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Impact of Diagnosed Diabetes on Premature Death among Middle-aged Japanese: Results from a Large-Scale Population-based Cohort Study in Japan (JPHC Study)

Running title: diabetes and death

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219 words in the abstract
3,004 words in the text
Three tables and one figure

Abstract

Objective

To examine the impact of diabetes on premature death for Japanese general people

Design

Prospective cohort study

Setting

The Japan Public Health Center-based prospective Study (JPHC Study), data collected between 1990 and 2010.

Population

A total of 46,017 men and 53,567 women, aged 40 to 69 years at the beginning of baseline survey

Main outcome measures

Overall and cause specific mortality. Cox proportional hazards models were used to calculate the relative risks of all cause and cause specific mortality associated with diabetes.

Results

The median follow-up period was 17.8 years. During the follow-up period, 8,223 men and 4,640 women have died. Diabetes increased the risk of death (856 men and 345 women) [hazard ratio (HR) 1.60, (95% confidence interval (95%CI) 1.49-1.71) for men and 1.98 (95%CI, 1.77-2.21) for women]. As for the cause of death, diabetes increased the risk of death by circulatory diseases [HR 1.76 (95%CI 1.53-2.02) for men and 2.49 (95%CI 2.06-3.01) for

women) while its impact on the risk of cancer death was moderate [HR 1.25 (95%CI 1.11-1.42) for men and 1.04 (95%CI 0.82-1.32) for women]. Diabetes also increased the risk of death for “non-cancer, non-circulatory system disease” [HR 1.91 (95%CI 1.71-2.14) for men and 2.67 (95%CI 2.25-3.17) for women].

Conclusions

Diabetes increased the risk of death, especially the risk of death by circulatory diseases.

Keywords

diabetes mellitus, mortality

List of acronyms and abbreviations

BMI, Body Mass Index

ERFC, Emerging Risk Factors Collabolation

JPHC study, The Japan Public Health Center-based prospective Study

Strengths and limitations of this study

▪ A large scale population-based prospective study, the study population was defined as all registered Japanese inhabitants in the 11 public health center areas, was conducted.

▪ In Japan, the registration of deaths is required by the Family Registration Law and is believed to be complete.

▪ The assessment of diabetes mellitus was based on a self-report. Although the sensitivity and specificity of diagnosed diabetes were reported to be high, the assessment of diabetes by self-report is most likely an underestimate.

▪ The association between mortality and glycemia was not examined because data about glycemia were not available for the entire population,

INTRODUCTION

Today, Japanese people, especially Japanese women, are one of the people who live longest in the world[1]. On the other hand, the prevalence of type 2 diabetes has increased over the past few decades in Japan and the total number of diabetic patients is estimated to have risen from 7.4 million in 2002 to 9.5 million in 2012[2]. Diabetes is an important cause of mortality and

morbidity and there are many literatures about diabetes and mortality. However, most of these literatures were focused on the Western people and the impact of diabetes on premature death among Japanese people was not well examined. Several genetic and environmental differences as well as causes of death between Japanese and Western people exist and in the present study we examined the impact of diagnosed diabetes on premature death for Japanese general people in a large scale population based cohort study.

METHODS

The Japan Public Health Centre-based prospective Study (JPHC Study) consists of two cohort, Cohort I and Cohort II that comprise five and six prefectural public health center areas, respectively. The study population was defined as all registered Japanese inhabitants in the 11 public health center areas, aged 40 to 69 years at the beginning of each baseline survey, that is, in 1990 for Cohort I and in 1993 for Cohort II. Details of the study design have been described elsewhere[3]. The study protocol was approved by the institutional review board of the National Cancer Center.

Initially, 140,420 subjects were identified as the study population. Subjects with non-Japanese nationality, duplicate enrollment, late report of emigration occurring before the start of follow-up or ineligibility because of incorrect birth date (n=260) were excluded.

Questionnaire

At the baseline survey, each participant completed a self-administered questionnaire that included questions about various lifestyle factors; such as medical history of major diseases, smoking and alcohol drinking status, height and weight and leisure-time physical activity. A similar survey was conducted at 5- and 10-years after the baseline survey.

At baseline, a total of 113,402 subjects responded to the questionnaire (response rate 80.9%). Subjects whose follow up period was not determined were excluded from further analysis (n=90). Subjects with any of the following conditions at baseline: cardiovascular disease, chronic liver disease, kidney disease and any type of cancer, were also excluded (n=8,049). Subjects who had missing baseline data for any of the exposure parameters described below (in Statistical Analysis) (n=5,049) or subjects with a body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 14 or more than 40 (n=1,363) were also excluded, because body mass index less than 14 or more than 40 in Japanese implies potentially unreliable data. After the above exclusions, the remaining cohort consisted of 99,584 subjects (46,017 men and 53,567 women).

Assessment of diabetes

We defined the subject as having diagnosed diabetes if he or she answered ‘yes’ to the question ‘Has a doctor ever told you that you have diabetes?’ or ‘Do you take any

anti-diabetic drugs?'. The sensitivity and specificity of diagnosed diabetes was reported as 82.9% and 99.7%, respectively[4].

Follow-up

Subjects were followed from the baseline survey up to December 31, 2010. All death certificates were forwarded centrally to the Ministry of Health, Welfare and Labor and coded for the National Vital Statistics. In Japan, the registration of deaths is required by the Family Registration Law and is believed to be complete. The underlying cause of death was determined by death certificates and was coded according to the tenth revision of the International Classification of Disease (ICD-10).

Statistical Analysis

Person-years of follow-up were counted from the date of the baseline survey until one of the following endpoints: the date of emigration from Japan, the date of death, or the end of the study period (December 31, 2010), whichever comes first. Age-standardized mortality rate was calculated using 5-year age category. The impact of diabetes on premature death was estimated as hazard ratios using Cox's proportional hazards model with age as the time scale[5]. We adjusted potential confounding factors: body mass index (categorized as 14-18.4, 18.5-24.9, 25-29.9, and 30-40), alcohol intake (categorized by weekly ethanol intake as

non-drinker, 1-149g/week, 150-299g/week, 300-449g/week and ≥450g/week for men and the last two categories were combined into a category ≥300g/week for women), smoking status (categorized as never smoker, past smoker, current smoker at < 20 and ≥ 20 cigarettes per day), leisure-time physical activity (dichotomized as participate in sports at least once a week or not) and history of hypertension. The public health center areas were included in the analysis as strata. Effect of birth cohort was also examined by including birth cohort (birth year of 1920-1929, 1930-1939, and 1940-). Difference of the impact of diabetes on mortality by diagnosed period was also examined by including information about diagnosis of diabetes at 5 and 10 year survey for subjects who responded to 5 and/or 10 year survey, that is, subjects were classified into four groups according to the period of diagnosis of diabetes: diagnosed before baseline, diagnosed between baseline and 5 year survey, diagnosed between 5 and 10 year survey, never diagnosed. Person-years of follow-up of subjects diagnosed between baseline and 5 year survey and diagnosed between 5 and 10 year survey were counted from five and ten years after the baseline survey, respectively.

Hazard ratios were calculated for death from all cause, circulatory system diseases (ICD10, I00-I99), all cancer (ICD10, C00-C97) and site-specific cancer if there were 5 or more cases in subjects with diabetes. Deaths from other than circulatory system disease or cancer were grouped as “non-cancer, non-circulatory system disease” and the hazard ratio for this group was also calculated. The proportional hazards assumption was checked graphically and by

using Schoenfeld residuals.

All analyses were performed separately for men and women.

RESULTS

The median follow-up period was 17.8 years both for men and women. During the follow-up period, 8,223 men and 4,640 women have died. The baseline characteristics of the study subjects are shown in Table 1. At baseline, 6.0% of men and 2.8% of women had diagnosed diabetes. Among men, age, proportion of subjects with leisure-time physical activity and history of hypertension were higher among subjects with diabetes. Among women, age, the body mass index, proportion of subjects with leisure-time physical activity and history of hypertension were higher among subjects with diabetes.

Among men without diabetes, 1,744 subjects died from circulatory system disease, 3,093 subjects died from cancer and 2,530 subjects died from other causes, while among men with diabetes, these numbers were 230, 283 and 343, respectively. Among women without diabetes, 1,084 subjects died from circulatory system disease, 1,841 subjects died from cancer and 1,370 subjects died from other causes, while among women with diabetes, these numbers were 123, 71 and 151, respectively.

Hazard ratios for major causes of death were shown in Table 2. As shown in Table 2, diabetes increased the risk of death both for men and women. The hazard ratio was high for circulatory

system disease (ischemic heart disease and cerebrovascular disease) among men and especially high for ischemic heart disease and cerebral infarction among women. The impact of diabetes on the risk of death from cancer was moderate and the hazard ratios were not high except some types of cancer (liver cancer both among men and women and pancreas, kidney and bladder cancer among men), while death from "multiple myeloma and malignant plasma cell neoplasms" in men and "malignant neoplasm of breast" in women was markedly lower among subjects with diabetes (46/0 cases for multiple myeloma and 135/1 cases for neoplasm of breast). Diabetes also increased the risk of death for "non-cancer, non-circulatory system disease". These results were almost unchanged when the deaths during the first five years were excluded. The major causes of death for "non-cancer, non-circulatory system disease" among subjects with diabetes were "unspecified diabetes mellitus" (E14) (men 17.8%, women 22.5%), "pneumonia, organism unspecified" (J18) (men 13.7%, women 13.9%) and "unknown causes" (men 6.4%, women 10.6%).

The hazard ratio of diabetes on mortality was larger among subjects with diabetes diagnosed before baseline than among subjects diagnosed after baseline (Table 3). Differences of hazard ratios between subjects diagnosed between baseline and 5 year survey and subjects diagnosed between 5 and 10 year survey were not clear.

No significant interaction was observed between adjustment factors and the results were essentially unchanged by including the effect of birth cohort. We found no violation of

proportionality assumption. However, although it was not confirmed statistically, there was a tendency that the hazard ratio of diabetes for death decreased as age increased. (Figure 1)

DISCUSSION

In this population-based prospective study of middle-aged Japanese, we observed the increased risk of death for subjects with diabetes. As for the cause of death, diabetes increased the risk of death by circulatory system diseases and "non-cancer, non-circulatory system disease", while the impact of diabetes on the risk of death from cancer was moderate.

There are many literatures about diabetes and mortality and substantial numbers of these results were combined into the ERFC (Emerging Risk Factors Collabolation)[6]. In ERFC, the hazard ratios among subjects with diabetes compared with subjects without diabetes were reported as 1.80 for all cause mortality, 1.25 for death from cancer, 2.32 for death from vascular causes and 1.73 for death from other causes.

