

Review

Effect of type-2 diabetes mellitus in long-term mortality in older adults: The NEDICES cohort study

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Dedicated to the memory of Professor Serrano Ríos.

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ABSTRACT

Aims: To describe the mortality associated with type-2 diabetes mellitus (T2DM) in a Spanish elderly population during a 22-year period.

Procedures: Prospective follow-up study (1994–95 to 2017) including 4,998 individuals (≥ 65 years old at baseline) of three communities (one rural) from central Spain. T2DM diagnosis was recorded during a clinical interview in 1994–95 (self-reported and information from their doctors, including treatment). Mortality incidence until 2017 was checked.

Results: A total of 4,038 subjects were included, with a mean age of 73.6 (± 6.6) years; 1,718 (42.5 %) were male and 685 (17.0 %) were diagnosed with T2DM. The mortality rate during follow-up was 85.2 %. Cardiovascular disease was the most frequent cause of death in DM2 subjects, followed by neoplasm. The mortality hazard ratio found for T2DM compared to non-T2DM subjects was 1.29 (1.16–1.45) after adjusting for multiple risk factors. The effect of TDM2 on the mortality rate remained significant in men (HR:1.27; CI 95 %:1.08–1.49; $p = 0.005$) and women (HR:1.32; CI 95 %:1.14–1.53; $p < 0.001$), with no differences between sexes ($p = 0.705$).

Main conclusion: The sustained reduction in T2DM elderly Spanish subjects' life expectancy address the necessity of community interventions and campaigns regarding lifestyle modifications and reinforce the need for an adequate and regular TDM2 subjects clinical follow-up.

1. Introduction

Diabetes mellitus (DM) is a major well-established cause of morbidity and mortality worldwide and it is included amongst the major preventable chronic conditions in the United States and around the world [1]. It is also one of the leading causes of death among elderly people [1], and it increases two to threefold the probability of functional disability and the medical spending compared to healthy individuals [2]. The highest expenditure per person with DM (20–79 years) in 2021 was in the high-income countries (1.16 % of the Gross Domestic

Product), followed by middle (1.08 %), and low-income countries (0.51 %) [3]. According to the International Diabetes Federation (IDF) [3], Spain was the 9th country with a higher expenditure in 2021 due to DM in subjects aged 20 to 79 years old.

With increasing ageing of the population and changes in lifestyle, the prevalence of DM is likely to increase [4], mainly in low and medium-income countries [5,6], but also in Spain [7]. One out of three individuals with DM lives in Western countries, according to the International Diabetes Federation (IDF) [3]. In 2021 the total number of people with DM in the world was 537 million, representing 10.5 % of the

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world population and significantly about 50 % of them being undiagnosed, mostly in low- and medium-income countries. Moreover, the prevalence of type 2 DM (T2DM) in the elderly is high, especially among older individuals aged ≥ 75 years [4]. In Europe, there is no adequate pooled data except for a study linking social inequalities to the prevalence and incidence of T2DM. In this study [8], the prevalence of T2DM in men aged 50 years and over ranged from 8.4 % [95 % CI: 6.3–10.4] in Denmark to 15.3 % [95 % CI: 12.5–18.1] in Spain, while in women ranged from 4.5 % [95 % CI: 2.6–6.5] in Switzerland to 14.2 % [95 % CI: 11.8–16.6] in Spain. In France the prevalence of DM peaks at age 75–79 years, affecting 19.7 % of men and 14.2 % of women at that age [4]. Regarding the elderly US people, it oscillates between 19.6 % and 21.6 % [9].

Nevertheless, only very few surveys have been carried out in Spain to describe the long-term mortality in adults with T2DM, specifically older subjects, that could show the correlation between expenditure in T2DM subjects and its outcomes. In general Spanish population, a cross-sectional descriptive observational study on 15 years waves (1998–2013) found that standardized mortality rates (SMR) were lower in the center and north-west of the national territory (Galicia, Castilla y León and Madrid Autonomous Communities) until 2008, a difference that partially disappeared in 2013 when 17 out of 50 provinces showed an SMR $< 20/100,000$ subjects. Moreover, SMR for DM fell markedly, by 25.3 % in men and by 41.4 % in women from 1998 to 2013 [10]. In another retrospective, observational study based on electronic medical records, HF and CKD were the first and most common manifestations during a seven-year follow-up in T2DM patients, with a significantly higher impact on mortality and rehospitalization rates [11]. Thus, information on long term T2DM mortality in Spain is limited, and to our knowledge, no prospective population-based studies have yet addressed this issue, even in the elderly.

The advances in primary, secondary and tertiary prevention [12,13], as well as the new drugs approved for DM treatment in these years [14–19], have smoothened the mortality rates between subjects with and without DM, as confirmed in some studies [20,21]. Therefore, a higher prevalence would not necessarily mean higher mortality. The scarce information on the T2DM elderly mortality in Spain convinced us to evaluate the data from the NEDICES (Neurological Disorders in Central Spain) study. This cohort is a sizeable population-prospective-based study carried out from 1994 until 2017 (last mortality evaluation) whose aim was the epidemiological study of elderly neurological and chronic disorders. It has contributed to the knowledge in Spain, of the epidemiology of cognitive impairment, dementia, stroke, and elderly neurodegenerative disorders (dementing disorders, Parkinson's disease, and essential tremor) [22–24] (more data in <https://www.cibernet.es/en/research-programmes/projects/nedices>).

Because of the uncertainties relating to survival in Spanish older adults with T2DM, which could have significant implications for health resources and policies, our aim was to study the effect of T2DM on the mortality during a long period of time in the NEDICES cohort, providing a more up-to-date assessment of the T2DM risk of mortality, and if this effect was different according to sex.

