Risk of cause-specific death in individuals with diabetes mellitus: a competing risks analysis

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OBJECTIVE

Diabetes is a common cause of shortened life expectancy. We aimed to assess the association between diabetes and cause-specific death.

RESEARCH DESIGN AND METHODS

We used the pooled analysis of individual data from 12 Spanish population cohorts with 10-year follow-up. Participants had no previous history of cardiovascular diseases and were 35-79 years old. Diabetes status was self-reported or defined as glycemia >125 mg/dl at baseline. Vital status and causes of death were ascertained by medical records review and linkage with the official death registry. The hazard ratios and cumulative mortality function were assessed with two approaches, with and without competing risks: proportional subdistribution hazard (PSH) and cause-specific hazard (CSH), respectively. Multivariate analyses were fitted for cardiovascular, cancer, and noncardiovascular noncancer deaths.

RESULTS

We included 55,292 individuals (15.6% diabetic with overall mortality of 9.1%). The adjusted hazard ratios showed that diabetes increased mortality risk: (1) cardiovascular death, CSH=2.03 (95% confidence interval=1.63-2.52) and PSH=1.99 (1.60-2.49) in men; CSH=2.28 (1.75-2.97) and PSH=2.23 (1.70-2.91) in women; (2) cancer death, CSH=1.37 (1.13-1.67) and PSH=1.35 (1.10-1.65)] in men; CSH=1.68 (1.29-2.20) and PSH=1.66 (1.25-2.19) in women; and (3) noncardiovascular noncancer death, CSH=1.53 (1.23-1.91) and PSH=1.50 (1.20-1.89) in men; CSH=1.89(1.43-2.48) and PSH=1.84 (1.39-2.45) in women. In all instances, the cumulative mortality function was significantly higher in individuals with diabetes.

CONCLUSIONS

Diabetes is associated with premature death from cardiovascular disease, cancer, and noncardiovascular noncancer causes. The use of CSH and PSH provides a comprehensive view of mortality dynamics in the diabetic population.

Keywords: Diabetes mellitus; Epidemiology; Mortality; Cardiovascular Diseases; Neoplasms; Risk Assessment; Competing Risks

Diabetes mellitus constitutes a worldwide public health problem (1) that affected 382 million people (8.3% of the world's population) in 2013 (2). Recent projections suggest that this prevalence is likely to increase in the next 20 years, affecting 592 million people (10.1%) in 2035. In Spain, diabetes affects 13.8% of individuals older than 18 years and is more prevalent in men than in women (3,4).

The average life expectancy of a 50-year-old individual with diabetes is 6 years shorter than it would be without the disease (5). Diabetes not only doubles or quadruples cardiovascular risk, compared with the general population (6,7), but also leads to an increased risk of cancer, as shown by some cohort studies (5,8).

The study of predictors of cause-specific death in individuals with diabetes in a cohort study is an example of competing risk analysis. Thus, a death due to the primary cause of interest (e.g. cancer) could be precluded by a death due to another cause (e.g. cardiovascular disease); the occurrence of the latter prevents us from observing the other. Two regression approaches have been widely used to study mortality risk with and without competing risks: proportional subdistribution hazard (PSH) and cause-specific hazard (CSH), respectively. The CSH quantifies the event rate among individuals at risk of developing the event, whereas the PSH estimates the probability of a particular event for an individual who has survived up to a given time without any event, or had the competing event prior to that given time. Thus, the PSH analysis can be used if different types of events are studied and the focus is on the time and type of the event of primary interest (9-12). Consequently, CSH and PSH yield different interpretations needed to understand the epidemiological event dynamics (13).

The aims of this study were to assess the association between exposure to diabetes at baseline, either self-reported or glycemia >125 mg/dl, and the risk of cause-specific

death in a population-based cohort with a median follow-up of 10 years, with and without competing risks (PSH and CSH methods, respectively).

RESEARCH DESIGN AND METHODS

Design and participants

We conducted a pooled analysis of individual data from 12 population cohorts in 7 Spanish regions examined with similar methods between 1991 and 2005. Participants in all cohorts were randomly selected from the general population, did not present previous symptoms or diagnosis of cardiovascular diseases, and were aged 35 to 79 years. All participants were examined at baseline and followed up for a median of 10 years. Supplementary Table 1 includes the characteristics of each cohort contributing to the FRESCO Study. The methodology of the FRESCO study has been explained in depth elsewhere (14). All the participants were duly informed and signed a consent form to participate in the component studies. The FRESCO study was approved by the local Parc de Salut Mar Ethics Committee (authorization #: 2009/3391/I).