Results of another large prospective cohort study of one million U.S. adults (CPS-II) was also published[7]. In the study, relative risk of all-cause mortality was 1.73 for men and 1.90 for women and that of cancer death was 1.07 for men and 1.11 for women and that of cardiovascular system death was 1.92 for men and 2.09 for women.

Recently published meta-analysis also reported increased mortality among diabetic subjects

and the relative risk for all-cause mortality was 1.57 for men and 2.00 for women and that of cardiovascular mortality was 1.76[8].

Although the results were almost similar, there is a difference of major causes of death between our study and these studies. In the present study, 41% and 25% of all deaths were caused by cancer and circulatory system disease, respectively, while these numbers were 34% and 36% in the ERFC and 15% and 50% in the CPS-II, respectively. This tendency that Japanese die from cancer more than from circulatory system disease and that this is opposite for western people (although ERFC was a collation of over 100 prospective studies, about 90% of the subjects were from North America or Europe), is also observed in the world statistics[9]. As discussed above, diabetes increases the risk of death by circulatory system disease more than death by cancer. This may seem as if the impact of diabetes on mortality is large in a population among which the major cause of death was circulatory system disease, that is, the impact of diabetes on mortality is larger among western people than Japanese. However, this is not true because the non-vascular, non-cancer death plays an unignorable part of death.

Our results were also almost consistent with the Japanese large scale cohort study (Takayama study)[10]. The most remarkable difference between the Takayama study and the present study was the risk of death by coronary heart disease among women. In the Takayama study, the risk of death by coronary heart disease among women were lower in subjects with

diabetes than subjects without diabetes (hazard ratio 0.49, 95% confidence interval 0.07-3.57). As shown in the wide confidence interval, this difference may come from the very low number of cases (only two cases) of coronary heart disease death among women with diabetes. The collaborate study in Asia[11] and meta-analysis including this collaborate study[12] and its update[13] reported the increased risk of coronary heart disease among diabetic women and our results were consistent with these reports. Our study revealed that the effect of diabetes on the risk of cardiovascular death was greater among women than among men. This is also consistent with the above mentioned meta-analysis[12,13]. Although several possible explanations, such as 1) a heavier burden of cardiovascular risk factors, 2) a major impact of some cardiovascular risk factors and/or diabetes per se on cardiovascular disease, 3) differences in the structure and function of heart and vessels, and 4) disparities in medical treatment as well as gender differences in treatment response, are postulated, the underlying mechanism of this sex difference in the impact of diabetes on cardiovascular disease is not elucidated well[14].

As for the death from cancer, our results were almost consistent with the report about the incidence of cancer in the same JPHC study[15]. In the case of incidence, diabetes moderately increased the risk of all cancer and the risk was especially high for cancer of the liver, pancreas and kidney among men and for cancer of the stomach, liver and ovary among women. In the present study, a similar tendency was observed among men, however the

number of death from cancer was small among women and the increased mortality risk associated with diabetes was observed only in liver cancer.

We found that the impact of diabetes on mortality was stronger among subjects diagnosed before baseline than among subjects diagnosed after baseline. This result suggests that the effect of diabetes on mortality becomes stronger as duration of diabetes becomes longer.

We also found, although not confirmed statistically, that the hazard ratio of diabetes for death decreased as age increased. The similar phenomenon was observed in the ERFC. The reason is unclear. However, one possible explanation is that diabetic patients who lived long managed their diabetes relatively well. Another possible explanation is that the diabetic patients with older age included more recently developed diabetes because the risk of diabetes increases as age increases and, as stated above, the impact of diabetes on mortality was relatively lower in newly developed diabetes.

The strength of our study was the large number of subjects. The number of subjects was about 3.4 times that of the Takayama study. Another strength of the present study was that it was based on the general population in Japan. Although this study was conducted on subjects who responded the baseline questionnaire, we believe that the high response rate (80.9%) makes it possible to assess the association between diabetes and mortality in the general population.

There are several methodological limitations in the present study. The assessment of diabetes mellitus was based on a self-report. Although the sensitivity (82.6%) and specificity (99.7%)

of diagnosed diabetes were reported to be high, the proportion of subjects with diabetes at baseline (6.0% for men and 2.8% for women) was low compared with the estimates in the same period (9.9-13.1% for men and 9.1-11.5% for women)[16]. The assessment of diabetes by self-report, therefore, is most likely an underestimate and our results may have been distorted toward null by this misclassification. However, in the above mentioned meta-analysis, sensitivity analyses were performed and no difference was found in the ratio of the relative risks for diabetes between the method of diabetes diagnosis (self-report versus glucose measured)[12]. Previous studies have revealed the association between mortality and glycemia in diabetic patients[17] and this association holds even in the non-diabetic range of glycemia[18,7]. Since we have no data about glycemia, we could not assess the association between mortality and glycemia in the present study.

Despite these limitations, our present study revealed the association between diabetes and mortality in the Japanese general population. Recent increase in diabetes patients will influence the longevity of Japanese people in the future and we believe that our study would provide useful information both for further research and treatment of diabetes.

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Competing interests:

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Ethical approval: This study was approved by the institutional review boards of the National Cancer Center, Japan, and the National Center for Global Health and Medicine, Japan.

Data sharing: no additional data available.

Declaration of transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1 Baseline characteristics according to diagnosed diabetes

	Men (n=46,017)				Women (n=53,567)			
	DM(-) (n=43,256)		DM(+) (n=2,761)		DM(-) (n=52,042)		DM(+) (n=1,525)	
Age	50	(44-56)	53	(49-59)	50	(44-57)	56	(50-62)
BMI	23.5	(2.8)	23.7	(3.0)	23.3	(3.1)	24.4	(3.6)
Smoking								
Never	10,175	(23.5)	577	(20.9)	47,347	(91.0)	1,363	(89.4)
Past	10,106	(23.4)	713	(25.8)	942	(1.8)	45	(3.0)
Current (<20 cigarettes/day)	5,913	(13.7)	398	(14.4)	2,422	(4.7)	64	(4.2)
Current (≥20 cigarettes/day)	17,062	(39.4)	1,073	(38.9)	1,331	(2.6)	53	(3.5)
Alcohol								
Non drinker	13,248	(30.6)	944	(34.2)	44,844	(86.2)	1,386	(90.9)
1-150 g/week	9,667	(22.4)	575	(20.8)	5,609	(10.8)	103	(6.8)
150-300 g/week	9,032	(20.9)	511	(18.5)	996	(1.9)	16	(1.0)
300-450 g/week (≥300 week for women)	5,325	(12.3)	273	(9.9)	593	(1.1)	20	(1.3)
≥450 g/week	5,984	(13.8)	458	(16.6)				
Physical activity (active)	8,188	(18.9)	682	(24.7)	9,629	(18.5)	381	(25.0)
Hypertension (+)	7,218	(16.7)	795	(28.8)	8,145	(15.7)	545	(35.7)

Table 2 Mortality according to diagnosed diabetes

Men	DM(-) (n=43,256)		DM(+) (n=2,761)		HR				excluding cases during first 5-years	
	cases	rate*	cases	rate*	crude		multivariate-adjusted*		multivariate-adjusted* HR	
All-cause	7,367	98.0	856	163.9	1.65	(1.54-1.77)	1.60	(1.49-1.71)	1.59	(1.47-1.71)
All circulatory system diseases (ICD10:I00-I99)	1,744	23.2	230	43.6	1.88	(1.63-2.15)	1.76	(1.53-2.02)	1.79	(1.54-2.09)
Ischemic heart disease (ICD10:I20-I25)	434	5.8	76	14.2	2.47	(1.93-3.15)	2.30	(1.80-2.95)	2.32	(1.78-3.03)
Cerebrovascular disease (ICD10:I60-I69)	705	9.4	88	16.7	1.78	(1.43-2.23)	1.68	(1.34-2.10)	1.75	(1.37-2.23)
Cerebral infarction (ICD10:I63)	176	2.3	27	4.9	2.07	(1.38-3.11)	1.87	(1.24-2.82)	1.76	(1.09-2.82)
Intracerebral haemorrhage (ICD10:I61)	227	3.0	27	5.6	1.86	(1.25-2.78)	1.73	(1.16-2.59)	2.00	(1.30-3.07)
All-cancer (ICD10:C00-C97)	3,093	41.2	283	53.6	1.28	(1.13-1.45)	1.25	(1.11-1.42)	1.22	(1.06-1.39)
All sites excluding the liver	2,850	37.9	244	46.0	1.20	(1.05-1.37)	1.18	(1.03-1.34)	1.16	(1.00-1.34)
All sites excluding the liver and pancreas	2,652	35.3	216	40.5	1.14	(0.99-1.31)	1.12	(0.97-1.29)	1.11	(0.95-1.29)
Esophagus (ICD10:C15)	171	2.3	16	3.0	1.35	(0.80-2.25)	1.31	(0.78-2.20)	1.01	(0.53-1.93)
Stomach (ICD10:C16)	543	7.2	37	7.2	0.95	(0.68-1.32)	0.92	(0.66-1.29)	0.73	(0.49-1.11)
Colon (ICD10:C18)	172	2.3	19	3.6	1.62	(1.01-2.61)	1.61	(1.00-2.60)	1.73	(1.04-2.87)
Rectum (ICD10:C19-C21)	146	1.9	12	2.3	1.20	(0.66-2.16)	1.17	(0.65-2.12)	1.29	(0.67-2.47)
Liver (ICD10:C22)	243	3.2	39	7.6	2.20	(1.57-3.10)	2.12	(1.50-2.98)	1.89	(1.27-2.80)
Bile duct (ICD10:C23-C24)	133	1.8	17	3.1	1.78	(1.07-2.96)	1.76	(1.06-2.92)	1.68	(0.96-2.94)
Pancreas (ICD10:C25)	198	2.6	28	5.4	1.98	(1.33-2.95)	1.95	(1.31-2.91)	1.80	(1.15-2.81)
Lung (ICD10:C33-C34)	778	10.4	49	9.1	0.85	(0.64-1.14)	0.84	(0.63-1.13)	0.87	(0.64-1.19)
Kidney (ICD10:C64-C66, C68)	51	0.7	10	2.1	2.75	(1.39-5.43)	2.50	(1.26-4.98)	2.32	(1.09-4.98)
Bladder (ICD10:C67)	39	0.5	10	1.8	3.38	(1.68-6.81)	3.29	(1.63-6.65)	3.63	(1.78-7.39)
Prostate (ICD10:C61)	107	1.4	10	1.7	1.29	(0.67-2.47)	1.24	(0.65-2.39)	1.31	(0.68-2.53)
Non-cancer, non-circulatory system disease	2,530	33.6	343	66.7	1.96	(1.75-2.19)	1.91	(1.71-2.14)	1.90	(1.67-2.15)