2. Material and methods

2.1. Sites and population of the NEDICES cohort

The NEDICES cohort sampled three geographic areas to obtain a cohort of older adults with different cultural and socioeconomic backgrounds. The study population comprised elderly participants over 65 years taken from the census of three communities in central Spain. A) Las Margaritas (approximately 14,800 inhabitants), a working-class neighborhood in Getafe (Greater South Madrid). B) Lista, high-income professional-class vicinity in Salamanca district in Central Madrid [approximately 150,000 inhabitants]. C) 38 villages of the agricultural region municipality of Arévalo (125 km northwest of Madrid)

(approximately 9,000 inhabitants, 24 % over 65 years of age). The three areas were selected according to the following criteria: a) there were approximately 2,000 elderly inhabitants; b) it existed a computer-based registry of elders' medical data in the primary care physician (PCP) setting, and c) there already existed a close relationship between the NEDICES investigators and the local PCP and health authorities. Moreover, these areas had sufficient differences in social structures to allow the study of elderly samples with different lifestyles and risk factors. There was no sampling in Margaritas and Arevalo County because the reference population was nearly 2,000 people (adequate sample for the objectives of the study). For Lista area, a representative and proportional random sample of 2,113 elderly subjects obtained from the municipal census of the neighborhood, and stratified by age and sex, was selected from the reference population (more than 24,000 elderly people). This survey covered the household and nursing home populations of the three communities. We have reported elsewhere a detailed account of the background, study population, and methods of the survey [22–24].

2.2. Participants and data collection

Up-to-date lists of residents were generated from population registers. In each community, survey eligibility was restricted to residents aged 65 years or older who were present there on December 31, 1993. Eligible persons who had moved away from the survey area were not traced. For the Lista area, a representative sample of 2,000 individuals, stratified by age and sex, was selected from the reference population (more than 24,000 older adults). In Margaritas and Arévalo, there was no sampling because the reference population was nearly 2,000 individuals. Each eligible individual was invited to participate in the survey by Post mail followed by telephone calls were used to invite participation and explain confidentiality procedures.

2.3. Community relations and ethical aspects

The survey was announced locally by newspapers, radio, and television. As previously mentioned, a letter from the local health and municipal authorities accompanied the invitation and telephone number to arrange an interview. The study, conducted following the principles of the Helsinki Declaration of 1975, was approved by two university hospitals' institutional ethical review committees, the University Hospital "12 de Octubre" and the University Hospital "La Princesa" both in Madrid. Every survey participant or their legal guardians gave written informed consent. In this informed consent, the name and address of the PCP were included. To avoid conflicts with local physicians, the medical staff of the NEDICES survey did not offer treatment. The newly detected cases of all chronic diseases (neurologic, psychiatric, or systemic) were communicated to each PCP.

2.4. Methods of the field survey and data on survival

This study consisted of a baseline survey (1994–1995) and data provided by the Spanish National Institute of Statistics (INE) on the population and its deaths (date and diagnosis) during the period from 1994–2017.

2.5. Cross-sectional survey (1994–1995)

At baseline, trained interviewers performed a face-to-face evaluation. The interviews were carried out at the Primary Care Centre closest to the subject's home and carried out with the elderly person and a companion. The evaluation comprised a 500-item screening questionnaire assessing demographic information, health status (including medical and neurologic disorders), cardiovascular and neurological disease risk factors, and variables about lifestyle (e.g., consumption of alcohol, smoking habits, self-reported health). Subjects were asked to provide the medication (and its containers) they had been taking during

the previous week, as well as any medical records available. A short form of the questionnaire was mailed to unavailable participants for face-to-face or telephone screening. The registered study population consisted of 6,395 participants, but 481 were ineligible (e.g., census issues, incorrect address, death), leaving 5,914 eligible participants. Of the 5,914 eligible participants, 52 (0.9 %) had died, 292 (4.9 %) refused, and 292 (4.9 %) were unreachable (contact failure). The remaining 5,278 [89.2 %] population-based older adults (of whom 57.6 % were women, with a mean age of 74.31 ± 6.97 years) agreed to participate.

For the main analyses of this study, the prevalence of T2DM in the cross-sectional survey was defined as a (self-reported) previous medical diagnosis of T2DM, the use of DM medication, or both. Diagnosis of hypertension and hypercholesterolemia were obtained following the same methodology, as appropriate questions were asked regarding the diagnosis, duration and treatment during the face-to-face interview. Regarding the smoking habit, it was categorized as “never” or “active” if he/she smokes or has smoked regularly during his/her lifetime, defined as at least one unit of any tobacco product per week. The consumption of ethanol was categorized as “never” or “active”, the latter defined as at least one cup of any alcoholic beverage per week during his/her lifetime. Physical activity was assessed using an adapted version (four items) of the Rosow-Breslau physical function measure [25] and classified as follows: (a) sedentary lifestyle (i.e., only minimal house chores or short walks at home); (b) light PA (i.e., regular house chores, walks independently at home); (c) moderate activity (i.e., regular house chores, walks up to one kilometer per day) and; (d) high activity) i.e., performs heavy housework, walks more than one kilometer, or engages in regular sports. The intensity level of PA was weighted based on the number of hours spent within the secondary category multiplied by 2; light PA by 1.2; moderate PA by 1.4; and high PA by 1.8. Next, different cut-off

points were calculated based on quartile distribution to classify the subjects as follows: ≤ 15.6 h (sedentary group), ≤ 17.6 h (light PA group), ≤ 19.4 h (high PA group) [24]. Regarding self-rated health, it was assessed with only one question: “In general terms, how would you describe your health: very good, good, fair, poor, or very poor?” that was rated with 1 [very good] to 5 [very poor] points. Measurements and anthropometric data were obtained from participants by their primary care physician.

