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

*Jose Miguel Baena-Díez,[1,2,3] Judit Peñafiel,[1] Isaac Subirana,[1,3] Rafel Ramos,[4,5] Roberto Elosua,[1] Alejandro Marín-Ibañez,[6] María Jesús Guembe,[7,8] Fernando Rigo,[9] María José Tormo-Díaz,[4,10,11,12] Conchi Moreno-Iribas,[13,14,15] Joan Josep Cabré,[16] Antonio Segura,[17] Manel García-Lareo,[2] Agustín Gómez de la Cámara,[3,18] José Lapetra,[19,20] Miquel Quesada[4], Jaume Marrugat,[1] Maria José Medrano,[21] Jesús Berjón,[7,15] Guiem Frontera,[9] Diana Gavrila,[3,22] Aurelio Barricarte,[3,13,15] Josep Basora,[23] Jose María García,[17] Natalia C. Pavone,[2] David Lora-Pablos,[3,18] Eduardo Mayoral,[19,24] Josep Franch,[25,26] Manel Mata,[27] Conxa Castell,[28] Albert Frances,[29] María Grau,[1,30] on behalf of the FRESCO Investigators**

[1]*REGICOR Study Group-Cardiovascular Epidemiology and Genetics, IMIM-Hospital del Mar Research Institute, Barcelona, Spain*
[2]*Primary Care Center La Marina and Primary Health Care Research Institute Jordi Gol, Catalan Institute of Health, Barcelona, Spain*
[3]*Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Spain*
[4]*Family Medicine Research Unit and Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Girona, Spain*
[5]*Univeristy of Girona, Spain*
[6]*San Jose Norte Health Centre, Zaragoza, Spain*
[7]*Vascular Risk in Navarra Research Group, Health Department, Navarra Government, Pamplona, Spain*
[8]*Knowledge Planning, Evaluation and Management, Health Department, Navarra Government, Pamplona, Spain*
[9]*Cardiovascular Group of Balearic Islands (REDIAP-IBSALUT), Palma de Mallorca, Spain*
[10]*Murcian Health Departament, Murcia, Spain*
[11]*University of Murcia, Spain*
[12]*Murcian Institute of Biomedical Research (IMIMB), Murcia, Spain*
[13]*Navarre Public Health Institute, Pamplona, Spain*
[14]*Research Network for Health Services in Chronic Disease (REDISSEC), Pamplona, Spain*
[15]*Navarra Health Research Institute (IdiSNA), Pamplona, Spain*
[16]*Primary Care Center Sant Pere Centre and Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Reus-Tarragona, Spain*
[17]*Health Science Institute, Department of Health and Social Affairs, Castille – La Mancha Government, Talavera de la Reina, Spain*

[18]*Clinical Research Department, Hospital 12 Octubre Research Institute, Madrid, Spain*
[19]*Consortium for Biomedical Research in Obesity and Nutrition (CIBEROBN), Spain*
[20] *Primary Care Center San Pablo, Department of Family Medicine, Primary Care Division, Sevilla, Spain*
[21]*Carlos III Health Institute, Madrid, Spain*
[22]*Health and Consumers Department, Murcia Government, Murcia, Spain*
[23]*Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Reus-Tarragona, Spain*
[24]*Diabetes Strategy, Andalusia Health Service, Sevilla, Spain*
[25]*Primary Care Center Raval Sud and Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Barcelona, Spain*
[26]*Consortium for Biomedical Research in Diabetes and Associated Metabolic Diseases (CIBERDEM), Spain*
[27]*Primary Care Center La Mina and Primary Health Care Research Unit Institute Jordi Gol, Catalan Institute of Health, Barcelona, Spain*
[28]*Public Health Agency, Government of Catalonia, Barcelona, Spain*
[29]*Department of Urology, Hospital del Mar, Barcelona, Spain*
[30]*University of Barcelona, Spain*
Corresponding author: Maria Grau, mgrau@imim.es

**A full roster of FRESCO Investigators can be found at www.regicor.org/fresco_inv*

OBJECTIVE

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

RESEARCH DESING AND METHODS

We used the pooled analysis of individual data from 11 Spanish population cohorts with 10-year follow-up. Participants had no previous history of cardiovascular diseases and were aged 35-79 years. 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. Sex-stratified cumulative mortality functions for all three causes of death were plotted.

