BMJ Open

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

Journal:	*BMJ Open*
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

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Manuscript category: Original research

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

Fumika Kamitani, MD[1], Yuichi Nishioka, MD, PhD[1,2], Tatsuya Noda, MD, PhD[2], Tomoya Myojin, MD [2], Shinichiro Kubo, MMedSc[2], Tsuneyuki Higashino, BE[3], Sadanori Okada, MD, PhD[1], Yasuhiro Akai, MD, PhD[1], Hitoshi Ishii, MD, PhD[1], Yutaka Takahashi, MD, PhD[1], Tomoaki Imamura, MD, PhD[2]

[1]Department of Diabetes and Endocrine Medicine, Nara Medical University, Nara, Japan

[2]Department of Public Health, Health Management and Policy, Nara Medical University, Nara, Japan

[3]Healthcare and Wellness Division, Mitsubishi Research Institute, Inc. Tokyo, Japan

Corresponding author:

Tatsuya Noda

Department of Public Health, Health Management and Policy, Nara Medical University, Nara, 634-8521, Japan

Email: tnodannn@gmail.com

Tel: +81-744-29-8811

Fax: +81-744-23-9945

Short Running Title: Incidence of limb amputation in Japan

Word count: 3113 words

Number of tables and figures: 4 tables and 1 figure.

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

times higher, respectively, in individuals with diabetes than in nondiabetic individuals. This information can help create an effective national healthcare strategy for preventing limb amputations, which affect the quality of life of patients with diabetes and add to the national healthcare expenditure.

Keywords: amputation, cohort study, diabetes mellitus

5

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

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

METHODS

Study design and population

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

The study cohort comprised individuals who are enrolled in the NDB; all patient data were anonymized. Japan has a universal public healthcare system, and the NDB includes almost all patients in Japan. The NDB data provided information on personal identifiers,[8] date, age group, sex, description of the medical procedures that were conducted, the World Health Organization International Classification of Diseases

diagnosis codes, the medical care that was received, medical examinations that were conducted that did not include test results, and prescribed drugs, which were independent of the doctor's or patient's reports.[9] Drug information included the prescription amount, brand name, generic name, dosage, and the number of days for which the medicine was prescribed.

We designed this cohort study to include all the data of LLA patients collected between April 2013 and March 2018 in the analysis. Japan has a population of approximately 127 million, although the total observable population of this study was approximately 150 million due to the inclusion of newborns within the 5-year observation period and the slight deficits in the linking of the NDB.

Criteria for diagnosing diabetes

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

Definition of LLA

The primary outcome was the first occurrence of each of the major or minor LLAs in the

study period. The amputation codes are shown in Supplementary Table S3. We defined major LLAs by the use of six medical procedure codes through, or proximal to, the ankle joint, as follows: Limb amputation (thigh), Limb amputation (below legs), Limb amputation (foot), Limb joint dissection (crotch), Limb joint dissection (knee), and Limb joint dissection (foot) indicated by 150051610, 150051710, 150051810, 150052210, 150052310, and 150052610 (in K084-00 and K085-00), respectively, which are Japanese original codes. In the Japanese medical code, finger and toe amputations are indicated by the same code, and it is impossible to distinguish between them. Therefore, we defined minor LLA as limb amputation (finger) and limb joint dissection (finger): 150051910 and 150052710 (in K084-00 and K085-00).

Statistical analyses

We defined the duration between dates of the first occurrence of the medical treatment code or drug code and the last occurrence as the risk period. If the first major LLA occurred during the observation period, the major LLA observation was terminated at that time. Similarly, if the first minor LLA occurred during the observation period, the minor LLA observation was terminated at the time. Therefore, even when the major and minor LLA occurred many times in the same person during the 5-year study period, we counted only the first major and minor LLAs. Moreover, even if a minor LLA occurred, the major LLA observation continued such that the incidence of the major LLA was not underestimated. The age recorded in this study was the age at the time of the last treatment

during the study period or the patient's age when the LLA was done. To calculate the rate of incidence of LLA, the denominator was extracted from the NDB dataset. Crude rates are presented as the number of amputations per 100,000 person-years. There were few LLAs in individuals younger than 44 years and in those aged 100 years or older during the study period; therefore, the crude rates were calculated for the diabetic and nondiabetic populations only in the age range of 45–100 years. Nonetheless, the sex- and age-adjusted LLA incidence rates were calculated for all age groups. To compare the LLA incidence rates between participants with and without diabetes, the incidence rates were evaluated, after adjusting for sex and age, at all ages, by using the direct method and the sex and age structure of the Japanese 1985 population model (A Virtual Population Model Based on population in 1985), which is commonly used in Japanese epidemiological studies (Supplementary Table S4).

RESULTS

Population included in the NDB and the diabetic population

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

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 groups and type of amputation.

	Major LLA			Minor LLA		
Age groups, years	**Total**	**Diabetic, n (%)**	**Nondiabetic, n (%)**	**Total**	**Diabetic, n (%)**	**Nondiabetic n (%)**
Total	34,773	20,777 (59.8)	13,996 (40.2)	24,904	16156 (64.9)	8748 (35.1)
Men, total	21149	14062 (66.5)	7087 (33.5)	16482	11832 (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)

65–74	6102	4599 (75.4)	1503 (25.6)	4986	3840 (77.0)	1146 (33.0)
75–84	6486	4148 (64.0)	2338 (36.0)	4629	3187 (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	4324 (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	1136 (68.9)	513 (31.1)
75–84	3840	2150 (56.0)	1690 (44.0)	2470	1371 (55.5)	1099 (44.5)

						17
≥85	6123	2002 (32.7)	4121 (67.3)	3134	1002 (32.0)	2132 (68.0)

LLA, lower limb amputation.

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.

	Major LLA				Minor LLA			
Men and women, age group, years	**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.

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.

	Incidence of Major LLA			Incidence of Minor LLA		
Groups	**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

future.[10–12] This study provides a more accurate incidence of LLA in the diabetic population and would be helpful for establishing a more effective healthcare strategy to prevent LLA, which could affect the quality of life of patients with diabetes.

Compared with the few previous studies that evaluated only the first amputation to calculate the incidence LLA, the results of this study showed a much lower incidence of LLA. The crude incidence of major and minor LLA per 100,000 person-years for diabetes was 49 and 38, respectively, in this study. In a previous systematic review where only the first amputation was evaluated to calculate the incidence of LLA, the crude incidence of major LLA per 100,000 person-years was 78–455 in the diabetic population.[5] Two studies from Japan have investigated the incidence of LLA by including only the first amputation. One of the studies was conducted in the southern part of Japan and showed that the incidence of major LLAs was 50 per 100,000 person-years in participants with type 2 diabetes.[13] Another study that used data from disabled person certifications revealed that the incidence of major LLAs, regardless of diabetes, was 5.8 per 100,000 person-years.[14] These results, in conjunction with the findings of this study, demonstrate a lower incidence of LLA in the Japanese population. There are several explanations for the observed lower incidence of LLA in Japanese patients. First, the Japanese population has a lower obesity rate than the Western populations.[15,16] Second, the incidence of cardiovascular disease is much lower in Japan;[17] and this contributes to a lower risk for the progression of atherosclerosis, which is the most prevalent etiology

of LLA. Third, many Japanese individuals tend to avoid amputations because of religious beliefs,[18] and doctors' resort to limb-preservation measures (intravascular therapy, such as stenting) to preserve the legs and feet and to delay amputation.

In this study, the incidence of major and minor LLA was approximately 20 and 30 times higher, respectively, in diabetic individuals compared to nondiabetic individuals. In Japan, foot care performed by trained nurses has been approved for medical insurance coverage since 2008,[19,20] and bypass surgery and intravascular treatment have become significantly advanced.[21,22] Despite these efforts, our data indicate that the risk of LLA in diabetic individuals remained significantly higher than it was in nondiabetic participants. This may be associated with the fact that despite the insurance coverage of nurse-provided foot care, only few patients actually avail foot care services. The medical expenses burden of LLA is large.[23] The LLA risk of diabetic patients is much higher and, therefore, more diligent screening and management of the diabetic population are important to reduce the burden of quality of life reduction and the national healthcare expenditure associated with LLA.[24]

A key strength of our study is that, by analyzing data from the nationwide NDB that encompasses almost the entire Japanese population, this study is the first to evaluate the true nationwide incidence of LLA in Japan. Nonetheless, this study has some limitations. First, there is no generally accepted definition of major or minor amputation.[5] We defined major LLA by the medical procedure codes that implied

amputation through or proximal to the ankle joint. Second, in minor amputation, we could not distinguish between upper and lower limb amputation because of the coding system of the NDB. The incidence of each limb amputation in the 5-year period is shown in Supplementary Table S5, which demonstrates a considerably lower incidence of upper limb amputation. These results could justify our definition of minor LLA. Finally, 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, with regard to the smoking rate, which can be an important confounding factor, a previous study in Japan reported that there was no difference between the diabetes group and the general population in terms of the current smoker rate in sex- and age-stratified analyses. Furthermore, NDB is a comprehensive survey and the likelihood of selection bias is relatively small; in addition, we adjusted for sex and age when comparing the LLA rates of diabetic and nondiabetic patients. Therefore, it is unlikely that the study results will be significantly affected even if the detailed medical information and parameters cannot be factored in.[25]

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

lower limb amputations, which affects the quality of life of the patient with diabetes and confers an increased burden on the national healthcare expenditure.

Data availability statement The research data are available from the corresponding authr on reasonable request.

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

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

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

Competing interests YN received consultant fees from Novo Nordisk. SO received speaker fees from Novo Nordisk, Mitsubishi Tanabe, Sumitomo Dainippon, Arkray, Bayer, Eli Lilly, Boehringer Ingelheim, Ono, AstraZeneca, Sanofi, and Takeda, outside of the submitted work. YA received lecture fees and consultant fees from MSD KK, Ono, Otsuka, Sumitomo Dainippon, Daiichi Sankyo, Eli Lilly, Sanofi S.A., Chugai, Novo Nordisk, Kissei, Nippon Boehringer Ingelheim, Astellas, Kyowa Hakko Kirin, Pfizer,

Takeda, Mitsubishi Tanabe, Novartis, Janssen Pharmaceutical K.K, Japanese Red Cross Society Nara Red Cross Blood Center, Sumitomo Dainippon, Ltd., Kissei. HI received lecture fees and consultant fees from Takeda, Eli Lilly Japan, Sanofi, Merck & Co., Astellas, Mitsubishi Tanabe, Daiichi Sankyo, Ono, AstraZeneca, Taisho Toyama, Shionogi, Kowa, Boehringer Ingelheim, Novo Nordisk, Sumitomo Dainippon, and Kyowa Hakko Kirin. YT received consultant fees from Novo Nordisk, Otsuka, and Recordati, and speaker fees from Novo Nordisk, Sumitomo Dainippon, Eli Lilly, Ono, Novartis, Nippon Boehringer Ingelheim, AstraZeneca, and Kyowa Kirin. The other authors declare that they have no conflict of interest.

Patient consent for publication Not required.

Data availability statement The research data are available from the corresponding authr on reasonable request.

Data availability statement The research data are available from the corresponding authr on reasonable request.

Data availability statement The research data are available from the corresponding authr on reasonable request.

References

1. Treatment Guide for Diabetes 2016-2017. 2017.

2. Bowling FL, Rashid ST, Boulton AJ. Preventing and treating foot complications associated with diabetes mellitus. Nat Rev Endocrinol 2015; 11: 606-616.

3. Alothman S, Alenazi A, Waitman LR et al. Neuropathy and Other Risk Factors for Lower Extremity Amputation in People with Diabetes Using a Clinical Data Repository System. J Allied Health 2018; 47: 217-221.

4. Fosse S, Hartemann-Heurtier A, Jacqueminet S et al. Incidence and characteristics of lower limb amputations in people with diabetes. Diabet Med 2009; 26: 391-396.

5. Narres M, Kvitkina T, Claessen H et al. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: A systematic review. PLoS One 2017; 12: e0182081.

6. Kroger K, Berg C, Santosa F et al. Lower Limb Amputation in Germany. Dtsch Arztebl Int 2017; 114: 130-136

7. Ministry of Health, Labour and welfare. 2019.

8. Kubo S. National Database of Health Insurance Claims and specific Health Checkups of Japan (NDB): 2018.

9. Nishioka Y, Okada S, Noda T et al. Absolute risk of acute coronary syndrome after severe hypoglycemia: A population-based 2-year cohort study using the National Database in Japan. J Diabetes Investig 2020; 11: 426-434.

10. Johannesson A, Larsson GU, Ramstrand N et al. Incidence of lower-limb amputation in the diabetic and nondiabetic general population: a 10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations. Diabetes Care 2009; 32: 275-280.

11. Larsson J, Apelqvist J. Towards less amputations in diabetic patients. Incidence, causes, cost, treatment, and prevention-a review. Acta Orthop Scand 1995; 66: 181-192.

12. Unwin N. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. Br J Surg 2000; 87: 328-337.

13. Iwase M, Fujii H, Nakamura U et al. Incidence of diabetic foot ulcer in Japanese patients with type 2 diabetes mellitus: The Fukuoka diabetes registry. Diabetes Res Clin Pract 2018; 137: 183-189.

14. Ohmine S, Kimura Y, Saeki S et al. Community-based survey of amputation derived from the physically disabled person's certification in Kitakyushu City, Japan. Prosthet Orthot Int 2012; 36: 196-202.

15. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016; 387: 1377-1396.

16. Yoon KH, Lee JH, Kim JW et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006; 368: 1681-1688.

17. Ueshima H, Sekikawa A, Miura K et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation 2008; 118: 2702-2709.

18. Maroukis BL, Shauver MJ, Nishizuka T et al. Cross-cultural variation in preference for replantation or revision amputation: Societal and surgeon views. Injury 2016; 47: 818-823.

19. Fujiwara Y, Kishida K, Terao M et al. Beneficial effects of foot care nursing for people with diabetes mellitus: an uncontrolled before and after intervention study. J Adv Nurs 2011; 67: 1952-1962.

20. Hingorani A, LaMuraglia GM, Henke P et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg 2016; 63: 3S-21S.

21. Iida O, Nakamura M, Yamauchi Y et al. 3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients With Critical Limb Ischemia: A Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia. JACC Cardiovasc Interv 2015; 8: 1493-1502.

22. Zayed H, Halawa M, Maillardet L et al. Improving limb salvage rate in diabetic patients with critical leg ischaemia using a multidisciplinary approach. Int J Clin Pract 2009; 63: 855-

858.

23. Franklin H, Rajan M, Tseng CL et al. Cost of lower-limb amputation in U.S. veterans with diabetes using health services data in fiscal years 2004 and 2010. J Rehabil Res Dev 2014; 51: 1325-1330.