2.5.1. Analytic sample construction

The flow chart at each step of the NEDICES survey is shown in Fig. 1. Of the 5,278 participants screened at baseline (1994 to 1995), 280 were excluded from the follow-up because there was no information regarding DM diagnosis at baseline, leaving in the study 4,998 from which 830 (16.6 %) were subjects with diabetes. Of these, 47 were excluded due to lack of information provided by the INE and 913 due to lack of information on any of the main risk factors with which the complete analysis was performed (hypertension, hypercholesterolemia, tobacco, and alcohol consumption). Thus, this analysis was performed in 4,038 subjects of which 685 (17.0 %) were subjects with T2DM. 596 subjects (14.8 %) remained alive in 2017.

2.6. Statistical analysis

Qualitative variables are shown with their absolute and relative frequency distribution. Quantitative variables are summarized with the mean and standard deviation (SD). For the comparison of baseline characteristics according to the diagnosis of T2DM, the chi-square test was used for qualitative variables, and the parametric Student's *t*-test for quantitative variables. The prevalence of T2DM diagnosis at baseline

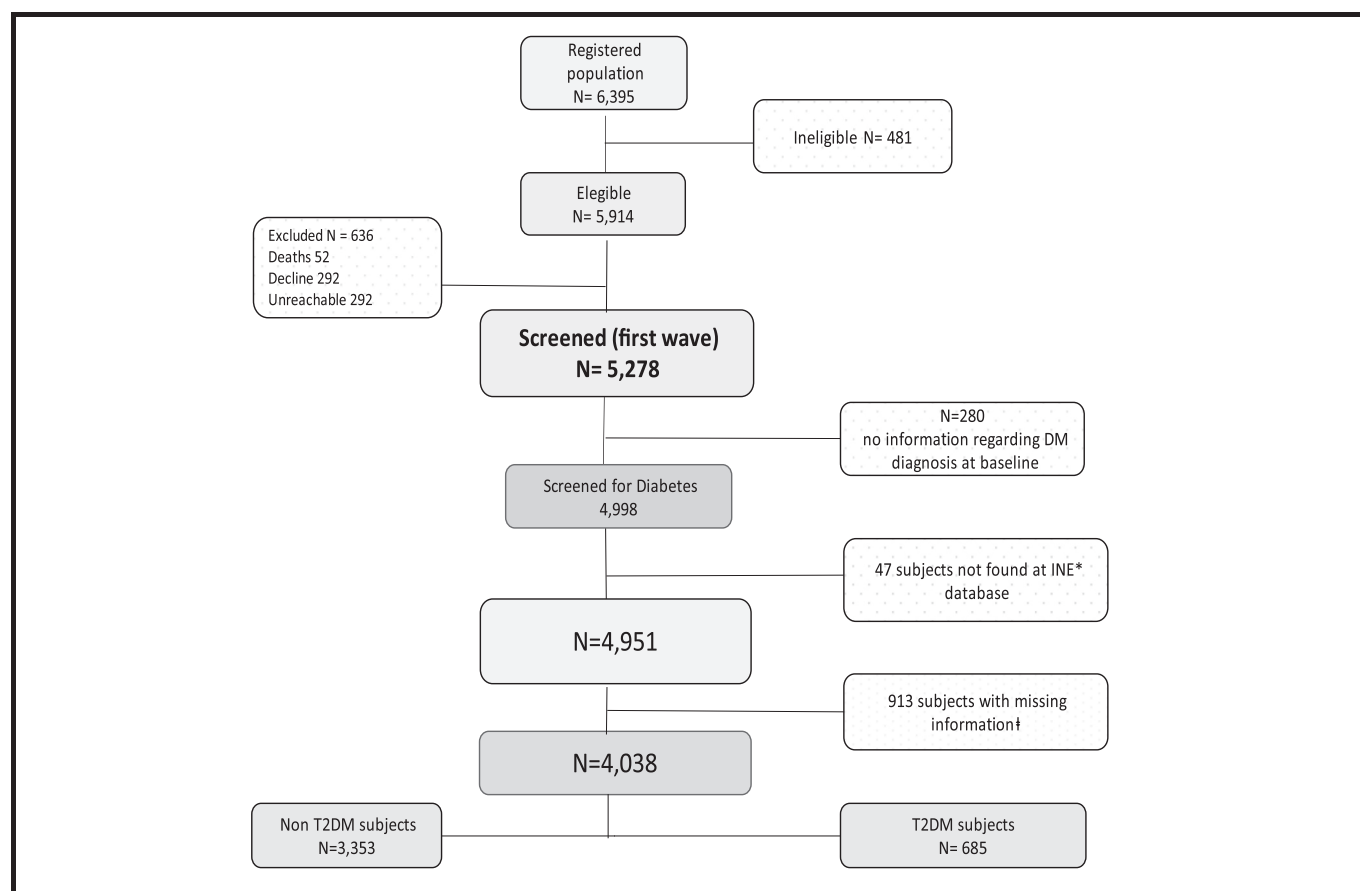


Fig. 1. Cohort study flowchart outlines and sample enrollment according to DM diagnosis. *DM: diabetes mellitus. * INE: Spain's National Statistics Institute. † Clinical missing information on alcohol, smoking habit, hypercholesterolemia or high blood pressure.

was compared by age group using the Cochran-Armitage test for trend.

The probability of survival was estimated depending on the T2DM diagnosis using the Kaplan-Meier method. Comparisons of the curves were performed using the log-rank test.

A Cox regression model was fitted to evaluate the effect of T2DM diagnosis on the mortality rate for any reason. Those baseline characteristics that presented statistically significant differences according to T2DM and/or were clinically relevant as factors related to mortality were included as confounders. The interaction term between T2DM and sex was included to explore differences in the mortality rate of T2DM by sex. As some of these confounding factors were missing in some subjects, we tested a crude model and several models including at least 70 % of the total subjects. Model 1 included age, sex, study area, hypertension, perceived health, cultural level and number of treatment drugs, including >90 % subjects; model 2 included the same variables as model 1 plus hypercholesterolemia, smoking status and alcohol consumption with >80 % included subjects; model 3 the same as model 2 plus the body mass index and the physical activity with >70 % included subjects. For all tests, a significant value of 5 % was accepted. Statistical analyses were performed with STATA software (15.1 version, StataCorp LLC, Texas, USA).

