relative risk (RR) of LLA among people with diabetes was calculated
22 by dividing amputation rates among people with diabetes by amputation rates among
23 those without diabetes.

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1 We used Microsoft SQL Server for our data processing and univariate analysis, and used
2 IBM SPSS for Windows (version 25.0; IBM, Armonk, NY, USA) for our multivariate
3 analysis.

4 Annual standardized major and minor LLAs were analysed from 2013 to 2016 fiscal year.
5 2017 was excluded because the observation period in 2017 was shorter than other years,
6 and the denominator was smaller, which could overestimate the LLA rate. To test for time
7 trends, we fitted Poisson regression models for major or minor amputation rate using year
8 of outcome (difference from the first fiscal year 2013 as an ordinal variable), age and sex,
9 and the population with and without diabetes as independent variables. All models were
10 adjusted for over-dispersion using a dispersion parameter.

12 **RESULTS**

13 **Population included in the NDB and the diabetic population**

14 Of the 150,328,339 people (186,819,100,972 person-days) included in the NDB,
15 9,962,459 had diabetes, which accounted for 6.6% of the total sample (Table 1). In the
16 subgroups of men and women, the proportion of diabetic patients was higher in the elderly
17 group (age ≥ 65 years).

19 **Incidence of LLAs**

20 Major LLAs occurred in 30,187 people, whereas minor LLAs occurred in 29,299 people
21 in the 5-year period. In Japan, a new major and minor LLA occurred in approximately

1 6,000 individuals per year. Table 2 shows the characteristics of LLA patients stratified
2 into subgroups of people with and without diabetes. Figures 1A and 1B show the sex and
3 age composition of the patient population with major and minor LLAs. In the overall
4 study population, the incidence of LLA was higher among men than in women. Patients
5 with diabetes accounted for 58% and 66% of the total major and minor LLAs,
6 respectively; the highest number of LLAs in men were performed around 65–84 years of
7 age, whereas, in women, the number was significantly associated with age. Therefore,
8 most amputations occurred in the elderly population.

9 10 **Age-adjusted incidence rate**

11 Throughout the observation period, the major amputation risk was 9.5 times higher in
12 people with diabetes compared with people without diabetes (people with diabetes, 21.8
13 vs. people without diabetes, 2.3, per 100,000 person-years); the minor amputation risk
14 was also 14.9 times higher among people with diabetes (people with diabetes, 28.4 vs.
15 people without diabetes, 1.9, per 100,000 person-years) (Table 3). This difference was
16 particularly pronounced in minor amputations than major amputations. Additionally, the
17 RR was higher in men than in women.

18 19 **Time trend**

20 We observed a significant decrease in the major amputation rate in the general population,
21 from 5.5 per 100,000 person-years in 2013 to 4.4 in 2016 ($p < 0.05$, for time trend, Poisson
22 model). The major amputation rate decreased among people with (2013:22.8; 2016:20.0)

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1 and without diabetes (2013:2.6; 2016: 2.1). In detail, there was a little change among men
2 with diabetes and a decreasing trend in women with diabetes for major amputation.
3 Furthermore, both men and women without diabetes showed a decreasing trend.

4 In contrast, the minor amputation rate remained stable in the general population, from
5 5.6 per 100,000 person-years in 2013 to 4.7 in 2016 ($p=0.63$, for time trend, Poisson
6 model). The minor amputation rate remained stable among people with (2013:29.0;
7 2016:28.9) and without diabetes (2013 2.1; 2016: 1.7) (Table 4, Figure 2).

9 **Patient and public involvement**

10 No patient involved.

1 DISCUSSION

2 The NDB is a comprehensive database of health insurance claims that are covered by the
3 Japanese National Health Insurance system. Japan has universal health coverage, with
4 local governments providing healthcare payments for approximately 2% of the population
5 who are on welfare, with the exception of accidents (which is covered by automobile
6 liability insurance or worker's accident compensation in a previous health insurance
7 plan); thus, the NDB is considered to be the representative of almost all health claims in
8 Japan [8,9]. Using information from the Japanese NDB dataset, we conducted cohort
9 studies that comprised almost all LLAs in Japan during the study period. This is the first
10 report of LLAs across Japan.

11 Although several studies have analysed amputation risk in people with diabetes,
12 population-based and nationwide studies analysing amputation risk in populations with
13 and without diabetes are still limited. Additionally, study design such as definition and
14 counting LLA (counting all, counting only the first of the observation period, counting
15 only the first of each year), sex- and age- adjustment method (all ages or only specific
16 ages) were different significantly, so accurately comparing them is difficult. Considering
17 this, compared with the few previous studies that evaluated only the first amputation in
18 the observation period or each year to calculate the LLA incidence, LLA rates in the
19 general population of this study were much lower (e.g., 7.4–41.4 and 8.0–46.7 per
20 100,000 person-years in Europe and Australasia in 2010–2014, major and minor
21 amputation, respectively [10]; 7.8–13.2 per 100,000 person-years in OECD in 2000–2011,
22 major amputation [11]; in our study 4.8 and 5.0 per 100,000 person-years, major and
23 minor amputation, respectively). Herein, the LLA rates among people with diabetes were

1 much lower than those of previous studies (e.g., 78–704 per 100,000 person-years in a
2 systematic review in 1990–2010, major amputation [5]; 7.8–13.2 per 100,000 person-
3 years in OECD in 2000–2011, major amputation [11]; in our study 21.8 and 28.4 per
4 100,000 person-years, major and minor amputation, respectively). There are several
5 explanations for the observed lower incidence of LLA in Japanese patients. First, the
6 Japanese population has a lower obesity rate than the Western population [12,13]. Second,
7 the incidence of cardiovascular disease is much lower in Japan [14]; this contributes to
8 lower risk for the progression of atherosclerosis, which is the most prevalent aetiology of
9 LLA.

10 In this study, the incidence of major and minor LLA was approximately 10 and 15
11 times higher, respectively, in people with diabetes compared to those without. Among
12 people with diabetes, both peripheral arterial disease and peripheral neuropathy can cause
13 foot ulceration and lower limb amputation. Strict chronic disease management (such as
14 plasma glucose, blood pressure, lipids, and renal failure control) is important to suppress
15 arteriosclerosis. Peripheral vascular disease is often not diagnosed in patients with
16 diabetes usually until the formation of a nonhealing ulcer. Therefore, identification of
17 patients with diabetes who are at high risk of ulceration is important and it can be achieved
18 through annual foot screening [2]. There is an emerging focus on lifestyle interventions
19 including weight loss and physical activity as well [15]. Further, in case of foot ulcer or
20 foot infection, many experts (diabetologists, vascular surgeons, orthopaedics,
21 interventional radiologists, infectious diseases specialists, specialised nurses, podiatrists,
22 and orthotic technicians) need to work together as a multidisciplinary team to prevent
23 LLA [16]. In Japan, foot care performed by trained nurses has been approved for medical

1 insurance coverage since 2008 [17,18], and bypass surgery and endovascular treatment
2 have become significantly advanced [19,20]. Despite these efforts, our data indicate that
3 the risk of LLA in people with diabetes remained significantly higher than in people
4 without diabetes. This may be associated with the fact that despite the insurance coverage
5 of nurse-provided foot care, only few patients actually availed foot care services. The
6 medical expenses burden of LLA is large [21]. The LLA risk among people with diabetes
7 is much higher and, therefore, more diligent screening and management of the people
8 with diabetes are important to reduce the burden of quality-of-life reduction and the
9 national healthcare expenditure associated with LLA [22]. The high risk of LLA in people
10 with diabetes clarified in this study will help to develop national medical strategies such
11 as more specialised diabetes treatments including insulin and foot care, expansion of team
12 medical care, and establishment of educational programmes and activities for patient
13 empowerment.

