Incidence of Idiopathic Cardiomyopathy in Type 2 Diabetes Patients: Age, Sex, and Urbanization status stratified Analysis

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Original investigation

Keywords: Type 2 Diabetes Mellitus, Cardiomyopathies, Cohort Studies, Epidemiology

Posted Date: April 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-23178/v1

Version of Record: A version of this preprint was published on October 14th, 2020. See the published version at https://doi.org/10.1186/s12933-020-01144-y.

Abstract

Background

There are limited data regarding epidemiology of diabetes and idiopathic cardiomyopathy. We investigated the overall and age, sex, and urbanization-specific incidence and relative hazard of idiopathic cardiomyopathy in association with type 2 diabetes in Taiwan.

Methods

A total of 474,268 type 2 diabetes patients were identified from ambulatory care and inpatient claims in 2007–2009 from Taiwan's National Health Insurance (NHI) database, and 474,266 age-, sex- and diagnosis date-matched controls were randomly selected from the registry of NHI beneficiaries. All study subjects were linked to ambulatory care and inpatient claims (up to the end of 2016) to identify possible diagnosis of idiopathic cardiomyopathy. The person-year approach with Poisson assumption was used to estimate the incidence; and Cox proportional hazard regression model with Fine and Gray's method was used to estimate the relative hazards of idiopathic cardiomyopathy in relation to type 2 diabetes.

Results

The overall incidence of idiopathic cardiomyopathy for men and women patients, respectively, was 4.26 and 3.34/10,000 person-years, which were higher than the corresponding men and women controls (2.40 and 1.69 per 10,000 person-years). Compared with control group, type 2 diabetes patients were significantly associated with an increased hazard of idiopathic cardiomyopathy (adjusted hazard ratio [aHR] 1.39, 95% confidence interval [CI] 1.28–1.51] in all age and sex stratifications except in those aged > 64 years. Type 2 diabetes aged < 45 years confronted the greatest increase in hazard of idiopathic cardiomyopathy, with an aHR of 2.36 (95% CI 1.68–3.32) and 3.72 (95% CI 1.86–7.44) for men and women, respectively. Patients living in rural areas tended to have higher HRs of idiopathic cardiomyopathy.

Conclusions

In Taiwan, diabetes increased the risk of idiopathic cardiomyopathy in both sexes as well as in all age groups except in those > 64 years. Younger patients and those living in rural areas were especially vulnerable to have higher HRs of idiopathic cardiomyopathy.

Background

Coronary heart disease is the most common cause of cardiovascular complications in diabetes [1], but still there is a myocardial disorder in which the heart muscle is structurally and functionally abnormal in

the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to explain the observed myocardial abnormality which might also be associated with diabetes [2]. Diabetic cardiomyopathy is characterized by lipid accumulation in cardiomyocytes, fetal gene reactivation, and left ventricular hypertrophy, which together result in contractile dysfunction [3].

The epidemiology of idiopathic cardiomyopathy in diabetes patients has not been clear since there is lack of large study outcomes from different diabetic populations. Previous studies were case-control studies [4, 5] or cross-sectional survey [6] with regional hospital- [4], or county [6]-based rather than the prospective population-based study design. In a cross-sectional study, the prevalence of diabetic cardiomyopathy was reported to be 1.1% in Olmsted County, Minnesota, USA [6] but there has been, to our best knowledge, no study yet estimated the incidence of diabetic cardiomyopathy at the population-based level with age and sex stratifications. Some studies [4, 5] did not exclude patients with diagnosis of hypertension which might also have predisposed to cardiomyopathy. In one study, the authors did not exclude ischemic heart disease and valvular heart disease in the control group [5], which might have affected the results of subsequent relative risk estimation. This same study [5] selected diagnoses of diabetes and cardiomyopathy from the US Nationwide Inpatient Sample which might have missed some patients with milder symptoms not admitted to the hospital. In addition to the above-mentioned methodological limitations, the urban-rural difference in incidence and relative risk of cardiomyopathy in relation to diabetes also have not been examined, given that the urban-rural difference was observed in some diabetes related complications [7].