3. Results

The demographic and lifestyle features of the 4,038 included subjects (57.5 % women) are depicted in Table 1. Slightly more than a third of the individuals (34.2 %) included at baseline were 65 to 69 years old. Regarding the study area, there was a significantly higher proportion of T2DM women in Margaritas working-class area (51 vs. 35.4 %, $p < 0.001$). A lower education level was found in T2DM2 as compared to non-T2DM women ($p < 0.001$) but not in men. A higher proportion of non-T2DM men and women felt in very good or good health as compared to T2DM counterparts ($p < 0.001$). Instead, a higher proportion of T2DM men and women were diagnosed with hypercholesterolemia and hypertension ($p < 0.001$). T2DM men and women were less frequently active alcohol drinkers than their non-T2DM counterparts ($p = 0.023$ and < 0.001 , respectively). Oppositely, no differences were found for smoking status in T2DM vs. non-T2DM men and women. Regarding BMI, more overweight and obese women were found in the T2DM group ($p < 0.001$). No differences in BMI were found for men. Moreover, sedentarism was more frequent in T2DM subjects ($p = 0.013$). As expected, the number of treatment drugs was higher in T2DM subjects ($p < 0.001$), that were treated with an average of 1.41 drugs per day.

The crude prevalence of T2DM, according to age categories is displayed in Table 2. The prevalence of T2DM in the survey (1994–1995) was 17.0 % (95 % CI: 15.8–18.2), higher in women than men: 18.7 % (95 % CI: 17.1–20.3) vs. 14.7 % (95 % CI: 13.1–16.4).

By 31st December 2017, 3,442 subjects (85.2 %) from the 4,038 followed subjects had died, 616 in the T2DM2 group (89.9 %). As of the subjects' death causes (Table 3), the most important aetiology in the T2DM group was the cardiovascular group (18.6 %), followed by neoplasms (14.4 %), oppositely to the non-T2DM group, where neoplasms were the main group (17.7 %). Regarding the cardiovascular group, stroke of ischemic origin, was significantly more frequent in the T2DM group ($p < 0.001$), especially women (Suppl. Table 1). Moreover, it is important to notice that T2DM was the third most frequent death diagnosis followed by main cognitive impairment (Table 3). The death reason was not found in 33 subjects (< 1 % of the dead subjects).

Cumulative survival of subjects according to Kaplan-Meier curves is shown in Fig. 2. Survival was higher in the non-T2DM group ($p < 0.001$). Similar trends were found in the Kaplan-Meier curves according to sex ($p < 0.001$, figures not shown). Mean individuals survival time was two years higher for non-T2DM subjects as compared to T2DM (Table 4): 14.08 vs. 11.99 years ($p < 0.001$). Women had a mean survival time more than two years higher in both groups: T2DM men 10.52 vs. women 12.72 years ($p < 0.001$); non-T2DM men 12.83 vs. women

15.13 years ($p < 0.001$).

The crude Cox regression (Table 5) showed a HR mortality of 1.37 for men and 1.38 for women with T2DM as compared to non-DM subjects ($p < 0.001$), that did not change after adjustment for several confounding factors in the three models. We also categorized subjects in quartiles according to the number of years after T2DM diagnosis at baseline (data not shown in Table 5), and found that there were no differences in the Cox regression, but a tendency towards a higher risk of mortality in those subjects with 5 or more years after diagnosis (quartiles 3 and 4): ≥ 5 years HR 1.21 (0.96–1.53), $p = 0.108$; ≥ 14 years HR 1.21 (0.94–1.55), $p = 0.140$. Considering vascular disease (coronary artery disease, stroke, or limb ischemia), a significant mortality HR was also found for T2DM individuals: 1.59 (1.31–1.94, $p < 0.001$). Interestingly, the highest mortality HR in T2DM individuals was found for ischemic stroke: 4.40 (2.60–7.46, $p < 0.001$).

Regarding the different models of mortality for T2DM subjects on the multivariate test, they demonstrated an increased risk independently of gender or the included covariates, similar across all models (Table 5). Model 1 ($n = 3,681$ subjects, 91.2 % of the total subjects) showed a statistically significant mortality HR 1.31 for T2DM subjects. Model 2 ($n = 3,370$ subjects, 83.5 % of the total subjects) and model 3 (2,388 subjects, 70.3 %) showed similar mortality HRs. All-cause mortality risk was slightly higher for women according to the three models (1.35, 1.36 and 1.32, respectively vs 1.28, 1.23 and 1.27 in men). Therefore, none of the models diverged significantly from the mortality HR without adjustment, neither by sex (Table 5).

4. Discussion

In this study, the participants were all individuals under care in the Spanish National Healthcare System. We have found that T2DM subjects have a 2-year reduced expected survival time as compared to non-T2DM subjects throughout for 22 years, after adjusting for several confounding factors, with no differences between sex (Table 4). To our knowledge, this is the first time that a sustained reduction in the associated life expectancy of T2DM elderly subjects (≥ 65 years old) is proven in Spain. We have also found a crude prevalence of T2DM of 17 % in this elderly population, which is in accordance with more recent data in Spain for this age strata [7,26]. T2DM subjects had a 4.1 % excess risk for cardiovascular disease, and 2.3 % for stroke, compared with non-T2DM subjects.