RESULTS

We included 55,292 individuals (15.6% diabetic with overall mortality 9.1%). Diabetes increased mortality risk as follows: (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

KEY MESSAGES

- Diabetes confers significantly higher risk of death, even after adjusting for risk factors.
- Mortality rate in individuals with diabetes is significantly higher for all causes, being cardiovascular death the one with the highest magnitude of association.
- An excess risk of death is observed for stomach, liver, colon-rectum and lung cancers in diabetic individuals.

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 (5,8-10).

The analysis of cause-specific death in individuals with diabetes in a cohort study is a case of competing risk events because each individual is exposed to different potential risks, although there is one main attributable cause of death (11-13). For instance, the observation of one particular risk of death (e.g., cancer) may be preceded by other events (e.g., cardiovascular death), the occurrence of which prevents us from observing the first cause. 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 (13,**¡Error! Marcador no definido.**). Thus, CSH and PSH yield different interpretations needed to understand the epidemiological event dynamics (14).

The aims of this study were to assess the association between baseline exposure to diabetes and the risk of cause-specific death in a population-based cohort followed up

for 10 years, on average, 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 11 population cohorts in 7 Spanish regions examined between 1992 and 2005 with similar methods; the methodology of the FRESCO study has been explained elsewhere (15). In summary, all the cohorts were randomly selected and included participants without previous symptoms or diagnosis of cardiovascular diseases, aged 35 to 79 years. 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 Ethics Committee of the Parc de Salut Mar (authorization #: 2009/3391/I).

Measurements

The following risk factors were measured at baseline using standardized methods based on World Health Organization recommendations (16). 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 causes of death during 10-year follow-up were ascertained by reviewing medical records and by linkage with the official death registry, coded according to the 10th revision of the International Classification of Diseases (ICD). 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).

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 risk factors prevalence, and death rate during follow-up according to diabetes at baseline and vital status at the end of the follow-up.

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 regression treats the competing events as censored at the time they occurred; the second divides the probability of death into the probability corresponding to each competing event. Assumptions of CSH and PSH were validated in Cox and Fine-Gray regressions, respectively. A multivariate sex-stratified model was fitted, adjusting for variables that showed a significant association with the exposure variable (diabetes) and outcome (10-year death). Finally, we plotted the sex-stratified cumulative hazard functions for all three causes of death and the hazard ratios of the most frequent single causes of death using both CSH and PSH methods.

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 average 9.3-year follow-up was 1710 (3.8%) among the 44,664 individuals without diabetes, and 781 (9.1%) in those with diabetes (Figure 1).

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

Participants who died during follow-up were significantly older, nonsmokers, and presented with diabetes and hypertension more frequently. In addition, systolic blood pressure and glycemia were significantly higher in those who died. Men who died presented significantly lower total and LDL cholesterol and diastolic blood pressure; women who died presented with significantly higher body mass index, triglycerides and lower HDL cholesterol (Supplementary Table 1).

The crude cumulative mortality functions showed that individuals with diabetes presented with significantly higher risk of cardiovascular, cancer, and noncardiovascular noncancer death in the 10-year follow-up. The estimates performed with the CSH approach were higher compared to the PSH method, considering the competing risks, particularly for individuals with diabetes (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, total cholesterol and HDL cholesterol. Diabetes significantly increased the risk of cardiovascular, cancer, and noncardiovascular noncancer death in both sexes. The hazard ratios performed with PSH were lower than those performed with CSH in all instances; however, the differences were small (Table 2). Single-cause analysis showed that individuals with diabetes presented significantly higher risk of fatal cardiovascular events (e.g., myocardial infarction, stroke, heart failure) than the nondiabetic population. Regarding cancer death, the individuals with diabetes presented significantly higher risk of death from liver, colon-rectum, and lung cancer. Finally, individuals with diabetes presented with higher risk of 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 3).