Women	DM(-) (n=52,042)		DM(+) (n=1,525)		HR				excluding cases during first 5-years	
	cases	rate*	cases	rate*	crude		multivariate-adjusted*		multivariate-adjusted* HR	
All-cause	4,295	45.9	345	102.3	2.11	(1.89-2.35)	1.98	(1.77-2.21)	2.02	(1.79-2.28)
All circulatory system diseases (ICD10:I00-I99)	1,084	11.6	123	36.6	2.82	(2.33-3.40)	2.49	(2.06-3.01)	2.56	(2.09-3.13)
Ischemic heart disease (ICD10:I20-I25)	196	2.1	42	13.4	5.10	(3.64-7.13)	4.52	(3.21-6.37)	4.56	(3.17-6.57)
Cerebrovascular disease (ICD10:I60-I69)	479	5.1	38	11.3	2.08	(1.49-2.90)	1.72	(1.23-2.40)	1.72	(1.19-2.47)
Cerebral infarction (ICD10:I63)	98	1.1	18	5.5	4.31	(2.60-7.15)	3.43	(2.05-5.74)	3.61	(2.12-6.15)
Intracerebral haemorrhage (ICD10:I61)	136	1.5	9	3.2	1.93	(0.98-3.81)	1.64	(0.83-3.24)	1.71	(0.83-3.54)
All-cancer (ICD10:C00-C97)	1,841	19.6	71	22.6	1.08	(0.85-1.37)	1.04	(0.82-1.32)	1.05	(0.81-1.36)
All sites excluding the liver	1,730	18.4	61	19.9	1.00	(0.77-1.29)	0.96	(0.74-1.24)	0.93	(0.70-1.24)
All sites excluding the liver and pancreas	1,540	16.4	52	17.3	0.97	(0.73-1.27)	0.93	(0.71-1.23)	0.90	(0.66-1.23)
Stomach (ICD10:C16)	224	2.4	8	3.4	1.05	(0.52-2.13)	1.10	(0.54-2.24)	1.21	(0.57-2.60)
Colon (ICD10:C18)	160	1.7	5	1.7	0.84	(0.35-2.06)	0.81	(0.33-2.00)	0.79	(0.29-2.15)
Liver (ICD10:C22)	111	1.2	10	2.6	2.30	(1.20-4.40)	2.21	(1.15-4.27)	2.66	(1.37-5.17)
Pancreas (ICD10:C25)	190	2	9	2.6	1.22	(0.62-2.39)	1.10	(0.56-2.16)	1.17	(0.57-2.39)
Lung (ICD10:C33-C34)	228	2.4	8	2.1	1.00	(0.49-2.02)	0.95	(0.47-2.40)	0.95	(0.35-2.61)
Non-cancer, non-circulatory system disease	1,370	14.7	151	43.2	2.79	(2.35-3.30)	2.67	(2.25-3.17)	2.66	(2.22-3.19)

rate*: per 10,000 person-years (age-standardized)

multivariate-adjusted*: adjsuted for BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

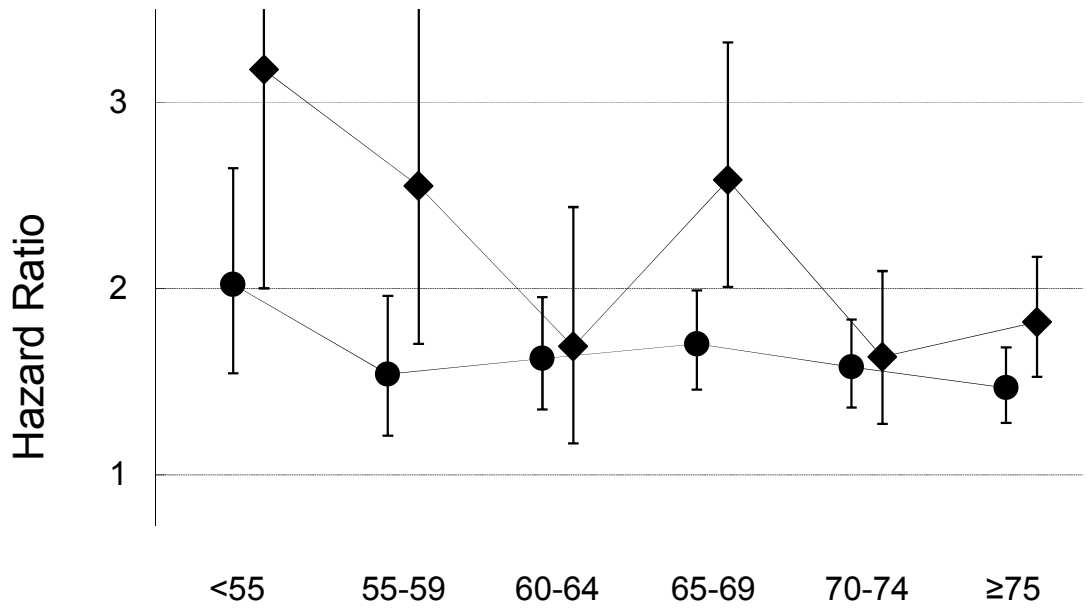
Table 3 Difference of the impact of diabetes by diagnosed period (All-cause mortality)

	Men				Women			
Diagnosed Period	n	cases	adjusted HR*		n	cases	adjusted HR*	
Never	41,036	6,975	1		50,555	4,106	1	
Before baseline	2,761	856	1.59	(1.48-1.71)	1,525	345	2.00	(1.79-2.23)
Between baseline and 5 year survey	1,341	254	1.20	(1.05-1.36)	861	123	1.55	(1.29-1.86)
Between 5 and 10 year survey	879	138	1.22	(1.03-1.44)	626	66	1.45	(1.14-1.86)

adjusted HR*: adjsuted for BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

Figure 1 Changes of hazard ratio of diabetes according to age (all-cause mortality)

(Men, circle; Women, diamond)



Appendix:

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*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	6-7
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	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	10
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	5-7
		(b) Give reasons for non-participation at each stage	5-7
		(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	9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
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	22
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
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	16-17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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Impact of Diagnosed Diabetes on Premature Death among Middle-aged Japanese: Results from a Large-Scale Population-based Cohort Study in Japan (JPHC Study)

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Impact of Diagnosed Diabetes on Premature Death among Middle-aged Japanese: Results from a Large-Scale Population-based Cohort Study in Japan (JPHC Study)

Running title: diabetes and death

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219 words in the abstract
3,211 words in the text
Three tables and one figure

Abstract

Objective

To examine the impact of diabetes on premature death for Japanese general people

Design

Prospective cohort study

Setting

The Japan Public Health Center-based prospective Study (JPHC Study), data collected between 1990 and 2010.

Population

A total of 46,017 men and 53,567 women, aged 40 to 69 years at the beginning of baseline survey

Main outcome measures

Overall and cause specific mortality. Cox proportional hazards models were used to calculate the relative risks of all cause and cause specific mortality associated with diabetes.

Results

The median follow-up period was 17.8 years. During the follow-up period, 8,223 men and 4,640 women have died. Diabetes increased the risk of death (856 men and 345 women) [hazard ratio (HR) 1.60, (95% confidence interval (95%CI) 1.49-1.71) for men and 1.98 (95%CI, 1.77-2.21) for women]. As for the cause of death, diabetes increased the risk of death by circulatory diseases [HR 1.76 (95%CI 1.53-2.02) for men and 2.49 (95%CI 2.06-3.01) for

women) while its impact on the risk of cancer death was moderate [HR 1.25 (95%CI 1.11-1.42) for men and 1.04 (95%CI 0.82-1.32) for women]. Diabetes also increased the risk of death for “non-cancer, non-circulatory system disease” [HR 1.91 (95%CI 1.71-2.14) for men and 2.67 (95%CI 2.25-3.17) for women].

Conclusions

Diabetes increased the risk of death, especially the risk of death by circulatory diseases.

Keywords

diabetes mellitus, mortality

List of acronyms and abbreviations

BMI, Body Mass Index

ERFC, Emerging Risk Factors Collabolation

JPHC study, The Japan Public Health Center-based prospective Study

Strengths and limitations of this study

▪ A large scale population-based prospective study, the study population was defined as all registered Japanese inhabitants in the 11 public health center areas, was conducted.

▪ In Japan, the registration of deaths is required by the Family Registration Law and is believed to be complete.

▪ The assessment of diabetes mellitus was based on a self-report. Although the sensitivity and specificity of diagnosed diabetes were reported to be high, the assessment of diabetes by self-report is most likely an underestimate.

▪ The association between mortality and glycemia was not examined because data about glycemia were not available for the entire population.

INTRODUCTION

Today, Japanese people, especially Japanese women, are one of the people who live longest in the world[1]. On the other hand, the prevalence of type 2 diabetes has increased over the past few decades in Japan and the total number of diabetic patients is estimated to have risen from 7.4 million in 2002 to 9.5 million in 2012[2]. Diabetes is an important cause of mortality and morbidity and there are many literatures about diabetes and mortality. However, most of these literatures were focused on the Western people and the impact of diabetes on premature death among Japanese people was not well examined. Several genetic and environmental differences as well as causes of death between Japanese and Western people exist and in the present study we examined the impact of diagnosed diabetes on premature death for Japanese general people in a large scale population based cohort study.

METHODS

The Japan Public Health Centre-based prospective Study (JPHC Study) consists of two cohort, Cohort I and Cohort II that comprise five and six prefectural public health center areas, respectively. The study population was defined as all registered Japanese inhabitants in the 11 public health center areas, aged 40 to 69 years at the beginning of each baseline survey, that is, in 1990 for Cohort I and in 1993 for Cohort II. Details of the study design have been described elsewhere[3]. The study protocol was approved by the institutional review board of

the National Cancer Center.

Initially, 140,420 subjects were identified as the study population. Subjects with non-Japanese nationality, duplicate enrollment, late report of emigration occurring before the start of follow-up or ineligibility because of incorrect birth date (n=260) were excluded.

Questionnaire

At the baseline survey, each participant completed a self-administered questionnaire that included questions about various lifestyle factors; such as medical history of major diseases, smoking and alcohol drinking status, height and weight and leisure-time physical activity. A similar survey was conducted at 5- and 10-years after the baseline survey.

At baseline, a total of 113,402 subjects responded to the questionnaire (response rate 80.9%). Subjects whose follow up period was not determined were excluded from further analysis (n=90). Subjects with any of the following conditions at baseline: cardiovascular disease, chronic liver disease, kidney disease and any type of cancer, were also excluded (n=8,049). Subjects who had missing baseline data for any of the exposure parameters described below (in Statistical Analysis) (n=5,049) or subjects with a body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 14 or more than 40 (n=1,363) were also excluded, because body mass index less than 14 or more than 40 in Japanese implies potentially unreliable data. After the above exclusions, the remaining cohort

consisted of 99,584 subjects (46,017 men and 53,567 women).