The expected survival time in T2DM subjects has been studied for more than 30 years ago, mainly in developed countries, with controversial results. In Europe, the most recent data on a retrospective study from the UK [27] over a 15-year follow-up period, showed a constant increase in mortality among individuals with T2DM (HR 1.21 and 1.52 among individuals with diagnosis at 50–59 years and 60–74 years, respectively), in accordance with the results herein provided. Nevertheless, these data showed an improvement in the all-cause T2DM subjects' mortality, as a previous report in the UK in 2014 [28] demonstrated a twofold increased risk (HR 2.07) of all-cause mortality after adjusting for smoking, in a 7-follow-up year period of subjects aged 40 to 65 years at baseline. Interestingly of this study, was the finding that T2DM with <55 years of age, were at a greater relative risk than older middle-aged people without T2DM. This is in accordance with a systematic review in 8 countries including the UK [29], that found that increased mortality was lower when the diagnosis of T2DM was made at an older age than that reported for the general older T2DM population.

That the over-mortality of established persons with T2DM decreases with age has been found in several studies carried out in developed countries [28–31]. Even more, in some studies, no excess mortality was found over the ages of 65 or 70 years, as compared with non-DM counterparts [29–31]. However, a significant increase has been reported only for elderly women as compared to men in some studies [32,33]. Nevertheless, the reasons why some studies found small or non-differences in mortality, even in subjects diagnosed at a later age, could

Table 1
Characteristics of the included participants from the baseline survey (1994–5), according to diabetes mellitus status and sex.

Characteristics		Men				Women				Total			
		Total (%)	Non-T2DM# n (%)	T2DM# n (%)	P	Total (%)	Non-T2DM# n (%)	T2DM# n (%)	p	Total (%)	Non-T2DM# n (%)	T2DM# n (%)	p
Demographics (n = 4,038)													
Age – mean ± SD –		73.1 ± 6.4	73.2 ± 6.4	72.3 ± 6.4	0.034	74.0 ± 6.8	74.0 ± 6.8	73.9 ± 6.6	0.766	73.6 ± 6.6	73.7 ± 6.7	73.3 (6.5)	0.207
Age groups – years –	65–69	633 (36.8)	522 (35.6)	111 (44.0)	0.059	747 (32.2)	611 (32.4)	136 (31.4)	0.723	1,380 (34.2)	1,133 (33.8)	247 (36.1)	0.708
	70–74	485 (28.2)	414 (28.2)	71 (28.2)		648 (27.9)	529 (28.0)	119 (27.5)		1,133 (28.1)	943 (28.1)	229 (27.7)	
	75–79	294 (17.1)	263 (17.9)	31 (12.3)		416 (17.9)	331 (17.5)	85 (19.6)		710 (17.6)	594 (17.7)	116 (16.9)	
	80–84	192 (11.2)	167 (11.4)	25 (9.9)		299 (12.9)	240 (12.7)	59 (13.6)		491 (12.2)	407 (12.1)	84 (12.3)	
	≥ 85	114 (6.6)	100 (6.8)	14 (5.6)		210 (9.1)	176 (9.3)	34 (7.9)		324 (8.0)	276 (8.2)	48 (7.0)	
	Total	1,718 (42.5)	1,466 (85.3)	252 (14.7)		2,320 (57.5)	1,887 (81.3)	433 (18.7)		4,038 (100)	3,353 (83.0)	685 (17.0)	
Study Area	Lista	493 (28.7)	423 (28.9)	70 (27.8)	0.143	714 (30.8)	641 (34.0)	73 (16.9)	<0.001	1,207 (29.9)	1,064 (31.7)	143 (20.9)	<0.001
	Arévalo Country	626 (36.4)	545 (37.2)	81 (32.1)		717 (30.9)	578 (30.6)	139 (32.1)		1,343 (33.3)	1,123 (33.5)	220 (32.1)	
	Margaritas	599 (34.9)	498 (34.0)	101 (40.1)		889 (38.3)	668 (35.4)	221 (51.0)		1,488 (36.8)	1,166 (34.8)	322 (47.0)	
Education*	Total	1,718 (42.5)	1,466 (85.3)	252 (14.7)		2,320 (57.5)	1,887 (81.3)	433 (18.7)		4,038 (100)	3,353 (83.0)	685 (17.0)	
	Illiterates**	128 (7.5)	111 (7.6)	17 (6.7)	0.577	399 (17.3)	283 (15.1)	116 (26.9)	<0.001	527 (13.1)	394 (11.8)	133 (19.4)	<0.001
	Able to read & write	732 (42.8)	615 (42.2)	117 (46.4)		939 (40.6)	763 (40.6)	176 (40.7)		1,671 (41.6)	1,378 (41.3)	293 (42.8)	
Perceived health	Primary	526 (30.8)	456 (31.3)	70 (27.8)		725 (31.4)	612 (32.6)	113 (26.2)		1,251 (31.1)	1,068 (32.0)	183 (26.8)	
	Secondary/University	323 (18.9)	275 (18.9)	48 (19.0)		247 (10.7)	220 (11.7)	27 (6.3)		570 (14.2)	495 (14.8)	75 (11.0)	
	Total*	1,709 (10.4)	1,457 (11.1)	252 (6.4)	<0.001	2,310 (10.0)	1,878 (11.1)	432 (5.4)	<0.001	4,019 (10.2)	3,335 (11.1)	684 (5.8)	<0.001
	Very Good	177 (10.4)	161 (11.1)	16 (6.4)		229 (10.0)	206 (11.1)	23 (5.4)		406 (10.2)	367 (11.1)	39 (5.8)	
	Good	921 (54.2)	803 (55.3)	118 (47.4)		1,008 (44.2)	859 (46.3)	149 (34.8)		1,929 (48.4)	1,662 (50.3)	267 (39.4)	
	Fair	444 (26.1)	369 (25.4)	75 (30.1)		735 (32.2)	560 (30.2)	175 (40.9)		1,179 (29.6)	929 (28.1)	250 (36.9)	
Hypercholesterolemia †	Bad	125 (7.4)	90 (6.2)	35 (14.1)		234 (10.3)	167 (9.0)	67 (15.7)		359 (9.0)	257 (7.8)	102 (15.1)	
	Very bad	33 (1.9)	28 (1.9)	5 (2.0)		76 (3.3)	62 (3.3)	14 (3.3)		109 (2.7)	90 (2.7)	19 (2.8)	
	Total*	1,700 (40.4)	1,451 (23.4)	249 (35.7)	<0.001	2,282 (34.6)	1,854 (32.3)	428 (44.7)	<0.001	3,982 (30.6)	3,305 (28.4)	677 (41.3)	<0.001
	Yes	404 (25.2)	320 (23.4)	84 (35.7)		741 (34.6)	565 (32.3)	176 (44.7)		1,145 (30.6)	885 (28.4)	260 (41.3)	
Alcohol intake *	No	1,200 (74.8)	1,049 (76.6)	151 (64.3)		1,402 (65.4)	1,184 (67.7)	218 (55.3)		2,602 (69.4)	2,233 (71.6)	369 (58.7)	
	Total	1,604 (42.8)	1,369 (85.3)	235 (14.7)		2,143 (57.2)	1,749 (81.6)	394 (18.4)		3,747 (100)	3,118 (83.2)	629 (16.8)	
	Yes	789 (45.9)	684 (46.7)	105 (41.7)	0.023	377 (16.3)	339 (18.0)	38 (8.8)	<0.001	1,166 (33.8)	1,023 (30.5)	143 (20.9)	<0.001
Alcohol intake *	No	689 (46.6)	568 (45.4)	121 (53.5)		1,590 (80.8)	1,260 (78.8)	330 (89.7)		2,279 (66.2)	1,828 (64.1)	451 (75.9)	
	Total	1,478	1,252	226		1,967	1,599	368		3,445	2,851	594	