DISCUSSION

Individuals with diabetes presented significantly higher risk of death than the population without diabetes, even after adjusting for risk factors that have individually shown a significant association with death (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 rest of 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. Likely, the steep decrease in cardiovascular deaths, particularly observed in Western countries (19), results in the emergence of other causes of death in individuals with diabetes. Nonetheless, this 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 those with history of such 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, with the digestive tract locations (liver and colon-rectum) having the greatest magnitude of association (5,8-10). A possible pathological mechanism that may explain this association is the increased insulin resistance and the alteration of insulin-like growth factors (9,10,23,24). In addition, the risk of lung cancer was increased in individuals with diabetes in our report. 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 (5,9,10). Finally, we did not find a significant association between diabetes and pancreatic cancer, despite a suggested link between the two diseases (9).

Regarding other causes of death, similarly to Emerging Risk Factor Collaboration, we observed a strong positive association of diabetes with deaths from infections, and from renal and liver diseases (5). These results may reflect associated diabetes complications such as suppression of cellular immunity, nephropathy, and fatty liver disease (19).

Competing risk analysis

The differences observed between the CSH and PSH methods highlights the differing interpretations of both estimates and therefore, their utility for understanding the cause-specific death dynamic in diabetes, compared with the general population (**¡Error! Marcador no definido.**). The estimates performed with CSH implied that, among any individuals who survived all events up to 10 years, the CSH rate among those with diabetes was CSH ratio×the CSH rate of those who do not have diabetes. This method yields a valid measure of association, being relevant to ascertain the disease etiology, but did not allow event prediction. On the other hand, PSH is more relevant for prediction because the estimate accounts for the competing event. This estimate yields a measure of association but the result is due to the exposure and the possibly differential impact of competing events on the risk set for exposed and unexposed individuals (i.e., with and without diabetes, respectively) (**¡Error! Marcador no definido.**).

To get a complete understanding of event dynamics in the diabetic population, the present report followed the recommendations by Latouche et al.: (1) Using a different terminology for each model of the hazard ratio (CSH for Cox model and PSH for Fine-Gray model); (2) Reporting all the CSH; (3) Reporting the PSH for the event of interest and the PSH for the competing event; (4) Presenting the results in a unified interpretation; (5) Explicitly checking the proportional hazards assumption for Cox and Fine-Gray models; (6) Providing plots of all cumulative mortalities using CSH and PSH (14).

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 patient support to achieve 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 the society (e.g., smoking ban policies) (25- 30). 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 (31-33). 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 (4,34).

More studies are needed to estimate the incidence rates of diabetes and its related complications. The final objective should be to achieve more efficient planning and prioritizing of resource assignment.

Characteristics and limitations

Our study has several limitations. First, we have used a single glycaemia measure to diagnose diabetes; however, this is the standardized method defined by World Health Organization recommendations for epidemiologic studies (16) Second, the component studies did not collect the type of diabetes (e.g. 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% (35). Indeed, the authors of the Emerging Risk Factors Collaboration did not distinguish between both types of diabetes diagnoses in their analysis (5).

CONCLUSIONS

Diabetes is associated with premature death from cardiovascular diseases (coronary heart disease, stroke, and heart failure), several cancers (liver, colon-rectum, 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 death dynamics in the diabetic population. This approach identifies the individuals with diabetes as a vulnerable population for several causes of death aside from cardiovascular death, traditionally reported. There is

a need for more efficient preventive activities for preventing such disease and its related complications.

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Conflict of interest: None to declare.

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FIGURE LEGENDS

Figure 1. Flow chart of participants in the FRESCO Study

Figure 2. 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 3. 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.