24. Hicks CW, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Curr Diab Rep 2019; 19: 86.

25. Hiroshi T, Koichi H, Koichi K et al. Current Status of Cigarette Smoking in Diabetes Patients in Japan: The Importance of Early Smoker Education. J Japan Diab Soc 2011; 54: 779-785.

Supporting information

Table S1. Diagnosis codes for diabetes.

Table S2. Medication codes for diabetes.

Table S3. Amputation codes.

Table S4. A standard Japanese population model (1985).

Table S5. Incidence of each type of limb amputation during the study period.

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.

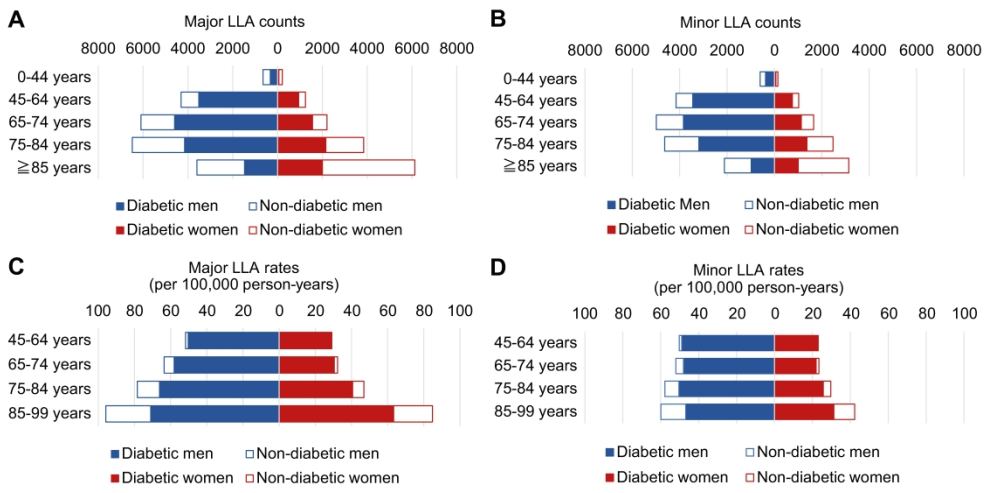


Figure 1. Results of sex- and age-stratified analyses: (A) number of major lower limb amputation (LLA); (B) number of minor LLA; (C) rates of incidence of major LLA; and (D) rates of incidence of minor LLA.

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.

１型糖尿病性腎症第２期	Type 1 diabetic nephropathy phase 2	E102	8843984
１型糖尿病性腎症第３期	Type 1 diabetic nephropathy phase 3	E102	8843985
１型糖尿病性腎症第３期Ａ	Type 1 diabetic nephropathy phase 3A	E102	8843986
１型糖尿病性腎症第３期Ｂ	Type 1 diabetic nephropathy phase 3B	E102	8843987
１型糖尿病性腎症第４期	Type 1 diabetic nephropathy phase 4	E102	8843988
１型糖尿病性腎症第５期	Type 1 diabetic nephropathy phase 5	E102	8843989
緩徐進行１型糖尿病・腎合併症あり	SPIDDM with nephropathy - [Slowly progressive insulin-dependent diabetes mellitus]	E102	8844028
１型糖尿病性腎硬化症	Type 1 diabetic nephrosclerosis	E102	8845058
１型糖尿病性腎不全	Type 1 diabetic kidney failure	E102	8845059
１型糖尿病性網膜症	Type 1 diabetic retinopathy	E103	8830033
１型糖尿病・眼合併症あり	Type 1 diabetes mellitus with eye complication	E103	8841682
１型糖尿病性黄斑浮腫	Type 1 diabetic macular edema	E103	8843982
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]	E103	8844024
１型糖尿病性白内障	Type 1 diabetic cataracts	E103	8844346
増殖性糖尿病性網膜症・１型糖尿病	Proliferative diabetic retinopathy, type 1 diabetes	E103	8844536
１型糖尿病黄斑症	Type 1 diabetic macular disease	E103	8845043
１型糖尿病性眼筋麻痺	Type 1 diabetic eye muscle paralysis	E103	8845049
１型糖尿病性虹彩炎	Type 1 diabetic iritis	E103	8845053
１型糖尿病性中心性網膜症	Type 1 diabetic central retinopathy	E103	8845064
１型糖尿病性ニューロパチー	Type 1 diabetic neuropathy	E104	8830032
１型糖尿病・神経学的合併症あり	Type 1 diabetes mellitus with neurological	E104	8841683

	complications		
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]	E104	8844027
１型糖尿病性筋萎縮症	Type 1 diabetic muscular atrophy	E104	8845050
１型糖尿病性神経因性膀胱	Type 1 diabetic neuropathic bladder	E104	8845055
１型糖尿病性神経痛	Type 1 diabetic neuralgia	E104	8845056
１型糖尿病性自律神経ニューロパチー	Type 1 diabetic autonomic neuropathy	E104	8845057
１型糖尿病性多発ニューロパチー	Type 1 diabetic polyneuropathy	E104	8845062
１型糖尿病性単ニューロパチー	Type 1 diabetic mononeuropathy	E104	8845063
１型糖尿病性末梢神経障害	Type 1 diabetic peripheral neuropathy	E104	8845071
１型糖尿病・末梢循環合併症あり	Type 1 diabetes mellitus with peripheral circulation complications	E104	8841684
１型糖尿病性壊疽	Type 1 diabetic gangrene	E105	8843105
緩徐進行１型糖尿病・末梢循環合併症あり	SPIDDM with peripheral circulation complications - [Slowly progressive insulin-dependent diabetes mellitus]	E105	8844031
１型糖尿病性潰瘍	Type 1 diabetic ulcer	E105	8845046
１型糖尿病性血管障害	Type 1 diabetic vascular disease	E105	8845051
１型糖尿病性動脈硬化症	Type 1 diabetic atherosclerosis	E105	8845066
１型糖尿病性動脈閉塞症	Type 1 diabetic arterial occlusion	E105	8845067
１型糖尿病性末梢血管症	Type 1 diabetic peripheral vascular disease	E105	8845069
１型糖尿病性末梢血管障害	Type 1 diabetic peripheral vascular disease	E105	8845070
１型糖尿病・関節合併症あり	Type 1 diabetes mellitus with joint complications	E105	8841685

１型糖尿病・糖尿病性合併症あり	Type 1 diabetes mellitus with diabetic complications	E106	8841686
緩徐進行１型糖尿病・関節合併症あり	SPIDDM with joint complications - [Slowly progressive insulin-dependent diabetes mellitus]	E106	8844023
１型糖尿病性水疱	Type 1 diabetic blister	E106	8844626
１型糖尿病性浮腫性硬化症	Type 1 diabetic edematous sclerosis	E106	8844627
１型糖尿病性肝障害	Type 1 diabetic liver injury	E106	8845047
１型糖尿病性関節症	Type 1 diabetic arthropathy	E106	8845048
１型糖尿病性高コレステロール血症	Type 1 diabetic hypercholesterolemia	E106	8845052
１型糖尿病性骨症	Type 1 diabetic osteopathy	E106	8845054
１型糖尿病性精神障害	Type 1 diabetic mental disorder	E106	8845060
１型糖尿病性そう痒症	Type 1 diabetic pruritus	E106	8845061
１型糖尿病性皮膚障害	Type 1 diabetic skin disorder	E106	8845068
１型糖尿病性胃腸症	Type 1 diabetic gastroenteritis	E106	8845842
１型糖尿病・多発糖尿病性合併症あり	Type 1 diabetes mellitus with multiple diabetic complications	E107	8841687
緩徐進行１型糖尿病・多発糖尿病性合併症あり	SPIDDM with multiple diabetic complications - [Slowly progressive insulin-dependent diabetes mellitus]	E107	8844029
１型糖尿病・糖尿病性合併症なし	Type 1 diabetes mellitus without diabetic complecations	E106	8841688
緩徐進行１型糖尿病・糖尿病性合併症なし	SPIDDM without diabetic complications - [Slowly progressive insulin-dependent diabetes mellitus]	E106	8844030
インスリン抵抗性糖尿病	Insulin resistant diabetes mellitus	E11	2500001

２型糖尿病	Type 2 diabetes mellitus	E11	2500015
安定型糖尿病	Stable diabetes mellitus	E11	8830405
若年２型糖尿病	Juvenile type 2 diabetes	E11	8835244
２型糖尿病性昏睡	Type 2 diabetic coma	E11	8830041
２型糖尿病・昏睡合併あり	Type 2 diabetes mellitus with coma	E11	8841689
２型糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of type 2 diabetes mellitus	E11	8845094
２型糖尿病性ケトアシドーシス	Type 2 diabetic ketoacidosis	E11	8830040
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
２型糖尿病性アシドーシス	Type 2 diabetic acidosis	E11	8845073
２型糖尿病性アセトン血症	Type 2 diabetic acetone hyperlipoproteinemia	E11	8845074
２型糖尿病性腎症	Type 2 diabetic nephropathy	E11	8830042
２型糖尿病・腎合併症あり	Type 2 diabetes mellitus with diabetic nephropathy	E11	8841691
２型糖尿病性腎症第１期	Type 2 diabetic nephropathy phase 1	E11	8843991
２型糖尿病性腎症第２期	Type 2 diabetic nephropathy phase 2	E11	8843992
２型糖尿病性腎症第３期	Type 2 diabetic nephropathy phase 3	E11	8843993
２型糖尿病性腎症第３期Ａ	Type 2 diabetic nephropathy phase 3A	E11	8843994
２型糖尿病性腎症第３期Ｂ	Type 2 diabetic nephropathy phase 3B	E11	8843995
２型糖尿病性腎症第４期	Type 2 diabetic nephropathy phase 4	E11	8843996
２型糖尿病性腎症第５期	Type 2 diabetic nephropathy phase 5	E11	8843997
２型糖尿病性腎硬化症	Type 2 diabetic nephrosclerosis	E11	8845087
２型糖尿病性腎不全	Type 2 diabetic kidney failure	E11	8845088
２型糖尿病性網膜症	Type 2 diabetic retinopathy	E11	8830045

２型糖尿病・眼合併症あり	Type 2 diabetes mellitus with eye complications	E11.3	8841692
２型糖尿病性黄斑浮腫	Type 2 diabetic macular edema	E11.3	8843990
２型糖尿病性白内障	Type 2 diabetic cataracts	E11.3	8844347
増殖性糖尿病性網膜症・２型糖尿病	Proliferative diabetic retinopathy, type 2 diabetes	E11.3	8844537
２型糖尿病黄斑症	Type 2 diabetic macular disease	E11.3	8845072
２型糖尿病性眼筋麻痺	Type 2 diabetic eye muscle paralysis	E11.3	8845078
２型糖尿病性虹彩炎	Type 2 diabetic iritis	E11.3	8845082
２型糖尿病性中心性網膜症	Type 2 diabetic central retinopathy	E11.3	8845093
２型糖尿病性ニューロパチー	Type 2 diabetic neuropathy	E11.4	8830043
２型糖尿病性ミオパチー	Type 2 diabetic myopathy	E11.4	8830044
２型糖尿病・神経学的合併症あり	Type 2 diabetes mellitus with neurological complications	E11.4	8841693
２型糖尿病性筋萎縮症	Type 2 diabetic muscular atrophy	E11.4	8845079
２型糖尿病性神経因性膀胱	Type 2 diabetic neuropathic bladder	E11.4	8845084
２型糖尿病性神経痛	Type 2 diabetic neuralgia	E11.4	8845085
２型糖尿病性自律神経ニューロパチー	Type 2 diabetic autonomic neuropathy	E11.4	8845086
２型糖尿病性多発ニューロパチー	Type 2 diabetic polyneuropathy	E11.4	8845091
２型糖尿病性単ニューロパチー	Type 2 diabetic mononeuropathy	E11.4	8845092
２型糖尿病性末梢神経障害	Type 2 diabetic peripheral neuropathy	E11.4	8845100
２型糖尿病・末梢循環合併症あり	Type 2 diabetes mellitus with peripheral circulation complications	E11.5	8841694
２型糖尿病性壊疽	Type 2 diabetic gangrene	E11.5	8843106

２型糖尿病性潰瘍	Type 2 diabetic ulcer	E11	8845075
２型糖尿病性血管障害	Type 2 diabetic vascular disease	E11	8845080
２型糖尿病性動脈硬化症	Type 2 diabetic atherosclerosis	E11	8845095
２型糖尿病性動脈閉塞症	Type 2 diabetic arterial occlusion	E11	8845096
２型糖尿病性末梢血管症	Type 2 diabetic peripheral vascular disease	E11	8845098
２型糖尿病性末梢血管障害	Type 2 diabetic peripheral vascular disease	E11	8845099
２型糖尿病・関節合併症あり	Type 2 diabetes mellitus with joint complications	E11	8841695
２型糖尿病・糖尿病性合併症あり	Type 2 diabetes mellitus with diabetic complications	E11	8841696
２型糖尿病性水疱	Type 2 diabetic blister	E11	8844628
２型糖尿病性浮腫性硬化症	Type 2 diabetic edematous sclerosis	E11	8844629
２型糖尿病性肝障害	Type 2 diabetic liver injury	E11	8845076
２型糖尿病性関節症	Type 2 diabetic arthropathy	E11	8845077
２型糖尿病性高コレステロール血症	Type 2 diabetic hypercholesterolemia	E11	8845081
２型糖尿病性骨症	Type 2 diabetic osteopathy	E11	8845083
２型糖尿病性精神障害	Type 2 diabetic mental disorder	E11	8845089
２型糖尿病性そう痒症	Type 2 diabetic pruritus	E11	8845090
２型糖尿病性皮膚障害	Type 2 diabetic skin disorder	E11	8845097
２型糖尿病性胃腸症	Type 2 diabetic gastroenteritis	E11	8848108
２型糖尿病・多発糖尿病性合併症あり	Type 2 diabetes mellitus with multiple diabetic complications	E11	8841697
２型糖尿病・糖尿病性合併症なし	Type 2 diabetes mellitus without diabetic complecations	E11	8841698
栄養不良関連糖尿病	Malnutrition-related diabetes mellitus	E12	2500037

