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Predictors of 15-year survival among Australian women with diabetes from age 76–81

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ABSTRACT

Aims: To assess the impact of diabetes on the survival of older women, adjusted for other all-cause mortality predictors.

Methods: Data were used from the 1921–26 cohort of the Australian Longitudinal Study on Women's Health, when the women were aged 76–81 years at baseline, with linkage to the National Death Index. Survival curves were plotted to compare the survival of women with no diabetes, incident diabetes and prevalent diabetes over 15 years. Cox proportional hazards models were used to examine the association between diabetes and all-cause mortality risks.

Results: A total of 972 (11.7%) of 8296 eligible women reported either incident, 522 (6.3%) or prevalent, 450 (5.4%) diabetes. The median survival times were 10.1, 11.4 and 12.7 years among women with prevalent, incident and no diabetes, respectively. The risks of death were 30% [HR: 1.30 (95% CI: 1.16–1.45)] and 73% [HR: 1.73 (CI: 1.57–1.92)] higher for women with incident and prevalent diabetes compared to women without diabetes. These associations were sustained after controlling for demographics, body mass index, smoking status, comorbidities and health care use.

Conclusions: This study revealed that diabetes is associated with reduced survival probabilities for older women with minimal moderation after adjustment for other predictors. Our findings suggest that diabetes management guidelines for older women need to integrate factors such as comorbidities, smoking and being underweight to reduce the risk of mortality.

1. Introduction

Diabetes is one of the major chronic diseases with an ever-increasing health and economic burden in all corners of the world [1]. Age-standardised adult prevalence of diabetes has increased or at least remained stable in every country since 1980. Coupled with ageing and population growth, this rise has led to an almost four-times (108 million in 1980 to 422

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million in 2014) increase in the number of adults with diabetes [2]. The number of adults with diabetes is expected to increase to 693 million by 2045. Globally, diabetes was a cause of death for approximately five million adults aged 20–99 years and resulted in an estimated healthcare expenditure of $850 billion in 2017 only [1]. Researchers in different countries found that diabetes is associated with lower patient quality of life [3] and survival reduction of up to 12 years [4].

Most survival studies related to diabetes focused on examining the contribution of diabetes as comorbid with an index condition such as heart failure [5], cancer [6], and coronary heart disease [7]. However, diabetes is associated with numerous fatal complications and therefore plays a critical role in patient survival. Consequently, it would be relevant to assess the primary impact of diabetes on survival [8,9]. Moreover, it is expected that there are factors other than diabetes that may affect survival. Previous researchers observed that lower body mass index (BMI) and smoking were associated with increased risk of all-cause mortality by up to 69% and 74%, respectively [10]. Risk of death was also 41% and 55% lower for patients with diabetes who have medium and highest level of social support compared to those with lowest level of support. In addition, older age and comorbidities such as cardiovascular disease and cancer were also among the predictors of increased risk of all-cause mortality for patients with diabetes [10–12].

Even though diabetes is a key public health problem among older women, there is a paucity of research focused on this population and the factors that contribute to increased risk of mortality. Previous studies did not have a focus or sub-analysis of older women, or did not look into predictors of increased risk of mortality or included too few of the potential predictors [13]. For instance, none of the above studies examined the potential contribution of level of health care access and use which are important predictors of mortality amenable to effective health care [10,14]. Furthermore, the expected increase in diabetes prevalence in the coming decades further underscores the importance of estimating the impact of diabetes on survival and better understanding of factors contributing to increased mortality risks, particularly among older women [1]. Therefore, this study aimed at estimating the impact of both prevalent and incident diabetes on the long-term survival of older women and assessing the contribution of other potential predictors of mortality in the presence of diabetes.

2. Methods

2.1. *Study population and data sources*

The Australian Longitudinal Study on Women's Health (ALSWH) is a prospective longitudinal study of Australian women, investigating the ongoing health and well-being of women as well as heath care service use (www.alswh.org.au). In 1996, three cohorts of community dwelling women (born 1921–26, 1946–51 and 1973–78) were randomly selected from Medicare Australia's database. The women have been regularly followed via postal and online surveys. Another cohort of women (born 1989–95) was recruited to ALSWH through social media in 2012–2013 and have been surveyed annually. To widen the scope of the study the survey data have been linked to several health care administrative databases such as Medicare Australia (MBS and PBS), hospital admissions and the National Death Index (NDI). Death dates were ascertained from the NDI which contains date of death and causes of death [15].