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

	Men			Women		
	Diabetes			Diabetes		
	Yes N=4595	No N=20845	p-value	Yes N=4032	No N=25811	p-value
Age, 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, 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, mean (SD)	143 (20)	135 (18)	<0.001	144 (22)	131 (20)	<0.001
Diastolic blood pressure, 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, mean (SD)	219 (43)	221 (40)	0.005	227 (43)	224 (41)	<0.001
HDL cholesterol, mean (SD)	46 (12)	50 (13)	<0.001	52 (13)	60 (14)	<0.001
LDL cholesterol, mean (SD)	147 (39)	148 (38)	0.225	150 (41)	146 (39)	<0.001
Triglycerides, median [IQR]	113 [83-162]	104 [78-143]	<0.001	118 [88-160]	87 [66-117]	<0.001
Glycemia, median [IQR]	147 [128-185]	95 [87-103]	<0.001	140 [123-172]	90 [84-97]	<0.001
Exitus, n (%)	483 (10.9)	1036 (5.2)	<0.001	298 (7.6)	674 (2.7)	<0.001
Cause of death, n (%)			<0.001			0.043

Cardiovascular	148 (34.6)	225 (24.9)	100 (37.8)	170 (29.1)
Malignant neoplasm	154 (36.0)	387 (42.8)	85 (31.7)	224 (38.3)
Other causes	126 (29.4)	293 (32.4)	85(31.0)	191 (32.6)

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			
	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**
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
Age	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
Smoker	1.52 (1.19-1.95)	<0.001	1.51 (1.17-1.94)	0.002	1.23 (1.00-1.52)	0.050	1.22 (0.99-1.51)	0.062
Body mass index	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
Systolic blood pressure	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
Total cholesterol	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
HDL cholesterol	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
Women	**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
Age	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
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
Body mass index	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
Systolic blood pressure	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
Total cholesterol	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
HDL cholesterol	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

CI, Confidence interval; HDL, High-density lipoprotein; LDL, Low-density lipoprotein. Systolic blood pressure, LDL and HDL cholesterol has been estimated for 10 unit increase

Figure 1.

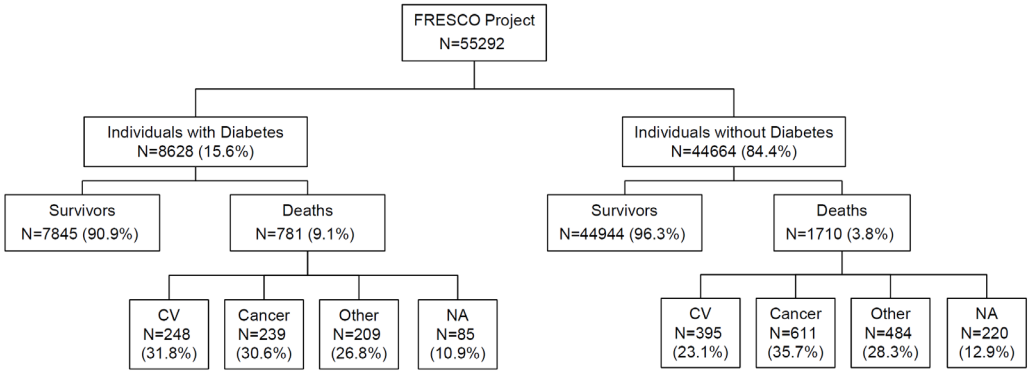

FRESCO Project
N=55292
Individuals with Diabetes
N=8628 (15.6%)
Individuals without Diabetes
N=44664 (84.4%)
Survivors
N=7845 (90.9%)
Deaths
N=781 (9.1%)
Survivors
N=44944 (96.3%)
Deaths
N=1710 (3.8%)
CV
N=248
(31.8%)
Cancer
N=239
(30.6%)
Other
N=209
(26.8%)
NA
N=85
(10.9%)
CV
N=395
(23.1%)
Cancer
N=611
(35.7%)
Other
N=484
(28.3%)
NA
N=220
(12.9%)

Figure 2.