The aim of our study was to use a nationally representative type 2 diabetes patient cohort selected from Taiwan's National Health Insurance (NHI) claims to investigate the incidence of idiopathic cardiomyopathy in association with type 2 diabetes, with particular interest in various age, sex and urbanization status stratified analyses.

Methods

Study design and subjects

By the end of 1995, approximately 96% of total Taiwanese population had enrolled in NHI Program [8], a universal health program which has been implemented by NHI Administration under the jurisdiction of Ministry of Health and Welfare. NHI Administration has had contracted 97% of hospitals and 90% of clinics all over Taiwan [9]. In addition, the NHI Administration performs quarterly expert reviews on a random sample for every 50 to 100 ambulatory and inpatient claims to ensure the accuracy of claim files so that information available is considered to be complete and accurate [10]. We used data of ambulatory care claims (2006–2016), inpatient claims (2006–2016), registry for beneficiaries (2007–2009), and death certificate registry (2007–2016) for this study. The ambulatory care claims record all outpatient (including emergency room visit) related information including personal identification number (PIN), date of birth, sex, and date of outpatient visit with a maximum of three leading diagnostic codes while the inpatient claims include all hospitalization information including PIN, date of birth, sex, date of

admission and discharge, with a maximum of five leading discharge diagnostic codes and four operation procedure codes. All the dataset can be inter-linked through PIN. The study proposal was approved by the Institutional Review Board of National Cheng Kung University Hospital (A-EX-104-008).

An individual was classified as a type 2 diabetic patient if he or she had an initial type 2 diabetes diagnosis (ICD-9-CM 250.x0, ICD-9-CM 250.x2 or ICD-10-CM E11) in ambulatory care and inpatient claims between 2007 and 2009 and then experienced another one or more diagnosis within the subsequent 12 months. Additionally, the first and last outpatient visits during the 12-month period had to be separated by at least 30 days to avoid accidental inclusion of miscoded patients. Initial diabetic cohort consisted of 1,431,903 patents. We excluded 4,023 subjects with missing information of sex or year of birth, 31,549 patients with type 1 diabetes, and 2,206 patients with gestational diabetes diagnosis between 1 January 2006 and the date of first type 2 diabetes diagnosis in 2007–2009 (i.e., the index date). We also excluded some patients recorded with cardiovascular risk factors for cardiomyopathy in either ambulatory care or inpatient claims before index date. After further excluding 284,255 patients with prior histories of ischemic heart disease, 628,713 patients with prior histories of hypertensive disease, 1,848 patients with prior histories of rheumatic heart disease, 4,025 patients with prior histories of valvular heart disease, 452 patients with prior histories of congenital heart disease, 51 patients with prior histories of acute myocarditis and 513 patients with prior histories of cardiomyopathy, the final diabetic cohort consisted of 474,268 patients (Fig. 1). Respective ICD-9 and ICD-9 codes are shown in Table 1.

Our control group was collected from registry of beneficiaries which contains information of PIN, date of birth, sex, geographic area of each member's NHI unit, and date of enrollment and withdrawal from NHI each time. Between 2007 and 2009, there were 23,328,994 individuals in the registry of beneficiaries. We excluded 1,029,105 subjects with missing information of sex or year of birth, 1,890,133 patients with either type 1 or type 2 diabetes, 168,681 patients with gestational diabetes, 1,041,366 patients with prior histories of ischemic heart disease, 1,880,906 patients with prior histories of hypertensive disease, 29,739 patients with prior histories of rheumatic heart disease, 199,060 patients with prior histories of valvular heart disease, 121,996 patients with prior histories of congenital heart disease, 1,227 patients with prior histories of acute myocarditis, 3,187 patients with prior histories of cardiomyopathy recorded in either ambulatory care or inpatient claims between 1 January 2006 and the index date (Fig. 1).

Using the individual matching technique, we randomly selected 1 control by matching 1 type 2 diabetes patient on age, sex, and the index date of type 2 diabetes diagnosis, totally 474,266 controls were selected from the 16,963,594 potential controls. The index date for subjects in the control group was the same as his/her matched type 2 diabetes.