膵性糖尿病	Pancreatic diabetes mellitus	E13	2500024
ステロイド糖尿病	Steroid diabetes mellitus	E13	2509003
二次性糖尿病	Secondary diabetes mellitus	E13	2509004
ウイルス性糖尿病	Viral diabetes mellitus	E13	8830756
薬剤性糖尿病	Drug-induced diabetes mellitus	E13	8840710
ウイルス性糖尿病・昏睡合併あり	Viral diabetes mellitus with coma	E13	8843122
膵性糖尿病・昏睡合併あり	Pancreatic diabetes mellitus with coma	E13	8843377
ステロイド糖尿病・昏睡合併あり	Steroid diabetes mellitus with coma	E13	8843390
二次性糖尿病・昏睡合併あり	Secondary diabetes mellitus with coma	E13	8843450
薬剤性糖尿病・昏睡合併あり	Drug-induced diabetes mellitus with coma	E13	8843621
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
膵性糖尿病・ケトアシドーシス合併あり	Pancreatic diabetes mellitus with ketoacidosis	E13	8843376
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
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
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
ウイルス性糖尿病・腎合併症あり	Viral diabetes mellitus with renal complications	E13	8843124
膵性糖尿病・腎合併症あり	Pancreatic diabetes mellitus with renal complications	E13	8843379
ステロイド糖尿病・腎合併症あり	Steroid diabetes mellitus with renal complications	E13	8843392
二次性糖尿病・腎合併症あり	Secondary diabetes mellitus with renal complications	E13	8843452

薬剤性糖尿病・腎合併症あり	Drug-induced diabetes mellitus with renal complications	E13	8843623
ウイルス性糖尿病・眼合併症あり	Viral diabetes mellitus with eye complications	E13	8843120
膵性糖尿病・眼合併症あり	Pancreatic diabetes mellitus with eye complications	E13	8843375
ステロイド糖尿病・眼合併症あり	Steroid diabetes mellitus with eye complications	E13	8843388
二次性糖尿病・眼合併症あり	Secondary diabetes mellitus with eye complications	E13	8843448
薬剤性糖尿病・眼合併症あり	Drug-induced diabetes mellitus with eye complications	E13	8843619
ウイルス性糖尿病・神経学的合併症あり	Viral diabetes mellitus with neurological complications	E13	8843123
膵性糖尿病・神経学的合併症あり	Pancreatic diabetes mellitus with neurological complications	E13	8843378
ステロイド糖尿病・神経学的合併症あり	Steroid diabetes mellitus with neurological complications	E13	8843391
二次性糖尿病・神経学的合併症あり	Secondary diabetes mellitus with neurological complications	E13	8843451
薬剤性糖尿病・神経学的合併症あり	Drug-induced diabetes mellitus with neurological complications	E13	8843622
ウイルス性糖尿病・末梢循環合併症あり	Viral diabetes mellitus with peripheral circulatory complications	E13	8843128
膵性糖尿病・末梢循環合併症あり	Pancreatic diabetes mellitus with peripheral circulatory complications	E13	8843383
ステロイド糖尿病・末梢循環合併症あり	Steroid diabetes mellitus with peripheral circulatory complications	E13	8843396
二次性糖尿病・末梢循環合併症あ	Secondary diabetes mellitus with peripheral circulatory	E13	8843456

り	complications		
薬剤性糖尿病・末梢循環合併症あり	Drug-induced diabetes mellitus with peripheral circulatory complications	E135	8843627
ウイルス性糖尿病・糖尿病性合併症あり	Viral diabetes mellitus with diabetic complications	E136	8843126
膵性糖尿病・糖尿病性合併症あり	Pancreatic diabetes mellitus with diabetic complications	E136	8843381
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
二次性糖尿病・糖尿病性合併症あり	Secondary diabetes mellitus with diabetic complications	E136	8843454
薬剤性糖尿病・糖尿病性合併症あり	Drug-induced diabetes mellitus with diabetic complications	E136	8843625
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	E137	8843125
膵性糖尿病・多発糖尿病性合併症あり	Pancreatic diabetes mellitus with multiple diabetic complications	E137	8843380
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	E137	8843393
二次性糖尿病・多発糖尿病性合併症あり	Secondary diabetes mellitus with multiple diabetic complications	E137	8843453
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	E137	8843624
ウイルス性糖尿病・糖尿病性合併症なし	Viral diabetes mellitus without diabetic complications	E139	8843127

膵性糖尿病・糖尿病性合併症なし	Pancreatic diabetes mellitus without diabetic complications	E139	8843382
ステロイド糖尿病・糖尿病性合併症なし	Steroid diabetes mellitus without diabetic complications	E139	8843395
二次性糖尿病・糖尿病性合併症なし	Secondary diabetes mellitus without diabetic complications	E139	8843455
薬剤性糖尿病・糖尿病性合併症なし	Drug-induced diabetes mellitus without diabetic complications	E139	8843626
糖尿病	Diabetes mellitus	E14	2500013
糖尿病合併症	Diabetic complications	E14	2507028
糖尿病性昏睡	Diabetic coma	E140	2502006
糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of diabetes mellitus	E140	8838076
糖尿病性アシドーシス	Diabetic acidosis	E141	2501002
糖尿病性アセトン血症	Diabetic acetonemia	E141	2501003
糖尿病性ケトアシドーシス	Diabetic ketoacidosis	E141	2501005
糖尿病性腎症	Diabetic nephropathy	E142	2503005
糖尿病性腎不全	Diabetic renal failure	E142	2503007
糖尿病性腎硬化症	Diabetic nephrosclerosis	E142	8838071
糖尿病性虹彩炎	Diabetic iritis	E143	2504004
糖尿病性中心性網膜症	Diabetic central retinopathy	E143	2504005
糖尿病性白内障	Diabetic cataract	E143	2504006
増殖性糖尿病性網膜症	Proliferative diabetic retinopathy	E143	2504010
糖尿病黄斑症	Diabetic maculopathy	E143	2504012
糖尿病網膜症	Diabetic retinopathy	E143	2504013

糖尿病性眼筋麻痺	Diabetic ophthalmoplegia	E143	8838065
糖尿病黄斑浮腫	Diabetic macular edema	E143	8844089
糖尿病性神経痛	Diabetic neuralgia	E144	2505011
糖尿病性末梢神経障害	Diabetic peripheral neuropathy	E144	2505018
糖尿病性筋萎縮症	Diabetic muscular atrophy	E144	2505021
糖尿病性神経因性膀胱	Diabetic neuropathic bladder	E144	8838069
糖尿病性自律神経ニューロパチー	Diabetic autonomic neuropathy	E144	8838070
糖尿病性多発ニューロパチー	Diabetic polyneuropathy	E144	8838074
糖尿病性単ニューロパチー	Diabetic mononeuropathy	E144	8838075
糖尿病性ニューロパチー	Diabetic neuropathy	E144	8838078
糖尿病足病変	Diabetic foot lesion	E144	8848634
糖尿病性神経障害性疼痛	Diabetic neuropathic pain	E144	8848768
糖尿病性壊疽	Diabetic gangrene	E145	2506006
糖尿病性動脈閉塞症	Diabetic arterial occlusion	E145	2506011
糖尿病性潰瘍	Diabetic ulcer	E147	8838063
糖尿病性血管障害	Diabetic angiopathy	E147	8838066
糖尿病性動脈硬化症	Diabetic arteriosclerosis	E147	8838077
糖尿病性末梢血管症	Diabetic peripheral vascular disease	E147	8838079
糖尿病性末梢血管障害	Diabetic peripheral vascular disease	E147	8838080
糖尿病足壊疽	Diabetic foot gangrene	E147	8848632
糖尿病足潰瘍	Diabetic foot ulcer	E147	8848633
糖尿病性関節症	Diabetic arthropathy	E148	2507025
糖尿病性皮膚障害	Diabetic skin disorders	E149	2507029
糖尿病性肝障害	Diabetic liver injury	E149	8838064

糖尿病性高コレステロール血症	Diabetic hypercholesterolemia	E146	8838067
糖尿病性骨症	Diabetic osteopathy	E146	8838068
糖尿病性精神障害	Diabetic mental disorder	E146	8838072
糖尿病性そう痒症	Diabetic pruritus	E146	8838073
糖尿病性水疱	Diabetic blister	E146	8844652
糖尿病性浮腫性硬化症	Diabetic edematous sclerosis	E146	8844653
高血糖高浸透圧症候群	Hyperglycemia hyperosmolarity syndrome	E146	8845128
糖尿病・糖尿病性合併症なし	Diabetes mellitus without diabetic complications	E149	8843439
非糖尿病性低血糖性昏睡	Hypoglycemic coma not in the context of diabetes mellitus	E151	8839324
果糖尿症	Levulosuria	E74	8831401
本態性果糖尿症	Essential levulosuria	E74	8840104
良性果糖尿症	Benign levulosuria	E74	8841021
腎性糖尿	Renal glycosuria	E74	2714002
青銅性糖尿病	Bronze diabetes mellitus	E83	8835941
膵全摘後二次性糖尿病	Secondary diabetes after pancreatectomy	E89	8835685
１型糖尿病合併妊娠	Pregnancy with type 1 diabetes	O240	8830029
２型糖尿病合併妊娠	ıith type 2 diabetes	O241	8830039
妊娠糖尿病	Pregnancy diabetes mellitus	O244	6489003
妊娠中の糖尿病	Overt diabetes in pregnancy	O244	8838621
妊娠中の耐糖能低下	Impaired glucose tolerance in pregnancy	O99	8838619
妊娠糖尿病母体児症候群	Gestational diabetes maternal syndrome	P70	8838633
糖尿病母体児	Diabetes maternal infant	P70	8838081
新生児一過性糖尿病	Neonatal transient diabetes mellitus	P70	7751001

新生児糖尿病	Neonatal diabetes mellitus	P70	7751002
新生児一過性高血糖症	Neonatal transient hyperglycemia	P70	8844233
境界型糖尿病	Borderline type diabetes mellitus	R73	2500031
耐糖能異常	Impaired glucose tolerance	R73	2713009
化学的糖尿病	Chemical diabetes mellitus	R73	8831132
潜在性糖尿病	Latent diabetes mellitus	R73	8836104
前糖尿病	Pre-diabetes mellitus	R73	8836563
高血糖症	Hyperglycemia	R73	8833419
一過性糖尿	Transient diabetes mellitus	R81	7915002
五炭糖尿症	L-Xylulosuria	R81	7915003
高血糖性糖尿	Hypoglycemic glycosuria	R81	8833420
食事性糖尿	Dietary glycosuria	R81	8834843
情動性糖尿	Emotional glycosuria	R81	8835464
正常血糖性糖尿	Euglycemic glycosuria	R81	8835871
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

,

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	17, Table3 17 20, Table4
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	25
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
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:	*BMJ Open*
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

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Manuscript category: Original research

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

Fumika Kamitani, MD[1], Yuichi Nishioka, MD, PhD[1,2], Tatsuya Noda, MD, PhD[2], Tomoya Myojin, MD [2], Shinichiro Kubo, MMedSc[2], Tsuneyuki Higashino, BE[3], Sadanori Okada, MD, PhD[1], Yasuhiro Akai, MD, PhD[1], Hitoshi Ishii, MD, PhD[1], Yutaka Takahashi, MD, PhD[1], Tomoaki Imamura, MD, PhD[2]

[1]Department of Diabetes and Endocrine Medicine, Nara Medical University, Nara, Japan

[2]Department of Public Health, Health Management and Policy, Nara Medical University, Nara, Japan

[3]Healthcare and Wellness Division, Mitsubishi Research Institute, Inc. Tokyo, Japan

Corresponding author:

Tatsuya Noda

Department of Public Health, Health Management and Policy, Nara Medical University,

Nara, 634-8521, Japan

Email: tnodannn@gmail.com

Tel: +81-744-29-8811

Fax: +81-744-23-9945

Short Running Title: Incidence of limb amputation in Japan

Word count: 3198 words

Number of tables and figures: 4 tables and 2 figures.

ABSTRACT

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

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. We analyzed the sex- and age-adjusted annual LLA rate (every fiscal year) in people with and without diabetes for major and minor amputation. To test for time trend, Poisson regression models were fitted.

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

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

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

Keywords: amputation, cohort study, diabetes mellitus

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.

INTRODUCTION

The objectives of diabetes management are to reduce the metabolic dysfunction that occurs because of hyperglycaemia, to prevent the development or progression of diabetes-related complications and conditions, and to enable the affected individuals to maintain their quality of life and life expectancy like 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 its incidence among people with diabetes [5]. It is important to understand the incidence rates of LLA in diabetic and nondiabetic populations to further improve the care of patients with diabetes and to avoid fatal outcomes, particularly regarding decisions associated with health policy and the economy [4,5].

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

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

METHODS

Study design and population

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

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

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

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

Criteria for diagnosing diabetes

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

Definition of LLA

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

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

Statistical analyses

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

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

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

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

Patient and Public Involvement.

Patients and the public were not involved.

RESULTS

Population included in the NDB and the diabetic population

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

group (age ≥65 years).

Incidence of LLAs

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

Age-adjusted incidence rate

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

RR was higher in men than in women.

Time trend

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

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

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 the representative of almost all health claims in Japan [8,9]. Using 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Contributions

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

Patient consent for publication Not required.

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

References

1. Treatment Guide for Diabetes 2016-2017. 2017.

2. Bowling FL, Rashid ST, Boulton AJ. Preventing and treating foot complications associated with diabetes mellitus. Nat Rev Endocrinol 2015; 11: 606-616.

3. Alothman S, Alenazi A, Waitman LR et al. Neuropathy and Other Risk Factors for Lower Extremity Amputation in People with Diabetes Using a Clinical Data Repository System. J Allied Health 2018; 47: 217-221.

4. Fosse S, Hartemann-Heurtier A, Jacqueminet S et al. Incidence and characteristics of lower limb amputations in people with diabetes. Diabet Med 2009; 26: 391-396.

5. Narres M, Kvitkina T, Claessen H et al. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: A systematic review. PLoS One 2017; 12: e0182081.

6. Kroger K, Berg C, Santosa F et al. Lower Limb Amputation in Germany. Dtsch Arztebl Int 2017; 114: 130-136

7. Ministry of Health, Labour and welfare. 2019.

8. Kubo S. National Database of Health Insurance Claims and specific Health Checkups of Japan (NDB): 2018.

9. Nishioka Y, Okada S, Noda T et al. Absolute risk of acute coronary syndrome after severe hypoglycemia: A population-based 2-year cohort study using the National Database in Japan. J Diabetes Investig 2020; 11: 426-434.

10. Christian-Alexander B, Birgitta S, Zoltan S et al. International Variations in Amputation Practice: A VASCUNET Report. Eur J Vasc Endovasc Surg 2018; 56: 391-399.

11. Carinci F, Massi Benedetti M, Klazinga NS et al. Lower extremity amputation rates in people with diabetes as an indicator of health systems performance. A critical appraisal of the

data collection 2000-2011 by the Organization for Economic Cooperation and Development (OECD). Acta Diabetol 2016; 53: 825-832.

12. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016; 387: 1377-1396.

13. Yoon KH, Lee JH, Kim JW et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006; 368: 1681-1688.

14. Ueshima H, Sekikawa A, Miura K et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation 2008; 118: 2702-2709.

15. Maroukis BL, Shauver MJ, Nishizuka T et al. Cross-cultural variation in preference for replantation or revision amputation: Societal and surgeon views. Injury 2016; 47: 818-823.