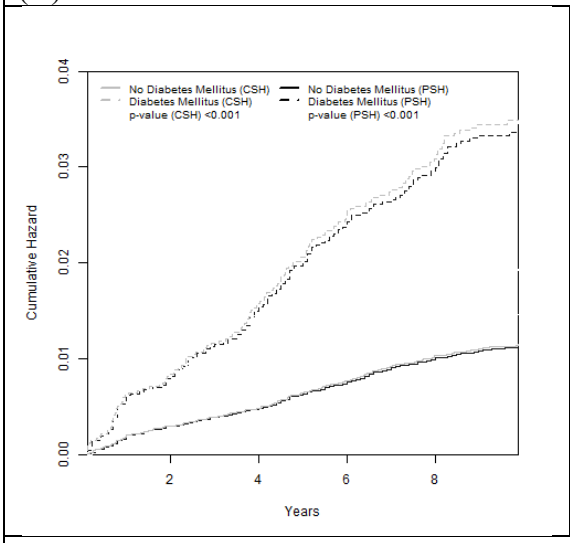
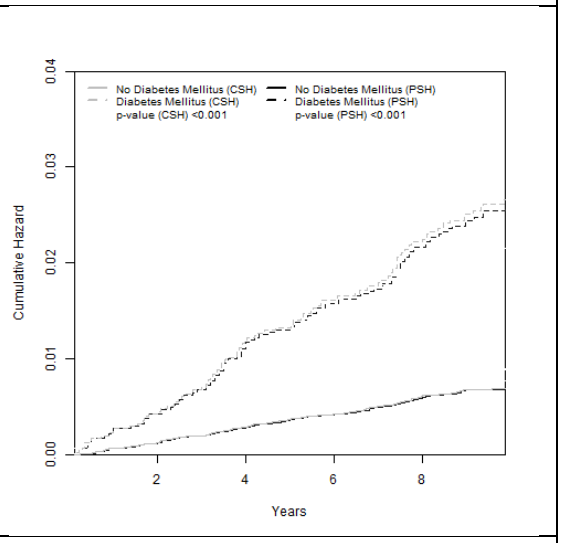
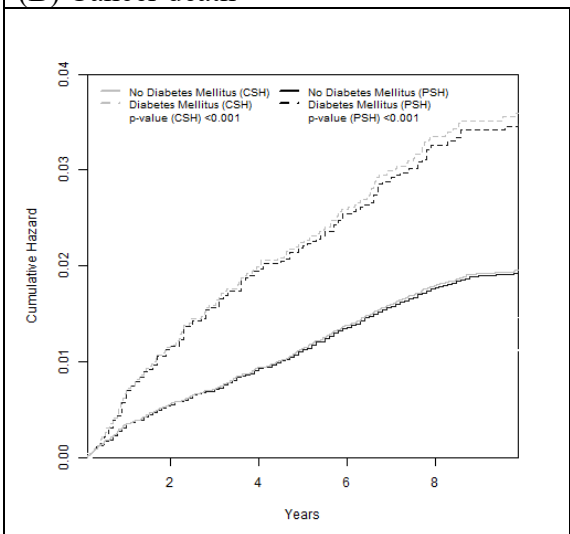
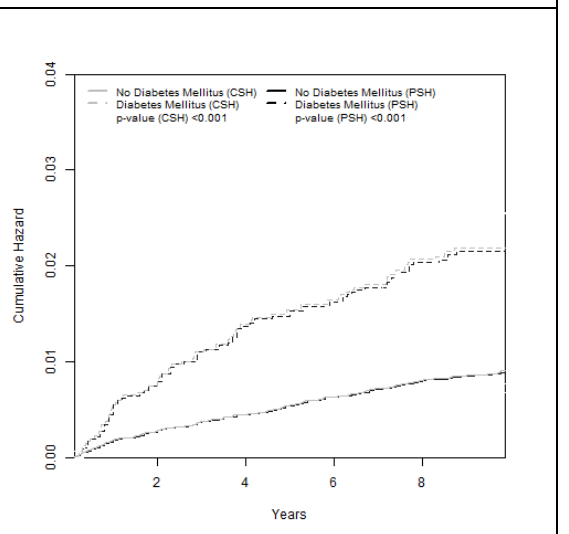