Assessment of diabetes

We defined the subject as having diagnosed diabetes if he or she marked on 'diabetes mellitus' to the question 'Has a doctor ever told you that you have any of the following diseases?' or on 'anti-diabetic drug' to the question 'Do you take any of the following drugs?' The sensitivity and specificity of diagnosed diabetes was reported as 82.9% and 99.7%, respectively[4]. The questionnaire did not distinguish type 1 and type 2 diabetes. However, the subjects of the present study were Japanese inhabitants aged 40 to 69 years and we believe that most of the subjects with diagnosed diabetes had type 2 diabetes.

Follow-up

Subjects were followed from the baseline survey up to December 31, 2010. All death certificates were forwarded centrally to the Ministry of Health, Welfare and Labor and coded for the National Vital Statistics. In Japan, the registration of deaths is required by the Family Registration Law and is believed to be complete. The underlying cause of death was determined by death certificates and was coded according to the tenth revision of the International Classification of Disease (ICD-10). Until 1995, the cause of death was determined according to the criteria of the ICD-9 and from 1995, the codes were translated

into the corresponding ICD-10 codes.

Statistical Analysis

Person-years of follow-up were counted from the date of the baseline survey until one of the following endpoints: the date of emigration from Japan, the date of death, or the end of the study period (December 31, 2010), whichever comes first. Age-standardized mortality rate was calculated by direct method using 5-year age specific mortality rate and the total population (subjects with and without diabetes) as standard. The impact of diabetes on premature death was estimated as hazard ratios using Cox's proportional hazards model with age as the time scale[5]. We adjusted potential confounding factors: body mass index (categorized as 14-18.4, 18.5-24.9, 25-29.9, and 30-40), alcohol intake (categorized by weekly ethanol intake as non-drinker, 1-149g/week, 150-299g/week, 300-449g/week and ≥ 450g/week for men and the last two categories were combined into a category ≥300g/week for women), smoking status (categorized as never smoker, past smoker, current smoker at < 20 and ≥ 20 cigarettes per day), leisure-time physical activity (dichotomized as participate in sports at least once a week or not) and history of hypertension. The public health center areas were included in the analysis as strata. Effect of birth cohort was also examined by including birth cohort (birth year of 1920-1929, 1930-1939, and 1940-). Difference of the impact of diabetes on mortality by diagnosed period was also examined by including information about

diagnosis of diabetes at 5 and 10 year survey for subjects who responded to 5 and/or 10 year survey, that is, subjects were classified into four groups according to the period of diagnosis of diabetes: diagnosed before baseline, diagnosed between baseline and 5 year survey, diagnosed between 5 and 10 year survey, never diagnosed. Person-years of follow-up of subjects diagnosed between baseline and 5 year survey and diagnosed between 5 and 10 year survey were counted from five and ten years after the baseline survey, respectively.

Hazard ratios were calculated for death from all cause, circulatory system diseases (ICD10, I00-I99), all cancer (ICD10, C00-C97) and site-specific cancer if there were 5 or more cases in subjects with diabetes. Deaths from other than circulatory system disease or cancer were grouped as “non-cancer, non-circulatory system disease” and the hazard ratio for this group was also calculated. The proportional hazards assumption was checked graphically and by using Schoenfeld residuals.

All analyses were performed separately for men and women.

RESULTS

The median follow-up period was 17.8 years both for men and women. During the follow-up period, 8,223 men and 4,640 women have died. The baseline characteristics of the study subjects are shown in Table 1. At baseline, 6.0% of men and 2.8% of women had diagnosed diabetes. Among men, age, proportion of subjects with leisure-time physical activity and

history of hypertension were higher among subjects with diabetes. Among women, age, the body mass index, proportion of subjects with leisure-time physical activity and history of hypertension were higher among subjects with diabetes. Besides these factors, medication about hypercholesterolemia was higher among subjects with diabetes (3.5% among diabetes and 1.2% among non-diabetes for men, and 5.5% among diabetes and 1.9% among non-diabetes for women).

Among men without diabetes, 1,744 subjects died from circulatory system disease, 3,093 subjects died from cancer and 2,530 subjects died from other causes, while among men with diabetes, these numbers were 230, 283 and 343, respectively. Among women without diabetes, 1,084 subjects died from circulatory system disease, 1,841 subjects died from cancer and 1,370 subjects died from other causes, while among women with diabetes, these numbers were 123, 71 and 151, respectively.

Hazard ratios for major causes of death were shown in Table 2. As shown in Table 2, diabetes increased the risk of death both for men and women. The hazard ratio was high for circulatory system disease (ischemic heart disease and cerebrovascular disease) among men and especially high for ischemic heart disease and cerebral infarction among women. The impact of diabetes on the risk of death from cancer was moderate and the hazard ratios were not high except some types of cancer (liver cancer both among men and women and pancreas, kidney and bladder cancer among men), while death from “multiple myeloma and malignant plasma

cell neoplasms" in men and "malignant neoplasm of breast" in women was markedly lower among subjects with diabetes (46/0 cases for multiple myeloma and 135/1 cases for neoplasm of breast). Diabetes also increased the risk of death for "non-cancer, non-circulatory system disease". These results were almost unchanged when the deaths during the first five years were excluded. The major causes of death for "non-cancer, non-circulatory system disease" among subjects with diabetes were "unspecified diabetes mellitus" (E14) (men 17.8%, women 22.5%), "pneumonia, organism unspecified" (J18) (men 13.7%, women 13.9%) and "unknown causes" (men 6.4%, women 10.6%).

The hazard ratio of diabetes on mortality was larger among subjects with diabetes diagnosed before baseline than among subjects diagnosed after baseline (Table 3). Differences of hazard ratios between subjects diagnosed between baseline and 5 year survey and subjects diagnosed between 5 and 10 year survey were not clear.

No significant interaction was observed between adjustment factors and the results were essentially unchanged by including the effect of birth cohort. Further adjustment for medication for hypercholesterolemia had little impact on our results. We found no violation of proportionality assumption. However, although it was not confirmed statistically, there was a tendency that the hazard ratio of diabetes for death decreased as age increased. (Figure 1)

DISCUSSION

In this population-based prospective study of middle-aged Japanese, we observed the increased risk of death for subjects with diabetes. As for the cause of death, diabetes increased the risk of death by circulatory system diseases and "non-cancer, non-circulatory system disease", while the impact of diabetes on the risk of death from cancer was moderate.

There are many literatures about diabetes and mortality and substantial numbers of these results were combined into the ERFC (Emerging Risk Factors Collabolation)[6]. In ERFC, the hazard ratios among subjects with diabetes compared with subjects without diabetes were reported as 1.80 for all cause mortality, 1.25 for death from cancer, 2.32 for death from vascular causes and 1.73 for death from other causes.

Results of another large prospective cohort study of one million U.S. adults (CPS-II) was also published[7]. In the study, relative risk of all-cause mortality was 1.73 for men and 1.90 for women and that of cancer death was 1.07 for men and 1.11 for women and that of cardiovascular system death was 1.92 for men and 2.09 for women.

Recently published meta-analysis also reported increased mortality among diabetic subjects and the relative risk for all-cause mortality was 1.57 for men and 2.00 for women and that of cardiovascular mortality was 1.76[8].

Although the results were almost similar, there is a difference of major causes of death between our study and these studies. In the present study, 41% and 25% of all deaths were

caused by cancer and circulatory system disease, respectively, while these numbers were 34% and 36% in the ERFC and 15% and 50% in the CPS-II, respectively. This tendency that Japanese die from cancer more than from circulatory system disease and that this is opposite for western people (although ERFC was a collation of over 100 prospective studies, about 90% of the subjects were from North America or Europe), is also observed in the world statistics[9]. As discussed above, diabetes increases the risk of death by circulatory system disease more than death by cancer. This may seem as if the impact of diabetes on mortality is large in a population among which the major cause of death was circulatory system disease, that is, the impact of diabetes on mortality is larger among western people than Japanese. However, this is not true because the non-vascular, non-cancer death plays an unignorable part of death.

Our results were also almost consistent with the Japanese large scale cohort study (Takayama study)[10]. The most remarkable difference between the Takayama study and the present study was the risk of death by coronary heart disease among women. In the Takayama study, the risk of death by coronary heart disease among women were lower in subjects with diabetes than subjects without diabetes (hazard ratio 0.49, 95% confidence interval 0.07-3.57). As shown in the wide confidence interval, this difference may come from the very low number of cases (only two cases) of coronary heart disease death among women with diabetes. The collaborate study in Asia[11] and meta-analysis including this collaborate study[12] and

its update[13] reported the increased risk of coronary heart disease among diabetic women and our results were consistent with these reports. Our study revealed that the effect of diabetes on the risk of cardiovascular death was greater among women than among men. This is also consistent with the above mentioned meta-analysis[12,13]. Although several possible explanations, such as 1) a heavier burden of cardiovascular risk factors, 2) a major impact of some cardiovascular risk factors and/or diabetes per se on cardiovascular disease, 3) differences in the structure and function of heart and vessels, and 4) disparities in medical treatment as well as gender differences in treatment response, are postulated, the underlying mechanism of this sex difference in the impact of diabetes on cardiovascular disease is not elucidated well[14].

As for the death from cancer, our results were almost consistent with the report about the incidence of cancer in the same JPHC study[15]. In the case of incidence, diabetes moderately increased the risk of all cancer and the risk was especially high for cancer of the liver, pancreas and kidney among men and for cancer of the stomach, liver and ovary among women. In the present study, a similar tendency was observed among men, however the number of death from cancer was small among women and the increased mortality risk associated with diabetes was observed only in liver cancer.

We found that the impact of diabetes on mortality was stronger among subjects diagnosed before baseline than among subjects diagnosed after baseline. This result suggests that the

effect of diabetes on mortality becomes stronger as duration of diabetes becomes longer.

We also found, although not confirmed statistically, that the hazard ratio of diabetes for death decreased as age increased. The similar phenomenon was observed in the ERFC. The reason is unclear. However, one possible explanation is that diabetic patients who lived long managed their diabetes relatively well. Another possible explanation is that the diabetic patients with older age included more recently developed diabetes because the risk of diabetes increases as age increases and, as stated above, the impact of diabetes on mortality was relatively lower in newly developed diabetes.