16. Shaima A, Aqeel A, L Russ W et al. Neuropathy and Other Risk Factors for Lower Extremity Amputation in People with Diabetes Using a Clinical Data Repository System. J Allied Health 2018; 47 (3): 217-221.

17. Enrico B, Sasa N, Mariagrazia M et al. Diabetic foot management: multidisciplinary approach for advanced lesion rescue. J Cardiovasc Surg (Torino) 2018; 59 (5): 670-684.

18. Fujiwara Y, Kishida K, Terao M et al. Beneficial effects of foot care nursing for people with diabetes mellitus: an uncontrolled before and after intervention study. J Adv Nurs 2011; 67: 1952-1962.

19. Hingorani A, LaMuraglia GM, Henke P et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg 2016; 63:

3S-21S.

20. Iida O, Nakamura M, Yamauchi Y et al. 3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients With Critical Limb Ischemia: A Prospective, Multi-Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia. JACC Cardiovasc Interv 2015; 8: 1493-1502.

21. Zayed H, Halawa M, Maillardet L et al. Improving limb salvage rate in diabetic patients with critical leg ischaemia using a multidisciplinary approach. Int J Clin Pract 2009; 63: 855-858.

22. Franklin H, Rajan M, Tseng CL et al. Cost of lower-limb amputation in U.S. veterans with diabetes using health services data in fiscal years 2004 and 2010. J Rehabil Res Dev 2014; 51: 1325-1330.

23. Hicks CW, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Curr Diab Rep 2019; 19: 86.

24. Melissa S, Ulrike N, Thomas M. Amputation rates of the lower limb by amputation level-observational study using German national hospital discharge data from 2005 to 2015. BHC Health Serv Res. 2019; 19 (1): 163-171.

25. Flavia L, Marina M, Alessandra De B et al. Lower extremity amputations in person with and without diabetes in Italy: 2001-2010. Pros One 2014; 9(1) :e86405.

26. Heiner C, Herve A, Joeri G et al. Decreasing rates of major lower-extremity amputation in people with diabetes but not in those without: a nationwide study in Belgium. Diabetologia 2018; 61(9),1966- 1977.

27. Hiroshi T, Koichi H, Koichi K et al. Current Status of Cigarette Smoking in Diabetes

Patients in Japan: The Importance of Early Smoker Education. J Japan Diab Soc 2011; 54: 779-785.

Supporting information

Table S1. Diagnosis codes for diabetes.

Table S2. Medication codes for diabetes.

Table S3. Amputation codes.

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

Figure legends

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

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

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)

≥ 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)

NDB, National Database.

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

	Major LLA			Minor LLA		
Age groups, years	**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	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						

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						

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**	**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

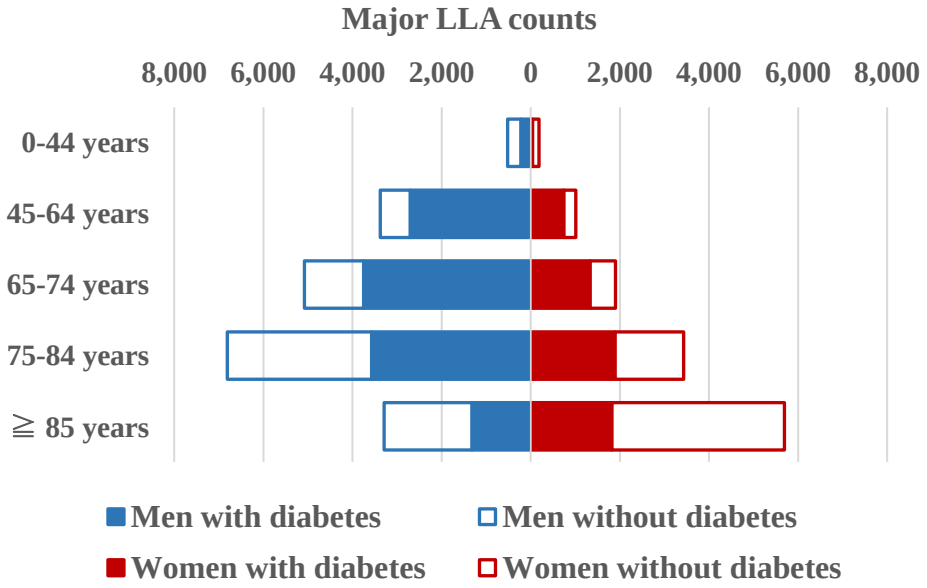
LLA, Lower limb amputation; CI, confidence interval.

Table 4 Time trend of age- and sex- standarized 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	10.4 - 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	20.7 - 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.



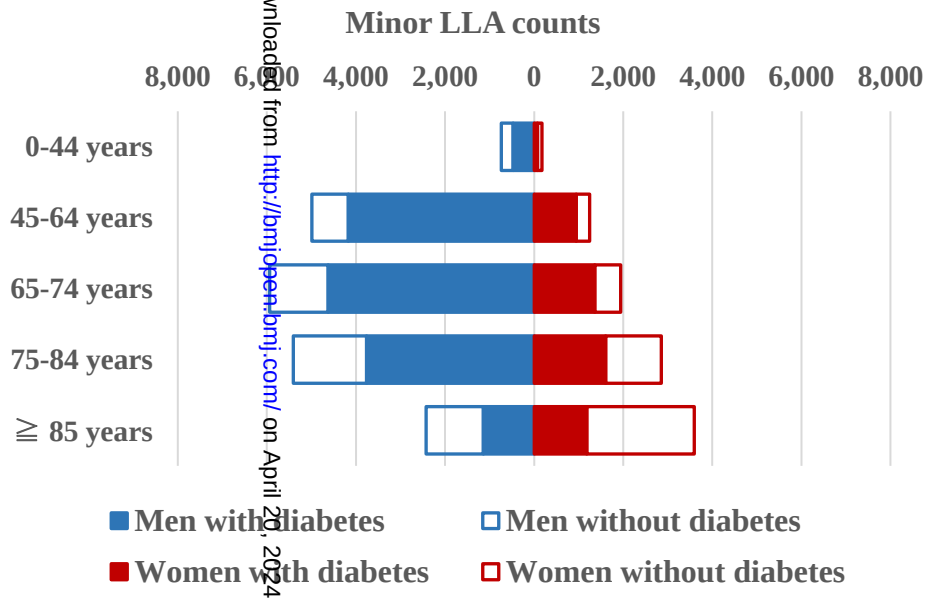


Figure 2. Time trend of age- and sex- standardized amputation rate: (A) major amputation; (B) minor amputation

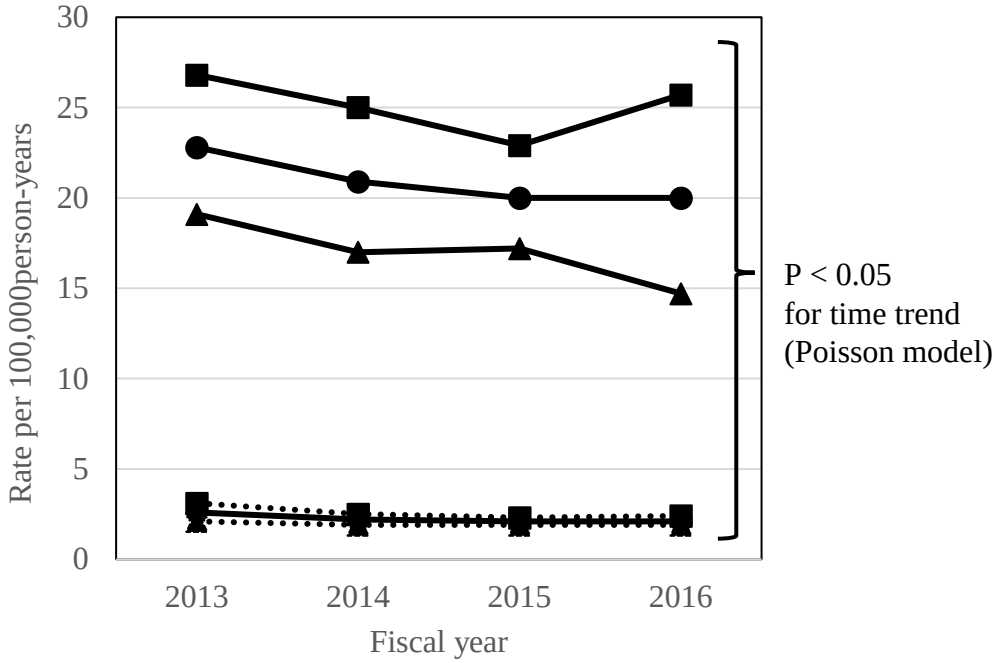


Fig.2-A Time trend of age- and sex- standardized major amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

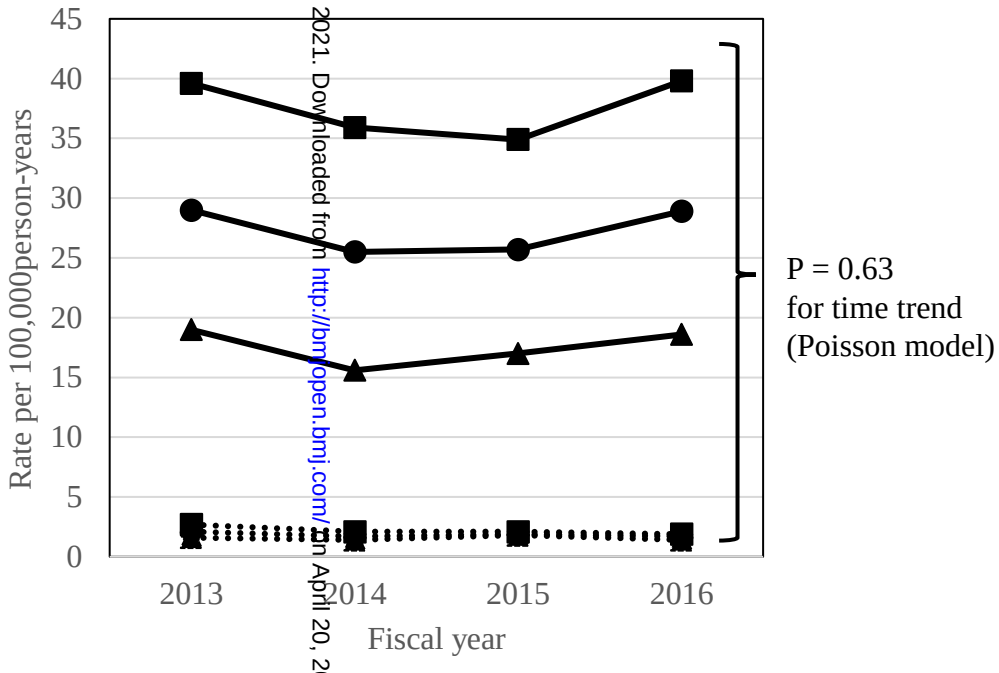


Fig.2-B Time trend of age- and sex- standardized minor amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

Supplementary Table S1 Diagnostic codes of diabetes.

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	E100	8830030
１型糖尿病・昏睡合併あり	Type 1 diabetes mellitus with coma	E100	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]	E100	8844026
１型糖尿病性低血糖性昏睡	Hypoglycemia in the context of type 1 diabetes mellitus	E106	8845065
１型糖尿病性ケトアシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus	E101	8830028
１型糖尿病・ケトアシドーシス合併あり	Type 1 diabetes mellitus with ketoacidosis	E101	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]	E101	8844025
劇症１型糖尿病	Fulminant type 1 diabetes mellitus	E101	8844045
１型糖尿病性アシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus	E101	8845044
１型糖尿病性アセトン血症	Type 1 diabetic acetone hyperlipoproteinemia	E101	8845045
１型糖尿病性腎症	Type 1 diabetic nephropathy	E102	8830031
１型糖尿病・腎合併症あり	Type 1 diabetes mellitus with diabetic nephropathy	E102	8841681
１型糖尿病性腎症第１期	Type 1 diabetic nephropathy phase 1	E102	8843983
１型糖尿病性腎症第２期	Type 1 diabetic nephropathy phase 2	E102	8843984
１型糖尿病性腎症第３期	Type 1 diabetic nephropathy phase 3	E102	8843985
１型糖尿病性腎症第３期Ａ	Type 1 diabetic nephropathy phase 3A	E102	8843986
１型糖尿病性腎症第３期Ｂ	Type 1 diabetic nephropathy phase 3B	E102	8843987
１型糖尿病性腎症第４期	Type 1 diabetic nephropathy phase 4	E102	8843988
１型糖尿病性腎症第５期	Type 1 diabetic nephropathy phase 5	E102	8843989

緩徐進行１型糖尿病・腎合併症あり	SPIDDM with nephropathy - [Slowly progressive insulin-dependent diabetes mellitus]	E102	8844028
１型糖尿病性腎硬化症	Type 1 diabetic nephrosclerosis	E102	8845058
１型糖尿病性腎不全	Type 1 diabetic kidney failure	E102	8845059
１型糖尿病性網膜症	Type 1 diabetic retinopathy	E102	8830033
１型糖尿病・眼合併症あり	Type 1 diabetes mellitus with eye complication	E102	8841682
１型糖尿病性黄斑浮腫	Type 1 diabetic macular edema	E102	8843982
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]	E102	8844024
１型糖尿病性白内障	Type 1 diabetic cataracts	E102	8844346
増殖性糖尿病性網膜症・１型糖尿病	Proliferative diabetic retinopathy, type 1 diabetes	E102	8844536
１型糖尿病黄斑症	Type 1 diabetic macular disease	E102	8845043
１型糖尿病性眼筋麻痺	Type 1 diabetic eye muscle paralysis	E102	8845049
１型糖尿病性虹彩炎	Type 1 diabetic iritis	E102	8845053
１型糖尿病性中心性網膜症	Type 1 diabetic central retinopathy	E102	8845064
１型糖尿病性ニューロパチー	Type 1 diabetic neuropathy	E104	8830032
１型糖尿病・神経学的合併症あり	Type 1 diabetes mellitus with neurological complications	E104	8841683
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]	E104	8844027
１型糖尿病性筋萎縮症	Type 1 diabetic muscular atrophy	E104	8845050
１型糖尿病性神経因性膀胱	Type 1 diabetic neuropathic bladder	E104	8845055
１型糖尿病性神経痛	Type 1 diabetic neuralgia	E104	8845056