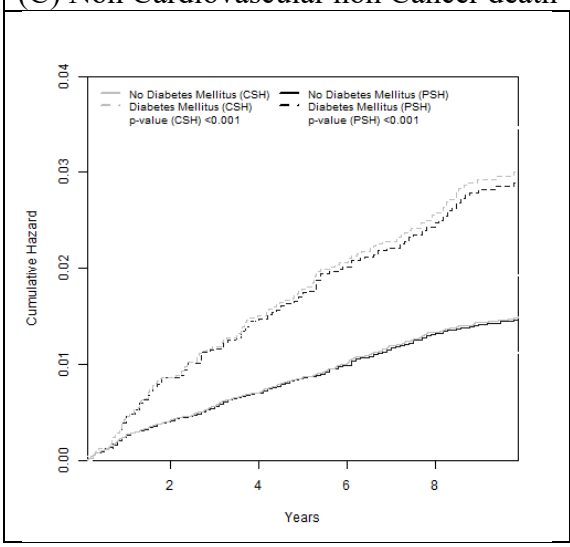
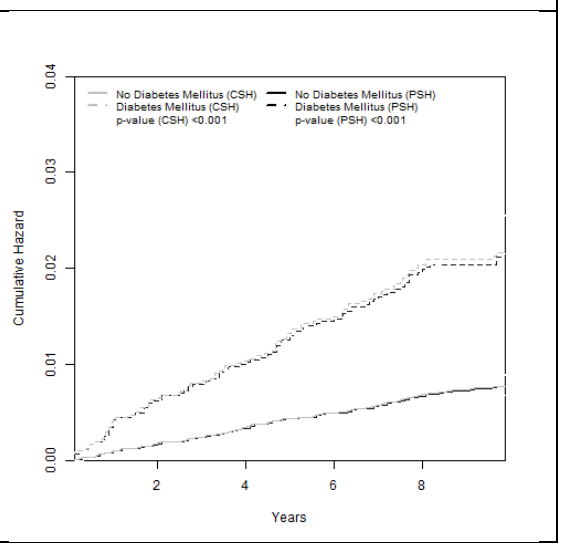
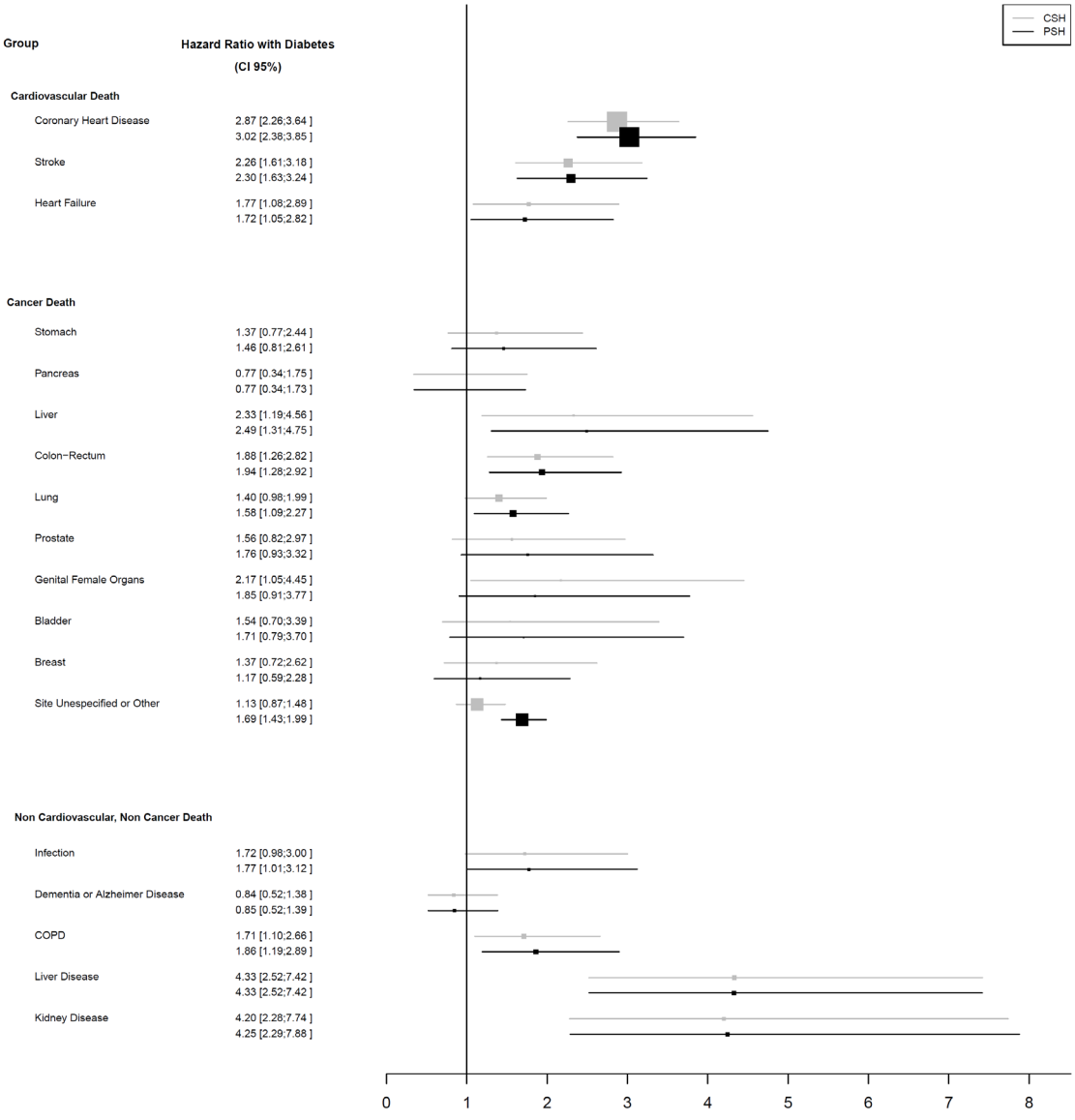
Men	Women
(A) Cardiovascular death	
	