14 In this study, a significant decline in the annual major amputation rate was
15 observed in Japan and the annual minor amputation rate remained stable. Our finding
16 concerning the time trend for major LLAs in people with and without diabetes is in line
17 with results from other international studies, which mainly demonstrated decreased
18 incidence of major LLAs. Major amputations decreased by 11.1% in 2005–2015 in the
19 general population of Germany [23]. A progressive decrease was observed for major
20 amputations among people with diabetes (-30.7%) and without diabetes (-12.5%) in
21 2001–2010 in Italy [24]. In detail, for major amputation, there was little change among
22 men with diabetes and a decreasing trend in women with diabetes and men and women
23 without diabetes in this study. These trends correspond to the findings of previous studies

1 [23], but biological factors might be contributing to sex differences in amputation rates
2 [25,26]. However, the causes of the sex differences still need further research. Minor
3 amputations in people with and without diabetes had different trends in each country. A
4 significant but weaker decrease was observed for minor amputations in 2009–2013 in
5 Belgium (5% and 3%, people with and without diabetes) [27]. A relative increase of
6 +12.8% was observed for minor amputations in 2005–2011 in Germany [23]. Minor
7 amputations may indicate better quality of care as they maybe interventions to prevent
8 major amputations and salvage the lower extremities. A stable number of the total
9 amputations, or even an increase, may actually hide a higher number of minor vs. major
10 amputations, which in turn would indicate better performance [11].

11 A key strength of our study is that, by analysing data from the nationwide NDB
12 that encompasses almost the entire Japanese population, this study is the first to evaluate
13 the nationwide incidence of LLA in Japan. Nonetheless, this study has some limitations.
14 First, many similar studies investigated only the amputations related to peripheral arterial
15 disease or diabetes by excluding amputations due to trauma or malignancy using
16 diagnosis codes attached to the amputation episodes; it was technically impossible to
17 exclude amputations due to trauma or malignancy in this study. Second, in minor
18 amputation, we could not distinguish between finger and toe amputations because of the
19 coding system of the NDB. This means that the minor amputation rate reported in this
20 study is overestimated, although toe amputations are more than finger amputations. Third,
21 the total observable population of this study was approximately 150 million, although
22 Japan has a population of approximately 127 million. Even considering new births,
23 marriages, divorces, and changes in family names due to social circumstances, there could

1 be slight deficits in the linking of the NDB. In the design of this study, at risk period was
2 set from the first insurance use date to the last insurance use date; therefore, even if one
3 person does have two IDs, it is not possible to count the same person more than once in
4 the same period. Since the LLA rate is also calculated by the person-year method, it is
5 considered that having two IDs does not affect the LLA rate. However, strictly speaking,
6 in very rare cases, it is possible to overestimate the incidence if two LLAs are performed
7 before and after the insurance change. Finally, the detailed medical information and
8 parameters of each patient, including glycated haemoglobin, body weight, smoking
9 history, and family history, could not be reviewed because of the nature of the database.
10 However, regarding smoking rate, which can be an important confounding factor, a
11 previous study in Japan reported no difference between the diabetes group and the general
12 population in terms of smoking status in sex- and age-stratified analyses [28].
13 Furthermore, NDB is a comprehensive survey and the likelihood of selection bias is
14 relatively small; additionally, we adjusted for sex and age while comparing LLA rates of
15 people with and without diabetes. Therefore, it is unlikely that the study results will be
16 significantly affected even if detailed medical information and parameters are considered
17 [29].

18 In conclusion, this is the first report of nationwide LLAs in Japan, and we found
19 that the incidence of major and minor LLAs was 10 and 15 times higher, respectively, in
20 people with diabetes compared to those without diabetes. A significant decline in the
21 major amputation rate was observed and the annual minor amputation rate remained
22 stable during the observation period. This information can help create an effective
23 national healthcare strategy for preventing limb amputations, which affect the quality of

- 1 life of patients with diabetes and add to the national healthcare expenditure.
- 2 **Data availability statement** The research data are available from the corresponding
- 3 author on reasonable request.

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1 **Ethics approval** This study was approved by the ethics committee of Nara Medical
2 University (approval no. 1123-5).

4 **Acknowledgments** We would like to thank Editage (www.editage.com) for English
5 language editing.

7 **Funding.** This study was supported by the Research for Infrastructure Construction of
8 Studies with the Next Generation NDB Data to Create New Evidence from the Japan
9 Agency for Medical Research and Development. This study was supported by the Project
10 for Accelerating Medical Research through Cross-regional ICT utilization from the Japan
11 Agency for Medical Research and Development and Japan Society for the Promotion of
12 Science KAKENHI (grant number: JP18K17390, 18H04126, 21K10451, 21K10474).

14 **Competing interests** YN received consultant fees from Novo Nordisk. SO received
15 speaker fees from Novo Nordisk, Mitsubishi Tanabe, Sumitomo Dainippon, Arkray,
16 Bayer, Eli Lilly, Boehringer Ingelheim, Ono, AstraZeneca, Sanofi, and Takeda, outside
17 of the submitted work. YA received lecture fees and consultant fees from MSD KK, Ono,
18 Otsuka, Sumitomo Dainippon, Daiichi Sankyo, Eli Lilly, Sanofi S.A., Chugai, Novo
19 Nordisk, Kissei, Nippon Boehringer Ingelheim, Astellas, Kyowa Hakko Kirin, Pfizer,
20 Takeda, Mitsubishi Tanabe, Novartis, Janssen Pharmaceutical K.K, Japanese Red Cross
21 Society Nara Red Cross Blood Center, Sumitomo Dainippon, Ltd., Kissei. HI received
22 lecture fees and consultant fees from Takeda, Eli Lilly Japan, Sanofi, Merck & Co.,

1 Astellas, Mitsubishi Tanabe, Daiichi Sankyo, Ono, AstraZeneca, Taisho Toyama,
2 Shionogi, Kowa, Boehringer Ingelheim, Novo Nordisk, Sumitomo Dainippon, and
3 Kyowa Hakko Kirin. YT received consultant fees from Novo Nordisk, Otsuka, and
4 Recordati, and speaker fees from Novo Nordisk, Sumitomo Dainippon, Eli Lilly, Ono,
5 Novartis, Nippon Boehringer Ingelheim, AstraZeneca, and Kyowa Kirin. The other
6 authors declare that they have no conflict of interest.

7 Contributorship statement

8
9 **Author's contribution** F.K. designed the study and wrote the manuscript. Y.N.
10 contributed to the study design, data analysis, and discussion. T.N. provided advice on
11 the study design and discussed the findings from an epidemiological perspective. T.M.,
12 S.K., and T.H. performed the initial NDB analysis and provided technical advice. S.O.,
13 Y.A., H.I., and Y.T. evaluated the results from a clinical perspective. T.I. provided advice
14 on the study design and discussed the findings from the public health viewpoint.

15
16 **Patient consent for publication** Not required.

17 **Data availability statement** The research data are available from the corresponding
18 author on reasonable request.

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25 **Supporting information**

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28 Table S1. Diagnosis codes for diabetes.

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31 Table S2. Medication codes for diabetes.

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34 Table S3. Amputation codes.

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37 Table S4. The population of Japanese national census (2015).
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6 **Figure legends**
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9 **Figure 1.** Results of sex- and age-stratified analyses: (A) number of major lower limb
10 amputation (LLA); (B) number of minor LLA.
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14 **Figure 2.** Time trend of age- and sex- standardized amputation rate: (A) major amputation; (B)
15 minor amputation
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Table 1 Characteristics of the NDB study population categorized into people with and without diabetes.

Age groups, years	Total	People with diabetes, n (%)	People without diabetes, n (%)
Total	150,328,339	9,962,459 (6.6)	140,365,880 (93.4)
Men, total	70,958,283	5,838,320 (8.2)	65,119,963 (91.8)
Men, age groups, years			
0 – 44	35,317,225	301,772 (0.9)	35,015,453 (99.1)
45 – 64	17,572,798	1,709,991 (9.7)	15,862,807 (90.3)
65 – 74	9,134,765	1,849,566 (20.2)	7,285,199 (79.8)
75 – 84	6,152,042	1,458,566 (23.7)	4,693,476 (76.3)

7	≥ 85	2,781,453	518,425 (18.6)	2,263,028 (81.4)
10	Women, total	79,370,056	4,124,139 (5.2)	75,245,917 (94.8)
14	Women, age groups, years			
17	0 – 44	37,492,073	212,476 (0.6)	37,279,597 (99.4)
20	45 – 64	18,906,831	792,993 (5.7)	18,113,838 (94.3)
24	65 – 74	9,860,220	1,154,454 (11.7)	8,705,766 (88.3)
27	75 – 84	7,538,821	1,191,531 (15.8)	6,347,290 (84.2)
30	≥ 85	5,572,111	772,685 (13.9)	4,799,426 (86.1)

NDB, National Database.

Table 2 Patients with lower limb amputations according to diagnosis of diabetes, sex, age.