1型糖尿病性自律神経ニューロパチー	Type 1 diabetic autonomic neuropathy	E104	8845057
1型糖尿病性多発ニューロパチー	Type 1 diabetic polyneuropathy	E104	8845062
1型糖尿病性単ニューロパチー	Type 1 diabetic mononeuropathy	E104	8845063
1型糖尿病性末梢神経障害	Type 1 diabetic peripheral neuropathy	E104	8845071
1型糖尿病・末梢循環合併症あり	Type 1 diabetes mellitus with peripheral circulation complications	E105	8841684
1型糖尿病性壊疽	Type 1 diabetic gangrene	E105	8843105
緩徐進行1型糖尿病・末梢循環合併症あり	SPIDDM with peripheral circulation complications - [Slowly progressive insulin-dependent diabetes mellitus]	E105	8844031
1型糖尿病性潰瘍	Type 1 diabetic ulcer	E105	8845046
1型糖尿病性血管障害	Type 1 diabetic vascular disease	E105	8845051
1型糖尿病性動脈硬化症	Type 1 diabetic atherosclerosis	E105	8845066
1型糖尿病性動脈閉塞症	Type 1 diabetic arterial occlusion	E105	8845067
1型糖尿病性末梢血管症	Type 1 diabetic peripheral vascular disease	E105	8845069
1型糖尿病性末梢血管障害	Type 1 diabetic peripheral vascular disease	E105	8845070
1型糖尿病・関節合併症あり	Type 1 diabetes mellitus with joint complications	E106	8841685
1型糖尿病・糖尿病性合併症あり	Type 1 diabetes mellitus with diabetic complications	E106	8841686
緩徐進行1型糖尿病・関節合併症あり	SPIDDM with joint complications - [Slowly progressive insulin-dependent diabetes mellitus]	E106	8844023
1型糖尿病性水疱	Type 1 diabetic blister	E106	8844626
1型糖尿病性浮腫性硬化症	Type 1 diabetic edematous sclerosis	E106	8844627
1型糖尿病性肝障害	Type 1 diabetic liver injury	E106	8845047

１型糖尿病性関節症	Type 1 diabetic arthropathy	E106	8845048
１型糖尿病性高コレステロール血症	Type 1 diabetic hypercholesterolemia	E106	8845052
１型糖尿病性骨症	Type 1 diabetic osteopathy	E106	8845054
１型糖尿病性精神障害	Type 1 diabetic mental disorder	E106	8845060
１型糖尿病性そう痒症	Type 1 diabetic pruritus	E106	8845061
１型糖尿病性皮膚障害	Type 1 diabetic skin disorder	E106	8845068
１型糖尿病性胃腸症	Type 1 diabetic gastroenteritis	E106	8845842
１型糖尿病・多発糖尿病性合併症あり	Type 1 diabetes mellitus with multiple diabetic complications	E104	8841687
緩徐進行１型糖尿病・多発糖尿病性合併症あり	SPIDDM with multiple diabetic complications - [Slowly progressive insulin-dependent diabetes mellitus]	E104	8844029
１型糖尿病・糖尿病性合併症なし	Type 1 diabetes mellitus without diabetic complecations	E105	8841688
緩徐進行１型糖尿病・糖尿病性合併症なし	SPIDDM without diabetic complications - [Slowly progressive insulin-dependent diabetes mellitus]	E105	8844030
インスリン抵抗性糖尿病	Insulin resistant diabetes mellitus	E11	2500001
２型糖尿病	Type 2 diabetes mellitus	E114	2500015
安定型糖尿病	Stable diabetes mellitus	E11	8830405
若年２型糖尿病	Juvenile type 2 diabetes	E11	8835244
２型糖尿病性昏睡	Type 2 diabetic coma	E116	8830041
２型糖尿病・昏睡合併あり	Type 2 diabetes mellitus with coma	E116	8841689

２型糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of type 2 diabetes mellitus	E116	8845094
２型糖尿病性ケトアシドーシス	Type 2 diabetic ketoacidosis	E117	8830040
２型糖尿病・ケトアシドーシス合併あり	Type 2 diabetes mellitus with ketoacidosis	E111	8841690
２型糖尿病性アシドーシス	Type 2 diabetic acidosis	E117	8845073
２型糖尿病性アセトン血症	Type 2 diabetic acetone hyperlipoproteinemia	E117	8845074
２型糖尿病性腎症	Type 2 diabetic nephropathy	E114	8830042
２型糖尿病・腎合併症あり	Type 2 diabetes mellitus with diabetic nephropathy	E111	8841691
２型糖尿病性腎症第１期	Type 2 diabetic nephropathy phase 1	E114	8843991
２型糖尿病性腎症第２期	Type 2 diabetic nephropathy phase 2	E114	8843992
２型糖尿病性腎症第３期	Type 2 diabetic nephropathy phase 3	E114	8843993
２型糖尿病性腎症第３期Ａ	Type 2 diabetic nephropathy phase 3A	E114	8843994
２型糖尿病性腎症第３期Ｂ	Type 2 diabetic nephropathy phase 3B	E114	8843995
２型糖尿病性腎症第４期	Type 2 diabetic nephropathy phase 4	E114	8843996
２型糖尿病性腎症第５期	Type 2 diabetic nephropathy phase 5	E114	8843997
２型糖尿病性腎硬化症	Type 2 diabetic nephrosclerosis	E114	8845087
２型糖尿病性腎不全	Type 2 diabetic kidney failure	E112	8845088
２型糖尿病性網膜症	Type 2 diabetic retinopathy	E113	8830045
２型糖尿病・眼合併症あり	Type 2 diabetes mellitus with eye complications	E118	8841692
２型糖尿病性黄斑浮腫	Type 2 diabetic macular edema	E113	8843990
２型糖尿病性白内障	Type 2 diabetic cataracts	E113	8844347
増殖性糖尿病性網膜症・２型糖尿病	Proliferative diabetic retinopathy, type 2 diabetes	E113	8844537

2型糖尿病黄斑症	Type 2 diabetic macular disease	E11.3	8845072
2型糖尿病性眼筋麻痺	Type 2 diabetic eye muscle paralysis	E11.3	8845078
2型糖尿病性虹彩炎	Type 2 diabetic iritis	E11.3	8845082
2型糖尿病性中心性網膜症	Type 2 diabetic central retinopathy	E11.3	8845093
2型糖尿病性ニューロパチー	Type 2 diabetic neuropathy	E11.4	8830043
2型糖尿病性ミオパチー	Type 2 diabetic myopathy	E11.4	8830044
2型糖尿病・神経学的合併症あり	Type 2 diabetes mellitus with neurological complications	E11.4	8841693
2型糖尿病性筋萎縮症	Type 2 diabetic muscular atrophy	E11.4	8845079
2型糖尿病性神経因性膀胱	Type 2 diabetic neuropathic bladder	E11.4	8845084
2型糖尿病性神経痛	Type 2 diabetic neuralgia	E11.4	8845085
2型糖尿病性自律神経ニューロパチー	Type 2 diabetic autonomic neuropathy	E11.4	8845086
2型糖尿病性多発ニューロパチー	Type 2 diabetic polyneuropathy	E11.4	8845091
2型糖尿病性単ニューロパチー	Type 2 diabetic mononeuropathy	E11.4	8845092
2型糖尿病性末梢神経障害	Type 2 diabetic peripheral neuropathy	E11.4	8845100
2型糖尿病・末梢循環合併症あり	Type 2 diabetes mellitus with peripheral circulation complications	E11.5	8841694
2型糖尿病性壊疽	Type 2 diabetic gangrene	E11.5	8843106
2型糖尿病性潰瘍	Type 2 diabetic ulcer	E11.5	8845075
2型糖尿病性血管障害	Type 2 diabetic vascular disease	E11.5	8845080
2型糖尿病性動脈硬化症	Type 2 diabetic atherosclerosis	E11.5	8845095
2型糖尿病性動脈閉塞症	Type 2 diabetic arterial occlusion	E11.5	8845096
2型糖尿病性末梢血管症	Type 2 diabetic peripheral vascular disease	E11.5	8845098

２型糖尿病性末梢血管障害	Type 2 diabetic peripheral vascular disease	E11	8845099
２型糖尿病・関節合併症あり	Type 2 diabetes mellitus with joint complications	E11	8841695
２型糖尿病・糖尿病性合併症あり	Type 2 diabetes mellitus with diabetic complications	E11	8841696
２型糖尿病性水疱	Type 2 diabetic blister	E11	8844628
２型糖尿病性浮腫性硬化症	Type 2 diabetic edematous sclerosis	E11	8844629
２型糖尿病性肝障害	Type 2 diabetic liver injury	E11	8845076
２型糖尿病性関節症	Type 2 diabetic arthropathy	E11	8845077
２型糖尿病性高コレステロール血症	Type 2 diabetic hypercholesterolemia	E11	8845081
２型糖尿病性骨症	Type 2 diabetic osteopathy	E11	8845083
２型糖尿病性精神障害	Type 2 diabetic mental disorder	E11	8845089
２型糖尿病性そう痒症	Type 2 diabetic pruritus	E11	8845090
２型糖尿病性皮膚障害	Type 2 diabetic skin disorder	E11	8845097
２型糖尿病性胃腸症	Type 2 diabetic gastroenteritis	E11	8848108
２型糖尿病・多発糖尿病性合併症あり	Type 2 diabetes mellitus with multiple diabetic complications	E11	8841697
２型糖尿病・糖尿病性合併症なし	Type 2 diabetes mellitus without diabetic complecations	E11	8841698
栄養不良関連糖尿病	Malnutrition-related diabetes mellitus	E12	2500037
膵性糖尿病	Pancreatic diabetes mellitus	E13	2500024
ステロイド糖尿病	Steroid diabetes mellitus	E13	2509003
二次性糖尿病	Secondary diabetes mellitus	E13	2509004
ウイルス性糖尿病	Viral diabetes mellitus	E13	8830756
薬剤性糖尿病	Drug-induced diabetes mellitus	E13	8840710

ウイルス性糖尿病・昏睡合併あり	Viral diabetes mellitus with coma	E130	8843122
膵性糖尿病・昏睡合併あり	Pancreatic diabetes mellitus with coma	E130	8843377
ステロイド糖尿病・昏睡合併あり	Steroid diabetes mellitus with coma	E130	8843390
二次性糖尿病・昏睡合併あり	Secondary diabetes mellitus with coma	E130	8843450
薬剤性糖尿病・昏睡合併あり	Drug-induced diabetes mellitus with coma	E130	8843621
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	E131	8843121
膵性糖尿病・ケトアシドーシス合併あり	Pancreatic diabetes mellitus with ketoacidosis	E131	8843376
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	E131	8843389
二次性糖尿病・ケトアシドーシス合併あり	Secondary diabetes mellitus with ketoacidosis	E131	8843449
薬剤性糖尿病・ケトアシドーシス合併あり	Drug-induced diabetes mellitus with ketoacidosis	E131	8843620
ウイルス性糖尿病・腎合併症あり	Viral diabetes mellitus with renal complications	E132	8843124
膵性糖尿病・腎合併症あり	Pancreatic diabetes mellitus with renal complications	E132	8843379
ステロイド糖尿病・腎合併症あり	Steroid diabetes mellitus with renal complications	E132	8843392
二次性糖尿病・腎合併症あり	Secondary diabetes mellitus with renal complications	E132	8843452
薬剤性糖尿病・腎合併症あり	Drug-induced diabetes mellitus with renal complications	E132	8843623
ウイルス性糖尿病・眼合併症あり	Viral diabetes mellitus with eye complications	E132	8843120
膵性糖尿病・眼合併症あり	Pancreatic diabetes mellitus with eye complications	E132	8843375
ステロイド糖尿病・眼合併症あり	Steroid diabetes mellitus with eye complications	E132	8843388

二次性糖尿病・眼合併症あり	Secondary diabetes mellitus with eye complications	E133	8843448
薬剤性糖尿病・眼合併症あり	Drug-induced diabetes mellitus with eye complications	E133	8843619
ウイルス性糖尿病・神経学的合併症あり	Viral diabetes mellitus with neurological complications	E134	8843123
膵性糖尿病・神経学的合併症あり	Pancreatic diabetes mellitus with neurological complications	E134	8843378
ステロイド糖尿病・神経学的合併症あり	Steroid diabetes mellitus with neurological complications	E134	8843391
二次性糖尿病・神経学的合併症あり	Secondary diabetes mellitus with neurological complications	E134	8843451
薬剤性糖尿病・神経学的合併症あり	Drug-induced diabetes mellitus with neurological complications	E134	8843622
ウイルス性糖尿病・末梢循環合併症あり	Viral diabetes mellitus with peripheral circulatory complications	E135	8843128
膵性糖尿病・末梢循環合併症あり	Pancreatic diabetes mellitus with peripheral circulatory complications	E135	8843383
ステロイド糖尿病・末梢循環合併症あり	Steroid diabetes mellitus with peripheral circulatory complications	E135	8843396
二次性糖尿病・末梢循環合併症あり	Secondary diabetes mellitus with peripheral circulatory complications	E135	8843456
薬剤性糖尿病・末梢循環合併症あり	Drug-induced diabetes mellitus with peripheral circulatory complications	E135	8843627
ウイルス性糖尿病・糖尿病性合併症あり	Viral diabetes mellitus with diabetic complications	E136	8843126

膵性糖尿病・糖尿病性合併症あり	Pancreatic diabetes mellitus with diabetic complications	E136	8843381
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
二次性糖尿病・糖尿病性合併症あり	Secondary diabetes mellitus with diabetic complications	E136	8843454
薬剤性糖尿病・糖尿病性合併症あり	Drug-induced diabetes mellitus with diabetic complications	E136	8843625
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	E137	8843125
膵性糖尿病・多発糖尿病性合併症あり	Pancreatic diabetes mellitus with multiple diabetic complications	E137	8843380
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	E137	8843393
二次性糖尿病・多発糖尿病性合併症あり	Secondary diabetes mellitus with multiple diabetic complications	E137	8843453
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	E137	8843624
ウイルス性糖尿病・糖尿病性合併症なし	Viral diabetes mellitus without diabetic complications	E139	8843127
膵性糖尿病・糖尿病性合併症なし	Pancreatic diabetes mellitus without diabetic complications	E139	8843382
ステロイド糖尿病・糖尿病性合併症なし	Steroid diabetes mellitus without diabetic complications	E139	8843395