(B) Cancer death	
	
(C) Non Cardiovascular non Cancer death	
	

Figure 3.


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]
Non Cardiovascular, Non Cancer 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

Supplementary table 1. Baseline characteristics of participants in the FRESCO Study, by vital status at the end of follow-up

	Men			Women		
	Death			Death		
	Yes N=1519	No N=23919	p-value	Yes N=972	No N=28870	p-value
Age, mean (SD)	65 (10)	55 (12)	<0.001	67 (10)	56 (12)	<0.001
Diabetes, n (%)	483 (31.8)	4112 (17.2)	<0.001	298 (30.7)	3733 (12.9)	<0.001
Smoker, n (%)	393 (26.1)	7208 (30.4)	<0.001	37 (3.8)	3813 (13.4)	<0.001
Body mass index, mean (SD)	27.8 (4.5)	27.8 (3.7)	0.657	28.8 (5.2)	28.0 (5.0)	<0.001
Systolic blood pressure, mean (SD)	144 (22)	136 (18)	<0.001	142 (23)	133 (21)	<0.001
Diastolic blood pressure, mean (SD)	79 (11)	81 (9)	<0.001	79 (11)	79 (10)	0.439
Hypertension, n (%)	1069 (71.7)	13040 (57.4)	<0.001	687 (72.4)	14110 (51.8)	<0.001
Total cholesterol, mean (SD)	216 (45)	221 (40)	<0.001	227 (46)	224 (41)	0.088
HDL cholesterol, mean (SD)	49 (14)	50 (13)	0.769	56 (14)	59 (15)	<0.001
LDL cholesterol, mean (SD)	144 (42)	148 (38)	0.002	149 (44)	147 (39)	0.221
Triglycerides, median [IQR]	105 [79-142]	105 [78-147]	0.172	101 [78-143]	90 [67-122]	<0.001

Glycemia, median [IQR]	101 [90-125]	98 [89-110]	<0.001	97 [86-120]	92 [85-102]	<0.001

IQR, Interquartile range; SD, Standard deviation