For this study, data were obtained for the 12,432 women born 1921–26 (aged 70–75 years in 1996). These women were largely representative of similarly aged women in Australia with the exception of the inclusion of slightly more women who were partnered (married/defacto) or had post-school educational qualification. Eligible women were those who were: [1] alive at Survey 3 (2002) and did not withdraw before the follow-up start date (survey 3 return date); and [2] completed Survey 1 (1996) and Survey 3 and responded to the diabetes question in both of these surveys.

2.2. *Variables/Measurements*

2.2.1. *Diabetes status*

Diabetes status was ascertained using responses to the question "Have you ever been told by a doctor that you have diabetes (high blood sugar)?" in the first survey; or "In the last three years, have you been diagnosed with or treated for diabetes?" in subsequent surveys. The women were categorised into three mutually exclusive groups based on their baseline self-reported diabetes status at Surveys 1–3 (i.e. in 1996, 1999 and 2002), namely (1) women with *no diabetes*, (i.e. those who did not report diabetes at any of the three surveys); (2) women with *prevalent diabetes* (i.e. those who reported diabetes at survey 1 and either at survey 2 or survey 3); and (3) women with *incident diabetes*, (i.e. those who reported diabetes at either survey 2 or survey 3 but not at survey 1) (Fig. 1). These diabetes status definitions were based on the enduring nature of the disease (i.e. a woman was considered to have diabetes from her first report forward). Therefore women who reported 'yes' at Survey 1 but 'no' at Survey 2 were considered as inconsistent and removed from analysis.

2.2.2. *Survival time*

All eligible women were followed for up to 15 years. Women who died between the start date (Survey 3 return date, 2002) and follow-up end date (31 December 2016) were censored on their date of death. Those who were alive after the end date of the follow-up were censored at the follow-up end date. Survival time was calculated for each participant from the follow-up start date and death/censored date.

2.2.3. *Causes of death*

Women who died during the follow-up period were grouped according to 29 causes of death categories based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes for their primary cause of death (https://www.accd.net.au/icd10.aspx). The top ten causes of death were identified for each of the diabetes groups (see Supplemental file: Table S1). Primary cause is a disease which had a principal contribution in causing the death whereas secondary causes are one or more diseases which assisted the

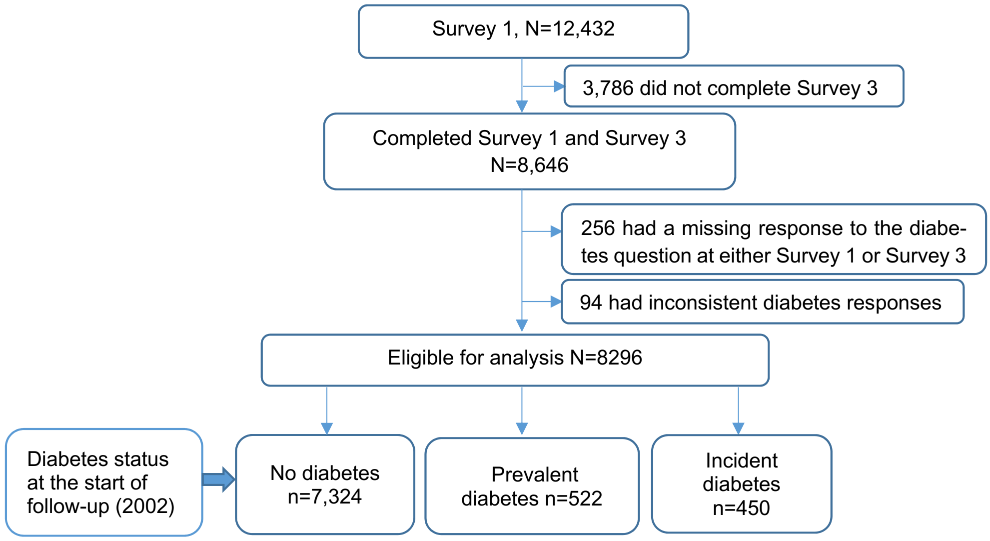

Fig. 1 – Determination of eligibility.

primary cause in resulting in the death as registered in the NDI [15].