The strength of our study was the large number of subjects. The number of subjects was about 3.4 times that of the Takayama study. Another strength of the present study was that it was based on the general population in Japan. Although this study was conducted on subjects who responded the baseline questionnaire, we believe that the high response rate (80.9%) makes it possible to assess the association between diabetes and mortality in the general population. In addition, the age-specific mortality rates in the present study were similar to those of Japanese general population. For example, age-specific mortality rates (per 10,000 person-years) in the present study in men were 15.5, 36.3, 83.0 and 224.0 for 40, 50, 60 and 70 years-old respectively and those of Japanese general population (Abridged Life Tables For Japan 2005) were 14.4, 35.8, 89.4 and 213.8. In women, the age-specific mortality rates (per 10,000 person-years) in the present study were 5.3, 17.4, 33.2 and 87.2 for 40, 50, 60 and 70

years-old respectively and those of Japanese general population were 7.5, 17.7, 36.6 and 89.3. No large discrepancies in mortality rates exist between our study and Japanese general population and this may also support the representativeness of our cohort.

There are several methodological limitations in the present study. The assessment of diabetes mellitus was based on a self-report. Although the sensitivity (82.6%) and specificity (99.7%) of diagnosed diabetes were reported to be high, the proportion of subjects with diabetes at baseline (6.0% for men and 2.8% for women) was low compared with the estimates in the same period (9.9-13.1% for men and 9.1-11.5% for women)[16]. The assessment of diabetes by self-report, therefore, is most likely an underestimate and our results may have been distorted toward null by this misclassification. However, in the above mentioned meta-analysis, sensitivity analyses were performed and no difference was found in the ratio of the relative risks for diabetes between the method of diabetes diagnosis (self-report versus glucose measured)[12]. Previous studies have revealed the association between mortality and glycemia in diabetic patients[17] and this association holds even in the non-diabetic range of glycemia[18,7]. Since we have no data about glycemia, we could not assess the association between mortality and glycemia in the present study.

Despite these limitations, our present study revealed the association between diabetes and mortality in the Japanese general population. Recent increase in diabetes patients will influence the longevity of Japanese people in the future and we believe that our study would

provide useful information both for further research and treatment of diabetes.

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Contributors: MK analysed data, drafted the manuscript, reviewed and edited the manuscript, and contributed to discussion; MN and ST conducted, designed, and supervised the study, and contributed to discussion; TM, AG, YT, YM, AN, HI, MI, and NS reviewed the manuscript, and contributed to discussion. NM is guarantors. All authors read and approved the final manuscript.

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Competing interests:

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Ethical approval: This study was approved by the institutional review boards of the National Cancer Center, Japan, and the National Center for Global Health and Medicine, Japan.

Data sharing: no additional data available.

Declaration of transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1 Baseline characteristics according to diagnosed diabetes

	Men (n=46,017)				Women (n=53,567)			
	DM(-) (n=43,256)		DM(+) (n=2,761)		DM(-) (n=52,042)		DM(+) (n=1,525)	
Age	50	(44-56)	53	(49-59)	50	(44-57)	56	(50-62)
BMI	23.5	(2.8)	23.7	(3.0)	23.3	(3.1)	24.4	(3.6)
Smoking								
Never	10,175	(23.5)	577	(20.9)	47,347	(91.0)	1,363	(89.4)
Past	10,106	(23.4)	713	(25.8)	942	(1.8)	45	(3.0)
Current（<20 cigarettes/day）	5,913	(13.7)	398	(14.4)	2,422	(4.7)	64	(4.2)
Current（≥20 cigarettes/day）	17,062	(39.4)	1,073	(38.9)	1,331	(2.6)	53	(3.5)
Alcohol								
Non drinker	13,248	(30.6)	944	(34.2)	44,844	(86.2)	1,386	(90.9)
1-150 g/week	9,667	(22.4)	575	(20.8)	5,609	(10.8)	103	(6.8)
150-300 g/week	9,032	(20.9)	511	(18.5)	996	(1.9)	16	(1.0)
300-450 g/week (≥300 week for women)	5,325	(12.3)	273	(9.9)	593	(1.1)	20	(1.3)
≥450 g/week	5,984	(13.8)	458	(16.6)				
Physical activity (active)	8,188	(18.9)	682	(24.7)	9,629	(18.5)	381	(25.0)
Hypertension (+)	7,218	(16.7)	795	(28.8)	8,145	(15.7)	545	(35.7)

Table 2 Mortality according to diagnosed diabetes

Men	DM(-) (n=43,256)		DM(+) (n=2,761)		HR				excluding cases during first 5-years	
	cases	rate*	cases	rate*	crude		multivariate-adjusted*		multivariate-adjusted* HR	
All-cause	7,367	98.0	856	163.9	1.65	(1.54-1.77)	1.60	(1.49-1.71)	1.59	(1.47-1.71)
All circulatory system diseases (ICD10:I00-I99)	1,744	23.2	230	43.6	1.88	(1.63-2.15)	1.76	(1.53-2.02)	1.79	(1.54-2.09)
Ischemic heart disease (ICD10:I20-I25)	434	5.8	76	14.2	2.47	(1.93-3.15)	2.30	(1.80-2.95)	2.32	(1.78-3.03)
Cerebrovascular disease (ICD10:I60-I69)	705	9.4	88	16.7	1.78	(1.43-2.23)	1.68	(1.34-2.10)	1.75	(1.37-2.23)
Cerebral infarction (ICD10:I63)	176	2.3	27	4.9	2.07	(1.38-3.11)	1.87	(1.24-2.82)	1.76	(1.09-2.82)
Intracerebral haemorrhage (ICD10:I61)	227	3.0	27	5.6	1.86	(1.25-2.78)	1.73	(1.16-2.59)	2.00	(1.30-3.07)
All-cancer (ICD10:C00-C97)	3,093	41.2	283	53.6	1.28	(1.13-1.45)	1.25	(1.11-1.42)	1.22	(1.06-1.39)
All sites excluding the liver	2,850	37.9	244	46.0	1.20	(1.05-1.37)	1.18	(1.03-1.34)	1.16	(1.00-1.34)
All sites excluding the liver and pancreas	2,652	35.3	216	40.5	1.14	(0.99-1.31)	1.12	(0.97-1.29)	1.11	(0.95-1.29)
Esophagus (ICD10:C15)	171	2.3	16	3.0	1.35	(0.80-2.25)	1.31	(0.78-2.20)	1.01	(0.53-1.93)
Stomach (ICD10:C16)	543	7.2	37	7.2	0.95	(0.68-1.32)	0.92	(0.66-1.29)	0.73	(0.49-1.11)
Colon (ICD10:C18)	172	2.3	19	3.6	1.62	(1.01-2.61)	1.61	(1.00-2.60)	1.73	(1.04-2.87)
Rectum (ICD10:C19-C21)	146	1.9	12	2.3	1.20	(0.66-2.16)	1.17	(0.65-2.12)	1.29	(0.67-2.47)
Liver (ICD10:C22)	243	3.2	39	7.6	2.20	(1.57-3.10)	2.12	(1.50-2.98)	1.89	(1.27-2.80)
Bile duct (ICD10:C23-C24)	133	1.8	17	3.1	1.78	(1.07-2.96)	1.76	(1.06-2.92)	1.68	(0.96-2.94)
Pancreas (ICD10:C25)	198	2.6	28	5.4	1.98	(1.33-2.95)	1.95	(1.31-2.91)	1.80	(1.15-2.81)
Lung (ICD10:C33-C34)	778	10.4	49	9.1	0.85	(0.64-1.14)	0.84	(0.63-1.13)	0.87	(0.64-1.19)
Kidney (ICD10:C64-C66, C68)	51	0.7	10	2.1	2.75	(1.39-5.43)	2.50	(1.26-4.98)	2.32	(1.09-4.98)
Bladder (ICD10:C67)	39	0.5	10	1.8	3.38	(1.68-6.81)	3.29	(1.63-6.65)	3.63	(1.78-7.39)
Prostate (ICD10:C61)	107	1.4	10	1.7	1.29	(0.67-2.47)	1.24	(0.65-2.39)	1.31	(0.68-2.53)
Non-cancer, non-circulatory system disease	2,530	33.6	343	66.7	1.96	(1.75-2.19)	1.91	(1.71-2.14)	1.90	(1.67-2.15)

rate*: per 10,000 person-years (age-standardized)

multivariate-adjusted*: adjsuted for age, BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

Women	DM(-) (n=52,042)		DM(+) (n=1,525)		HR				excluding cases during first 5-years	
	cases	rate*	cases	rate*	crude		multivariate-adjusted*		multivariate-adjusted* HR	
All-cause	4,295	45.9	345	102.3	2.11	(1.89-2.35)	1.98	(1.77-2.21)	2.02	(1.79-2.28)
All circulatory system diseases (ICD10:I00-I99)	1,084	11.6	123	36.6	2.82	(2.33-3.40)	2.49	(2.06-3.01)	2.56	(2.09-3.13)
Ischemic heart disease (ICD10:I20-I25)	196	2.1	42	13.4	5.10	(3.64-7.13)	4.52	(3.21-6.37)	4.56	(3.17-6.57)
Cerebrovascular disease (ICD10:I60-I69)	479	5.1	38	11.3	2.08	(1.49-2.90)	1.72	(1.23-2.40)	1.72	(1.19-2.47)
Cerebral infarction (ICD10:I63)	98	1.1	18	5.5	4.31	(2.60-7.15)	3.43	(2.05-5.74)	3.61	(2.12-6.15)
Intracerebral haemorrhage (ICD10:I61)	136	1.5	9	3.2	1.93	(0.98-3.81)	1.64	(0.83-3.24)	1.71	(0.83-3.54)
All-cancer (ICD10:C00-C97)	1,841	19.6	71	22.6	1.08	(0.85-1.37)	1.04	(0.82-1.32)	1.05	(0.81-1.36)
All sites excluding the liver	1,730	18.4	61	19.9	1.00	(0.77-1.29)	0.96	(0.74-1.24)	0.93	(0.70-1.24)
All sites excluding the liver and pancreas	1,540	16.4	52	17.3	0.97	(0.73-1.27)	0.93	(0.71-1.23)	0.90	(0.66-1.23)
Stomach (ICD10:C16)	224	2.4	8	3.4	1.05	(0.52-2.13)	1.10	(0.54-2.24)	1.21	(0.57-2.60)
Colon (ICD10:C18)	160	1.7	5	1.7	0.84	(0.35-2.06)	0.81	(0.33-2.00)	0.79	(0.29-2.15)
Liver (ICD10:C22)	111	1.2	10	2.6	2.30	(1.20-4.40)	2.21	(1.15-4.27)	2.66	(1.37-5.17)
Pancreas (ICD10:C25)	190	2	9	2.6	1.22	(0.62-2.39)	1.10	(0.56-2.16)	1.17	(0.57-2.39)
Lung (ICD10:C33-C34)	228	2.4	8	2.1	1.00	(0.49-2.02)	0.95	(0.47-2.40)	0.95	(0.35-2.61)
Non-cancer, non-circulatory system disease	1,370	14.7	151	43.2	2.79	(2.35-3.30)	2.67	(2.25-3.17)	2.66	(2.22-3.19)

rate*: per 10,000 person-years (age-standardized)

multivariate-adjusted*: adjsuted for age, BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