Measurements

The following risk factors were measured at baseline using standardized methods based on World Health Organization recommendations (15). Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m2). Using a standardized smoking questionnaire, participants were classified as smokers (current or quit <1 year) or nonsmokers (quit ≥1 year or never smoked). Blood pressure was determined from the average of 2 separate readings taken at least 5 min apart. Blood was withdrawn after 10–14 hours fasting. Total and high-density lipoprotein (HDL)

cholesterol concentrations were measured in serum sample aliquots stored at −80 °C. Friedewald formula was used to estimate low-density lipoprotein (LDL) cholesterol whenever triglycerides were <300 mg/dl. A previous study, in which 9 of the 11 FRESCO cohorts participated, obtained good agreement in the measurement of frozen samples from a random subset of participants, establishing that the study's laboratory measurements can be reliably pooled (4).

Assessment of diabetes mellitus status and plasma glucose level

Diabetes and type of treatment were self-reported by the participants in all studies. We also considered diabetic those participants in whom glycemia >125 mg/dl was observed at the time of baseline examination, regardless of their awareness of this glycemic disorder.

Mortality ascertainment

Vital status and cause of death during 10-year follow-up were ascertained by examining the corresponding electronic medical record for in-hospital deaths and by reviewing death certificates from regional and national mortality offices and autopsy for out-of-hospital deaths. All deaths were coded according to the 10th revision of the International Classification of Diseases (ICD) (14). Mortality was classified as being due to cardiovascular diseases (ICD F01, G45, I00-I99, Q20, Q28, R96), all malignant neoplasms (ICD C00-C99, D1-D48), and other diseases (rest of ICD codes). The cardiovascular group was subdivided by coronary heart disease (ICD I20-I25), cerebrovascular disease (ICD F01, I60-I69, G45), and heart failure (ICD I50-I52). Malignant neoplasms were subdivided into 10 individual sites: stomach (ICD C16),

pancreas (ICD C25), liver and intrahepatic bile ducts (ICD C22), colon and rectum (ICD C18-C21), bronchus and lung (ICD C33-C34), prostate (ICD C61), female genital organs (ICD C51-C58), bladder (ICD C67), breast (ICD C50), and deaths due to malignancies at all other sites. Noncardiovascular and noncancer causes were grouped as “rest of causes” and were subdivided into infections (ICD A00-A99, B00-B99, J12-J18), dementia and Alzheimer disease (ICD F00-F03, G30-G32), chronic obstructive pulmonary disease (ICD J41-J47), diseases of the liver (ICD K70-K77), and diseases of the genitourinary system (ICD N00-N39). All causes of death and the corresponding ICD codes have been included in Supplementary Table 2.

Statistical analysis

All analyses were stratified by sex. Age was summarized as mean and standard deviation, and categorical variables as proportions. Chi-square tests for categorical variables and Student t test for continuous variables were computed to test differences in sociodemographic variables and risk factors prevalence according to diabetes at baseline. Additionally, differences in vital status at the end of the follow-up were estimated with the log-rank test. The sex-specific all-cause, cardiovascular, cancer and noncardiovascular noncancer mortality rates were calculated for the population with and without diabetes by 10-year age intervals and age-standardized by the direct method using a European standard population aged 35 to 79 years (16).The sex difference in absolute age-standardized mortality rates was assessed by the ratio of men and women in a population.

All multivariate analyses were fitted for death occurrence, divided in 3 groups: cardiovascular, cancer, and noncardiovascular noncancer death. The hazard ratios and

cumulative mortality function were assessed by Cox (CSH) and Fine-Gray (PSH) regressions using the "cmprsk" R package (17,18). The first provides a direct measure of the association of diabetes with a single cause of death (i.e. treats any competing events as censored at the time they occurred). The second considers as a single cause of death both the association of diabetes with a single cause of death and the contribution of another competing event by actively maintaining individuals in the risk sets (i.e. divides the probability of death into the probability corresponding to each competing event). Proportional hazards assumption of CSH and PSH were validated in Cox and Fine-Gray regressions, respectively. A multivariable sex-stratified model was fitted, adjusting for potential confounders: age, smoking status, body mass index, systolic blood pressure, and total and HDL cholesterol. Finally, we plotted the sex-stratified cumulative hazard functions for all three causes of death and the sex- and age-adjusted hazard ratios of the most frequent single causes of death according to the CSH and PSH methods. A sensitivity analysis was performed excluding those individuals who died of cancer during the first year of follow-up, as a proxy of disease severity.

All calculations were made with R statistical package (R Foundation for Statistical Computing, Vienna, Austria; version 3.1.1).

RESULTS

The FRESCO cohort included 55,292 individuals (15.6% with diabetes). The number of deaths in the 10-year median follow-up [interquartile range 8.8-10] was 1710 (3.8%) among the 44,664 individuals without diabetes and 781 (9.1%) in those with diabetes. Finally, no cause of death information was available for 85 (10.9%) and 220 (12.9%) of the deaths with and without diabetes, respectively (Supplementary Figure 1).