2.2.4. *Other predictor variables for survival*

Predictor variables assessed for their impact on survival included demographic characteristics, comorbidities, proxy status (whether the study participants needed others' help to respond to the questions and or complete the surveys), BMI, smoking status social support and health service use. Unless otherwise specified, these predictor variables were obtained from Survey 3 of the ALSWH, with missing values filled in by using Survey 2 initially and using Survey 1 if necessary. The inclusion of these variables was dictated by previous mortality and survival studies [10–12,16].

Demographics: Marital status was dichotomised as partnered (married and de facto relationship); and not partnered (separated, divorced, widowed). Area of residence was categorised as major cities, inner regional and outer regional/remote/very remote; while age at Survey 3 was collected as continuous variable. Education status was collected at Survey 1 and was categorised into three levels: Year 12 or below, trade certificate/diploma and University degree or above. Self-reported ***comorbidities*** at Survey 3 for doctor-diagnosis or treatment included hypertension, heart attack, asthma, stroke, cancers other than non-melanocytic cancer, depression and Alzheimer's disease or dementia. ***Proxy status*** was indicated when a survey was completed by others on behalf of a participant. BMI and smoking status were also included in the model as such. BMI was calculated from self-reported height and weight questions and categorised according to WHO guidelines [17], while smoking status was classified as current smoker, ex-smoker and never smoked. ***Social support*** was measured using the Duke Social Support Scale [18]. Health service use was determined using survey self-report. Women were asked to indicate the number of annual general practitioner (GP) visits they had in the 12-month periods prior to surveys, which was then categorised as low use (0–4 times) or high use (5 or more times), based on a mean of 5.1 GP visits/person in Australia [19]. The women also indicated if they visited a specialist doctor in the 12-month period prior to each of the surveys (yes/no).

2.3. *Statistical analysis*

Chi-square tests and ANOVA were used to compare the predictor variables between the three groups of women according to diabetes status. Statistical significance was set at $P < 0.01$. Kaplan Meier survival curves were plotted and compared according to diabetes status. Differences in median survival times between the groups were assessed using the log-rank test. Cox regression models [20] were fitted to assess the effect of diabetes status on mortality, with other predictors sequentially included in the model. The models built and the sequence of predictor inclusion were as follows:

Model 1: Diabetes
Model 2: Diabetes + comorbidities + BMI + smoking status
Model 3: Diabetes + comorbidities + BMI + smoking status + demographic factors + social support + health care use

The hazard ratios (HR) for all models were reported with 95% CIs. All statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

2.4. *Ethical approval*

The ALSWH has an ongoing ethical approval from the University of Newcastle (H-076-0795 and H-2012-0256) and the University of Queensland (2004000224 and 2012000950) Human Research Ethics Committee. Ethical approval for the linkage of ALSWH survey data to the NDI was obtained from the AIHW Ethics Committee.

3. Results

Of the 12,432 women in the cohort, 8646 completed both Survey 1 and Survey 3. Of these women, 256 had missing responses to the diabetes questions and were excluded, while an additional 94 women were excluded since their responses were inconsistent across Surveys 1–3, leaving 8296 women eligible for analysis. Of these women, 522 (6.3%) and 450 (5.4%) reported prevalent and incident diabetes respectively, while 7324 (88.3%) women did not report diabetes (Fig. 1).

3.1. Baseline characteristics

The percentage of women with incident (3.3%) and prevalent (1.8%) diabetes who reported tertiary level of education was lower than that of the women with no diabetes (4.5%) ($p = 0.02$). A slightly higher percentage of the women with no diabetes (44.5%) were residents of major cities compared to the women with diabetes (incident: 42.4% and prevalent: 38.1%) ($p = 0.05$). The women with diabetes were more likely to have comorbidities including hypertension ($p < 0.0001$), heart attack ($p < 0.0001$), cancer ($p = 0.03$), and depression ($p = 0.0022$) with the exception of stroke ($p = 0.32$), dementia ($p = 0.32$) and asthma ($p = 0.25$). Women who reported diabetes were also more likely to be overweight or obese ($p < 0.0001$) and use more health care ($p < 0.0001$) (Table 1).

3.2. Survival

The survival of women with prevalent diabetes was significantly lower than that of women with incident diabetes throughout the follow-up period and this rate in turn was lower than that of women without diabetes ($p < 0.0001$, Fig. 2). Median survival for women in the prevalent, incident and no diabetes groups were 10.1 [interquartile range (IQR): 5.5–13.8], 11.4 (IQR: 6.9–14.7) and 12.7 (IQR: 8.5–14.8) years, respectively. At the end of 15 years of follow up, a total of 3376 (40.7%) women were alive, with 42.4% of women without diabetes still alive compared with 32.7% and 23.8% in the incident and prevalent diabetes groups, respectively.