Age groups, years	Major LLA			Minor LLA		
	Total	People with diabetes, n (%)	People without diabetes, n (%)	Total	People with diabetes, n (%)	People without diabetes, n (%)
Total	30,187	17,390 (57.6)	12,797 (42.4)	29,299	9,331 (66.0)	9,968 (34.0)
Men, total	17,971	11,545 (64.2)	6,426 (35.8)	19,485	4,163 (72.7)	5,322 (27.3)
Men, age groups, years						
0–44	515	218 (42.3)	297 (57.7)	736	468 (63.6)	268 (36.4)

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45–64	3,376	2,699 (79.9)	677 (20.1)	4,989	4,173 (83.6)	816 (16.4)
65–74	5,077	3,748 (73.8)	1,329 (26.2)	5,934	4,621 (77.9)	1,313 (22.1)
75–84	5,710	3,568 (62.5)	2,142 (37.5)	5,404	3,761 (69.6)	1,643 (30.4)
≥85	3,293	1,312 (39.8)	1,981 (60.2)	2,422	1,140 (47.1)	1,282 (52.9)
Women, total	12,216	5845 (47.8)	6371 (52.2)	9,814	5,168 (52.7)	4646 (47.3)
Women, age groups, years						
0–44	183	44 (24.0)	139 (76.0)	177	72 (40.7)	105 (59.3)
45–64	1,011	747 (73.9)	264 (26.1)	1,243	946 (76.1)	297 (23.9)

65–74	1,900	1,335 (70.3)	565 (29.7)	1,945	1,361 (70.0)	584 (30.0)
75–84	3,429	1,894 (55.2)	1,535 (44.8)	2,854	1,606 (56.3)	1248 (43.7)
≥85	5,693	1,825 (32.1)	3,868 (67.9)	3,595	1,183 (32.9)	2412 (67.1)

LLA, lower limb amputation.

Table 3 Age-adjusted incidence rate (per 100,000 person-year) of LLA in people with and without diabetes.

Incidence of Major LLA							
Groups	Total	95%CI	With diabetes	95% CI	Without diabetes	95% CI	Relative risk (With / Without)
Men	6.2	5.9 - 6.5	26.4	23.4 - 29.5	2.6	2.3 - 2.8	10.2
Women	3.5	3.3 - 3.7	17.3	14.5 - 20.1	2.0	1.8 - 2.2	8.7
Total	4.8	4.5 - 5.1	21.8	18.9 - 24.7	2.3	2.1 - 2.5	9.5

Incidence of Minor LLA							
Groups	Total	95% CI	With diabetes	95% CI	Without diabetes	95% CI	Relative risk (With / Without)
Men	7.1	6.7 - 7.5	39.3	35.7 - 43.0	2.2	2.0 - 2.5	17.9
Women	3.0	2.7 - 3.2	18.0	15.4 - 20.5	1.5	1.3 - 1.7	12.0
Total	5.0	4.7 - 5.3	28.4	25.3 - 31.4	1.9	1.7 - 2.1	14.9

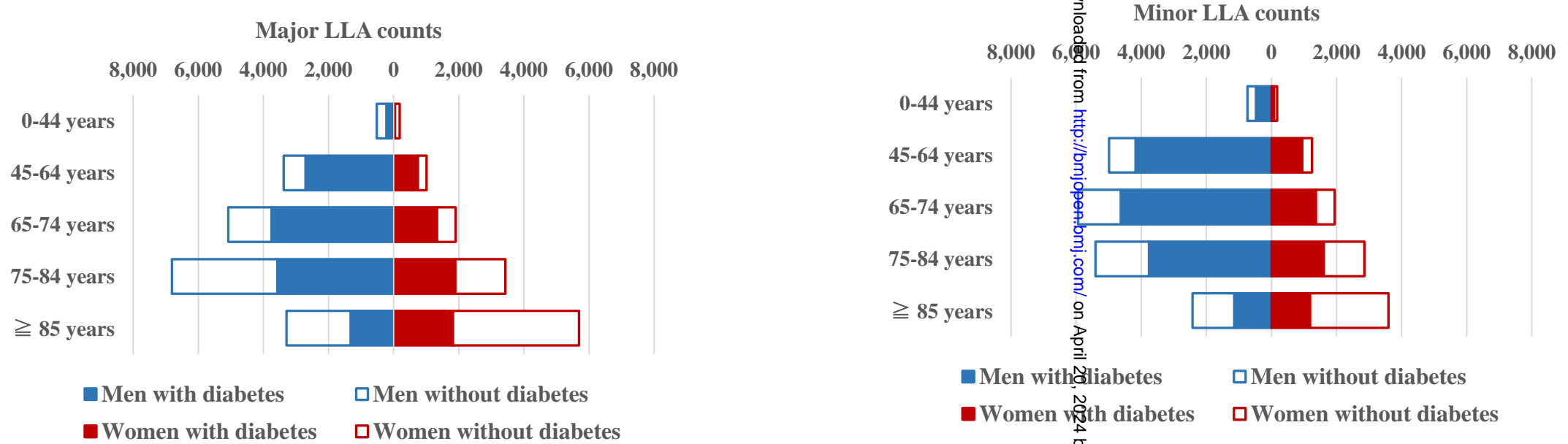
LLA, Lower limb amputation; CI, confidence interval.

Table 4 Time trend of age- and sex- standardized amputation rates (/100,000 person-years, annual fiscal year)

Fiscal year	2013	2014	2015	2016
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	rate	95% CI	rate	95% CI	rate	95% CI	rate	95% CI
Major amputation								
Men and women with diabetes	22.8	17.3 - 28.3	20.9	15.6 - 26.1	20.0	14.9 - 26.1	20.0	14.7 - 25.4
Men with diabetes	26.8	22.2 - 31.4	25.0	19.0 - 31.0	22.9	17.7 - 28.2	25.7	19.1 - 32.3
Women with diabetes	19.1	12.8 - 25.4	17.0	12.4 - 21.6	17.2	12.4 - 24.1	14.7	10.6 - 18.8
Men and women without diabetes	2.6	2.0 - 3.1	2.2	1.7 - 2.6	2.1	1.7 - 2.5	2.1	1.7 - 2.6
Men without diabetes	3.1	2.4 - 3.7	2.5	2.0 - 3.0	2.3	1.8 - 2.8	2.4	1.8 - 2.9
Women without diabetes	2.1	1.7 - 2.5	1.9	1.5 - 2.3	1.9	1.5 - 2.2	1.9	1.5 - 2.3
Minor amputation								
Men and women with diabetes	29.0	21.7 - 36.4	25.5	19.4 - 31.6	25.7	19.7 - 31.7	28.9	22.0 - 35.8
Men with diabetes	39.6	30.9 - 48.4	35.9	28.1 - 43.6	34.9	27.8 - 42.0	39.8	31.7 - 47.9
Women with diabetes	19.0	13.1 - 25.0	15.6	11.1 - 20.2	17.0	12.0 - 22.0	18.6	12.8 - 24.4
Men and women without diabetes	2.1	1.6 - 2.6	1.7	1.3 - 2.1	1.9	1.2 - 2.7	1.7	1.3 - 2.1
Men without diabetes	2.7	2.1 - 3.3	2.1	1.6 - 2.6	2.1	1.6 - 2.5	1.9	1.5 - 2.4
Women without diabetes	1.6	1.2 - 2.0	1.4	1.0 - 1.7	1.8	0.7 - 2.8	1.4	1.1 - 1.8

Figure 1. Results of sex- and age-stratified analyses:
 (A) number of major lower limb amputation (LLA); (B) number of minor LLA.