Individuals with diabetes were significantly older, less likely to smoke, had higher body mass index, systolic blood pressure, triglycerides, and glycemia, and more often presented with hypertension, compared to individuals without diabetes. In addition, individuals with diabetes had significantly lower HDL cholesterol values, while total cholesterol values were significantly lower in men but significantly higher in women, compared to the population without diabetes. In addition, women with diabetes presented with significantly higher diastolic blood pressure and LDL cholesterol, compared to women without diabetes. The overall mortality rate was significantly higher in individuals with diabetes, whereas only cardiovascular disease showed a higher unadjusted mortality rate in individuals with diabetes compared to those without (Table 1).

Men had higher mortality rates than women (i.e. sex ratio >1 in all instances). However, the lower sex ratio found in the population with diabetes reflects an attenuation of the mortality differences, probably driven by the diabetic status (Supplementary Table 3).

The crude cumulative mortality functions showed that individuals with diabetes presented with significantly higher risk of cardiovascular, cancer, noncardiovascular noncancer, and overall death in the 10-year follow-up. The estimates performed with both methods (i.e. CSH and PSH) were similar in individuals without diabetes and slightly higher with the CSH approach in those with diabetes (Figure 1 and Supplementary Figure 2).

To ascertain the association between diabetes status and mortality, we fitted a multivariate model for every cause of death adjusted for age, smoking status, body mass index, systolic blood pressure, and total and HDL cholesterol. Diabetes significantly

increased the risk of cardiovascular, cancer, noncardiovascular noncancer, and overall death in both sexes. The hazard ratios performed with PSH were lower than those performed with CSH in all instances; however, these differences were small (Table 2 and Supplementary Table 4). The sensitivity analysis including all individuals that had not died of cancer within the first year of follow-up yielded similar results (Supplementary Table 5). Single-cause analysis showed that, compared to the nondiabetic population, individuals with diabetes had significantly higher risk of cardiovascular death (e.g., myocardial infarction, stroke, heart failure), death due to liver, colon-rectum, and lung cancer, and death from infections, chronic obstructive pulmonary disease, and liver and kidney disease. Again, small differences were found between the PSH and the CSH results (Figure 2).

CONCLUSIONS

Individuals with diabetes had significantly higher risk of death than the population without diabetes, even after adjusting for risk factors that have individually shown a significant association with mortality rates (i.e. age, smoking status, body mass index, systolic blood pressure, total and HDL cholesterol). Mortality rate was significantly higher for all causes, as classified in three groups: cardiovascular diseases, cancer, and all other causes. The highest magnitude of association was found for cardiovascular death, but the excess risk also observed for some cancer locations (e.g., stomach, liver, colon-rectum or lung) or other pathologies (e.g., liver and kidney disease) points out the vulnerability that diabetes confers. The steep decrease in cardiovascular deaths, particularly observed in Western countries (19), likely results in the emergence of other

causes of death in individuals with diabetes. Nonetheless, the disorder is still associated with shorter life expectancy.

Most common causes of death in diabetes

The risk of death from coronary heart disease was almost 3-fold higher in individuals with diabetes. This observation has traditionally lead to controversial interpretations pointing out that individuals with diabetes and no coronary heart disease should be managed with a cardiovascular secondary prevention strategy (20). However, more recent publications have shown that coronary risk in individuals with diabetes and no coronary heart disease was significantly lower than that observed in patients with a history of coronary heart disease (21,22). Although the magnitude of the association was lower, diabetes was also significantly related with higher mortality from stroke and heart failure (6).

Concurring with previous reports, our results showed a moderate association of diabetes with death from cancer, particularly in the liver and colon-rectum (5). A possible pathological mechanism that may explain this association with the digestive tract is the increased insulin resistance and the alteration of insulin-like growth factors (8,23,24). In addition, the risk of lung cancer was increased in individuals with diabetes in our study results. However, this association is not consistent in the literature, with studies showing both decreased and increased risks of this type of cancer in individuals with diabetes (5,8). Finally, we did not find a significant association between diabetes and pancreatic cancer, despite a suggested link between the two diseases (8).

Regarding other causes of death, we observed a strong positive association of diabetes with deaths from infections and from renal and liver diseases, similarly to the

Emerging Risk Factor Collaboration findings (5). These results may reflect associated diabetes complications such as suppression of cellular immunity, nephropathy, and fatty liver disease (19).

Finally, the hazard ratios for mortality in participants with diabetes compared with those without were always higher in women than in men for all groups of causes assessed. This observation suggests that insulin resistance may have a greater effect in women. In the case of cardiovascular mortality, the hyperinsulinemia and hyperglycemia environment is likely to worsen the effect of cardiovascular risk factors (25,26). On the other hand, tumor cell proliferation and metastases may also increase, enhancing cancer risk (27,28). As a result, diabetes seems to attenuate the mortality risk gap between men and women observed in the general population (29).