二次性糖尿病・糖尿病性合併症なし	Secondary diabetes mellitus without diabetic complications	E139	8843455
薬剤性糖尿病・糖尿病性合併症なし	Drug-induced diabetes mellitus without diabetic complications	E139	8843626
糖尿病	Diabetes mellitus	E14	2500013
糖尿病合併症	Diabetic complications	E14	2507028
糖尿病性昏睡	Diabetic coma	E140	2502006
糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of diabetes mellitus	E160	8838076
糖尿病性アシドーシス	Diabetic acidosis	E141	2501002
糖尿病性アセトン血症	Diabetic acetonemia	E141	2501003
糖尿病性ケトアシドーシス	Diabetic ketoacidosis	E141	2501005
糖尿病性腎症	Diabetic nephropathy	E142	2503005
糖尿病性腎不全	Diabetic renal failure	E142	2503007
糖尿病性腎硬化症	Diabetic nephrosclerosis	E142	8838071
糖尿病性虹彩炎	Diabetic iritis	E143	2504004
糖尿病性中心性網膜症	Diabetic central retinopathy	E143	2504005
糖尿病性白内障	Diabetic cataract	E143	2504006
増殖性糖尿病性網膜症	Proliferative diabetic retinopathy	E143	2504010
糖尿病黄斑症	Diabetic maculopathy	E143	2504012
糖尿病網膜症	Diabetic retinopathy	E143	2504013
糖尿病性眼筋麻痺	Diabetic ophthalmoplegia	E143	8838065
糖尿病黄斑浮腫	Diabetic macular edema	E143	8844089
糖尿病性神経痛	Diabetic neuralgia	E144	2505011
糖尿病性末梢神経障害	Diabetic peripheral neuropathy	E144	2505018

糖尿病性筋萎縮症	Diabetic muscular atrophy	E144	2505021
糖尿病性神経因性膀胱	Diabetic neuropathic bladder	E144	8838069
糖尿病性自律神経ニューロパチー	Diabetic autonomic neuropathy	E144	8838070
糖尿病性多発ニューロパチー	Diabetic polyneuropathy	E144	8838074
糖尿病性単ニューロパチー	Diabetic mononeuropathy	E144	8838075
糖尿病性ニューロパチー	Diabetic neuropathy	E144	8838078
糖尿病足病変	Diabetic foot lesion	E144	8848634
糖尿病性神経障害性疼痛	Diabetic neuropathic pain	E144	8848768
糖尿病性壊疽	Diabetic gangrene	E145	2506006
糖尿病性動脈閉塞症	Diabetic arterial occlusion	E145	2506011
糖尿病性潰瘍	Diabetic ulcer	E145	8838063
糖尿病性血管障害	Diabetic angiopathy	E145	8838066
糖尿病性動脈硬化症	Diabetic arteriosclerosis	E145	8838077
糖尿病性末梢血管症	Diabetic peripheral vascular disease	E145	8838079
糖尿病性末梢血管障害	Diabetic peripheral vascular disease	E145	8838080
糖尿病足壊疽	Diabetic foot gangrene	E145	8848632
糖尿病足潰瘍	Diabetic foot ulcer	E145	8848633
糖尿病性関節症	Diabetic arthropathy	E146	2507025
糖尿病性皮膚障害	Diabetic skin disorders	E146	2507029
糖尿病性肝障害	Diabetic liver injury	E146	8838064
糖尿病性高コレステロール血症	Diabetic hypercholesterolemia	E146	8838067
糖尿病性骨症	Diabetic osteopathy	E146	8838068
糖尿病性精神障害	Diabetic mental disorder	E146	8838072
糖尿病性そう痒症	Diabetic pruritus	E146	8838073

糖尿病性水疱	Diabetic blister	E146	8844652
糖尿病性浮腫性硬化症	Diabetic edematous sclerosis	E146	8844653
高血糖高浸透圧症候群	Hyperglycemia hyperosmolarity syndrome	E146	8845128
糖尿病・糖尿病性合併症なし	Diabetes mellitus without diabetic complications	E149	8843439
非糖尿病性低血糖性昏睡	Hypoglycemic coma not in the context of diabetes mellitus	E151	8839324
果糖尿症	Levulosuria	E741	8831401
本態性果糖尿症	Essential levulosuria	E741	8840104
良性果糖尿症	Benign levulosuria	E741	8841021
腎性糖尿	Renal glycosuria	E743	2714002
青銅性糖尿病	Bronze diabetes mellitus	E83	8835941
膵全摘後二次性糖尿病	Secondary diabetes after pancreatectomy	E895	8835685
１型糖尿病合併妊娠	Pregnancy with type 1 diabetes	O240	8830029
２型糖尿病合併妊娠	ith type 2 diabetes	O241	8830039
妊娠糖尿病	Pregnancy diabetes mellitus	O244	6489003
妊娠中の糖尿病	Overt diabetes in pregnancy	O249	8838621
妊娠中の耐糖能低下	Impaired glucose tolerance in pregnancy	O998	8838619
妊娠糖尿病母体児症候群	Gestational diabetes maternal syndrome	P700	8838633
糖尿病母体児	Diabetes maternal infant	P701	8838081
新生児一過性糖尿病	Neonatal transient diabetes mellitus	P704	7751001
新生児糖尿病	Neonatal diabetes mellitus	P702	7751002
新生児一過性高血糖症	Neonatal transient hyperglycemia	P708	8844233
境界型糖尿病	Borderline type diabetes mellitus	R730	2500031
耐糖能異常	Impaired glucose tolerance	R730	2713009

化学的糖尿病	Chemical diabetes mellitus	R73H	8831132
潜在性糖尿病	Latent diabetes mellitus	R73H	8836104
前糖尿病	Pre-diabetes mellitus	R73H	8836563
高血糖症	Hyperglycemia	R73H	8833419
一過性糖尿	Transient diabetes mellitus	R81	7915002
五炭糖尿症	L-Xylulosuria	R81	7915003
高血糖性糖尿	Hypoglycemic glycosuria	R81	8833420
食事性糖尿	Dietary glycosuria	R81	8834843
情動性糖尿	Emotional glycosuria	R81	8835464
正常血糖性糖尿	Euglycemic glycosuria	R81	8835871
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

	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**	7,695,811	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**	6,276,856	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

,

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	17, Table3 17 20, Table4
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	25
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
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:	*BMJ Open*
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

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Manuscript category: Original research

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

Fumika Kamitani, MD[1], Yuichi Nishioka, MD, PhD[1,2], Tatsuya Noda, MD, PhD[2], Tomoya Myojin, MD [2], Shinichiro Kubo, MMedSc[2], Tsuneyuki Higashino, BE[3], Sadanori Okada, MD, PhD[1], Yasuhiro Akai, MD, PhD[1], Hitoshi Ishii, MD, PhD[1], Yutaka Takahashi, MD, PhD[1], Tomoaki Imamura, MD, PhD[2]

[1]Department of Diabetes and Endocrine Medicine, Nara Medical University, Nara, Japan

[2]Department of Public Health, Health Management and Policy, Nara Medical University, Nara, Japan

[3]Healthcare and Wellness Division, Mitsubishi Research Institute, Inc. Tokyo, Japan

Corresponding author:

Tatsuya Noda

Department of Public Health, Health Management and Policy, Nara Medical University,

Nara, 634-8521, Japan

Email: tnodannn@gmail.com

Tel: +81-744-29-8811

Fax: +81-744-23-9945

Short Running Title: Incidence of limb amputation in Japan

Word count: 3352 words

Number of tables and figures: 4 tables and 2 figures.

ABSTRACT

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

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. We analyzed the sex- and age-adjusted annual LLA rate (every fiscal year) in people with and without diabetes for major and minor amputation. To test for time trend, Poisson regression models were fitted.

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

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

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

Keywords: amputation, cohort study, diabetes mellitus

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.

INTRODUCTION

The objectives of diabetes management are to reduce the metabolic dysfunction that occurs because of hyperglycaemia, to prevent the development or progression of diabetes-related complications and conditions, and to enable the affected individuals to maintain their quality of life and life expectancy like 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 its incidence among people with diabetes [5]. It is important to understand the incidence rates of LLA in diabetic and nondiabetic populations to further improve the care of patients with diabetes and to avoid fatal outcomes, particularly regarding decisions associated with health policy and the economy [4,5].

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

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

METHODS

Study design and population

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

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

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

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

Criteria for diagnosing diabetes

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

Definition of LLA

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

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

Statistical analyses

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

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

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

RESULTS

Population included in the NDB and the diabetic population

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

Incidence of LLAs

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

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

Age-adjusted incidence rate

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

Time trend

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

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

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

Patient and public involvement

No patient involved.

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 the representative of almost all health claims in Japan [8,9]. Using 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.

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

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

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

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

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

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

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

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

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

life of patients with diabetes and add to the national healthcare expenditure.

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

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

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

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

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

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

Contributorship statement

Author's contribution 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.

Patient consent for publication Not required.

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

References

1. Treatment Guide for Diabetes 2016-2017. 2017.

2. Bowling FL, Rashid ST, Boulton AJ. Preventing and treating foot complications associated with diabetes mellitus. Nat Rev Endocrinol 2015; 11: 606-616.

3. Alothman S, Alenazi A, Waitman LR et al. Neuropathy and Other Risk Factors for Lower Extremity Amputation in People with Diabetes Using a Clinical Data Repository System. J Allied Health 2018; 47: 217-221.

4. Fosse S, Hartemann-Heurtier A, Jacqueminet S et al. Incidence and characteristics of lower limb amputations in people with diabetes. Diabet Med 2009; 26: 391-396.

5. Narres M, Kvitkina T, Claessen H et al. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: A systematic review. PLoS One 2017; 12: e0182081.

6. Kroger K, Berg C, Santosa F et al. Lower Limb Amputation in Germany. Dtsch Arztebl Int 2017; 114: 130-136

7. Ministry of Health, Labour and welfare. 2019.

8. Kubo S. National Database of Health Insurance Claims and specific Health Checkups of Japan (NDB): 2018.

9. Nishioka Y, Okada S, Noda T et al. Absolute risk of acute coronary syndrome after severe hypoglycemia: A population-based 2-year cohort study using the National Database in Japan. J Diabetes Investig 2020; 11: 426-434.

10. Christian-Alexander B, Birgitta S, Zoltan S et al. International Variations in Amputation Practice: A VASCUNET Report. Eur J Vasc Endovasc Surg 2018; 56: 391-399.

11. Carinci F, Massi Benedetti M, Klazinga NS et al. Lower extremity amputation rates in people with diabetes as an indicator of health systems performance. A critical appraisal of the

data collection 2000-2011 by the Organization for Economic Cooperation and Development (OECD). Acta Diabetol 2016; 53: 825-832.

12. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016; 387: 1377-1396.

13. Yoon KH, Lee JH, Kim JW et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006; 368: 1681-1688.

14. Ueshima H, Sekikawa A, Miura K et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation 2008; 118: 2702-2709.

15. Shaima A, Aqeel A, L Russ W et al. Neuropathy and Other Risk Factors for Lower Extremity Amputation in People with Diabetes Using a Clinical Data Repository System. J Allied Health 2018; 47 (3): 217-221.

16. Enrico B, Sasa N, Mariagrazia M et al. Diabetic foot management: multidisciplinary approach for advanced lesion rescue. J Cardiovasc Surg (Torino) 2018; 59 (5): 670-684.

17. Fujiwara Y, Kishida K, Terao M et al. Beneficial effects of foot care nursing for people with diabetes mellitus: an uncontrolled before and after intervention study. J Adv Nurs 2011; 67: 1952-1962.

18. Hingorani A, LaMuraglia GM, Henke P et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg 2016; 63: 3S-21S.

19. Iida O, Nakamura M, Yamauchi Y et al. 3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients With Critical Limb Ischemia: A Prospective, Multi-

Center, Three-Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia. JACC Cardiovasc Interv 2015; 8: 1493-1502.

20. Zayed H, Halawa M, Maillardet L et al. Improving limb salvage rate in diabetic patients with critical leg ischaemia using a multidisciplinary approach. Int J Clin Pract 2009; 63: 855-858.

21. Franklin H, Rajan M, Tseng CL et al. Cost of lower-limb amputation in U.S. veterans with diabetes using health services data in fiscal years 2004 and 2010. J Rehabil Res Dev 2014; 51: 1325-1330.

22. Hicks CW, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Curr Diab Rep 2019; 19: 86.

23. Melissa S, Ulrike N, Thomas M. Amputation rates of the lower limb by amputation level-observational study using German national hospital discharge data from 2005 to 2015. BHC Health Serv Res. 2019; 19 (1): 163-171.

24. Flavia L, Marina M, Alessandra De B et al. Lower extremity amputations in person with and without diabetes in Italy: 2001-2010. Pros One 2014; 9(1) :e86405.

25. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study.Diabetologia.2008;51:747-755.

26. Takamura H, Hirao K, Kawai K, et al. Current Status of Cigarette Smoking in Diabetic Patients in Japan -The Importance of Early Smoker Education. J Japan Diab Soc 2011;54(10):779-785.

27. Heiner C, Herve A, Joeri G et al. Decreasing rates of major lower-extremity amputation in people with diabetes but not in those without: a nationwide study in Belgium. Diabetologia

2018; 61(9),1966- 1977.

28. Dinh T, Veves A. The influence of gender as a risk factor in diabetic foot ulceration. Wounds. 2008;20(5):127-131.

29. Hiroshi T, Koichi H, Koichi K et al. Current Status of Cigarette Smoking in Diabetes Patients in Japan: The Importance of Early Smoker Education. J Japan Diab Soc 2011; 54: 779-785.

Supporting information

Table S1. Diagnosis codes for diabetes.

Table S2. Medication codes for diabetes.

Table S3. Amputation codes.

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

Figure legends

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

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

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)

≧ 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)

NDB, National Database.

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

	Major LLA			Minor LLA		
Age groups, years	**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	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						
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						
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- standarized 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	10.4 - 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.