Table 3 Difference of the impact of diabetes by diagnosed period (All-cause mortality)

	Men				Women			
Diagnosed Period	n	cases	adjusted HR*		n	cases	adjusted HR*	
Never	41,036	6,975	1		50,555	4,106	1	
Before baseline	2,761	856	1.59	(1.48-1.71)	1,525	345	2.00	(1.79-2.23)
Between baseline and 5 year survey	1,341	254	1.20	(1.05-1.36)	861	123	1.55	(1.29-1.86)
Between 5 and 10 year survey	879	138	1.22	(1.03-1.44)	626	66	1.45	(1.14-1.86)

adjusted HR*: adjsuted for BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

Figure caption

Figure 1 Changes of hazard ratio of diabetes according to age (all-cause mortality)

(Men, circle; Women, diamond)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*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	6-7
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	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	10
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	5-7
		(b) Give reasons for non-participation at each stage	5-7
		(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	9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
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	22
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
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	16-17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

Appendix:

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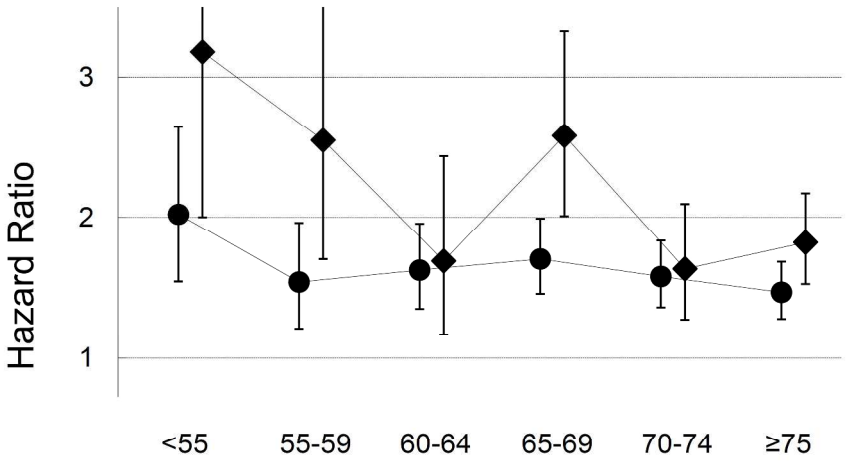

Changes of hazard ratio of diabetes according to age (all-cause mortality)
(Men, circle; Women, diamond)

277x173mm (300 x 300 DPI)

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Diagnosed Diabetes on Premature Death among Middle-aged Japanese: Results from a Large-Scale Population-based Cohort Study in Japan (JPHC Study)

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Diagnosed Diabetes and Premature Death among Middle-aged Japanese: Results from a Large-Scale Population-based Cohort Study in Japan (JPHC Study)

Running title: diabetes and death

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227 words in the abstract
3,222 words in the text
Three tables and one figure

Abstract

Objective

To examine the association between diabetes and premature death for Japanese general people

Design

Prospective cohort study

Setting

The Japan Public Health Center-based prospective Study (JPHC Study), data collected between 1990 and 2010.

Population

A total of 46,017 men and 53,567 women, aged 40 to 69 years at the beginning of baseline survey

Main outcome measures

Overall and cause specific mortality. Cox proportional hazards models were used to calculate the hazard ratios of all cause and cause specific mortality associated with diabetes.

Results

The median follow-up period was 17.8 years. During the follow-up period, 8,223 men and 4,640 women have died. Diabetes was associated with increased risk of death (856 men and 345 women) [hazard ratio (HR) 1.60, (95% confidence interval (95%CI) 1.49-1.71) for men and 1.98 (95%CI, 1.77-2.21) for women]. As for the cause of death, diabetes was associated with increased risk of death by circulatory diseases [HR 1.76 (95%CI 1.53-2.02) for men and

2.49 (95%CI 2.06-3.01) for women) while its association with the risk of cancer death was moderate [HR 1.25 (95%CI 1.11-1.42) for men and 1.04 (95%CI 0.82-1.32) for women]. Diabetes was also associated with increased risk of death for "non-cancer, non-circulatory system disease" [HR 1.91 (95%CI 1.71-2.14) for men and 2.67 (95%CI 2.25-3.17) for women].

Conclusions

Diabetes was associated with increased risk of death, especially the risk of death by circulatory diseases.

Keywords

diabetes mellitus, mortality

List of acronyms and abbreviations

BMI, Body Mass Index

ERFC, Emerging Risk Factors Collabolation

JPHC study, The Japan Public Health Center-based prospective Study

Strengths and limitations of this study

▪ A large scale population-based prospective study, the study population was defined as all registered Japanese inhabitants in the 11 public health center areas, was conducted.

▪ In Japan, the registration of deaths is required by the Family Registration Law and is believed to be complete.

▪ The assessment of diabetes mellitus was based on a self-report. Although the sensitivity and specificity of diagnosed diabetes were reported to be high, the assessment of diabetes by self-report is most likely an underestimate.

▪ The association between mortality and glycemia was not examined because data about glycemia were not available for the entire population.

INTRODUCTION

Today, Japanese people, especially Japanese women, are one of the people who live longest in the world[1]. On the other hand, the prevalence of type 2 diabetes has increased over the past few decades in Japan and the total number of diabetic patients is estimated to have risen from 7.4 million in 2002 to 9.5 million in 2012[2]. Diabetes is an important cause of mortality and morbidity and there are many literatures about diabetes and mortality. However, most of these literatures were focused on the Western people and the impact of diabetes on premature death among Japanese people was not well examined. Several genetic and environmental differences as well as causes of death between Japanese and Western people exist and in the present study we examined the association between diagnosed diabetes and premature death for Japanese general people in a large scale population based cohort study.

METHODS

The Japan Public Health Centre-based prospective Study (JPHC Study) consists of two cohort, Cohort I and Cohort II that comprise five and six prefectural public health center areas, respectively. The JPHC Study group members are listed in Appendix. The study population was defined as all registered Japanese inhabitants in the 11 public health center areas, aged 40 to 69 years at the beginning of each baseline survey, that is, in 1990 for Cohort I and in 1993 for Cohort II. Details of the study design have been described elsewhere[3]. The study

protocol was approved by the institutional review board of the National Cancer Center.

Initially, 140,420 subjects were identified as the study population. Subjects with non-Japanese nationality, duplicate enrollment, late report of emigration occurring before the start of follow-up or ineligibility because of incorrect birth date (n=260) were excluded.

Questionnaire

At the baseline survey, each participant completed a self-administered questionnaire that included questions about various lifestyle factors; such as medical history of major diseases, smoking and alcohol drinking status, height and weight and leisure-time physical activity. A similar survey was conducted at 5- and 10-years after the baseline survey.

At baseline, a total of 113,402 subjects responded to the questionnaire (response rate 80.9%). Subjects whose follow up period was not determined were excluded from further analysis (n=90). Subjects with any of the following conditions at baseline: cardiovascular disease, chronic liver disease, kidney disease and any type of cancer, were also excluded (n=8,049). Subjects who had missing baseline data for any of the exposure parameters described below (in Statistical Analysis) (n=5,049) or subjects with a body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 14 or more than 40 (n=1,363) were also excluded, because body mass index less than 14 or more than 40 in Japanese implies potentially unreliable data. After the above exclusions, the remaining cohort

consisted of 99,584 subjects (46,017 men and 53,567 women).

Assessment of diabetes

We defined the subject as having diagnosed diabetes if he or she marked on 'diabetes mellitus' to the question 'Has a doctor ever told you that you have any of the following diseases?' or on 'anti-diabetic drug' to the question 'Do you take any of the following drugs?' The sensitivity and specificity of diagnosed diabetes was reported as 82.9% and 99.7%, respectively[4]. The questionnaire did not distinguish type 1 and type 2 diabetes. However, the subjects of the present study were Japanese inhabitants aged 40 to 69 years and we believe that most of the subjects with diagnosed diabetes had type 2 diabetes.

Follow-up

Subjects were followed from the baseline survey up to December 31, 2010. All death certificates were forwarded centrally to the Ministry of Health, Welfare and Labor and coded for the National Vital Statistics. In Japan, the registration of deaths is required by the Family Registration Law and is believed to be complete. The underlying cause of death was determined by death certificates and was coded according to the tenth revision of the International Classification of Disease (ICD-10). Until 1995, the cause of death was determined according to the criteria of the ICD-9 and from 1995, the codes were translated

into the corresponding ICD-10 codes.

Statistical Analysis

Person-years of follow-up were counted from the date of the baseline survey until one of the following endpoints: the date of emigration from Japan, the date of death, or the end of the study period (December 31, 2010), whichever comes first. Age-standardized mortality rate was calculated by direct method using 5-year age specific mortality rate and the total population (subjects with and without diabetes) as standard. The association between diabetes and premature death was estimated as hazard ratios using Cox's proportional hazards model with age as the time scale[5]. We adjusted potential confounding factors: body mass index (categorized as 14-18.4, 18.5-24.9, 25-29.9, and 30-40), alcohol intake (categorized by weekly ethanol intake as non-drinker, 1-149g/week, 150-299g/week, 300-449g/week and ≥ 450g/week for men and the last two categories were combined into a category ≥300g/week for women), smoking status (categorized as never smoker, past smoker, current smoker at < 20 and ≥ 20 cigarettes per day), leisure-time physical activity (dichotomized as participate in sports at least once a week or not) and history of hypertension. The public health center areas were included in the analysis as strata. Effect of birth cohort was also examined by including birth cohort (birth year of 1920-1929, 1930-1939, and 1940-). Difference of the association between diabetes and mortality by diagnosed period was also examined by including

information about diagnosis of diabetes at 5 and 10 year survey for subjects who responded to 5 and/or 10 year survey, that is, subjects were classified into four groups according to the period of diagnosis of diabetes: diagnosed before baseline, diagnosed between baseline and 5 year survey, diagnosed between 5 and 10 year survey, never diagnosed. Person-years of follow-up of subjects diagnosed between baseline and 5 year survey and diagnosed between 5 and 10 year survey were counted from five and ten years after the baseline survey, respectively.

Hazard ratios were calculated for death from all cause, circulatory system diseases (ICD10, I00-I99), all cancer (ICD10, C00-C97) and site-specific cancer if there were 5 or more cases in subjects with diabetes. Deaths from other than circulatory system disease or cancer were grouped as “non-cancer, non-circulatory system disease” and the hazard ratio for this group was also calculated. The proportional hazards assumption was checked graphically and by using Schoenfeld residuals.