(continued on next page)

Table 1 (continued)

Characteristics		Men				Women				Total			
		Total (%)	Non-T2DM# n (%)	T2DM# n (%)	P	Total (%)	Non-T2DM# n (%)	T2DM# n (%)	p	Total (%)	Non-T2DM# n (%)	T2DM# n (%)	p
Smoking status*	Current smoker	330	283 (22.6)	47 (20.6)	0.510	70	61 (3.8)	9 (2.4)	0.202	400 (11.6)	344 (12.1)	56 (9.4)	0.065
	Non-smoker (including former smokers)	1,151	970 (77.4)	181 (79.4)		1,898	1,539 (96.2)	359 (97.6)		3,049 (85.4)	2,509 (87.9)	540 (90.6)	
Hypertension*‡	Total	1,481	1,253	228		1,968	1,600	368		3,449	2,853	596	
	Yes	726 (42.4)	592 (40.5)	134 (53.4)	< 0.001	1,324 (42.7)	1,025 (54.6)	299 (69.5)	< 0.001	2,050 (50.8)	1,617 (48.4)	433 (63.6)	< 0.001
	No	986 (57.6)	869 (59.5)	117 (46.6)		985 (42.7)	299 (69.5)	131 (30.5)		1,971 (48.8)	1,723 (51.6)	248 (36.4)	
	Total	1,712	1,461	251		2,309	1,879	430		4,021	3,340	681	
Body Mass Index		26.9 ± 4.0	26.9 ± 4.0	27.4 ± 4.0	0.092	28.0 ± 5.6	27.8 ± 5.5	28.9 ± 6.2	0.002	27.5 ± 5.0	27.3 ± 4.9	28.3 ± 5.5	< 0.001
- Kg/m ² – mean ± SD –													
Body Mass Index *	< 20	14 (1.0)	12 (1.0)	2 (0.9)	0.517	27 (1.6)	25 (1.8)	2 (0.7)	0.015	41 (1.3)	37 (1.5)	4 (0.8)	0.080
	20 – 24.99	417 (30.0)	362 (30.8)	55 (25.7)		505 (30.3)	432 (31.7)	73 (24.2)		922 (30.2)	794 (31.2)	128 (24.8)	
	25–30	696 (50.0)	583 (49.5)	113 (52.8)		619 (37.2)	499 (36.6)	120 (39.7)		1,315 (43.0)	1,082 (42.6)	233 (45.2)	
	>30	264 (19.0)	220 (18.7)	44 (20.6)		515 (30.9)	408 (29.9)	107 (35.4)		779 (25.5)	628 (24.7)	151 (29.3)	
Physical Activity*	Total	1,391	1,177	214		1,666	1,364	302		3,057	2,541	516	
	Sedentary	428 (30.7)	349 (29.5)	79 (37.6)	0.084	445 (24.5)	348 (23.4)	97 (29.8)	0.062	873 (21.6)	697 (26.1)	176 (32.8)	0.013
	Low	374 (26.9)	319 (27.0)	55 (26.2)		499 (27.5)	417 (28.0)	82 (25.2)		873 (21.6)	736 (27.6)	137 (25.6)	
	Moderate	316 (22.7)	272 (23.0)	44 (21.0)		383 (21.1)	325 (21.8)	58 (17.8)		699 (17.3)	597 (22.4)	102 (19.0)	
	High	274 (19.7)	242 (20.5)	32 (15.2)		487 (26.8)	398 (26.7)	89 (27.3)		761 (18.8)	640 (24.0)	121 (22.6)	
	Total	1,392	1,182	210		1,814	1,488	326		3,206	2670	536	
Treatment	Number of drugs mean (SD)		0.55 (± 0.77)	1.24 (± 1.12)	< 0.001		0.76 (± 0.84)	1.51 (± 1.07)	< 0.001	0.79 (± 0.91)	0.66 (± 0.82)	1.41 (± 1.09)	< 0.001

*Non-T2DM; participants without diabetes. T2DM: participants with diabetes.

*For diverse reasons, not all participants had information on each characteristic.

‡Blood pressure ≥ 140/90 mm hg.

†Total Cholesterol ≥ 200 mg/dl.

††Standard deviation.