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Figure 2. Time trend of age- and sex- standardized amputation rate:
(A) major amputation; (B) minor amputation

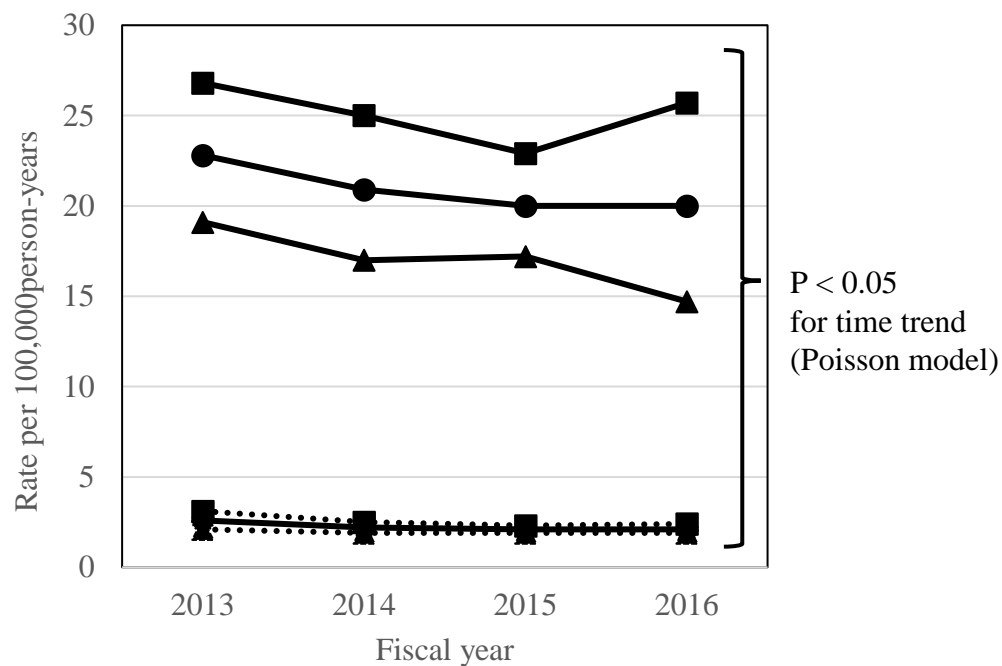


Fig.2-A Time trend of age- and sex- standardized major amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

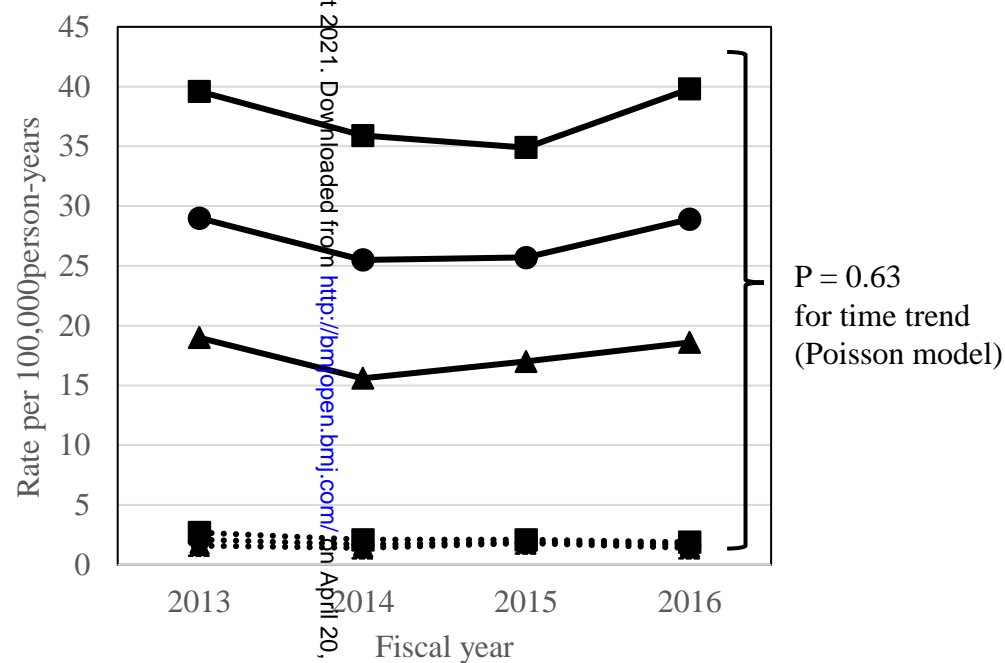


Fig.2-B Time trend of age- and sex- standardized minor amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

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Supplementary Table S1 Diagnostic codes of diabetes.