Competing risk analysis

The differences observed between the CSH and PSH methods highlight the differing interpretations of both estimates and therefore, their utility for understanding cause-specific death dynamic in diabetes, compared with the general population (12). The estimates performed with CSH implied that, among individuals who survived all events during the 10-year follow-up, the CSH rate in those with diabetes was the CSH ratio multiplied by the CSH rate of those who do not have diabetes. This method is appropriate to ascertain the disease etiology and therefore yields a valid measure of association. However, CSH did not allow event prediction because it measures the association of diabetes with a cause-specific death; a competing event contributes only by passively removing individuals from the risk set (i.e. the cause of death is irrelevant to the analysis). The PSH approach is more relevant for prediction because it yields a

measure of association that reflects both the association of diabetes with a certain cause-specific death (e.g., lung cancer) and the contribution of another cause-specific death (e.g., coronary heart disease) by actively maintaining diabetic and nondiabetic individuals in the risk set (12).

To get a complete understanding of event dynamics in the diabetic population, the present report followed the recommendations by Latouche et al.: (1) Use a different terminology for each model of the hazard ratio (CSH for Cox model and PSH for Fine-Gray model); (2) Report all the CSH; (3) Report the PSH for the event of interest and the PSH for the competing event; (4) Present the results in a unified interpretation; (5) Explicitly check the proportional hazards assumption for Cox and Fine-Gray models; (6) Provide plots of all cumulative mortalities using CSH and PSH (13).

The differences between methods observed in our study were not larger because of the low mortality rate, particularly in individuals with no diabetes. Indeed, we observed the biggest differences for the most common single causes of death: coronary heart disease and unspecified site or other cancers.

Public health implications

Several studies have shown alteration in the diabetes course by introducing changes in health promotion activities (e.g., screening and support in achieving lifestyle modifications), in the clinical management of such diseases (e.g., intensive control of cardiovascular risk factors), in health systems (e.g., functional multidisciplinary units for the management of diabetes) and in society as a whole (e.g., smoking ban policies) (30-35). This multidisciplinary approach may partially explain the annual 3% decrease in cardiovascular mortality observed in individuals with diabetes in the US; however,

the pattern in individuals without such disease has been much lower (36-38). In Spain, particularly, despite the improvements observed in the control of cardiovascular risk factors in individuals with diabetes, there is still room for preventive activity (4,39).

Characteristics and limitations

Our study has several limitations. First, we used a single glycemia measure to diagnose diabetes; however, this is the standardized method defined by World Health Organization recommendations for epidemiologic studies (15). Second, the component studies did not register the specific type of diabetes (1 or 2). However, the prevalence of type 1 diabetes in our country ranged between 0.08% and 0.2% whereas type 2 diabetes affects between 4.8% and 18.7% (40). Indeed, the Emerging Risk Factors Collaboration authors did not distinguish between the types of diabetes in their analysis (5). Third, individuals with previous history of cancer were not excluded from the FRESCO Study. However, the impact of such individuals on the results seems minimal, based on the sensitivity analysis that excluded those who died of cancer in the first year of follow-up (i.e. proxy of disease severity). Finally, diabetes status was diagnosed only at baseline and individuals who developed the disorder during follow-up were considered nonexposed. Although this could represent a misclassification bias, the impact on the final result is minimal. On the one hand, the risk of diabetes in our sample was low because 50% of those without diabetes were younger than 55 years. On the other hand, the inclusion of incident cases of diabetes as exposed would prevent us from observing the outcome due to the short time elapsed from diagnosis.

Summary

Diabetes is associated with premature death from cardiovascular diseases (coronary heart disease, stroke, and heart failure), several cancers (liver, colorectal, and lung), and other diseases (chronic obstructive pulmonary disease, liver and kidney disease). In addition, the cause-specific cumulative mortality for cardiovascular, cancer, and noncardiovascular noncancer causes was significantly higher in individuals with diabetes, compared with the general population. The dual analysis with CSH and PSH methods provides a comprehensive view of mortality dynamics in the diabetic population. This approach identifies the individuals with diabetes as a vulnerable population for several causes of death aside from the traditionally reported cardiovascular death. There is a need for more efficient preventive activities to reduce the incidence of this disease and its related complications.

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Author Contributions

J.M.B. and M.G. wrote the manuscript, J.P., I.S., M.G. performed the statistical analysis, and all co-authors researched data, contributed to discussion, and reviewed/edited manuscript.