The difference in time between the index date and the date of birth were set as the age of each study subject. We grouped the township/city of each member's NHI unit, either the beneficiaries' residential area or location of their employment, into two urbanization statuses (urban and rural) according to the classification scheme by Liu et al [11].

Follow-up, study end-points, and covariate

With the unique PIN, we linked study subjects to both ambulatory and inpatient claims from the index date to the last day of 2016 to identify the primary or secondary diagnostic codes of the following idiopathic cardiomyopathy diagnoses as the end point of this study: other primary cardiomyopathies (ICD-9-CM: 425.4), hypertrophic obstructive cardiomyopathy (ICD-9CM: 425.1; ICD-10-CM: I42.1), dilated cardiomyopathy (ICD-10-CM: I42.0), other hypertrophic cardiomyopathy (ICD-10-CM: I42.2) or other restrictive cardiomyopathy (ICD-10-CM: I42.5). Each study subject was followed from the index date to date of idiopathic cardiomyopathy occurrence, death censoring, or the last day of 2016, whichever came first. The information on various cardiovascular risk factors for cardiomyopathy including ischemic heart disease, hypertensive disease, rheumatic heart disease, valvular heart disease, congenital heart disease, acute myocarditis were retrieved from ambulatory care and inpatient claims between index date and date of end-of-follow-up, and were considered as potential confounders.

Statistical Analysis

The age- and sex-specific incidence density estimate was calculated with person-years as the denominator under the Poisson assumption. To assess the independent association of type 2 diabetes with the risk cardiomyopathy, we conducted Cox proportional hazard regression model with Fine and Gray's method and adjusted age, sex, urbanization status and cardiovascular risk factors simultaneously in the model. Adjustment for the geographic variables may help reduce the presence of an urban-rural difference in accessibility to medical health services in Taiwan [12]. We adjusted cardiovascular risk factors that occurred after baseline type 2 diabetes, which might results in a potential for over-adjustment of these comorbidities as some of these cardiovascular risk factors could play a role of mediator located on the causal pathway from type 2 diabetes to cardiomyopathy. To address this potential problem, we conducted a sensitivity analysis that removed adjustment for these confounders.

All statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC). A P value < 0.05 was considered statistically significant.

Results

The mean age ± SD of the type 2 diabetic and control group was similar at 55.84 ± 13.20 years, and male predominant. The urban-rural differences for the two groups were also comparable. Type 2 diabetes patients tended to have higher prevalence of ischemic heart disease and hypertensive disease, but comparable prevalence of rheumatic, valvular, congenital heart diseases and acute myocarditis after the index date. The median time of follow-up was 9.15 ± 1.36 years and 8.91 ± 1.68 years in control and type 2 diabetes group, respectively (Table 2).

The overall and age- and sex-specific incidence densities and hazard ratios (HRs) of idiopathic cardiomyopathy are presented in Table 2. The overall incidence density for men and women with type 2 diabetes was 4.26 and 3.34 per 10,000 person-years, respectively while the corresponding figures for control men and women were lower at 2.40 and 1.69 per 10,000 person-years. In both groups, incidence density of idiopathic cardiomyopathy increased with age, and the highest incidence density was found in

the age group > 64 years irrespective of age and diabetic status. Generally, the age- and sex-specific incidence density of idiopathic cardiomyopathy in type 2 diabetes patients was higher than those of control subjects, but the difference of incidences in both groups became narrower with increasing age.

Men and women with type 2 diabetes were observed to experience increased hazard of idiopathic cardiomyopathy with crude HR of 1.73 [95% confidence interval (CI) 1.56–1.91] and HR: 1.93 (95% CI 1.69–2.21), respectively. Further adjustment for age, sex, urbanization status, and cardiovascular risk factors attenuated the HRs to 1.33 (95% CI 1.20–1.48) and 1.50 (95% CI 1.30–1.73) in male and female type 2 diabetes, respectively. Because of a significant interaction of type 2 diabetes status with age ($P < 0.0001$) for both men and women, we performed stratified analysis to estimate the age-specific HR for each sex. The type 2 diabetes patients aged < 45 years had the highest adjusted HRs [aHR: 2.36 (95% CI 1.68–3.32) in men and aHR: 3.72 (95% CI 1.86–7.44) in women]. The HRs attenuated with increasing age and it became insignificant after adjustment for covariates (Table 3) in those over aged 64 years old for both men and women.