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	Diagnosis in Japanese	Diagnosis in English	BMJ Open	ICD-10 code	diagnosis code
	1 型糖尿病	Type 1 diabetes mellitus		E10	2500014
1	不安定型糖尿病	Brittle diabetes		E10	2500027
2					
3	緩徐進行 1 型糖尿病	SPIDDM - [Slowly progressive insulin-dependent diabetes mellitus]		E10	8844022
4					
5	1 型糖尿病性昏睡	Type 1 diabetic coma		E10	8830030
6					
7	1 型糖尿病・昏睡合併あり	Type 1 diabetes mellitus with coma		E10	8841679
8	緩徐進行 1 型糖尿病・昏睡合併あり	SPIDDM with coma - [Slowly progressive insulin-dependent diabetes mellitus]		E10	8844026
9					
10					
11	1 型糖尿病性低血糖性昏睡	Hypoglycemia in the context of type 1 diabetes mellitus		E10	8845065
12					
13	1 型糖尿病性ケトアシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus		E10	8830028
14					
15	1 型糖尿病・ケトアシドーシス合併あり	Type 1 diabetes mellitus with ketoacidosis		E10	8841680
16					
17	緩徐進行 1 型糖尿病・ケトアシドーシス合併あり	SPIDDM with ketoacidosis - [Slowly progressive insulin-dependent diabetes mellitus]		E10	8844025
18					
19	劇症 1 型糖尿病	Fulminant type 1 diabetes mellitus		E10	8844045
20					
21	1 型糖尿病性アシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus		E10	8845044
22					
23	1 型糖尿病性アセトン血症	Type 1 diabetic acetone hyperlipoproteinemia		E10	8845045
24					
25	1 型糖尿病性腎症	Type 1 diabetic nephropathy		E10	8830031
26					
27	1 型糖尿病・腎合併症あり	Type 1 diabetes mellitus with diabetic nephropathy		E10	8841681
28					
29	1 型糖尿病性腎症第 1 期	Type 1 diabetic nephropathy phase 1		E10	8843983
30					
31	1 型糖尿病性腎症第 2 期	Type 1 diabetic nephropathy phase 2		E10	8843984
32					
33	1 型糖尿病性腎症第 3 期	Type 1 diabetic nephropathy phase 3		E10	8843985
34					
35	1 型糖尿病性腎症第 3 期 A	Type 1 diabetic nephropathy phase 3A		E10	8843986
36					
37	1 型糖尿病性腎症第 3 期 B	Type 1 diabetic nephropathy phase 3B		E10	8843987
38					
39	1 型糖尿病性腎症第 4 期	Type 1 diabetic nephropathy phase 4		E10	8843988
40					
41	1 型糖尿病性腎症第 5 期	Type 1 diabetic nephropathy phase 5		E10	8843989
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3	緩徐進行 1 型糖尿病・腎合併症あり	SPIDDM with nephropathy - [Slowly progressive insulin-dependent diabetes mellitus]	E10369	8844028
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6	1 型糖尿病性腎硬化症	Type 1 diabetic nephrosclerosis	E10370	8845058
7				
8	1 型糖尿病性腎不全	Type 1 diabetic kidney failure	E10371	8845059
9				
10	1 型糖尿病性網膜症	Type 1 diabetic retinopathy	E10372	8830033
11	1 型糖尿病・眼合併症あり	Type 1 diabetes mellitus with eye complication	E10373	8841682
12				
13	1 型糖尿病性黄斑浮腫	Type 1 diabetic macular edema	E10374	8843982
14	緩徐進行 1 型糖尿病・眼合併症あり	SPIDDM with eye complication - [Slowly progressive insulin-dependent diabetes mellitus]	E10375	8844024
15				
16				
17	1 型糖尿病性白内障	Type 1 diabetic cataracts	E10376	8844346
18				
19	増殖性糖尿病性網膜症・1 型糖尿病	Proliferative diabetic retinopathy, type 1 diabetes	E10377	8844536
20				
21				
22	1 型糖尿病黄斑症	Type 1 diabetic macular disease	E10378	8845043
23				
24	1 型糖尿病性眼筋麻痺	Type 1 diabetic eye muscle paralysis	E10379	8845049
25				
26	1 型糖尿病性虹彩炎	Type 1 diabetic iritis	E10380	8845053
27				
28	1 型糖尿病性中心性網膜症	Type 1 diabetic central retinopathy	E10381	8845064
29				
30	1 型糖尿病性ニューロパチー	Type 1 diabetic neuropathy	E10382	8830032
31				
32	1 型糖尿病・神経学的合併症あり	Type 1 diabetes mellitus with neurological complications	E10383	8841683
33	緩徐進行 1 型糖尿病・神経学的合併症あり	SPIDDM with neurological complications - [Slowly progressive insulin-dependent diabetes mellitus]	E10384	8844027
34				
35				
36	1 型糖尿病性筋萎縮症	Type 1 diabetic muscular atrophy	E10385	8845050
37				
38	1 型糖尿病性神経因性膀胱	Type 1 diabetic neuropathic bladder	E10386	8845055
39				
40	1 型糖尿病性神経痛	Type 1 diabetic neuralgia	E10387	8845056
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3	1 型糖尿病性自律神経ニューロパ	Type 1 diabetic autonomic neuropathy	E10436	8845057
4	チー			
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6	1 型糖尿病性多発ニューロパチー	Type 1 diabetic polyneuropathy	E10437	8845062
7				
8	1 型糖尿病性単ニューロパチー	Type 1 diabetic mononeuropathy	E10438	8845063
9				
10	1 型糖尿病性末梢神経障害	Type 1 diabetic peripheral neuropathy	E10439	8845071
11				
12	1 型糖尿病・末梢循環合併症あり	Type 1 diabetes mellitus with peripheral circulation complications	E10440	8841684
13				
14	1 型糖尿病性壊疽	Type 1 diabetic gangrene	E10441	8843105
15				
16	緩徐進行 1 型糖尿病・末梢循環合	SPIDDM with peripheral circulation complications -		
17	併症あり	[Slowly progressive insulin-dependent diabetes mellitus]	E10442	8844031
18				
19				
20	1 型糖尿病性潰瘍	Type 1 diabetic ulcer	E10443	8845046
21				
22	1 型糖尿病性血管障害	Type 1 diabetic vascular disease	E10444	8845051
23				
24	1 型糖尿病性動脈硬化症	Type 1 diabetic atherosclerosis	E10445	8845066
25				
26	1 型糖尿病性動脈閉塞症	Type 1 diabetic arterial occlusion	E10446	8845067
27				
28	1 型糖尿病性末梢血管症	Type 1 diabetic peripheral vascular disease	E10447	8845069
29				
30	1 型糖尿病性末梢血管障害	Type 1 diabetic peripheral vascular disease	E10448	8845070
31				
32	1 型糖尿病・関節合併症あり	Type 1 diabetes mellitus with joint complications	E10449	8841685
33				
34	1 型糖尿病・糖尿病性合併症あり	Type 1 diabetes mellitus with diabetic complications	E10450	8841686
35				
36	緩徐進行 1 型糖尿病・関節合併症	SPIDDM with joint complications - [Slowly		
37	あり	progressive insulin-dependent diabetes mellitus]	E10451	8844023
38				
39	1 型糖尿病性水疱	Type 1 diabetic blister	E10452	8844626
40				
41	1 型糖尿病性浮腫性硬化症	Type 1 diabetic edematous sclerosis	E10453	8844627
42				
43	1 型糖尿病性肝障害	Type 1 diabetic liver injury	E10454	8845047
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3	1 型糖尿病性関節症	Type 1 diabetic arthropathy	E10436	8845048
4	1 型糖尿病性高コレステロール血	Type 1 diabetic hypercholesterolemia	E10437	8845052
5	症			
6	1 型糖尿病性骨症	Type 1 diabetic osteopathy	E10438	8845054
7	1 型糖尿病性精神障害	Type 1 diabetic mental disorder	E10439	8845060
8	1 型糖尿病性そう痒症	Type 1 diabetic pruritus	E10440	8845061
9	1 型糖尿病性皮膚障害	Type 1 diabetic skin disorder	E10441	8845068
10	1 型糖尿病性胃腸症	Type 1 diabetic gastroenteritis	E10442	8845842
11	1 型糖尿病・多発糖尿病性合併症	Type 1 diabetes mellitus with multiple diabetic	E10443	8841687
12	あり	complications		
13	緩徐進行 1 型糖尿病・多発糖尿病	SPIDDM with multiple diabetic complications -	E10444	8844029
14	性合併症あり	[Slowly progressive insulin-dependent diabetes		
15		mellitus]		
16	1 型糖尿病・糖尿病性合併症なし	Type 1 diabetes mellitus without diabetic	E10445	8841688
17		complications		
18	緩徐進行 1 型糖尿病・糖尿病性合	SPIDDM without diabetic complications - [Slowly	E10446	8844030
19	併症なし	progressive insulin-dependent diabetes mellitus]		
20	インスリン抵抗性糖尿病	Insulin resistant diabetes mellitus	E11436	2500001
21	2 型糖尿病	Type 2 diabetes mellitus	E11437	2500015
22	安定型糖尿病	Stable diabetes mellitus	E11438	8830405
23	若年 2 型糖尿病	Juvenile type 2 diabetes	E11439	8835244
24	2 型糖尿病性昏睡	Type 2 diabetic coma	E11440	8830041
25	2 型糖尿病・昏睡合併あり	Type 2 diabetes mellitus with coma	E11441	8841689
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4	2 型糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of type 2 diabetes mellitus	E1116	8845094
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6	2 型糖尿病性ケトアシドーシス	Type 2 diabetic ketoacidosis	E1117	8830040
7				
8	2 型糖尿病・ケトアシドーシス合	Type 2 diabetes mellitus with ketoacidosis	E1118	8841690
9	併あり			
10				
11	2 型糖尿病性アシドーシス	Type 2 diabetic acidosis	E1119	8845073
12				
13	2 型糖尿病性アセトン血症	Type 2 diabetic acetone hyperlipoproteinemia	E1120	8845074
14				
15	2 型糖尿病性腎症	Type 2 diabetic nephropathy	E1121	8830042
16	2 型糖尿病・腎合併症あり	Type 2 diabetes mellitus with diabetic nephropathy	E1122	8841691
17	2 型糖尿病性腎症第 1 期	Type 2 diabetic nephropathy phase 1	E1123	8843991
18				
19	2 型糖尿病性腎症第 2 期	Type 2 diabetic nephropathy phase 2	E1124	8843992
20				
21	2 型糖尿病性腎症第 3 期	Type 2 diabetic nephropathy phase 3	E1125	8843993
22	2 型糖尿病性腎症第 3 期 A	Type 2 diabetic nephropathy phase 3A	E1126	8843994
23				
24	2 型糖尿病性腎症第 3 期 B	Type 2 diabetic nephropathy phase 3B	E1127	8843995
25	2 型糖尿病性腎症第 4 期	Type 2 diabetic nephropathy phase 4	E1128	8843996
26				
27	2 型糖尿病性腎症第 5 期	Type 2 diabetic nephropathy phase 5	E1129	8843997
28	2 型糖尿病性腎硬化症	Type 2 diabetic nephrosclerosis	E1130	8845087
29				
30	2 型糖尿病性腎不全	Type 2 diabetic kidney failure	E1131	8845088
31	2 型糖尿病性網膜症	Type 2 diabetic retinopathy	E1132	8830045
32				
33	2 型糖尿病・眼合併症あり	Type 2 diabetes mellitus with eye complications	E1133	8841692
34	2 型糖尿病性黄斑浮腫	Type 2 diabetic macular edema	E1134	8843990
35				
36	2 型糖尿病性白内障	Type 2 diabetic cataracts	E1135	8844347
37	増殖性糖尿病性網膜症・2 型糖尿	Proliferative diabetic retinopathy, type 2 diabetes	E1136	8844537
38	病			
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4	2 型糖尿病黄斑症	Type 2 diabetic macular disease	E11436	8845072
5	2 型糖尿病性眼筋麻痺	Type 2 diabetic eye muscle paralysis	E11437	8845078
6	2 型糖尿病性虹彩炎	Type 2 diabetic iritis	E11438	8845082
7				
8	2 型糖尿病性中心性網膜症	Type 2 diabetic central retinopathy	E11439	8845093
9				
10	2 型糖尿病性ニューロパチー	Type 2 diabetic neuropathy	E11440	8830043
11	2 型糖尿病性ミオパチー	Type 2 diabetic myopathy	E11441	8830044
12				
13	2 型糖尿病・神経学的合併症あり	Type 2 diabetes mellitus with neurological complications	E11442	8841693
14				
15	2 型糖尿病性筋萎縮症	Type 2 diabetic muscular atrophy	E11443	8845079
16	2 型糖尿病性神経因性膀胱	Type 2 diabetic neuropathic bladder	E11444	8845084
17	2 型糖尿病性神経痛	Type 2 diabetic neuralgia	E11445	8845085
18				
19	2 型糖尿病性自律神経ニューロパチー	Type 2 diabetic autonomic neuropathy	E11446	8845086
20				
21	2 型糖尿病性多発ニューロパチー	Type 2 diabetic polyneuropathy	E11447	8845091
22	2 型糖尿病性単ニューロパチー	Type 2 diabetic mononeuropathy	E11448	8845092
23	2 型糖尿病性末梢神経障害	Type 2 diabetic peripheral neuropathy	E11449	8845100
24				
25	2 型糖尿病・末梢循環合併症あり	Type 2 diabetes mellitus with peripheral circulation complications	E11450	8841694
26				
27	2 型糖尿病性壊疽	Type 2 diabetic gangrene	E11451	8843106
28	2 型糖尿病性潰瘍	Type 2 diabetic ulcer	E11452	8845075
29	2 型糖尿病性血管障害	Type 2 diabetic vascular disease	E11453	8845080
30	2 型糖尿病性動脈硬化症	Type 2 diabetic atherosclerosis	E11454	8845095
31	2 型糖尿病性動脈閉塞症	Type 2 diabetic arterial occlusion	E11455	8845096
32	2 型糖尿病性末梢血管症	Type 2 diabetic peripheral vascular disease	E11456	8845098
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3	2 型糖尿病性末梢血管障害	Type 2 diabetic peripheral vascular disease	E11436	8845099
4	2 型糖尿病・関節合併症あり	Type 2 diabetes mellitus with joint complications	E11436	8841695
5	2 型糖尿病・糖尿病性合併症あり	Type 2 diabetes mellitus with diabetic complications	E11436	8841696
6	2 型糖尿病性水疱	Type 2 diabetic blister	E11436	8844628
7	2 型糖尿病性浮腫性硬化症	Type 2 diabetic edematous sclerosis	E11436	8844629
8	2 型糖尿病性肝障害	Type 2 diabetic liver injury	E11436	8845076
9	2 型糖尿病性関節症	Type 2 diabetic arthropathy	E11436	8845077
10	2 型糖尿病性高コレステロール血症	Type 2 diabetic hypercholesterolemia	E11436	8845081
11	2 型糖尿病性骨症	Type 2 diabetic osteopathy	E11436	8845083
12	2 型糖尿病性精神障害	Type 2 diabetic mental disorder	E11436	8845089
13	2 型糖尿病性そう痒症	Type 2 diabetic pruritus	E11436	8845090
14	2 型糖尿病性皮膚障害	Type 2 diabetic skin disorder	E11436	8845097
15	2 型糖尿病性胃腸症	Type 2 diabetic gastroenteritis	E11436	8848108
16	2 型糖尿病・多発糖尿病性合併症あり	Type 2 diabetes mellitus with multiple diabetic complications	E11436	8841697
17	2 型糖尿病・糖尿病性合併症なし	Type 2 diabetes mellitus without diabetic complications	E11436	8841698
18	栄養不良関連糖尿病	Malnutrition-related diabetes mellitus	E12436	2500037
19	膵性糖尿病	Pancreatic diabetes mellitus	E13436	2500024
20	ステロイド糖尿病	Steroid diabetes mellitus	E13436	2509003
21	二次性糖尿病	Secondary diabetes mellitus	E13436	2509004
22	ウイルス性糖尿病	Viral diabetes mellitus	E13436	8830756
23	薬剤性糖尿病	Drug-induced diabetes mellitus	E13436	8840710
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1	ウイルス性糖尿病・昏睡合併あり	Viral diabetes mellitus with coma	E13	8843122
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3	膵性糖尿病・昏睡合併あり	Pancreatic diabetes mellitus with coma	E13	8843377
4				
5	ステロイド糖尿病・昏睡合併あり	Steroid diabetes mellitus with coma	E13	8843390
6				
7	二次性糖尿病・昏睡合併あり	Secondary diabetes mellitus with coma	E13	8843450
8				
9	薬剤性糖尿病・昏睡合併あり	Drug-induced diabetes mellitus with coma	E13	8843621
10				
11	ウイルス性糖尿病・ケトアシドーシス合併あり	Viral diabetes mellitus with ketoacidosis	E13	8843121
12				
13	膵性糖尿病・ケトアシドーシス合併あり	Pancreatic diabetes mellitus with ketoacidosis	E13	8843376
14				
15	ステロイド糖尿病・ケトアシドーシス合併あり	Steroid diabetes mellitus with ketoacidosis	E13	8843389
16				
17	二次性糖尿病・ケトアシドーシス合併あり	Secondary diabetes mellitus with ketoacidosis	E13	8843449
18				
19	薬剤性糖尿病・ケトアシドーシス合併あり	Drug-induced diabetes mellitus with ketoacidosis	E13	8843620
20				
21	ウイルス性糖尿病・腎合併症あり	Viral diabetes mellitus with renal complications	E13	8843124
22				
23	膵性糖尿病・腎合併症あり	Pancreatic diabetes mellitus with renal complications	E13	8843379
24				
25	ステロイド糖尿病・腎合併症あり	Steroid diabetes mellitus with renal complications	E13	8843392
26				
27	二次性糖尿病・腎合併症あり	Secondary diabetes mellitus with renal complications	E13	8843452
28				
29	薬剤性糖尿病・腎合併症あり	Drug-induced diabetes mellitus with renal complications	E13	8843623
30				
31	ウイルス性糖尿病・眼合併症あり	Viral diabetes mellitus with eye complications	E13	8843120
32				
33	膵性糖尿病・眼合併症あり	Pancreatic diabetes mellitus with eye complications	E13	8843375
34				
35	ステロイド糖尿病・眼合併症あり	Steroid diabetes mellitus with eye complications	E13	8843388
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3	二次性糖尿病・眼合併症あり	Secondary diabetes mellitus with eye complications	E13436	8843448
4	薬剤性糖尿病・眼合併症あり	Drug-induced diabetes mellitus with eye complications	E13436	8843619
5	ウイルス性糖尿病・神経学的合併症あり	Viral diabetes mellitus with neurological complications	E13436	8843123
6				
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9	膵性糖尿病・神経学的合併症あり	Pancreatic diabetes mellitus with neurological complications	E13436	8843378
10				
11	ステロイド糖尿病・神経学的合併症あり	Steroid diabetes mellitus with neurological complications	E13436	8843391
12				
13	二次性糖尿病・神経学的合併症あり	Secondary diabetes mellitus with neurological complications	E13436	8843451
14				
15	薬剤性糖尿病・神経学的合併症あり	Drug-induced diabetes mellitus with neurological complications	E13436	8843622
16				
17	ウイルス性糖尿病・末梢循環合併症あり	Viral diabetes mellitus with peripheral circulatory complications	E13436	8843128
18				
19				
20	膵性糖尿病・末梢循環合併症あり	Pancreatic diabetes mellitus with peripheral circulatory complications	E13436	8843383
21				
22	ステロイド糖尿病・末梢循環合併症あり	Steroid diabetes mellitus with peripheral circulatory complications	E13436	8843396
23				
24	二次性糖尿病・末梢循環合併症あり	Secondary diabetes mellitus with peripheral circulatory complications	E13436	8843456
25				
26	薬剤性糖尿病・末梢循環合併症あり	Drug-induced diabetes mellitus with peripheral circulatory complications	E13436	8843627
27				
28	ウイルス性糖尿病・糖尿病性合併症あり	Viral diabetes mellitus with diabetic complications	E13436	8843126
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4	膵性糖尿病・糖尿病性合併症あり	Pancreatic diabetes mellitus with diabetic complications	E136	8843381
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6	ステロイド糖尿病・糖尿病性合併症あり	Steroid diabetes mellitus with diabetic complications	E136	8843394
7				
8	二次性糖尿病・糖尿病性合併症あり	Secondary diabetes mellitus with diabetic complications	E136	8843454
9				
10	薬剤性糖尿病・糖尿病性合併症あり	Drug-induced diabetes mellitus with diabetic complications	E136	8843625
11				
12	ウイルス性糖尿病・多発糖尿病性合併症あり	Viral diabetes mellitus with multiple diabetic complications	E136	8843125
13				
14	膵性糖尿病・多発糖尿病性合併症あり	Pancreatic diabetes mellitus with multiple diabetic complications	E136	8843380
15				
16	ステロイド糖尿病・多発糖尿病性合併症あり	Steroid diabetes mellitus with multiple diabetic complications	E136	8843393
17				
18	二次性糖尿病・多発糖尿病性合併症あり	Secondary diabetes mellitus with multiple diabetic complications	E136	8843453
19				
20	薬剤性糖尿病・多発糖尿病性合併症あり	Drug-induced diabetes mellitus with multiple diabetic complications	E136	8843624
21				
22	ウイルス性糖尿病・糖尿病性合併症なし	Viral diabetes mellitus without diabetic complications	E136	8843127
23				
24	膵性糖尿病・糖尿病性合併症なし	Pancreatic diabetes mellitus without diabetic complications	E136	8843382
25				
26	ステロイド糖尿病・糖尿病性合併症なし	Steroid diabetes mellitus without diabetic complications	E136	8843395
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3	二次性糖尿病・糖尿病性合併症な	Secondary diabetes mellitus without diabetic		
4	し	complications	E136	8843455
5	薬剤性糖尿病・糖尿病性合併症な	Drug-induced diabetes mellitus without diabetic		
6	し	complications	E136	8843626
7	糖尿病	Diabetes mellitus	E14	2500013
8	糖尿病合併症	Diabetic complications	E14	2507028
9	糖尿病性昏睡	Diabetic coma	E14	2502006
10	糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of diabetes mellitus	E14	8838076
11	糖尿病性アシドーシス	Diabetic acidosis	E14	2501002
12	糖尿病性アセトン血症	Diabetic acetonemia	E14	2501003
13	糖尿病性ケトアシドーシス	Diabetic ketoacidosis	E14	2501005
14	糖尿病性腎症	Diabetic nephropathy	E14	2503005
15	糖尿病性腎不全	Diabetic renal failure	E14	2503007
16	糖尿病性腎硬化症	Diabetic nephrosclerosis	E14	8838071
17	糖尿病性虹彩炎	Diabetic iritis	E14	2504004
18	糖尿病性中心性網膜症	Diabetic central retinopathy	E14	2504005
19	糖尿病性白内障	Diabetic cataract	E14	2504006
20	増殖性糖尿病性網膜症	Proliferative diabetic retinopathy	E14	2504010
21	糖尿病黄斑症	Diabetic maculopathy	E14	2504012
22	糖尿病網膜症	Diabetic retinopathy	E14	2504013
23	糖尿病性眼筋麻痺	Diabetic ophthalmoplegia	E14	8838065
24	糖尿病黄斑浮腫	Diabetic macular edema	E14	8844089
25	糖尿病性神経痛	Diabetic neuralgia	E14	2505011
26	糖尿病性末梢神経障害	Diabetic peripheral neuropathy	E14	2505018
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3	糖尿病性筋萎縮症	Diabetic muscular atrophy	E14436	2505021
4	糖尿病性神経因性膀胱	Diabetic neuropathic bladder	E14436	8838069
5	糖尿病性自律神経ニューロパチー	Diabetic autonomic neuropathy	E14436	8838070
6	糖尿病性多発ニューロパチー	Diabetic polyneuropathy	E14436	8838074
7	糖尿病性単ニューロパチー	Diabetic mononeuropathy	E14436	8838075
8	糖尿病性ニューロパチー	Diabetic neuropathy	E14436	8838078
9	糖尿病足病変	Diabetic foot lesion	E14436	8848634
10	糖尿病性神経障害性疼痛	Diabetic neuropathic pain	E14436	8848768
11	糖尿病性壊疽	Diabetic gangrene	E14436	2506006
12	糖尿病性動脈閉塞症	Diabetic arterial occlusion	E14436	2506011
13	糖尿病性潰瘍	Diabetic ulcer	E14436	8838063
14	糖尿病性血管障害	Diabetic angiopathy	E14436	8838066
15	糖尿病性動脈硬化症	Diabetic arteriosclerosis	E14436	8838077
16	糖尿病性末梢血管症	Diabetic peripheral vascular disease	E14436	8838079
17	糖尿病性末梢血管障害	Diabetic peripheral vascular disease	E14436	8838080
18	糖尿病足壊疽	Diabetic foot gangrene	E14436	8848632
19	糖尿病足潰瘍	Diabetic foot ulcer	E14436	8848633
20	糖尿病性関節症	Diabetic arthropathy	E14436	2507025
21	糖尿病性皮膚障害	Diabetic skin disorders	E14436	2507029
22	糖尿病性肝障害	Diabetic liver injury	E14436	8838064
23	糖尿病性高コレステロール血症	Diabetic hypercholesterolemia	E14436	8838067
24	糖尿病性骨症	Diabetic osteopathy	E14436	8838068
25	糖尿病性精神障害	Diabetic mental disorder	E14436	8838072
26	糖尿病性そう痒症	Diabetic pruritus	E14436	8838073
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3	糖尿病性水疱	Diabetic blister	E14	8844652
4	糖尿病性浮腫性硬化症	Diabetic edematous sclerosis	E14	8844653
5	高血糖高浸透圧症候群	Hyperglycemia hyperosmolarity syndrome	E14	8845128
6	糖尿病・糖尿病性合併症なし	Diabetes mellitus without diabetic complications	E14	8843439
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8	非糖尿病性低血糖性昏睡	Hypoglycemic coma not in the context of diabetes mellitus	E15	8839324
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10	果糖尿症	Levulosuria	E74	8831401
11	本態性果糖尿症	Essential levulosuria	E74	8840104
12	良性果糖尿症	Benign levulosuria	E74	8841021
13	腎性糖尿	Renal glycosuria	E74	2714002
14	青銅性糖尿病	Bronze diabetes mellitus	E83	8835941
15	膵全摘後二次性糖尿病	Secondary diabetes after pancreatectomy	E89	8835685
16	1型糖尿病合併妊娠	Pregnancy with type 1 diabetes	O24	8830029
17	2型糖尿病合併妊娠	Pregnancy with type 2 diabetes	O24	8830039
18	妊娠糖尿病	Pregnancy diabetes mellitus	O24	6489003
19	妊娠中の糖尿病	Overt diabetes in pregnancy	O24	8838621
20	妊娠中の耐糖能低下	Impaired glucose tolerance in pregnancy	O99	8838619
21	妊娠糖尿病母体児症候群	Gestational diabetes maternal syndrome	P70	8838633
22	糖尿病母体児	Diabetes maternal infant	P70	8838081
23	新生児一過性糖尿病	Neonatal transient diabetes mellitus	P70	7751001
24	新生児糖尿病	Neonatal diabetes mellitus	P70	7751002
25	新生児一過性高血糖症	Neonatal transient hyperglycemia	P70	8844233
26	境界型糖尿病	Borderline type diabetes mellitus	R73	2500031
27	耐糖能異常	Impaired glucose tolerance	R73	2713009
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4	化学的糖尿病	Chemical diabetes mellitus	R734.36	8831132
5	潜在性糖尿病	Latent diabetes mellitus	R734.09	8836104
6	前糖尿病	Pre-diabetes mellitus	R734.1	8836563
7	高血糖症	Hyperglycemia	R734.3	8833419
8	一過性糖尿	Transient diabetes mellitus	R812.1	7915002
9				
10	五炭糖尿症	L-Xylulosemia	R812.1	7915003
11				
12	高血糖性糖尿	Hypoglycemic glycosuria	R812.1	8833420
13				
14	食事性糖尿	Dietary glycosuria	R812.1	8834843
15				
16	情動性糖尿	Emotional glycosuria	R812.1	8835464
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18	正常血糖性糖尿	Euglycemic glycosuria	R812.1	8835871
19	糖尿	Glycosuria	R812.1	8838062
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Supplementary Table S2 Codes of antidiabetic medications