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Table 1. Baseline characteristic of the participants in the FRESCO Study by sex and diabetes status

	Men			Women		
	Diabetes			Diabetes		
	Yes N=4595	No N=20845	p-value	Yes N=4032	No N=25811	p-value
Age (years), mean (SD)	60 (11)	55 (12)	<0.001	62 (11)	55 (12)	<0.001
Smoker, n (%)	1197 (26.2)	6405 (31.0)	<0.001	218 (5.5)	3632 (14.3)	<0.001
Body mass index (kg/m^2), mean (SD)	28.8 (4.0)	27.6 (3.7)	<0.001	30.4 (5.4)	27.6 (4.8)	<0.001
Systolic blood pressure (mmHg), mean (SD)	143 (20)	135 (18)	<0.001	144 (22)	131 (20)	<0.001
Diastolic blood pressure (mmHg), mean (SD)	81 (9)	81 (9)	0.138	80 (10)	79 (10)	<0.001
Hypertension, n (%)	3838 (84.9)	10275 (52.2)	<0.001	3377 (84.9)	11426 (47.2)	<0.001
Total cholesterol (mg/dl), mean (SD)	219 (43)	221 (40)	0.005	227 (43)	224 (41)	<0.001
HDL cholesterol (mg/dl), mean (SD)	46 (12)	50 (13)	<0.001	52 (13)	60 (14)	<0.001
LDL cholesterol (mg/dl), mean (SD)	147 (39)	148 (38)	0.225	150 (41)	146 (39)	<0.001
Triglycerides (mg/dl), median [IQR]	113 [83-162]	104 [78-143]	<0.001	118 [88-160]	87 [66-117]	<0.001
Glycemia (mg/dl), median [IQR]	147 [128-185]	95 [87-103]	<0.001	140 [123-172]	90 [84-97]	<0.001
Overall mortality, n (rate)	483 (10.9)	1036 (5.2)	<0.001	298 (7.6)	674 (2.7)	<0.001
Cardiovascular mortality, n (rate)	148 (3.6)	225 (1.2)	<0.001	100 (2.7)	170 (0.7)	<0.001
Cancer mortality rate, n (rate)	154 (3.7)	387 (2.0)	<0.001	85 (2.3)	224 (0.9)	<0.001
Other causes, mortality rate, n (rate)	126 (3.1)	293 (1.5)	<0.001	83 (2.2)	191 (0.8)	<0.001

IQR, Interquartile range; SD, Standard deviation

Table 2. Hazard Ratios for death among participants with diabetes compared with those without diabetes at baseline, estimated by Cox regression (cause-specific hazard) and Fine -Gray regression (proportional subdistribution hazard), after adjustment for potential risk factors according to cause of death

	Cardiovascular Death				Cancer Death				Noncardiovascular Noncancer Death			
	Cause-Specific Hazard		Proportional Subdistribution Hazard		Cause-Specific Hazard		Proportional Subdistribution Hazard		Cause-Specific Hazard		Proportional Subdistribution Hazard	
Men	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Diabetes	2.03 (1.63-2.52)	<0.001	1.99 (1.60-2.49)	<0.001	1.37 (1.13-1.67)	0.002	1.35 (1.10-1.65)	0.004	1.53 (1.23-1.91)	<0.001	1.50 (1.20-1.89)	<0.001
Age (1 year)	1.11 (1.10-1.13)	<0.001	1.11 (1.10-1.12)	<0.001	1.07 (1.06-1.08)	<0.001	1.07 (1.06-1.08)	<0.001	1.07 (1.06-1.08)	<0.001	1.07 (1.06-1.08)	<0.001
Smoker (ref. nonsmoker)	1.52 (1.19-1.95)	<0.001	1.51 (1.17-1.94)	0.002	1.23 (1.00-1.52)	0.048	1.22 (0.99-1.51)	0.062	1.17 (0.92-1.48)	0.209	1.15 (0.90-1.48)	0.260
Body mass index ($1\ kg/m^2$ change)	0.98 (0.95-1.01)	0.269	0.98 (0.95-1.02)	0.410	0.98 (0.96-1.01)	0.135	0.98 (0.95-1.01)	0.230	1.00 (0.97-1.02)	0.756	1.00 (0.96-1.03)	0.840
Systolic blood pressure (10 mmHg change)	1.05 (0.99-1.11)	0.081	1.05 (0.98-1.13)	0.150	1.02 (0.98-1.07)	0.346	1.03 (0.97-1.09)	0.400	0.99 (0.94-1.04)	0.653	0.99 (0.93-1.05)	0.700
Total cholesterol (10 mg/dl change)	1.00 (0.97-1.02)	0.924	1.00 (0.97-1.03)	0.999	0.97 (0.95-1.00)	0.017	0.98 (0.95-1.00)	0.037	0.97 (0.94-0.99)	0.009	0.97 (0.94-1.00)	0.032
HDL cholesterol (10 mg/dl change)	0.91 (0.83-1.00)	0.040	0.91 (0.83-0.99)	0.037	1.02 (0.95-1.10)	0.546	1.02 (0.98-0.95)	0.580	1.04 (0.96-1.12)	0.384	1.04 (0.95-1.13)	0.450
Women	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Diabetes	2.28 (1.75-2.97)	<0.001	2.23 (1.70-2.91)	<0.001	1.68 (1.29-2.20)	<0.001	1.66 (1.25-2.19)	<0.001	1.89 (1.43-2.48)	<0.001	1.84 (1.39-2.45)	<0.001
Age (1 year)	1.14 (1.12-1.16)	<0.001	1.14 (1.11-1.16)	<0.001	1.06 (1.05-1.08)	<0.001	1.06 (1.05-1.08)	<0.001	1.12 (1.10-1.14)	<0.001	1.12 (1.10-1.14)	<0.001
Smoker (ref. no smoker)	0.92 (0.40-2.11)	0.841	0.92 (0.38-2.20)	0.840	0.91 (0.54-1.53)	0.724	0.91 (0.53-1.55)	0.710	0.75 (0.35-1.64)	0.478	0.74 (0.34-1.61)	0.450
Body mass index ($1\ kg/m^2$ change)	0.99 (0.96-1.02)	0.512	0.99 (0.96-1.02)	0.580	1.01 (0.99-1.04)	0.285	1.01 (0.99-1.04)	0.310	0.99 (0.96-1.02)	0.440	0.99 (0.96-1.02)	0.540
Systolic blood pressure (10 mmHg change)	0.92 (0.87-0.98)	0.014	0.93 (0.87-1.00)	0.054	0.93 (0.87-0.99)	0.018	0.93 (0.86-1.01)	0.091	0.88 (0.83-0.94)	<0.001	0.89 (0.82-0.96)	0.002
Total cholesterol (10 mg/dl change)	1.00 (0.97-1.03)	0.808	1.00 (0.96-1.03)	0.860	0.99 (0.96-1.01)	0.346	0.99 (0.96-1.02)	0.430	0.96 (0.93-0.99)	0.006	0.96 (0.93-0.99)	0.016
HDL cholesterol (10 mg/dl change)	0.87 (0.79-0.96)	0.004	0.87 (0.78-0.96)	0.008	0.92 (0.84-1.00)	0.052	0.92 (0.84-1.01)	0.076	0.99 (0.91-1.08)	0.815	0.99 (0.90-1.09)	0.870