As there was also a significant interaction of type 2 diabetes status with urbanization status ($P < 0.0001$) for both men and women, we performed stratified analyses to estimate the urbanization status-specific HRs for each sex. (Table 4). A higher incidence of idiopathic cardiomyopathy was observed in both men and women from the rural areas than in those from the urban areas irrespective of their diabetes status. The adjusted HR of idiopathic cardiomyopathy was slightly higher in men of rural area (HR: 1.39; 95% CI 1.15–1.68) than those of urban are (HR: 1.31; 95% CI 1.15–1.49). Similarly, the adjusted HRs of cardiomyopathy was higher in women from rural areas than those urban counterparts (HR 1.70 vs. 1.38).

Discussion

In our study, the overall incidence densities of idiopathic cardiomyopathy were higher in type 2 diabetes patients than in controls. The incidence increased with age, and those aged > 64 had the highest incidence in both groups. Furthermore, men tended to have higher incidence rate than women regardless of diabetic status. Our data also demonstrated that diabetes increased the risk of idiopathic cardiomyopathy, and those aged < 45 had the highest increased risk. The relative risk attenuated with increasing age, and it became insignificant in those > 64 years old in both men and women subjects.

The incidence estimates of idiopathic cardiomyopathy in the control group in our study was lower than that of previous general population-based studies from Minnesota, USA [13], and Japan [14], higher than that of western Denmark [15], and comparable to that of Qatar study between 1996–2002 [16]. Men were reported to have higher incidence of cardiomyopathy [14] like the results of ours. Direct comparisons of the incidence densities of idiopathic cardiomyopathy between ours and that of previous general population-based studies might be inappropriate because of dissimilarity in baseline demographic status, variations in methods of outcome ascertainment, and length of follow-up.

To the best of knowledge, it is the first population-based study that evaluated the incidence of idiopathic cardiomyopathy in diabetes patients. In Olmsted County, Minnesota, USA, the authors estimated that the prevalence of diabetic cardiomyopathy was 1.1% in community population and 16.9% in diabetes patients [6]. Annual hospital discharge rate of idiopathic cardiomyopathy in the Nationwide Inpatient Sample was ascertained to be quite high at around 76 per 10,000 diabetes patients in the USA [5]. Inclusion of patients with hypertension, which is also a predisposing factor of cardiomyopathy, as well as inability to identify multiple hospitalizations by the same individual in their study, might have overestimated the discharge rate of cardiomyopathy.

In our study, the crude estimate of HR of idiopathic cardiomyopathy in diabetes patients (HR: 1.80) was comparable with univariate odd ratio (OR) of idiopathic cardiomyopathy in Bertoni et al.'s study (1.75) [5], but lower than OR of Coughlin's Washington DC Dilated Cardiomyopathy Study in the USA (2.6) [4]. Bertoni and our studies used ICD codes for outcome ascertainment while Coughlin et al. restricted their cases to echocardiographic evidence of regional wall motion abnormality, ventricular dilatation and hypokinesia. Such difference in definition of outcome might have affected the results. We adjusted all cardiovascular risk factors predisposing to cardiomyopathy in our analysis while Bertoni et al., adjusted only diabetes and hypertension apart from age, sex, race, and income in their model. Consequently, the adjusted HR of our estimates was lower than the adjusted OR of Bertoni et al.'s [5]. The HR became insignificant in both men and women after 64 years in our study. Two previous case-control studies recruiting subjects older than 60 years of age also found out that the association of idiopathic dilated cardiomyopathy with diabetes was of only borderline significance ($p < 0.10$) [17]. The insignificant association between diabetes and idiopathic cardiomyopathy in the elderly population may have highlighted a greater association between age and cardiomyopathy. In addition, subsequent sensitivity analysis in our study showed that the HRs of idiopathic cardiomyopathy only slightly elevated, suggesting no important mediation by those cardiovascular comorbidities for the association between diabetes and idiopathic cardiomyopathy.