Table 2
Total crude prevalence of type 2 diabetes mellitus in the baseline survey according to age categories.

% (95 % CI)	Age (years)	Men		Women		Total	
		Crude	p [†]	Crude	p [†]	Crude	p [†]
Cross-sectional (1994)	65–69	17.5 (14.8–20.8)	0.014	18.4 (15.6–21.5)	0.948	17.9 (16.0–20.0)	0.226
	70–74	14.6 (11.8–18.1)		18.4 (15.6–21.5)		16.8 (14.7–19.1)	
	75–79	10.5 (7.5–14.6)		20.4 (16.8–24.6)		16.3 (13.8–19.2)	
	80–84	13.0 (8.9–18.6)		19.7 (15.6–24.6)		17.1 (14.0–20.7)	
	>84	12.3 (7.3–19.7)		16.2 (11.8–21.8)		14.8 (11.3–19.1)	
	Total	14.7(13.1–16.4)		18.7 (17.1–20.3)		17.0 (15.8–18.2)	

†Cochran-Armitage test for trend.

Table 3
Subjects' death causes.

Cause				DM (%) [†]	Non-T2DM (%) [†]	Total (%) [†]	p
Cardiovascular disease	Subtype	Ischemic cardiomyopathy	Acute myocardial infarct	42 (6.2)	154 (4.6)	196 (4.9)	0.091
			Angor	0 (0)	2 (0.1)	2 (0)	--
			Other	19 (2.8)	93 (2.8)	112 (2.8)	0.991
			Total	61 (9.0)	249 (7.5)	310 (7.7)	0.192
		Stroke	Ischemic	24 (3.5)	33 (1.0)	57 (1.4)	<0.001
			Haemorrhagic	12 (1.8)	48 (1.4)	60 (1.5)	0.534
			Others	23 (3.4)	131 (3.9)	154 (3.8)	0.486
			Total	59 (8.7)	212 (6.4)	271 (6.8)	0.030
	Total	Ischemic lower limb		6 (0.9)	17 (0.5)	23 (0.6)	0.262
				126 (18.5)	478 (14.4)	604 (15.1)	0.006
Neoplasm			98 (14.4)	592 (17.8)	690 (17.2)	0.034	
Main cognitive impairment			40 (5.9)	198 (6.0)	238 (5.9)	0.934	
Diabetes mellitus			45 (6.6)	32 (1.0)	77 (1.9)	<0.001	
High blood pressure			13 (1.9)	89 (2.7)	102 (2.5)	0.286	
Others			290 (42.3)	1,408 (42.0)	1,698 (42,1)	0.868	
Unknown			4 (0.6)	29 (0.9)	33 (0.8)	0.641	
Death			616 (89.9)	2,826 (84.3)	3,442 (85.2)	<0.001	
Total			685	3,353	4,038		

DM: diabetes mellitus. Death causes according to the Spanish National Statistics Institute (INE) by 31st December 2017. In 33 cases (4 DM subjects) the cause of death is unknown. †Percentage of the whole subjects excluding unknown cases.

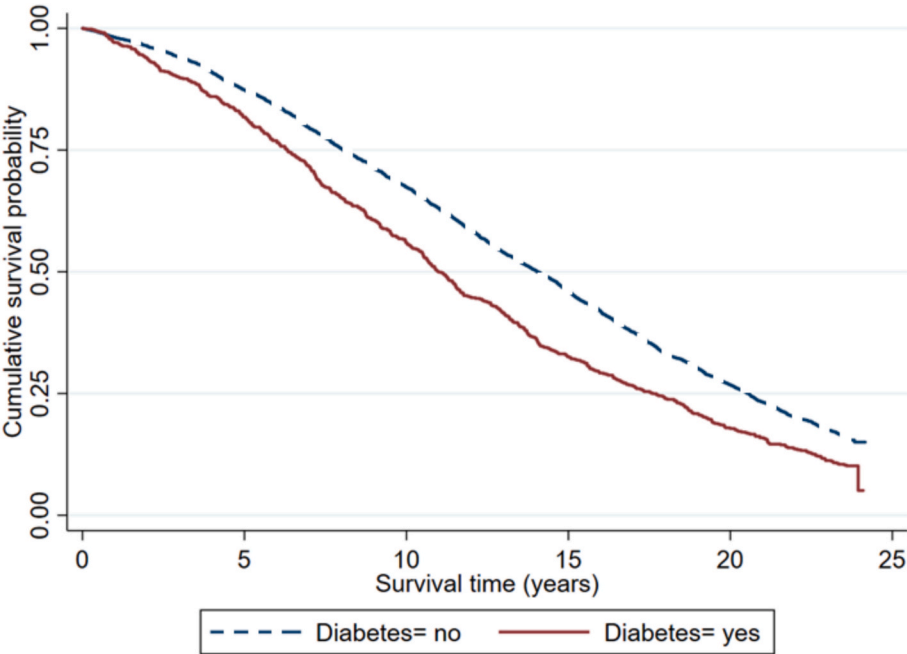


Fig. 2. Cumulative survival of subjects categorized according to DM diagnosis.

be because there was no adjustment for the confounding effect of deprivation [34], perhaps a degree of under-ascertainment of T2DM in the non-DM cohort [35,36], or alternatively there was a low mean year follow-up period [29,32,37]. In fact, it may be that mortality of T2DM

and non-T2DM subjects diverges in later years after diagnosis, starting at least 7 years following diagnosis [32]. It could possibly be explained because, in younger T2DM subjects, there is less additional risk besides hyperglycemia compared to older T2DM individuals.

Table 4
Subjects' survival time according to T2DM diagnosis.