All models are mutually adjusted. CI, Confidence interval; HDL, High-density lipoprotein; HR, Hazard ratio. Systolic blood pressure, total and HDL cholesterol has been estimated for 10 unit increase.

FIGURE LEGENDS

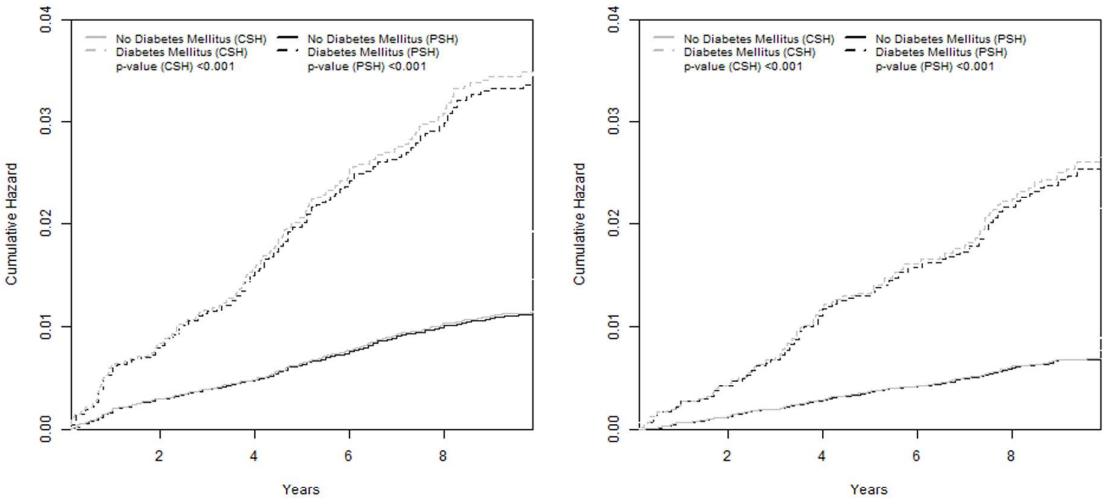
Figure 1 - Cumulative mortality function for cardiovascular (A), cancer (B) and noncardiovascular noncancer (C) causes in men and in women assessed with cause-specific hazard (CSH) and proportional subdistribution hazard (PSH) approaches.

Figure 2 - Hazard ratios for death from cardiovascular, cancer, and noncardiovascular noncancer causes among participants with diabetes mellitus compared with those without diabetes mellitus at baseline. Models have been adjusted by age and sex. The size of the data markers is proportional to the number of each cause-specific death in individuals with diabetes.