The pathophysiological mechanisms of diabetic cardiomyopathy have not been clearly elucidated. Oxidative stress induced by hyperglycemia leads to reduced myocardial contractility and fibrosis [18]. Insulin resistance and subsequent hyperinsulinemia are associated with reduced bioavailability of nitric oxide [19] and increased incidence and progression of coronary artery calcification [20]. Metabolic abnormalities involving endoplasmic reticulum stress, impaired handling, and mitochondrial dysfunction are also associated with pathogenesis of diabetic cardiomyopathy [3]. Diabetes associated lipotoxicity reduces normal physiological autophagy and impairs insulin signaling, which leads to structural and morphological alterations and impaired myocardial performance [21]. Cardiac automatic neuropathy [22], activation of intracardiac renin-angiotensin-aldosterone system [23], and maladaptive immune responses [24] may also contribute subsequent cardiac dysfunction.

Urban-rural differences in the incidence and relative risk of idiopathic cardiomyopathy in diabetes patients were rarely discussed before. Rural patients in Taiwan were older and had more chronic diseases than urban and suburban counterparts [25], but rural diabetes patients were less likely to receive

guideline-recommended examinations or tests [26]. Although the universal health insurance has largely removed financial barriers to health care, the urban-rural disparity in prevalence of diabetic complications still exists after nearly two decades of implementation of the NHI program in Taiwan [27]. Further studies are necessary to detect the definite underlying etiologies and measures to eliminate such urban-rural difference in various diabetic complications, including idiopathic cardiomyopathy.

There were several methodological strengths in our study. First, both type 2 diabetes and control groups were retrieved from the NHI database, which is population based and is highly representative, causing little possibility of selection biases. In addition, there is also little likelihood of non-response and lost to follow-up of cohort members. Information of disease was obtained from medical claims rather than self-reports, which may largely reduce the chance of recall bias. Second, one of the potential advantages of using insurance claim datasets in clinical research is easy access to the longitudinal records for a large sample of patients from different geographic areas [28]. Third, such a large number of study subjects also made it possible for us to make age- and sex-stratified analyses without compromising the statistical power. Fourth, since the diagnostic procedures of cardiomyopathy can be dependent on medical resources and physicians' behavior, adjustment for urbanization status made it possible in reducing such urbanization-related confounding.

In spite of the above strengths, several limitations should be noted in our study. First, exclusive reliance on the claim data might have resulted in potential disease misclassification bias in our study. Previous study reported the accuracy of a single diabetes diagnosis in the NHI claim data was 74.6% [29], but we used at least two diagnoses of type 2 diabetes with the first and the last visits > 30 days apart, which might have largely reduced the likelihood of disease misclassification. Despite that, the control group might still have been mixed up with new onset or undiagnosed diabetes. Such misclassification bias, however, was likely to be non-differential, which tends to underestimate rather overestimate the true relative risks [30]. Second, a number of potential confounders including BMI, duration and treatment regimens of diabetes, smoking, alcohol consumption, other socioeconomic characteristics as well as blood pressure, lipid profile and blood sugar status in our study, which might have also resulted in residual confounding. Last, data analyzed in this study were totally based on ethnic Chinese, generalizability of study findings to other ethnic population should be cautious.

Conclusions

After a maximum of 10 years of follow-up, except in those patients aged > 64 years, the men and women with type 2 diabetes were observed to have increased risk of idiopathic cardiomyopathy by 33% and 50%, respectively, even after adjustment of underlying cardiovascular risk factors. Those diabetes patients resided in rural areas had higher absolute and relative risk of idiopathic cardiomyopathy especially in female patients. Because of potentially serious medical and economic outcomes of diabetic cardiomyopathy, this study suggested a need to implement the multifaceted interventional program with particular focus on younger and rural type 2 diabetes patients in daily clinical practice.

Abbreviations

CI
Confidence Intervals
HR
Hazard Ratios
ICD-9-CM
International Classifications of Diseases, Ninth Revision Clinical Modification,
ICD-10-CM
International Classifications of Diseases, Tenth Revision Clinical Modification,
NHI
National Health Insurance,

Declarations

Acknowledgments

This research has been conducted using Taiwan's National Health Insurance database.