Types of antidiabetic medication	Medicine codes
Sulfonylureas	610412056, 610443002, 610443003, 613960002, 613960003, 613960008, 613960017, 613960026, 613960027, 613960028, 613960038, 613960039, 613960078, 620000048, 620002031, 620002032, 620003159, 620003160, 620003947, 620003948, 620006030, 620006890, 620009209, 620871601, 620872002, 620872003, 620872004, 620872009, 620872016, 620873202, 620873301, 620873402, 620873702, 621982701, 621997001, 621997101, 621998701, 621998801, 621998901, 621999001, 621999301, 621999401, 621999701, 621999801, 622000601, 622000701, 622001701, 622001801, 622004701, 622004801, 622005501, 622005601, 622005802, 622009802, 622009901, 622010001, 622011401, 622011501, 622011601, 622011701, 622013401, 622013501, 622013601, 622016001, 622016101, 622017301, 622017401, 622017501, 622017901, 622018001, 622018802, 622020903, 622021003, 622021801, 622021901, 622022001, 622022101, 622023501, 622023601, 622025201, 622025301, 622025801, 622025901, 622026501, 622026601, 622029901, 622030001, 622031401, 622031501, 622033001, 622033101, 622033201, 622033701, 622033801, 622035701, 622035801, 622036002, 622037901, 622038001, 622039901, 622048401, 622048501, 622058801, 622058901, 622059002, 622059102, 622075601, 622088301, 622088401, 622103201, 622114701, 622114801, 622118501, 622122201, 622122301, 622127301, 622127401, 622127501, 622128101, 622137701, 622141101, 622141302, 622143402, 622144001, 622159301, 622169102, 622169301, 622176301, 622177501, 622186201, 622187301, 622190001, 622190801,