Diabetes	Men*		Women*		Total*	
	x ⁻	M	x ⁻	M	x ⁻	M
No	12.72 (12.36–13.08)	12.01 (11.49–12.53)	15.13 (14.81–15.45)	15.52 (15.04–16.01)	14.08 (13.83–14.32)	14.04 (13.63–14.46)
Yes	10.52 (9.69–11.35)	9.18 (7.87–10.49)	12.83 (12.17–13.50)	11.75 (10.83–12.67)	11.99 (11.46–12.51)	10.99 (10.35–11.63)
Overall	12.40 (12.07–12.73)	11.62 (11.15–12.08)	14.70 (14.41–14.99)	14.94 (14.46–15.42)	13.72 (13.50–13.94)	13.46 (13.09–13.84)

n = 4,038. x⁻: mean. M: median. 95 % CI in brackets. *p < 0.001 for the comparisons of DM against non-T2DM.

Table 5
HRs of all-cause mortality.

	Crude	p	Model 1	p	Model 2	p	Model 3	p
All participants	1.34 (1.23–1.46)	<0.001	1.31 (1.19–1.44)	<0.001	1.29 (1.16–1.42)	<0.001	1.29 (1.16–1.45)	<0.001
Men	1.37 (1.22–1.53)	<0.001	1.28 (1.13–1.44)	<0.001	1.23 (1.08–1.40)	0.001	1.27 (1.08–1.49)	0.005
Women	1.38 (1.20–1.59)	<0.001	1.35 (1.17–1.57)	<0.001	1.36 (1.17–1.59)	<0.001	1.32 (1.14–1.53)	<0.001
p-interaction*		0.928		0.553		0.321		0.705

Data are HRs (95% CI) for people with type 2 diabetes compared with people without diabetes and non-unadjusted (crude model) or adjusted for age, sex, study area, hypercholesterolemia, hypertension, perceived health, cultural level and number of treatment drugs (model 1), or adjusted for the same variables as model 1 plus the smoking status and alcohol consumption (model 2) or adjusted for the same variables as model 2 plus the body mass index and the physical activity (model 3).

*The interaction p-value assesses whether the hazard associated with T2DM differs significantly between sexes.

Oppositely, in our elderly cohort, we found an increase in mortality only 1 year after diagnosis of DM as it occurred in a study conducted in Germany, where interestingly it was higher than the increased mortality found for the same cohort—10 years post-diagnosis [38]. Similarly, in our study the survival curves of T2DM and non-T2DM groups tended to converge after 20 years of follow-up (Fig. 2), indicating that above the age of 85 mortality is only slightly or not increased. Interventions such as smoking cessation, lifestyle modifications, and more efficacy in drugs for diabetes, have led to a reduction in risk factors for this disease, and therefore for cardiovascular diseases and diabetes associated mortality.

On the other hand, we have found that cardiovascular diseases are the major cause of premature death in subjects with T2DM, with a 1.59-fold increased risk of cardiovascular mortality and 4.4-fold increased risk for ischemic stroke. The increased mortality of older T2DM people may be up to four times higher than that of older non-DM people [29]. These results are in accordance with previous studies [28–31], although patterns in high income countries, including Spain, show declining rates of vascular complications and its hospitalizations, as well as death from cardiovascular causes since 2000. This information has been mostly obtained from registries or administrative data sources until 2021 and demonstrates that the largest declines in vascular complications have been observed for older adults [39].

The strengths of our study included the data sources, with high-quality data on a large representative sample of the central Spanish elderly population, and complete and accurate data on the date and cause of death in the certification by their PCP and provided by the INE. Moreover, we were able to adjust for the most important cardiovascular risk factors at baseline. Another significant strength is the long-term subject's follow-up, very unusual over a period longer than 15 years in other cohorts. However, we were limited by the extent of missing data for some covariates of interest in several subjects at the first wave carried out in 1994–95. Another possible flaw is that our cohort lacks information on the effect of T2DM drugs and T2DM control during the long follow-up period. No information on other important covariates such as hypertension, hypercholesterolemia, BMI, and physical activity levels during the long follow-up has neither been considered. Effectively, considering changes during the follow-up in those factors could potentially have influenced the mortality outcomes.

In conclusion, this is a unique study that demonstrates for the first time a sustained reduction in Spanish T2DM elderly subjects (≥65 years) life expectancy after more than 20 years follow-up. Nevertheless, above the age of 85, mortality is only slightly or not increased. Cardiovascular diseases, followed by neoplasms, are the major cause of mortality among

elderly individuals with T2DM, while in non-T2DM subjects' neoplasms were the most frequent cause. Amongst cardiovascular diseases, T2DM elderly subjects are at significant risk of death from ischemic stroke. Therefore, community interventions and campaigns addressing lifestyle modifications, alcohol and smoking cessation and promotion of an adequate and regular TDM2 clinical follow-up, should be reinforced by authorities to reduce the risk factors for this disease, as well as to improve its control and the associated morbidity and mortality.

5. Data

The datasets generated and analyzed during the current study are not publicly available as they contain information that could compromise research participants privacy, but they are available from the corresponding author upon reasonable request.

Author contributions

FBP and MSR are responsible for conceiving and designing the study. SVQ, FBP and JBL participated actively in the development of the field study. ACA, SVQ, JBL and MAG extracted and curated the data. ACA, SVQ and MFF are responsible for the integrity of the analyses and interpretation of the data. ACA, SVQ and FHC are responsible for the preparation of the draft of the manuscript. FHC and FBP participated in the critical revision and gave final approval of the manuscript to be published.

CRedit authorship contribution statement

A. Corbatón-Anchuelo: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **S. Vega-Quiroga:** Visualization, Methodology, Investigation, Funding acquisition, Data curation. **F. Bermejo-Pareja:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **M. Fuentes-Ferrer:** Writing – original draft, Methodology, Formal analysis, Data curation. **M. Álvarez-González:** Investigation, Formal analysis. **J. Benito-León:** Methodology, Funding acquisition, Data curation. **F. Hawkins-Carranza:** Writing – review & editing, Methodology. **M. Serrano-Ríos:** Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2025.112291>.

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