Authors' contributions

HFC and HJL designed the study, conducted literature research and wrote the manuscript. YHC acquired data and performed statistical analyses. CYL interpreted the data and critically revised the manuscript. All authors contributed to critical revision of the manuscript. CYL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Funding

This study was supported by a grant from the Ministry of Science and Technology (MOST 106-2314-B-006-025).

Availability of data and materials

The data sets analyzed during the current study are not publicly available because of information governance restrictions.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of National Cheng Kung University Hospital (A-EX-104-008) with no informed consent required.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no duality of interest associated with this manuscript.

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Tables

Table 1: ICD codes for diseases analyzed in this study

Diseases	ICD-9-CM	ICD-10-CM
Type 2 diabetes	250.x0, 250.x2	E11
Type 1 diabetes	250.x1, 250.x3	E10
Gestational diabetes	648.xx	O24.4
Comorbidities		
Ischemic heart disease	410-414	I20-I25
Hypertensive disease	401-405	I10-I16
Rheumatic heart disease	390, 391, 394-398	I00, I01, I05-I09
Valvular heart disease	424	I34-I39
Congenital heart disease	745-747	Q20-Q28
Acute myocarditis	422	I40, I41
Cardiomyopathy	425	I42, I43
End-point		
Other primary cardiomyopathies	425.4	
Dilated cardiomyopathy		I42.0
Hypertrophic obstructive cardiomyopathy	425.1	I42.1
Other hypertrophic cardiomyopathy		I42.2
Other restrictive cardiomyopathy		I42.5

Abbreviations: ICD-9-CM: International Classifications of Diseases, Ninth Revision Clinical Modification, ICD-10-CM: International Classifications of Diseases, Tenth Revision Clinical Modification,

Table 2: Characteristics of the study subjects

Variables [a]	Control group		Diabetic group	
	n	%	n	%
General Characteristics				
Age				
<45	85872	18.11	85872	18.11
45-64	268869	56.69	268869	56.69
>64	119525	25.20	119527	25.20
Mean age (±SD)	55.84	13.20	55.84	13.20
Sex				
Male	267161	56.33	267163	56.33
Female	207105	43.67	207105	43.67
Urbanization status				
Urban area	342117	72.14	332301	70.07
Rural area	132144	27.86	141963	29.93
Follow-up period (year)	9.15	1.36	8.91	1.68
Comorbidities				
Ischemic heart disease	55224	11.64	104857	22.11
Hypertensive disease	141639	29.86	267425	56.39
Rheumatic heart disease	4413	0.93	5466	1.15
Valvular heart disease	17717	3.74	18464	3.89
Congenital heart disease	1398	0.29	1901	0.40
Acute myocarditis	62	0.01	114	0.02
Total	474266	100.00	474268	100.00

[a] Inconsistency between total population and population summed for individual variable was due to missing information.

Table 3: Overall and age- and sex-specific incidence densities and relative hazards of Idiopathic Cardiomyopathy (ICD9=425.1, 425.4; ICD10=I42.0, I42.1, I42.2, I42.5) in the diabetic and control groups. (Fine and Gray's method)

Variables	Control group				Diabetic group				Crude	Adjusted
	No of patients	No of events	ID[a] (per 10,000 patient-years)	(95%CI[a])	No of patients	No of events	ID[a] (per 10,000 patient-years)	(95%CI[a])	HR[a]	HR[a]
Men										
<45	54958	48	0.96	(0.71-1.27)	54958	189	3.86	(3.33-4.45)	3.96(2.88-5.43)	2.36(1.68-3.32)[b]
45-64	152390	323	2.30	(2.06-2.57)	152390	553	4.04	(3.71-4.39)	1.72(1.50-1.97)	1.29(1.12-1.49)[b]
>64	59813	212	4.06	(3.53-4.64)	59815	261	5.24	(4.62-5.91)	1.24(1.03-1.48)	1.09(0.90-1.31)[b]
Total	267161	583	2.40	(2.21-2.61)	267163	1003	4.26	(4.00-4.53)	1.73(1.56-1.91)	1.33(1.20-1.48)[c]
Women										
<45	30914	9	0.32	(0.15-0.60)	30914	64	2.28	(1.76-2.92)	7.13(3.55-14.33)	3.72(1.86-7.44)[b]
45-64	116479	126	1.16	(0.96-1.38)	116479	308	2.87	(2.56-3.21)	2.45(1.99-3.02)	1.69(1.35-2.11)[b]
>64	59712	189	3.49	(3.01-4.02)	59712	252	4.88	(4.29-5.52)	1.34(1.11-1.62)	1.20(0.99-1.46)[b]
Total	207105	324	1.69	(1.51-1.89)	207105	624	3.34	(3.08-3.61)	1.93(1.69-2.21)	1.50(1.31-1.73)[c]
Overall	474266	907	2.09	(1.96-2.23)	474268	1627	3.85	(3.67-4.04)	1.80(1.66-1.96)	1.39(1.28-1.51)[d]