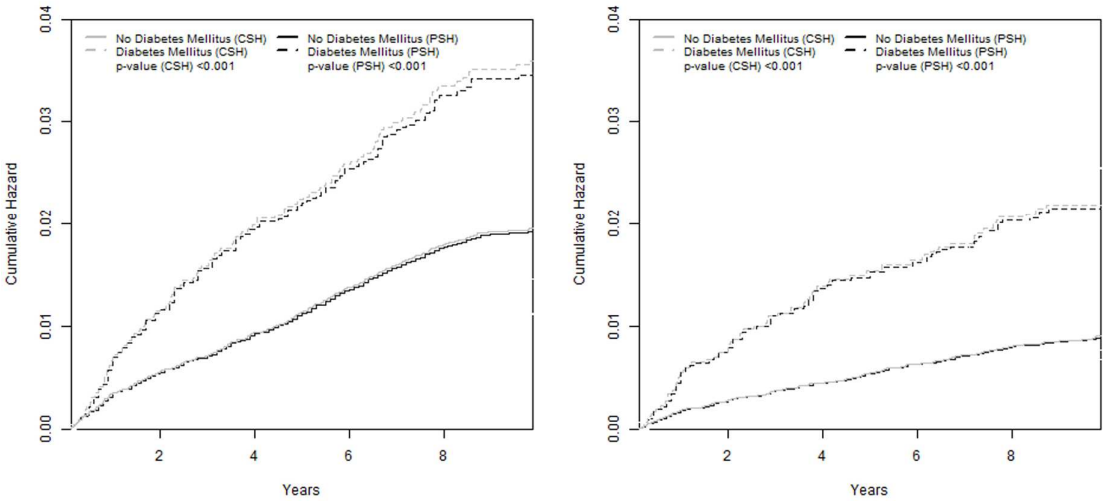
Figure 1.