3.3. Causes of death

The top five primary causes of death across all women in the study were heart diseases, cancer, cerebrovascular diseases, dementia and COPD (see Supplementary file Table S1). Diabetes was the eighth primary cause of death for all women, contributing 3.0% of the total deaths. However, it was the second and third primary cause of death for women with prevalent and incident diabetes, respectively. When secondary causes of death were included in the analysis, the contribution of diabetes rose to 10.1% of the total deceased women in the study. The leading primary cause of death in these women were also heart diseases, for which diabetes is a common risk factor.

3.4. All-cause mortality and its predictors

Compared to women with no diabetes, the risk of death over the fifteen year follow-up period was 30% higher for women with incident diabetes [HR: 1.30 (95% CI: 1.16–1.45)] and 73% higher for women with prevalent diabetes [HR: 1.73 (CI: 1.57–1.92)] (see Table 2, Model 1). After controlling for comorbidities, BMI and smoking status, both the HRs of all-cause mortality and the statistical significance remained stable, with only minor reductions in the hazard ratios (see Table 2, Model 2). Most of the comorbidities were also significant risk factors for all-cause mortality. The risk of death increased by 54% for women with heart attack, 57% for women with stroke, 78% for women with cancer; and was 2–3 times more likely for women with Alzheimer's disease or dementia compared to women without these conditions (see Table 2, Model 2). Mortality over the follow-up period was also 63% higher for women who dictated their survey responses and 46% higher for those whose surveys were filled in based on proxies' judgement.

When all other predictors were included in the model (see Table 2, Model 3), the risk of death remained 23% higher for women with incident diabetes and 55% higher for women with prevalent diabetes, compared to women with no diabetes. As expected, history of smoking and current smoking were both associated with increased risk of mortality (17% and 73% respectively), while being underweight was associated with a 77% risk of early mortality. Women who had high GP use (five or more visits in a 12-month period) and those who visited specialists in the 12-month period before the survey had 23% and 12% increased mortality risk respectively.

4. Discussion

This study demonstrated the impact of diabetes on long-term survival probability among older Australian women and the contribution of other all-cause mortality predictors. Women with incident or prevalent diabetes had a lower and increasingly declining survival probability compared to women with no diabetes, with women with prevalent diabetes having the worst survival probability. More importantly, this study found a number of factors contributing to and/or independently associated with increased risk of mortality among the women with diabetes including comorbidities, BMI, smoking status, level of social support and health care use.

The current study did not find significant associations between the women's all-cause mortality risks and their education level or residence area. In a US study, individuals with less than high school education had a twofold higher mortality from diabetes compared to those educated to college level [21]. The absence of association between education level, an important indicator of socioeconomic status, and diabetes mortality in the current study may be due to the universal health insurance system in Australia that is not available in most other countries including the US.

Women with diabetes were more likely to have other comorbid conditions, which were significant individual predictors of all-cause mortality. Comorbidities such as cancer and Alzheimer's disease/dementia contributed to increased risk of all-cause mortality. The reporting of multiple comorbidities by the majority of women who have diabetes accords with the fact that the disease has a very strong association with several other conditions [22]. However, adjustment of the model for comorbidities and respondent status (participant/proxy) resulted in minimal reduction in the risk of mortality among the incident and prevalent diabetes cases. This suggests that the effect of diabetes on mortality may be independent of other comorbid conditions.

Table 1 – Baseline characteristics of women with no, prevalent and incident diabetes.