All analyses were performed separately for men and women.

RESULTS

The median follow-up period was 17.8 years both for men and women. During the follow-up period, 8,223 men and 4,640 women have died. The baseline characteristics of the study subjects are shown in Table 1. At baseline, 6.0% of men and 2.8% of women had diagnosed

diabetes. Among men, age, proportion of subjects with leisure-time physical activity and history of hypertension were higher among subjects with diabetes. Among women, age, the body mass index, proportion of subjects with leisure-time physical activity and history of hypertension were higher among subjects with diabetes. Besides these factors, medication about hypercholesterolemia was higher among subjects with diabetes (3.5% among diabetes and 1.2% among non-diabetes for men, and 5.5% among diabetes and 1.9% among non-diabetes for women).

Among men without diabetes, 1,744 subjects died from circulatory system disease, 3,093 subjects died from cancer and 2,530 subjects died from other causes, while among men with diabetes, these numbers were 230, 283 and 343, respectively. Among women without diabetes, 1,084 subjects died from circulatory system disease, 1,841 subjects died from cancer and 1,370 subjects died from other causes, while among women with diabetes, these numbers were 123, 71 and 151, respectively.

Hazard ratios for major causes of death were shown in Table 2. As shown in Table 2, diabetes was associated with increased risk of death both for men and women. The hazard ratio was high for circulatory system disease (ischemic heart disease and cerebrovascular disease) among men and especially high for ischemic heart disease and cerebral infarction among women. The association between diabetes and the risk of death from cancer was moderate and the hazard ratios were not high except some types of cancer (liver cancer both among men

and women and pancreas, kidney and bladder cancer among men), while death from "multiple myeloma and malignant plasma cell neoplasms" in men and "malignant neoplasm of breast" in women was markedly lower among subjects with diabetes (46/0 cases for multiple myeloma and 135/1 cases for neoplasm of breast). Diabetes was also associated with increased risk of death for "non-cancer, non-circulatory system disease". These results were almost unchanged when the deaths during the first five years were excluded. The major causes of death for "non-cancer, non-circulatory system disease" among subjects with diabetes were "unspecified diabetes mellitus" (E14) (men 17.8%, women 22.5%), "pneumonia, organism unspecified" (J18) (men 13.7%, women 13.9%) and "unknown causes" (men 6.4%, women 10.6%).

The hazard ratio of diabetes on mortality was larger among subjects with diabetes diagnosed before baseline than among subjects diagnosed after baseline (Table 3). Differences of hazard ratios between subjects diagnosed between baseline and 5 year survey and subjects diagnosed between 5 and 10 year survey were not clear.

No significant interaction was observed between adjustment factors and the results were essentially unchanged by including the effect of birth cohort. Further adjustment for medication for hypercholesterolemia had little impact on our results. We found no violation of proportionality assumption. However, although it was not confirmed statistically, there was a tendency that the hazard ratio of diabetes for death decreased as age increased. (Figure 1)

DISCUSSION

In this population-based prospective study of middle-aged Japanese, we observed the increased risk of death for subjects with diabetes. As for the cause of death, diabetes was associated with increased risk of death by circulatory system diseases and "non-cancer, non-circulatory system disease", while the association with the risk of death from cancer was moderate.

There are many literatures about diabetes and mortality and substantial numbers of these results were combined into the ERFC (Emerging Risk Factors Collabolation)[6]. In ERFC, the hazard ratios among subjects with diabetes compared with subjects without diabetes were reported as 1.80 for all cause mortality, 1.25 for death from cancer, 2.32 for death from vascular causes and 1.73 for death from other causes.

Results of another large prospective cohort study of one million U.S. adults (CPS-II) was also published[7]. In the study, relative risk of all-cause mortality was 1.73 for men and 1.90 for women and that of cancer death was 1.07 for men and 1.11 for women and that of cardiovascular system death was 1.92 for men and 2.09 for women.

Recently published meta-analysis also reported increased mortality among diabetic subjects and the relative risk for all-cause mortality was 1.57 for men and 2.00 for women and that of

cardiovascular mortality was 1.76[8].

Although the results were almost similar, there is a difference of major causes of death between our study and these studies. In the present study, 41% and 25% of all deaths were caused by cancer and circulatory system disease, respectively, while these numbers were 34% and 36% in the ERFC and 15% and 50% in the CPS-II, respectively. This tendency that Japanese die from cancer more than from circulatory system disease and that this is opposite for western people (although ERFC was a collation of over 100 prospective studies, about 90% of the subjects were from North America or Europe), is also observed in the world statistics[9]. As discussed above, diabetes was associated with increased risk of death by circulatory system disease more than death by cancer. This may seem as if the association between diabetes and mortality is stronger in a population among which the major cause of death was circulatory system disease, that is, the association is stronger among western people than Japanese. However, this is not true because the non-vascular, non-cancer death plays an unignorable part of death.

Our results were also almost consistent with the Japanese large scale cohort study (Takayama study)[10]. The most remarkable difference between the Takayama study and the present study was the risk of death by coronary heart disease among women. In the Takayama study, the risk of death by coronary heart disease among women were lower in subjects with diabetes than subjects without diabetes (hazard ratio 0.49, 95% confidence interval 0.07-3.57).

As shown in the wide confidence interval, this difference may come from the very low number of cases (only two cases) of coronary heart disease death among women with diabetes. The collaborate study in Asia[11] and meta-analysis including this collaborate study[12] and its update[13] reported the increased risk of coronary heart disease among diabetic women and our results were consistent with these reports. Our study revealed that the effect of diabetes on the risk of cardiovascular death was greater among women than among men. This is also consistent with the above mentioned meta-analysis[12,13]. Although several possible explanations, such as 1) a heavier burden of cardiovascular risk factors, 2) a major impact of some cardiovascular risk factors and/or diabetes per se on cardiovascular disease, 3) differences in the structure and function of heart and vessels, and 4) disparities in medical treatment as well as gender differences in treatment response, are postulated, the underlying mechanism of this sex difference in the impact of diabetes on cardiovascular disease is not elucidated well[14].

As for the death from cancer, our results were almost consistent with the report about the incidence of cancer in the same JPHC study[15]. In the case of incidence, diabetes moderately increased the risk of all cancer and the risk was especially high for cancer of the liver, pancreas and kidney among men and for cancer of the stomach, liver and ovary among women. In the present study, a similar tendency was observed among men, however the number of death from cancer was small among women and the increased mortality risk

associated with diabetes was observed only in liver cancer.

We found that the association between diabetes and mortality was stronger among subjects diagnosed before baseline than among subjects diagnosed after baseline. This result suggests that the effect of diabetes on mortality becomes stronger as duration of diabetes becomes longer.

We also found, although not confirmed statistically, that the hazard ratio of diabetes for death decreased as age increased. The similar phenomenon was observed in the ERFC. The reason is unclear. However, one possible explanation is that diabetic patients who lived long managed their diabetes relatively well. Another possible explanation is that the diabetic patients with older age included more recently developed diabetes because the risk of diabetes increases as age increases and, as stated above, the association between diabetes and mortality was relatively weaker in newly developed diabetes.

The strength of our study was the large number of subjects. The number of subjects was about 3.4 times that of the Takayama study. Another strength of the present study was that it was based on the general population in Japan. Although this study was conducted on subjects who responded the baseline questionnaire, we believe that the high response rate (80.9%) makes it possible to assess the association between diabetes and mortality in the general population. In addition, the age-specific mortality rates in the present study were similar to those of Japanese general population. For example, age-specific mortality rates (per 10,000 person-years) in the

present study in men were 15.5, 36.3, 83.0 and 224.0 for 40, 50, 60 and 70 years-old respectively and those of Japanese general population (Abridged Life Tables For Japan 2005) were 14.4, 35.8, 89.4 and 213.8. In women, the age-specific mortality rates (per 10,000 person-years) in the present study were 5.3, 17.4, 33.2 and 87.2 for 40, 50, 60 and 70 years-old respectively and those of Japanese general population were 7.5, 17.7, 36.6 and 89.3. No large discrepancies in mortality rates exist between our study and Japanese general population and this may also support the representativeness of our cohort.

There are several methodological limitations in the present study. The assessment of diabetes mellitus was based on a self-report. Although the sensitivity (82.6%) and specificity (99.7%) of diagnosed diabetes were reported to be high, the proportion of subjects with diabetes at baseline (6.0% for men and 2.8% for women) was low compared with the estimates in the same period (9.9-13.1% for men and 9.1-11.5% for women)[16]. The assessment of diabetes by self-report, therefore, is most likely an underestimate and our results may have been distorted toward null by this misclassification. However, in the above mentioned meta-analysis, sensitivity analyses were performed and no difference was found in the ratio of the relative risks for diabetes between the method of diabetes diagnosis (self-report versus glucose measured)[12]. Previous studies have revealed the association between mortality and glycemia in diabetic patients[17] and this association holds even in the non-diabetic range of glycemia[18,7]. Since we have no data about glycemia, we could not assess the association

between mortality and glycemia in the present study.

Despite these limitations, our present study revealed the association between diabetes and mortality in the Japanese general population. Recent increase in diabetes patients will influence the longevity of Japanese people in the future and we believe that our study would provide useful information both for further research and treatment of diabetes.

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Contributors: MK analysed data, drafted the manuscript, reviewed and edited the manuscript, and contributed to discussion; MN and ST conducted, designed, and supervised the study, and contributed to discussion; TM, AG, YT, YM, AN, HI, MI, and NS reviewed the manuscript, and contributed to discussion. NM is guarantors. All authors read and approved the final

manuscript.

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Competing interests:

MI is the beneficiary of a financial contribution from the AXA Research fund as a chair holder on the AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo. The AXA Research Fund had no role in the design, data collection, analysis, interpretation or manuscript drafting, or in the decision to submit the manuscript for publication.

Ethical approval: This study was approved by the institutional review boards of the National Cancer Center, Japan, and the National Center for Global Health and Medicine, Japan.

Data sharing: no additional data available.