	622193301, 622194901, 622198001, 622202201, 622202801, 622205101, 622205501, 622208901, 622211501, 622217701, 622219701, 622221001, 622222001, 622242001, 622246801, 622252501, 622254701, 622271101, 622271201, 622271301, 622313200, 622313300, 622338501, 622338601, 622338701
Meglitinides	622462501, 622462401, 620001908, 620001907, 622053601, 622040901, 622041001, 610432026, 610432027, 622196601, 622119301, 622230001, 622196701, 622119401, 622230101, 610432032, 610432033, 622518201, 622525401, 622515301, 622523401, 622521001, 622518101, 622525301, 622515201, 622523301, 622520901
α -glucosidase inhibitors	610406390, 620002841, 620002843, 620004045, 620004072, 620004071, 620008727, 620008726, 621665301, 621683401, 621673501, 621691201, 622090001, 621689303, 621689001, 621690402, 621690901, 621690203, 620002120, 620004069, 620005557, 620005558, 620005559, 620005560, 620005561, 620008071, 620008072, 620008073, 621953301, 621943301, 620009287, 621896502, 622008602, 620009286, 621896402, 622008502, 620009296, 620009294, 620009293, 622302301, 620009297, 621958801, 620005360, 621785002, 621942202, 620009295, 620009291, 620009289, 620009288, 622302201, 620009292, 621958701, 620005359, 621784902, 621942102, 620009290, 621937201, 621937101, 613960082, 613960081, 622053601, 622432501, 622426601, 622426701, 620003127, 620003128, 620003129, 620002121, 610406391, 621953401, 620004046, 620004070, 620005562, 620008074, 620005563, 620005564, 620005565, 620008075, 620005566, 621943401, 620008076, 620004073, 620002845, 621690303, 620008729, 620008728, 620004074, 621689403, 621689101, 621691001, 621691601, 621665401, 621683501, 620002847, 622090101, 621690502, 621673601
Biguanides	622517101, 622450401, 622450301, 620004480, 620004502, 620005979, 610463145, 621986401, 621986301, 610444147, 621974701, 622242501, 622070801, 621676001,