Men **Women**

(A) Cardiovascular Death



(B) Cancer Death



(C) Noncardiovascular Noncancer Death

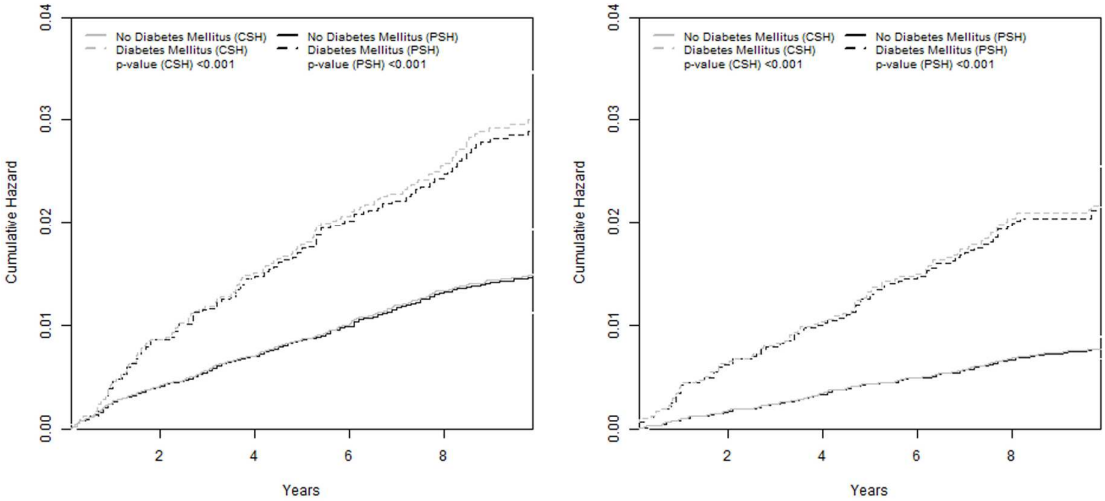
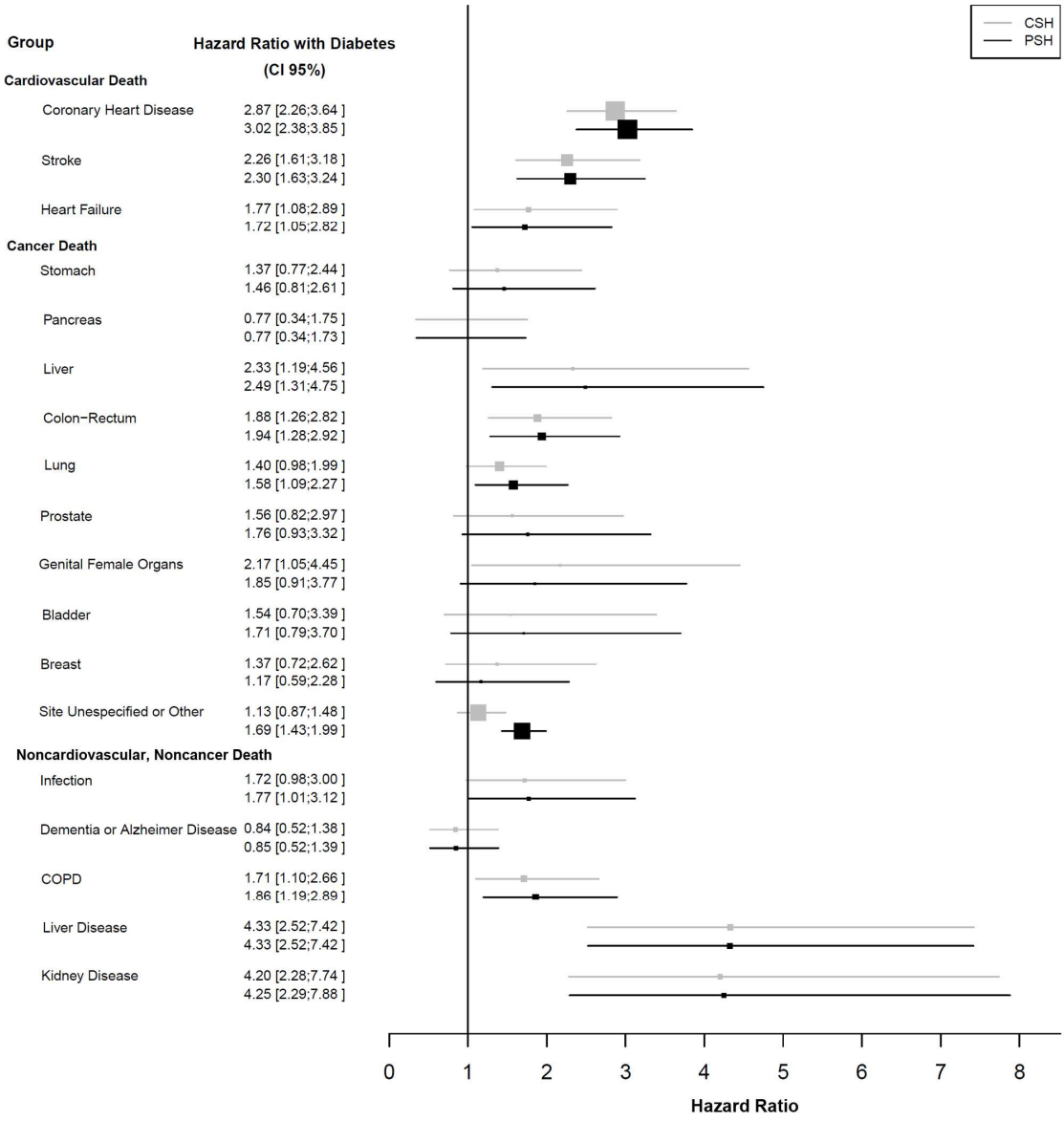


Figure 2.


Group
Hazard Ratio with Diabetes
(CI 95%)
CSH
PSH
Cardiovascular Death
Coronary Heart Disease
2.87 [2.26;3.64]
3.02 [2.38;3.85]
Stroke
2.26 [1.61;3.18]
2.30 [1.63;3.24]
Heart Failure
1.77 [1.08;2.89]
1.72 [1.05;2.82]
Cancer Death
Stomach
1.37 [0.77;2.44]
1.46 [0.81;2.61]
Pancreas
0.77 [0.34;1.75]
0.77 [0.34;1.73]
Liver
2.33 [1.19;4.56]
2.49 [1.31;4.75]
Colon−Rectum
1.88 [1.26;2.82]
1.94 [1.28;2.92]
Lung
1.40 [0.98;1.99]
1.58 [1.09;2.27]
Prostate
1.56 [0.82;2.97]
1.76 [0.93;3.32]
Genital Female Organs
2.17 [1.05;4.45]
1.85 [0.91;3.77]
Bladder
1.54 [0.70;3.39]
1.71 [0.79;3.70]
Breast
1.37 [0.72;2.62]
1.17 [0.59;2.28]
Site Unespecified or Other
1.13 [0.87;1.48]
1.69 [1.43;1.99]
Noncardiovascular, Noncancer Death
Infection
1.72 [0.98;3.00]
1.77 [1.01;3.12]
Dementia or Alzheimer Disease
0.84 [0.52;1.38]
0.85 [0.52;1.39]
COPD
1.71 [1.10;2.66]
1.86 [1.19;2.89]
Liver Disease
4.33 [2.52;7.42]
4.33 [2.52;7.42]
Kidney Disease
4.20 [2.28;7.74]
4.25 [2.29;7.88]
0
1
2
3
4
5
6
7
8
Hazard Ratio