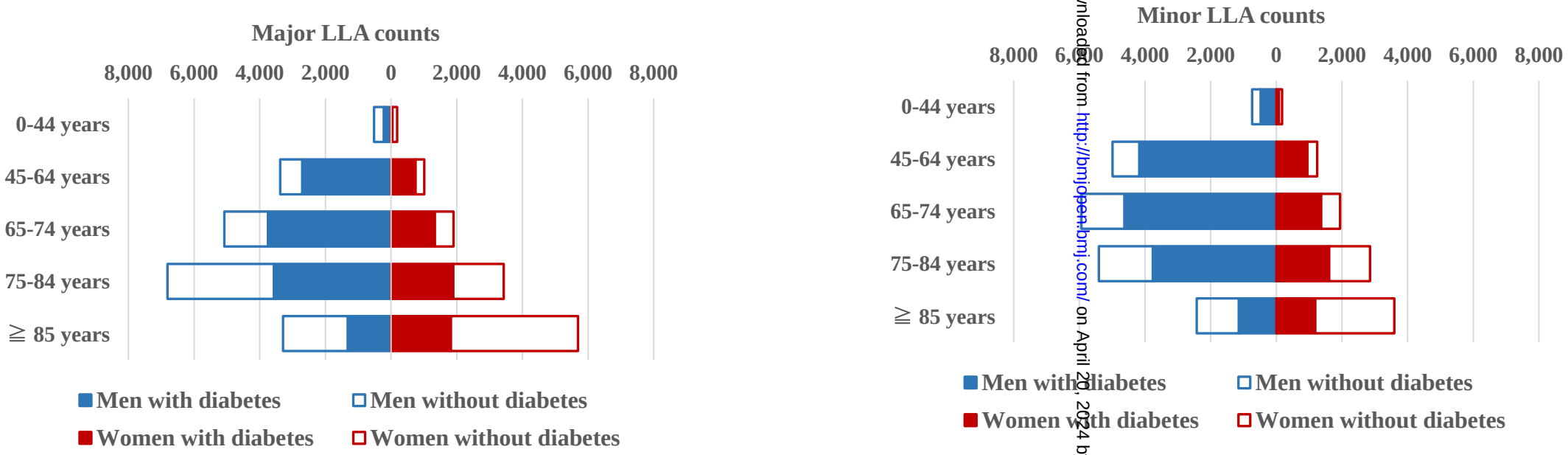


Figure 2. Time trend of age- and sex- standardized amputation rate: (A) major amputation; (B) minor amputation

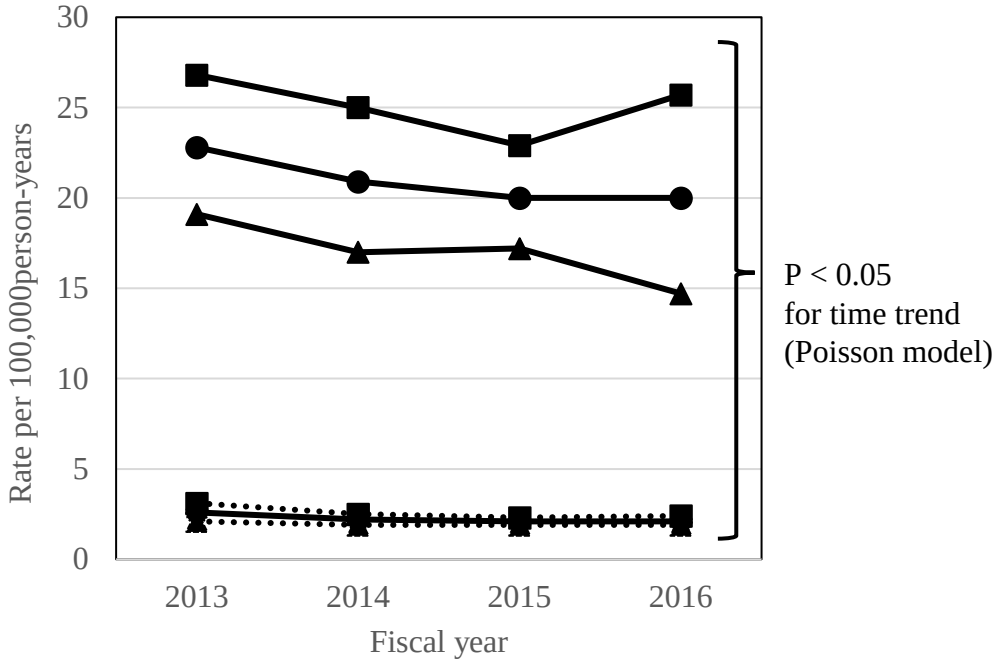


Fig.2-A Time trend of age- and sex- standardized major amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

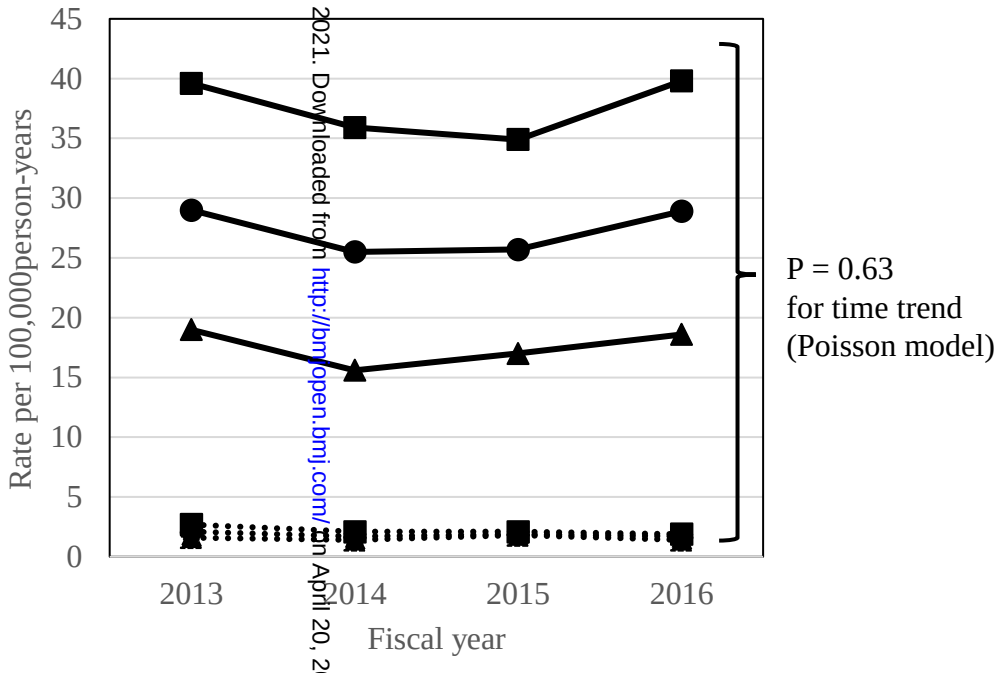


Fig.2-B Time trend of age- and sex- standardized minor amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women .

Supplementary Table S1 Diagnostic codes of diabetes.

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	E100	8830030
１型糖尿病・昏睡合併あり	Type 1 diabetes mellitus with coma	E100	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]	E100	8844026
１型糖尿病性低血糖性昏睡	Hypoglycemia in the context of type 1 diabetes mellitus	E100	8845065
１型糖尿病性ケトアシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus	E101	8830028
１型糖尿病・ケトアシドーシス合併あり	Type 1 diabetes mellitus with ketoacidosis	E101	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]	E101	8844025
劇症１型糖尿病	Fulminant type 1 diabetes mellitus	E101	8844045
１型糖尿病性アシドーシス	Diabetic ketoacidosis in type 1 diabetes mellitus	E101	8845044
１型糖尿病性アセトン血症	Type 1 diabetic acetone hyperlipoproteinemia	E101	8845045
１型糖尿病性腎症	Type 1 diabetic nephropathy	E102	8830031
１型糖尿病・腎合併症あり	Type 1 diabetes mellitus with diabetic nephropathy	E102	8841681
１型糖尿病性腎症第１期	Type 1 diabetic nephropathy phase 1	E102	8843983
１型糖尿病性腎症第２期	Type 1 diabetic nephropathy phase 2	E102	8843984
１型糖尿病性腎症第３期	Type 1 diabetic nephropathy phase 3	E102	8843985
１型糖尿病性腎症第３期Ａ	Type 1 diabetic nephropathy phase 3A	E102	8843986
１型糖尿病性腎症第３期Ｂ	Type 1 diabetic nephropathy phase 3B	E102	8843987
１型糖尿病性腎症第４期	Type 1 diabetic nephropathy phase 4	E102	8843988
１型糖尿病性腎症第５期	Type 1 diabetic nephropathy phase 5	E102	8843989

緩徐進行１型糖尿病・腎合併症あり	SPIDDM with nephropathy - [Slowly progressive insulin-dependent diabetes mellitus]	E102	8844028
１型糖尿病性腎硬化症	Type 1 diabetic nephrosclerosis	E102	8845058
１型糖尿病性腎不全	Type 1 diabetic kidney failure	E102	8845059
１型糖尿病性網膜症	Type 1 diabetic retinopathy	E102	8830033
１型糖尿病・眼合併症あり	Type 1 diabetes mellitus with eye complication	E102	8841682
１型糖尿病性黄斑浮腫	Type 1 diabetic macular edema	E102	8843982
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]	E102	8844024
１型糖尿病性白内障	Type 1 diabetic cataracts	E102	8844346
増殖性糖尿病性網膜症・１型糖尿病	Proliferative diabetic retinopathy, type 1 diabetes	E102	8844536
１型糖尿病黄斑症	Type 1 diabetic macular disease	E102	8845043
１型糖尿病性眼筋麻痺	Type 1 diabetic eye muscle paralysis	E102	8845049
１型糖尿病性虹彩炎	Type 1 diabetic iritis	E102	8845053
１型糖尿病性中心性網膜症	Type 1 diabetic central retinopathy	E102	8845064
１型糖尿病性ニューロパチー	Type 1 diabetic neuropathy	E104	8830032
１型糖尿病・神経学的合併症あり	Type 1 diabetes mellitus with neurological complications	E104	8841683
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]	E104	8844027
１型糖尿病性筋萎縮症	Type 1 diabetic muscular atrophy	E104	8845050
１型糖尿病性神経因性膀胱	Type 1 diabetic neuropathic bladder	E104	8845055
１型糖尿病性神経痛	Type 1 diabetic neuralgia	E104	8845056

1型糖尿病性自律神経ニューロパチー	Type 1 diabetic autonomic neuropathy	E104	8845057
1型糖尿病性多発ニューロパチー	Type 1 diabetic polyneuropathy	E104	8845062
1型糖尿病性単ニューロパチー	Type 1 diabetic mononeuropathy	E104	8845063
1型糖尿病性末梢神経障害	Type 1 diabetic peripheral neuropathy	E104	8845071
1型糖尿病・末梢循環合併症あり	Type 1 diabetes mellitus with peripheral circulation complications	E105	8841684
1型糖尿病性壊疽	Type 1 diabetic gangrene	E105	8843105
緩徐進行1型糖尿病・末梢循環合併症あり	SPIDDM with peripheral circulation complications - [Slowly progressive insulin-dependent diabetes mellitus]	E105	8844031
1型糖尿病性潰瘍	Type 1 diabetic ulcer	E105	8845046
1型糖尿病性血管障害	Type 1 diabetic vascular disease	E105	8845051
1型糖尿病性動脈硬化症	Type 1 diabetic atherosclerosis	E105	8845066
1型糖尿病性動脈閉塞症	Type 1 diabetic arterial occlusion	E105	8845067
1型糖尿病性末梢血管症	Type 1 diabetic peripheral vascular disease	E105	8845069
1型糖尿病性末梢血管障害	Type 1 diabetic peripheral vascular disease	E105	8845070
1型糖尿病・関節合併症あり	Type 1 diabetes mellitus with joint complications	E106	8841685
1型糖尿病・糖尿病性合併症あり	Type 1 diabetes mellitus with diabetic complications	E106	8841686
緩徐進行1型糖尿病・関節合併症あり	SPIDDM with joint complications - [Slowly progressive insulin-dependent diabetes mellitus]	E106	8844023
1型糖尿病性水疱	Type 1 diabetic blister	E106	8844626
1型糖尿病性浮腫性硬化症	Type 1 diabetic edematous sclerosis	E106	8844627
1型糖尿病性肝障害	Type 1 diabetic liver injury	E106	8845047

１型糖尿病性関節症	Type 1 diabetic arthropathy	E106	8845048
１型糖尿病性高コレステロール血症	Type 1 diabetic hypercholesterolemia	E106	8845052
１型糖尿病性骨症	Type 1 diabetic osteopathy	E106	8845054
１型糖尿病性精神障害	Type 1 diabetic mental disorder	E106	8845060
１型糖尿病性そう痒症	Type 1 diabetic pruritus	E106	8845061
１型糖尿病性皮膚障害	Type 1 diabetic skin disorder	E106	8845068
１型糖尿病性胃腸症	Type 1 diabetic gastroenteritis	E106	8845842
１型糖尿病・多発糖尿病性合併症あり	Type 1 diabetes mellitus with multiple diabetic complications	E107	8841687
緩徐進行１型糖尿病・多発糖尿病性合併症あり	SPIDDM with multiple diabetic complications - [Slowly progressive insulin-dependent diabetes mellitus]	E107	8844029
１型糖尿病・糖尿病性合併症なし	Type 1 diabetes mellitus without diabetic complecations	E109	8841688
緩徐進行１型糖尿病・糖尿病性合併症なし	SPIDDM without diabetic complications - [Slowly progressive insulin-dependent diabetes mellitus]	E109	8844030
インスリン抵抗性糖尿病	Insulin resistant diabetes mellitus	E11	2500001
２型糖尿病	Type 2 diabetes mellitus	E11	2500015
安定型糖尿病	Stable diabetes mellitus	E11	8830405
若年２型糖尿病	Juvenile type 2 diabetes	E11	8835244
２型糖尿病性昏睡	Type 2 diabetic coma	E110	8830041
２型糖尿病・昏睡合併あり	Type 2 diabetes mellitus with coma	E110	8841689

２型糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of type 2 diabetes mellitus	E116	8845094
２型糖尿病性ケトアシドーシス	Type 2 diabetic ketoacidosis	E117	8830040
２型糖尿病・ケトアシドーシス合併あり	Type 2 diabetes mellitus with ketoacidosis	E111	8841690
２型糖尿病性アシドーシス	Type 2 diabetic acidosis	E117	8845073
２型糖尿病性アセトン血症	Type 2 diabetic acetone hyperlipoproteinemia	E117	8845074
２型糖尿病性腎症	Type 2 diabetic nephropathy	E114	8830042
２型糖尿病・腎合併症あり	Type 2 diabetes mellitus with diabetic nephropathy	E111	8841691
２型糖尿病性腎症第１期	Type 2 diabetic nephropathy phase 1	E114	8843991
２型糖尿病性腎症第２期	Type 2 diabetic nephropathy phase 2	E114	8843992
２型糖尿病性腎症第３期	Type 2 diabetic nephropathy phase 3	E114	8843993
２型糖尿病性腎症第３期Ａ	Type 2 diabetic nephropathy phase 3A	E114	8843994
２型糖尿病性腎症第３期Ｂ	Type 2 diabetic nephropathy phase 3B	E114	8843995
２型糖尿病性腎症第４期	Type 2 diabetic nephropathy phase 4	E114	8843996
２型糖尿病性腎症第５期	Type 2 diabetic nephropathy phase 5	E114	8843997
２型糖尿病性腎硬化症	Type 2 diabetic nephrosclerosis	E112	8845087
２型糖尿病性腎不全	Type 2 diabetic kidney failure	E112	8845088
２型糖尿病性網膜症	Type 2 diabetic retinopathy	E113	8830045
２型糖尿病・眼合併症あり	Type 2 diabetes mellitus with eye complications	E119	8841692
２型糖尿病性黄斑浮腫	Type 2 diabetic macular edema	E113	8843990
２型糖尿病性白内障	Type 2 diabetic cataracts	E113	8844347
増殖性糖尿病性網膜症・２型糖尿病	Proliferative diabetic retinopathy, type 2 diabetes	E113	8844537