Characteristics	No diabetes (n = 7324)	Prevalent diabetes (n = 522)	Incident diabetes (n = 450)	p
Demographics				
Age in years, mean (SD)	78.3 (1.5)	78.30 (1.5)	78.2(1.5)	0.31
Education				0.02
Year 12 or below	83.2	87.0	86.3	
Trade certificate/ diploma	12.3	11.2	10.5	
University degree or above	4.5	1.8	3.3	
Marital status				0.20
Partnered*	45.0	46.0	40.9	
Not partnered	55.0	54.0	59.1	
Area of residence				0.05
Major cities	44.5	38.1	42.4	
Inner regional	37.0	39.7	37.8	
Outer regional/remote/very remote	18.5	22.2	19.8	
Comorbidities, %				
Hypertension	50.6	68.4	66.4	<0.0001
Heart attack	3.1	8.1	5.3	<0.0001
Stroke	3.2	4.2	4.0	0.32
Non-melanoma cancer	4.1	4.6	6.7	0.03
Depression	6.8	10.7	8.4	0.0022
Asthma	9.1	11.3	8.9	0.25
Alzheimer's disease or dementia	0.9	1.3	0.4	0.32
Proxy status				<0.0001
Completed by participant alone	7.4	14.9	10.9	
Participants provided answers, proxy completed survey	6.0	11.5	7.6	
Proxy provided answers & completed survey on behalf of participant	1.4	3.5	3.3	
Smoking status and body mass index				
Smoking status				0.03
Never smoked	64.3	64.2	68.8	
Ex-smoker	29.0	31.9	26.6	
Current smoker	6.6	3.9	4.7	
Body mass index (BMI)				<0.0001
Underweight (BMI < 18.5)	4.1	1.2	2.0	
Normal weight (18.5 ≤ BMI < 25)	49.8	36.9	36.7	
Overweight (25 ≤ BMI < 30)	32.9	34.3	35.1	
Obese (BMI ≥ 30)	13.2	27.6	26.1	
Duke Social Support Scale, mean (SD)	8.8 (1.6)	8.6 (1.6)	8.6 (1.6)	0.0019
Health care use				
Annual number of GP visits†				<0.0001
Low	40.9	23.4	25.6	
High	59.1	76.6	74.4	
Visited specialist doctor in 12 months, %	45.0	57.8	51.3	<0.0001

* Married or in a de facto relationship.

† Low: 0–4 times/ year, high: ≥5 times/year.

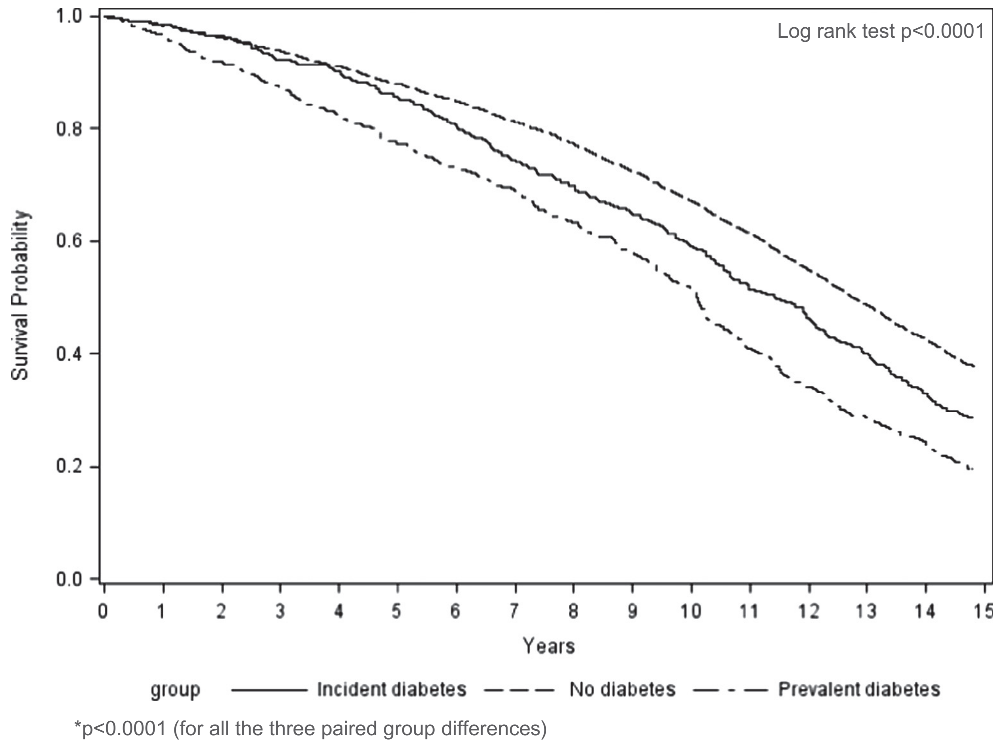

Fig. 2 – Kaplan-Meier survival curves of older women (aged 76–81 in 2002), according to diabetes group.