	620005570, 622427201, 622421901, 622424401, 622421101, 622412701, 622438401, 622417101, 622432601, 622436301, 622427301, 622422001, 622424501, 622421201, 622448601, 622438501, 622417201, 622432701, 622466601
Thiazolidinediones	621990901, 621991001, 610432040, 610432041, 622048501, 622048401, 622065301, 622061601, 622041402, 622155901, 622063201, 622156901, 622144601, 622167201, 622045401, 622159401, 622056001, 622147501, 622175601, 622071901, 622065401, 622061701, 622041502, 622156001, 622063301, 622157001, 622144701, 622167301, 622045501, 622159501, 622056101, 622147601, 622175701, 622072001, 622320800, 622320900, 622065101, 622042901, 622061401, 622166801, 622182401, 622041202, 622079101, 622155701, 622063001, 622066201, 622164301, 622062302, 622047701, 622049901, 622046801, 622163301, 622053101, 622081801, 622059201, 622045201, 622053801, 622055801, 622147301, 622078301, 622175401, 622071701, 622065201, 622043001, 622061501, 622166901, 622182501, 622041302, 622079201, 622155801, 622063101, 622066301, 622164401, 622062402, 622047801, 622050001, 622046901, 622163401, 622053201, 622081901, 622059301, 622045301, 622061001, 622055901, 622147401, 622078401, 622175501, 622071801, 621986401, 621986301, 622086101, 622086001
Dipeptidyl peptidase-4 inhibitors	621950901, 621951001, 621951101, 621970601, 621970701, 621970801, 621980701, 621986001, 621986101, 621986201, 622086001, 622086101, 622093501, 622182601, 622201701, 622245601, 622245701, 622277501, 622288401, 622415401, 622415501, 622448901, 622449001, 622450301, 622450401, 622517101
Sodium glucose cotransporter 2 inhibitor	622340101, 622360601, 622401201, 622401301, 622306601, 622306701, 622336801, 622342001, 622341901, 622335701, 622335801

Rapid-acting insulin	621911101, 621911301, 621911201, 620008895, 621926901, 622252701, 620008893, 620008894, 620008916, 640451027, 620007460
Short-acting insulin	620008897, 620000265, 620008909, 620008907, 622114401
Long-acting insulin	622440701, 620008945, 620008943, 620007536, 622198901, 622199001, 622410901, 622484801, 622411001, 621927001, 620008952, 620008953
Immediate-acting insulin	620000266, 620008912, 620008910, 622114501, 620002441, 620007459
Premixed insulin	620002439, 620007461, 620002440, 620007462, 620008915, 620008913, 622114601, 620000269, 620000448, 620008896, 621973201, 621973301, 640453023
Combination-acting insulin	622451001, 622450901
Glucagon-like peptide-1 receptor agonist	622038401, 622038301, 621974801, 622229001, 622406001, 622267001, 622442201

Supplementary Table S3 Amputation codes

	Medical procedure receipt codes (in Japan)
Major LLA	
above-knee/transfemoral amputation	150051610
below-knee/transtibial amputation	150051710
Hindquarter amputation/ Hip disarticulation	150052210
through-knee amputation	150052310
Minor LLA	
Foot amputation, trans-metatarsal amputation, Lisfranc disarticulation	150051810
Foot joint disarticulation	150052610
Finger and toe amputation	150051910
Finger and toe joint disarticulation	150052710

Supplementary Table S4 The population of Japanese national census (2015)

Age group, years	total	men	women	Age group, years	total	men	women	Age group, years	total	men	women
0–4	4,987,706	2,550,921	2,436,785	35–39	8,316,157	4,204,202	4,111,955	70–74	6,695,811	3,582,440	4,113,371
5–9	5,299,787	2,714,591	2,585,196	40–44	9,732,218	4,914,018	4,818,200	75–79	5,276,856	2,787,417	3,489,439
10–14	5,599,317	2,868,024	2,731,293	45–49	8,662,804	4,354,877	4,307,927	80–84	4,961,420	1,994,326	2,967,094
15–19	6,008,388	3,085,416	2,922,972	50–54	7,930,296	3,968,311	3,961,985	≥85	4,887,487	1,461,624	3,425,863
20–24	5,968,127	3,046,392	2,921,735	55–59	7,515,246	3,729,523	3,785,723	Total	127,094,745	61,841,738	65,253,007
25–29	6,409,612	3,255,717	3,153,895	60–64	8,455,010	4,151,119	4,303,891				
30–34	7,290,878	3,684,747		60–65	9,643,867	4,659,662	4,984,205				

Contributorship statement

All authors contributed significantly. F.K. designed the study and wrote the manuscript. Y.N. contributed to the study design, data analysis, and discussion. T.N. provided advice on the study design and discussed the findings from an epidemiological perspective. T.M., S.K., and T.H. performed the initial NDB analysis and provided technical advice. S.O., Y.A., H.I., and Y.T. evaluated the results from a clinical perspective. T.I. provided advice on the study design and discussed the findings from the public health viewpoint.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9,10
Bias	9	Describe any efforts to address potential sources of bias	7,8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9,10
		(b) Describe any methods used to examine subgroups and interactions	9,10
		(c) Explain how missing data were addressed	9,10
		(d) If applicable, explain how loss to follow-up was addressed	9,10
		(e) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	No participants
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	13, Table2

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17, Table3
2			(b) Report category boundaries when continuous variables were categorized	17
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	20, Table4
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	25
13	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	24,25
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22-24
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	24
16				
17	Other information			
18	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26
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26 *Give information separately for exposed and unexposed groups.

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28 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
29 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
30 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
31 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
32 available at <http://www.strobe-statement.org>.
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