Declaration of transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1 Baseline characteristics according to diagnosed diabetes

	Men (n=46,017)				Women (n=53,567)			
	DM(-) (n=43,256)		DM(+) (n=2,761)		DM(-) (n=52,042)		DM(+) (n=1,525)	
Age	50	(44-56)	53	(49-59)	50	(44-57)	56	(50-62)
BMI	23.5	(2.8)	23.7	(3.0)	23.3	(3.1)	24.4	(3.6)
Smoking								
Never	10,175	(23.5)	577	(20.9)	47,347	(91.0)	1,363	(89.4)
Past	10,106	(23.4)	713	(25.8)	942	(1.8)	45	(3.0)
Current（<20 cigarettes/day）	5,913	(13.7)	398	(14.4)	2,422	(4.7)	64	(4.2)
Current（≥20 cigarettes/day）	17,062	(39.4)	1,073	(38.9)	1,331	(2.6)	53	(3.5)
Alcohol								
Non drinker	13,248	(30.6)	944	(34.2)	44,844	(86.2)	1,386	(90.9)
1-150 g/week	9,667	(22.4)	575	(20.8)	5,609	(10.8)	103	(6.8)
150-300 g/week	9,032	(20.9)	511	(18.5)	996	(1.9)	16	(1.0)
300-450 g/week (≥300 week for women)	5,325	(12.3)	273	(9.9)	593	(1.1)	20	(1.3)
≥450 g/week	5,984	(13.8)	458	(16.6)				
Physical activity (active)	8,188	(18.9)	682	(24.7)	9,629	(18.5)	381	(25.0)
Hypertension (+)	7,218	(16.7)	795	(28.8)	8,145	(15.7)	545	(35.7)

Table 2 Mortality according to diagnosed diabetes

Men	DM(-) (n=43,256)		DM(+) (n=2,761)		HR				excluding cases during first 5-years	
	cases	rate*	cases	rate*	crude		multivariate-adjusted*		multivariate-adjusted* HR	
All-cause	7,367	98.0	856	163.9	1.65	(1.54-1.77)	1.60	(1.49-1.71)	1.59	(1.47-1.71)
All circulatory system diseases (ICD10:I00-I99)	1,744	23.2	230	43.6	1.88	(1.63-2.15)	1.76	(1.53-2.02)	1.79	(1.54-2.09)
Ischemic heart disease (ICD10:I20-I25)	434	5.8	76	14.2	2.47	(1.93-3.15)	2.30	(1.80-2.95)	2.32	(1.78-3.03)
Cerebrovascular disease (ICD10:I60-I69)	705	9.4	88	16.7	1.78	(1.43-2.23)	1.68	(1.34-2.10)	1.75	(1.37-2.23)
Cerebral infarction (ICD10:I63)	176	2.3	27	4.9	2.07	(1.38-3.11)	1.87	(1.24-2.82)	1.76	(1.09-2.82)
Intracerebral haemorrhage (ICD10:I61)	227	3.0	27	5.6	1.86	(1.25-2.78)	1.73	(1.16-2.59)	2.00	(1.30-3.07)
All-cancer (ICD10:C00-C97)	3,093	41.2	283	53.6	1.28	(1.13-1.45)	1.25	(1.11-1.42)	1.22	(1.06-1.39)
All sites excluding the liver	2,850	37.9	244	46.0	1.20	(1.05-1.37)	1.18	(1.03-1.34)	1.16	(1.00-1.34)
All sites excluding the liver and pancreas	2,652	35.3	216	40.5	1.14	(0.99-1.31)	1.12	(0.97-1.29)	1.11	(0.95-1.29)
Esophagus (ICD10:C15)	171	2.3	16	3.0	1.35	(0.80-2.25)	1.31	(0.78-2.20)	1.01	(0.53-1.93)
Stomach (ICD10:C16)	543	7.2	37	7.2	0.95	(0.68-1.32)	0.92	(0.66-1.29)	0.73	(0.49-1.11)
Colon (ICD10:C18)	172	2.3	19	3.6	1.62	(1.01-2.61)	1.61	(1.00-2.60)	1.73	(1.04-2.87)
Rectum (ICD10:C19-C21)	146	1.9	12	2.3	1.20	(0.66-2.16)	1.17	(0.65-2.12)	1.29	(0.67-2.47)
Liver (ICD10:C22)	243	3.2	39	7.6	2.20	(1.57-3.10)	2.12	(1.50-2.98)	1.89	(1.27-2.80)
Bile duct (ICD10:C23-C24)	133	1.8	17	3.1	1.78	(1.07-2.96)	1.76	(1.06-2.92)	1.68	(0.96-2.94)
Pancreas (ICD10:C25)	198	2.6	28	5.4	1.98	(1.33-2.95)	1.95	(1.31-2.91)	1.80	(1.15-2.81)
Lung (ICD10:C33-C34)	778	10.4	49	9.1	0.85	(0.64-1.14)	0.84	(0.63-1.13)	0.87	(0.64-1.19)
Kidney (ICD10:C64-C66, C68)	51	0.7	10	2.1	2.75	(1.39-5.43)	2.50	(1.26-4.98)	2.32	(1.09-4.98)
Bladder (ICD10:C67)	39	0.5	10	1.8	3.38	(1.68-6.81)	3.29	(1.63-6.65)	3.63	(1.78-7.39)
Prostate (ICD10:C61)	107	1.4	10	1.7	1.29	(0.67-2.47)	1.24	(0.65-2.39)	1.31	(0.68-2.53)
Non-cancer, non-circulatory system disease	2,530	33.6	343	66.7	1.96	(1.75-2.19)	1.91	(1.71-2.14)	1.90	(1.67-2.15)

rate*: per 10,000 person-years (age-standardized)

multivariate-adjusted*: adjsuted for age, BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

Women	DM(-) (n=52,042)		DM(+) (n=1,525)		HR				excluding cases during first 5-years	
	cases	rate*	cases	rate*	crude		multivariate-adjusted*		multivariate-adjusted* HR	
All-cause	4,295	45.9	345	102.3	2.11	(1.89-2.35)	1.98	(1.77-2.21)	2.02	(1.79-2.28)
All circulatory system diseases (ICD10:I00-I99)	1,084	11.6	123	36.6	2.82	(2.33-3.40)	2.49	(2.06-3.01)	2.56	(2.09-3.13)
Ischemic heart disease (ICD10:I20-I25)	196	2.1	42	13.4	5.10	(3.64-7.13)	4.52	(3.21-6.37)	4.56	(3.17-6.57)
Cerebrovascular disease (ICD10:I60-I69)	479	5.1	38	11.3	2.08	(1.49-2.90)	1.72	(1.23-2.40)	1.72	(1.19-2.47)
Cerebral infarction (ICD10:I63)	98	1.1	18	5.5	4.31	(2.60-7.15)	3.43	(2.05-5.74)	3.61	(2.12-6.15)
Intracerebral haemorrhage (ICD10:I61)	136	1.5	9	3.2	1.93	(0.98-3.81)	1.64	(0.83-3.24)	1.71	(0.83-3.54)
All-cancer (ICD10:C00-C97)	1,841	19.6	71	22.6	1.08	(0.85-1.37)	1.04	(0.82-1.32)	1.05	(0.81-1.36)
All sites excluding the liver	1,730	18.4	61	19.9	1.00	(0.77-1.29)	0.96	(0.74-1.24)	0.93	(0.70-1.24)
All sites excluding the liver and pancreas	1,540	16.4	52	17.3	0.97	(0.73-1.27)	0.93	(0.71-1.23)	0.90	(0.66-1.23)
Stomach (ICD10:C16)	224	2.4	8	3.4	1.05	(0.52-2.13)	1.10	(0.54-2.24)	1.21	(0.57-2.60)
Colon (ICD10:C18)	160	1.7	5	1.7	0.84	(0.35-2.06)	0.81	(0.33-2.00)	0.79	(0.29-2.15)
Liver (ICD10:C22)	111	1.2	10	2.6	2.30	(1.20-4.40)	2.21	(1.15-4.27)	2.66	(1.37-5.17)
Pancreas (ICD10:C25)	190	2	9	2.6	1.22	(0.62-2.39)	1.10	(0.56-2.16)	1.17	(0.57-2.39)
Lung (ICD10:C33-C34)	228	2.4	8	2.1	1.00	(0.49-2.02)	0.95	(0.47-2.40)	0.95	(0.35-2.61)
Non-cancer, non-circulatory system disease	1,370	14.7	151	43.2	2.79	(2.35-3.30)	2.67	(2.25-3.17)	2.66	(2.22-3.19)

rate*: per 10,000 person-years (age-standardized)

multivariate-adjusted*: adjsuted for age, BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

Table 3 Difference of the association between diabetes and mortality by diagnosed period (All-cause mortality)

	Men				Women			
Diagnosed Period	n	cases	adjusted HR*		n	cases	adjusted HR*	
Never	41,036	6,975	1		50,555	4,106	1	
Before baseline	2,761	856	1.59	(1.48-1.71)	1,525	345	2.00	(1.79-2.23)
Between baseline and 5 year survey	1,341	254	1.20	(1.05-1.36)	861	123	1.55	(1.29-1.86)
Between 5 and 10 year survey	879	138	1.22	(1.03-1.44)	626	66	1.45	(1.14-1.86)

adjusted HR*: adjsuted for BMI (<18, 18-20.9, 21-22.9, 23-24.9, 25-26.9, ≥27), alcohol intake(non-drinker, <150, 150-299, 300-450, ≥450 g/week (women, ≥300 g/week)), smoking (never, past, <20, ≥20 cigarettes /day), history of hypertension, leisure-time physical activity. Stratified by area.

Figure caption

Figure 1 Changes of hazard ratio of diabetes according to age (all-cause mortality)

(Men, circle; Women, diamond)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*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	6-7
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	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	10
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	5-7
		(b) Give reasons for non-participation at each stage	5-7
		(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	9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
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	22
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
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	16-17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

Appendix:

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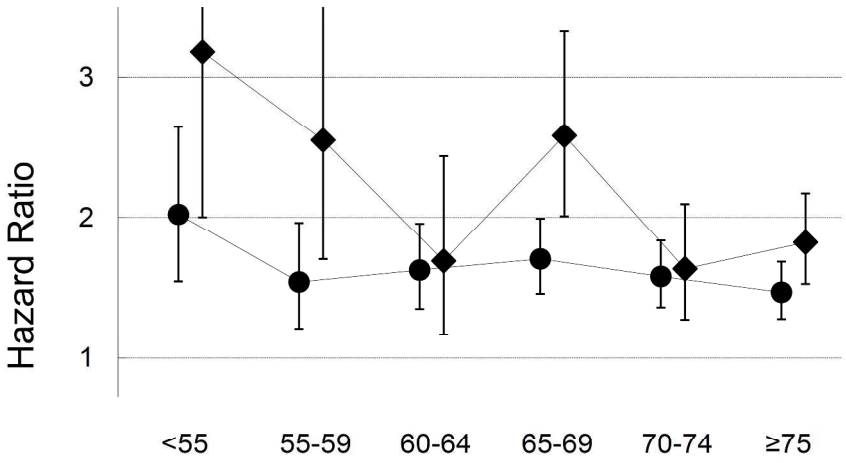

Changes of hazard ratio of diabetes according to age (all-cause mortality)
(Men, circle; Women, diamond)

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