[a] Based on Poisson assumption, ID= incidence density, CI=confidence interval; HR= hazard ratio.

[b] Based on Cox proportional hazard regression with adjustment for urbanization status, status of Ischemic heart disease, Hypertensive disease, Rheumatic heart disease, Valvular heart disease, Congenital heart disease and Acute myocarditis.

[c] Based on Cox proportional hazard regression with adjustment for age and urbanization status, status of Ischemic heart disease, Hypertensive disease, Rheumatic heart disease, Valvular heart disease, Congenital heart disease and Acute myocarditis.

[d] Based on Cox proportional hazard regression with adjustment for age, sex and urbanization status, status of Ischemic heart disease, Hypertensive disease, Rheumatic heart disease, Valvular heart disease, Congenital heart disease and Acute myocarditis.

Table 4: Overall and urbanization- and sex-specific incidence densities and relative hazards of Idiopathic Cardiomyopathy (ICD9=425.1, 425.4; ICD10=I42.0, I42.1, I42.2, I42.5) in the diabetic and control groups. (Fine and Gray's method)

Variables[a]	Control group				Diabetic group				Crude	Adjusted
	No of patients	No of events	ID[b] (per 10,000 patient-years)	(95%CI[b])	No of patients	No of events	ID[b] (per 10,000 patient-years)	(95%CI[b])	HR[b]	HR[b]
Men										
Urban	190969	397	2.29	(2.07-2.52)	187691	668	4.02	(3.72-4.34)	1.72(1.52-1.95)	1.31(1.15-1.49) [c]
Rural	76189	186	2.70	(2.33-3.12)	79468	335	4.82	(4.32-5.37)	1.74(1.45-2.08)	1.39(1.15-1.68) [c]
Total	267161	583	2.40	(2.21-2.61)	267163	1003	4.26	(4.00-4.53)	1.73(1.56-1.91)	1.33(1.20-1.48) [d]
Women										
Urban	151148	207	1.48	(1.29-1.70)	144610	371	2.84	(2.56-3.14)	1.88(1.59-2.23)	1.38(1.15-1.64) [c]
Rural	55955	117	2.27	(1.88-2.72)	62495	253	4.50	(3.96-5.09)	1.94(1.56-2.42)	1.70(1.35-2.13) [c]
Total	207105	324	1.69	(1.51-1.89)	207105	624	3.34	(3.08-3.61)	1.93(1.69-2.21)	1.50(1.30-1.73) [d]
Overall	474266	907	2.09	(1.96-2.23)	474268	1627	3.85	(3.67-4.04)	1.80(1.66-1.96)	1.39(1.28-1.51) [e]

[a] Inconsistency between total population and population summed for individual variable was due to missing information.

[b] Based on Poisson assumption, ID= incidence density, CI=confidence interval; HR= hazard ratio.

[c] Based on Cox proportional hazard regression with adjustment for age, status of Ischemic heart disease, Hypertensive disease, Rheumatic heart disease, Valvular heart disease, Congenital heart disease and Acute myocarditis.

[d] Based on Cox proportional hazard regression with adjustment for age and urbanization status, status of Ischemic heart disease, Hypertensive disease, Rheumatic heart disease, Valvular heart disease, Congenital heart disease and Acute myocarditis.