2型糖尿病黄斑症	Type 2 diabetic macular disease	E11.3	8845072
2型糖尿病性眼筋麻痺	Type 2 diabetic eye muscle paralysis	E11.3	8845078
2型糖尿病性虹彩炎	Type 2 diabetic iritis	E11.3	8845082
2型糖尿病性中心性網膜症	Type 2 diabetic central retinopathy	E11.3	8845093
2型糖尿病性ニューロパチー	Type 2 diabetic neuropathy	E11.4	8830043
2型糖尿病性ミオパチー	Type 2 diabetic myopathy	E11.4	8830044
2型糖尿病・神経学的合併症あり	Type 2 diabetes mellitus with neurological complications	E11.4	8841693
2型糖尿病性筋萎縮症	Type 2 diabetic muscular atrophy	E11.4	8845079
2型糖尿病性神経因性膀胱	Type 2 diabetic neuropathic bladder	E11.4	8845084
2型糖尿病性神経痛	Type 2 diabetic neuralgia	E11.4	8845085
2型糖尿病性自律神経ニューロパチー	Type 2 diabetic autonomic neuropathy	E11.4	8845086
2型糖尿病性多発ニューロパチー	Type 2 diabetic polyneuropathy	E11.4	8845091
2型糖尿病性単ニューロパチー	Type 2 diabetic mononeuropathy	E11.4	8845092
2型糖尿病性末梢神経障害	Type 2 diabetic peripheral neuropathy	E11.4	8845100
2型糖尿病・末梢循環合併症あり	Type 2 diabetes mellitus with peripheral circulation complications	E11.5	8841694
2型糖尿病性壊疽	Type 2 diabetic gangrene	E11.5	8843106
2型糖尿病性潰瘍	Type 2 diabetic ulcer	E11.5	8845075
2型糖尿病性血管障害	Type 2 diabetic vascular disease	E11.5	8845080
2型糖尿病性動脈硬化症	Type 2 diabetic atherosclerosis	E11.5	8845095
2型糖尿病性動脈閉塞症	Type 2 diabetic arterial occlusion	E11.5	8845096
2型糖尿病性末梢血管症	Type 2 diabetic peripheral vascular disease	E11.5	8845098

２型糖尿病性末梢血管障害	Type 2 diabetic peripheral vascular disease	E11	8845099
２型糖尿病・関節合併症あり	Type 2 diabetes mellitus with joint complications	E11	8841695
２型糖尿病・糖尿病性合併症あり	Type 2 diabetes mellitus with diabetic complications	E11	8841696
２型糖尿病性水疱	Type 2 diabetic blister	E11	8844628
２型糖尿病性浮腫性硬化症	Type 2 diabetic edematous sclerosis	E11	8844629
２型糖尿病性肝障害	Type 2 diabetic liver injury	E11	8845076
２型糖尿病性関節症	Type 2 diabetic arthropathy	E11	8845077
２型糖尿病性高コレステロール血症	Type 2 diabetic hypercholesterolemia	E11	8845081
２型糖尿病性骨症	Type 2 diabetic osteopathy	E11	8845083
２型糖尿病性精神障害	Type 2 diabetic mental disorder	E11	8845089
２型糖尿病性そう痒症	Type 2 diabetic pruritus	E11	8845090
２型糖尿病性皮膚障害	Type 2 diabetic skin disorder	E11	8845097
２型糖尿病性胃腸症	Type 2 diabetic gastroenteritis	E11	8848108
２型糖尿病・多発糖尿病性合併症あり	Type 2 diabetes mellitus with multiple diabetic complications	E11	8841697
２型糖尿病・糖尿病性合併症なし	Type 2 diabetes mellitus without diabetic complecations	E11	8841698
栄養不良関連糖尿病	Malnutrition-related diabetes mellitus	E12	2500037
膵性糖尿病	Pancreatic diabetes mellitus	E13	2500024
ステロイド糖尿病	Steroid diabetes mellitus	E13	2509003
二次性糖尿病	Secondary diabetes mellitus	E13	2509004
ウイルス性糖尿病	Viral diabetes mellitus	E13	8830756
薬剤性糖尿病	Drug-induced diabetes mellitus	E13	8840710

ウイルス性糖尿病・昏睡合併あり	Viral diabetes mellitus with coma	E13[illegible]	8843122
膵性糖尿病・昏睡合併あり	Pancreatic diabetes mellitus with coma	E13[illegible]	8843377
ステロイド糖尿病・昏睡合併あり	Steroid diabetes mellitus with coma	E13[illegible]	8843390
二次性糖尿病・昏睡合併あり	Secondary diabetes mellitus with coma	E13[illegible]	8843450
薬剤性糖尿病・昏睡合併あり	Drug-induced diabetes mellitus with coma	E13[illegible]	8843621
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[illegible]	8843121
膵性糖尿病・ケトアシドーシス合併あり	Pancreatic diabetes mellitus with ketoacidosis	E13[illegible]	8843376
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[illegible]	8843389
二次性糖尿病・ケトアシドーシス合併あり	Secondary diabetes mellitus with ketoacidosis	E13[illegible]	8843449
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[illegible]	8843620
ウイルス性糖尿病・腎合併症あり	Viral diabetes mellitus with renal complications	E13[illegible]	8843124
膵性糖尿病・腎合併症あり	Pancreatic diabetes mellitus with renal complications	E13[illegible]	8843379
ステロイド糖尿病・腎合併症あり	Steroid diabetes mellitus with renal complications	E13[illegible]	8843392
二次性糖尿病・腎合併症あり	Secondary diabetes mellitus with renal complications	E13[illegible]	8843452
薬剤性糖尿病・腎合併症あり	Drug-induced diabetes mellitus with renal complications	E13[illegible]	8843623
ウイルス性糖尿病・眼合併症あり	Viral diabetes mellitus with eye complications	E13[illegible]	8843120
膵性糖尿病・眼合併症あり	Pancreatic diabetes mellitus with eye complications	E13[illegible]	8843375
ステロイド糖尿病・眼合併症あり	Steroid diabetes mellitus with eye complications	E13[illegible]	8843388

二次性糖尿病・眼合併症あり	Secondary diabetes mellitus with eye complications	E133	8843448
薬剤性糖尿病・眼合併症あり	Drug-induced diabetes mellitus with eye complications	E133	8843619
ウイルス性糖尿病・神経学的合併症あり	Viral diabetes mellitus with neurological complications	E134	8843123
膵性糖尿病・神経学的合併症あり	Pancreatic diabetes mellitus with neurological complications	E134	8843378
ステロイド糖尿病・神経学的合併症あり	Steroid diabetes mellitus with neurological complications	E134	8843391
二次性糖尿病・神経学的合併症あり	Secondary diabetes mellitus with neurological complications	E134	8843451
薬剤性糖尿病・神経学的合併症あり	Drug-induced diabetes mellitus with neurological complications	E134	8843622
ウイルス性糖尿病・末梢循環合併症あり	Viral diabetes mellitus with peripheral circulatory complications	E135	8843128
膵性糖尿病・末梢循環合併症あり	Pancreatic diabetes mellitus with peripheral circulatory complications	E135	8843383
ステロイド糖尿病・末梢循環合併症あり	Steroid diabetes mellitus with peripheral circulatory complications	E135	8843396
二次性糖尿病・末梢循環合併症あり	Secondary diabetes mellitus with peripheral circulatory complications	E135	8843456
薬剤性糖尿病・末梢循環合併症あり	Drug-induced diabetes mellitus with peripheral circulatory complications	E135	8843627
ウイルス性糖尿病・糖尿病性合併症あり	Viral diabetes mellitus with diabetic complications	E136	8843126

膵性糖尿病・糖尿病性合併症あり	Pancreatic diabetes mellitus with diabetic complications	E136	8843381
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
二次性糖尿病・糖尿病性合併症あり	Secondary diabetes mellitus with diabetic complications	E136	8843454
薬剤性糖尿病・糖尿病性合併症あり	Drug-induced diabetes mellitus with diabetic complications	E136	8843625
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	E137	8843125
膵性糖尿病・多発糖尿病性合併症あり	Pancreatic diabetes mellitus with multiple diabetic complications	E137	8843380
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	E137	8843393
二次性糖尿病・多発糖尿病性合併症あり	Secondary diabetes mellitus with multiple diabetic complications	E137	8843453
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	E137	8843624
ウイルス性糖尿病・糖尿病性合併症なし	Viral diabetes mellitus without diabetic complications	E139	8843127
膵性糖尿病・糖尿病性合併症なし	Pancreatic diabetes mellitus without diabetic complications	E139	8843382
ステロイド糖尿病・糖尿病性合併症なし	Steroid diabetes mellitus without diabetic complications	E139	8843395

二次性糖尿病・糖尿病性合併症なし	Secondary diabetes mellitus without diabetic complications	E139	8843455
薬剤性糖尿病・糖尿病性合併症なし	Drug-induced diabetes mellitus without diabetic complications	E139	8843626
糖尿病	Diabetes mellitus	E14	2500013
糖尿病合併症	Diabetic complications	E14	2507028
糖尿病性昏睡	Diabetic coma	E140	2502006
糖尿病性低血糖性昏睡	Hypoglycemic coma in the context of diabetes mellitus	E140	8838076
糖尿病性アシドーシス	Diabetic acidosis	E141	2501002
糖尿病性アセトン血症	Diabetic acetonemia	E141	2501003
糖尿病性ケトアシドーシス	Diabetic ketoacidosis	E141	2501005
糖尿病性腎症	Diabetic nephropathy	E142	2503005
糖尿病性腎不全	Diabetic renal failure	E142	2503007
糖尿病性腎硬化症	Diabetic nephrosclerosis	E142	8838071
糖尿病性虹彩炎	Diabetic iritis	E143	2504004
糖尿病性中心性網膜症	Diabetic central retinopathy	E143	2504005
糖尿病性白内障	Diabetic cataract	E143	2504006
増殖性糖尿病性網膜症	Proliferative diabetic retinopathy	E143	2504010
糖尿病黄斑症	Diabetic maculopathy	E143	2504012
糖尿病網膜症	Diabetic retinopathy	E143	2504013
糖尿病性眼筋麻痺	Diabetic ophthalmoplegia	E143	8838065
糖尿病黄斑浮腫	Diabetic macular edema	E143	8844089
糖尿病性神経痛	Diabetic neuralgia	E144	2505011
糖尿病性末梢神経障害	Diabetic peripheral neuropathy	E144	2505018

糖尿病性筋萎縮症	Diabetic muscular atrophy	E144	2505021
糖尿病性神経因性膀胱	Diabetic neuropathic bladder	E144	8838069
糖尿病性自律神経ニューロパチー	Diabetic autonomic neuropathy	E144	8838070
糖尿病性多発ニューロパチー	Diabetic polyneuropathy	E144	8838074
糖尿病性単ニューロパチー	Diabetic mononeuropathy	E144	8838075
糖尿病性ニューロパチー	Diabetic neuropathy	E144	8838078
糖尿病足病変	Diabetic foot lesion	E144	8848634
糖尿病性神経障害性疼痛	Diabetic neuropathic pain	E144	8848768
糖尿病性壊疽	Diabetic gangrene	E145	2506006
糖尿病性動脈閉塞症	Diabetic arterial occlusion	E145	2506011
糖尿病性潰瘍	Diabetic ulcer	E145	8838063
糖尿病性血管障害	Diabetic angiopathy	E145	8838066
糖尿病性動脈硬化症	Diabetic arteriosclerosis	E145	8838077
糖尿病性末梢血管症	Diabetic peripheral vascular disease	E145	8838079
糖尿病性末梢血管障害	Diabetic peripheral vascular disease	E145	8838080
糖尿病足壊疽	Diabetic foot gangrene	E145	8848632
糖尿病足潰瘍	Diabetic foot ulcer	E145	8848633
糖尿病性関節症	Diabetic arthropathy	E146	2507025
糖尿病性皮膚障害	Diabetic skin disorders	E146	2507029
糖尿病性肝障害	Diabetic liver injury	E146	8838064
糖尿病性高コレステロール血症	Diabetic hypercholesterolemia	E146	8838067
糖尿病性骨症	Diabetic osteopathy	E146	8838068
糖尿病性精神障害	Diabetic mental disorder	E146	8838072
糖尿病性そう痒症	Diabetic pruritus	E146	8838073

糖尿病性水疱	Diabetic blister	E146	8844652
糖尿病性浮腫性硬化症	Diabetic edematous sclerosis	E146	8844653
高血糖高浸透圧症候群	Hyperglycemia hyperosmolarity syndrome	E146	8845128
糖尿病・糖尿病性合併症なし	Diabetes mellitus without diabetic complications	E149	8843439
非糖尿病性低血糖性昏睡	Hypoglycemic coma not in the context of diabetes mellitus	E151	8839324
果糖尿症	Levulosuria	E741	8831401
本態性果糖尿症	Essential levulosuria	E741	8840104
良性果糖尿症	Benign levulosuria	E741	8841021
腎性糖尿	Renal glycosuria	E743	2714002
青銅性糖尿病	Bronze diabetes mellitus	E83	8835941
膵全摘後二次性糖尿病	Secondary diabetes after pancreatectomy	E895	8835685
１型糖尿病合併妊娠	Pregnancy with type 1 diabetes	O240	8830029
２型糖尿病合併妊娠	ith type 2 diabetes	O241	8830039
妊娠糖尿病	Pregnancy diabetes mellitus	O244	6489003
妊娠中の糖尿病	Overt diabetes in pregnancy	O245	8838621
妊娠中の耐糖能低下	Impaired glucose tolerance in pregnancy	O998	8838619
妊娠糖尿病母体児症候群	Gestational diabetes maternal syndrome	P700	8838633
糖尿病母体児	Diabetes maternal infant	P701	8838081
新生児一過性糖尿病	Neonatal transient diabetes mellitus	P704	7751001
新生児糖尿病	Neonatal diabetes mellitus	P702	7751002
新生児一過性高血糖症	Neonatal transient hyperglycemia	P708	8844233
境界型糖尿病	Borderline type diabetes mellitus	R730	2500031
耐糖能異常	Impaired glucose tolerance	R730	2713009

化学的糖尿病	Chemical diabetes mellitus	R73H	8831132
潜在性糖尿病	Latent diabetes mellitus	R73H	8836104
前糖尿病	Pre-diabetes mellitus	R73H	8836563
高血糖症	Hyperglycemia	R73H	8833419
一過性糖尿	Transient diabetes mellitus	R81	7915002
五炭糖尿症	L-Xylulosuria	R81	7915003
高血糖性糖尿	Hypoglycemic glycosuria	R81	8833420
食事性糖尿	Dietary glycosuria	R81	8834843
情動性糖尿	Emotional glycosuria	R81	8835464
正常血糖性糖尿	Euglycemic glycosuria	R81	8835871
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

	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**	7,695,811	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**	6,276,856	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

,

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	17, Table3 17 20, Table4
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	25
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
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.