[e] Based on Cox proportional hazard regression with adjustment for age, sex and urbanization status, status of Ischemic heart disease, Hypertensive disease, Rheumatic heart disease, Valvular heart disease, Congenital heart disease and Acute myocarditis.

Figures

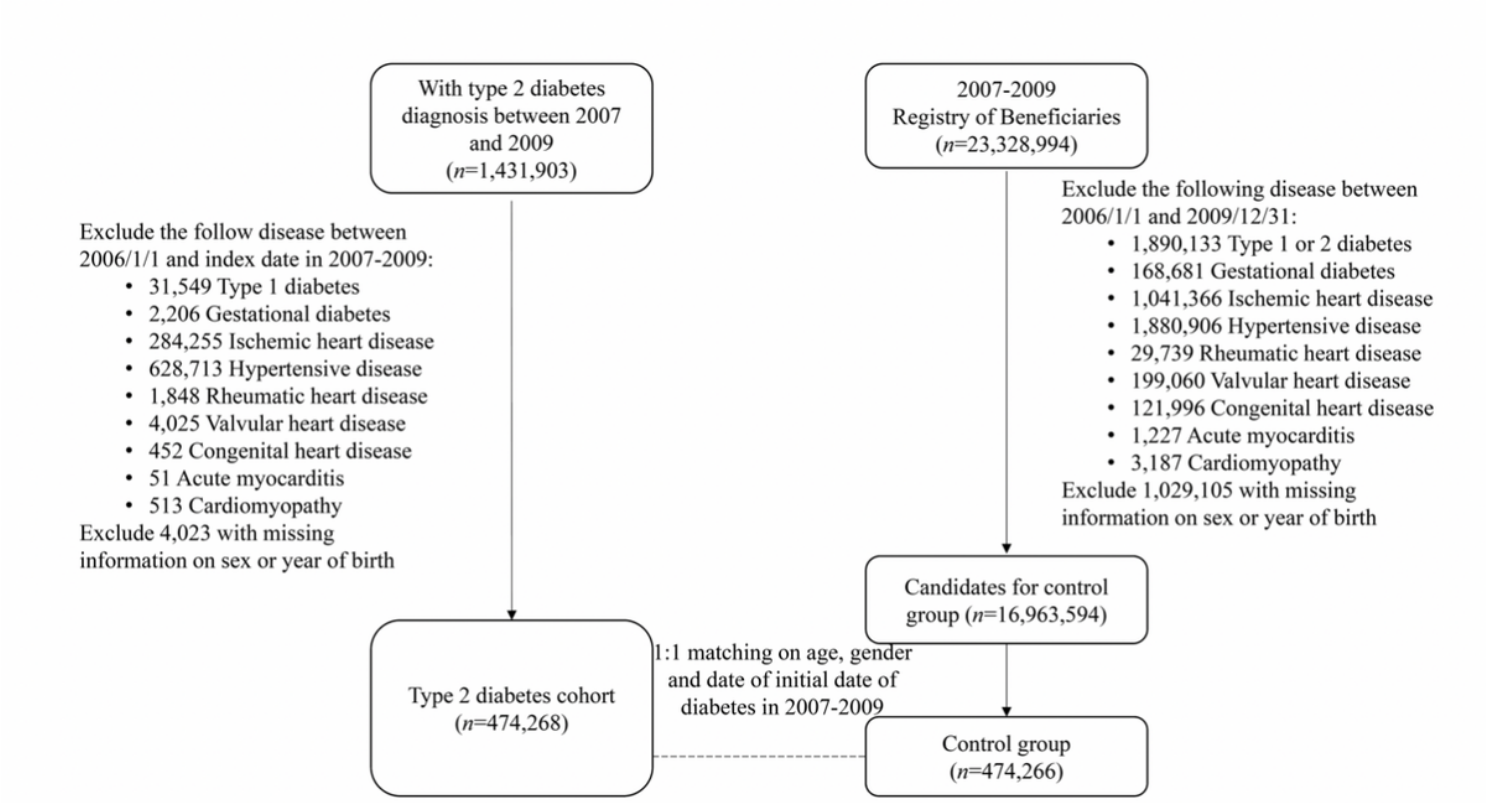

Figure 1

Flowchart for selection of type 2 diabetes cohort and control group