In this study, women with incident and prevalent diabetes had a 23% and 55% increased risk compared to women without diabetes, respectively. This is similar to the increment in mortality risk (1.6 times) among Australians with diabetes, compared to the general population, reported by AusDiab [23] In this study even those women with either prevalent or incident diabetes survived for more than a decade (median survival), which provides a long lead-time for prevention and control of risk factors that contribute to increased mortality risk. In a recent Swedish study it was reported that patients with diabetes in whom five major risk factors (smoking, elevated glycated hemoglobin level, albuminuria, elevated low-density lipoprotein cholesterol level, and elevated blood pressure) were controlled within target ranges had only a marginally increased risk of mortality (6%) [24]. Therefore, the higher risk of mortality for women with diabetes in the current study may be partly due to less optimal control of the risk factors. This calls for more investment into the delivery of strategies to prevent and control these risk factors for older women, including encouraging better uptake of,- and adherence to, the annual cycle of care services for patients with diabetes.

Heart diseases, cancer, cerebrovascular diseases, dementia and chronic obstructive pulmonary disease (COPD) were the leading primary causes of death among all women in the study in keeping with the top five causes of death in Australia for both men and women [25]. Diabetes accounted for 10.1% of all deaths as a primary or associated cause and this is consistent with national figures [26]. Among women with prevalent or incident diabetes, those who died had diabetes as a primary (2.4%) or secondary (7.7%) cause of death. In most of these cases diabetes was coded as "diabetes without complications" (75%). Other diabetes associated immediate causes include kidney- (4.7%), cardiovascular- (14.2%), and multiple complications (3.4%).

Compared to women with no diabetes, there were more women with diabetes who were overweight or obese (i.e. had a BMI over 25). Despite this, no association between risk of death and being obese was observed and overweight was protective against mortality risk among women with diabetes. In other research there is lack of conclusive evidence on the nature of the association between BMI and mortality risk among people with diabetes [27]. Even though being overweight, and especially obese, are important risk factors in the development of diabetes and cardiovascular diseases, higher BMI may be associated with lower mortality. This protective effect of higher BMI is described as "the obesity paradox" [28,29]. This study found a higher mortality risk for underweight individuals, which is consistent with the findings of many previous studies [30,31], and which may indicate underlying pathological processes.

This study revealed an increased likelihood of more health care use among women with diabetes compared to those without the disease. The risk of mortality was also higher among women who had a 'high' number of annual GP visits and those who visited a specialist doctor in the 12-month period before the survey. A possible explanation for this is that those women who are sicker and thus more likely to die may have constituted the group which had more health care use.

Strengths and limitations: One of the strengths of our study is that it involved a large population representative cohort of women (over 8000) followed for a long time. Second, a comprehensive list of all-cause mortality predictors, including those which were not included in previous studies such as

Table 2 – Cox-proportional hazards models for the effect of diabetes and other predictors of all-cause mortality [Hazard ratio (95% CI)].

Characteristics	Model 1 (N = 8296)	Model 2 (N = 7715)	Model 3 (N = 7073)
Diabetes (ref = No diabetes)			
Incident diabetes	1.30 (1.16–1.45)	1.25 (1.11–1.41)	1.23 (1.09–1.39)
Prevalent diabetes	1.73 (1.57–1.92)	1.62 (1.45–1.80)	1.55 (1.39–1.74)
Comorbidities (ref = No disease)			
Hypertension		1.14 (1.07–1.21)	1.11 (1.04–1.18)
Heart attack		1.54 (1.34–1.77)	1.50 (1.29–1.74)
Stroke		1.57 (1.37–1.81)	1.48 (1.27–1.72)
Cancer (excluding skin cancer)		1.78 (1.57–2.02)	1.61 (1.41–1.85)
Depression		1.16 (1.05–1.29)	1.09 (0.97–1.22)
Asthma		1.19 (1.08–1.30)	1.13 (1.02–1.25)
Alzheimer's disease or dementia		2.4 (1.91–3.24)	2.16 (1.63–2.86)
Participant status (ref = study participants)			
Proxy answers—participants provided answers		1.63 (1.33–1.99)	1.63 (1.31–2.02)
Proxy used judgement		1.46 (1.31–1.63)	1.32 (1.18–1.49)
Smoking status and body mass index			
Smoking status (ref = Never smoked)			
Current smoker		1.74 (1.56–1.93)	1.73 (1.54–1.93)
Ex-smoker		1.20 (1.13–1.28)	1.17 (1.10–1.25)
Body mass index [ref = normal weight (18.5 ≤ BMI < 25)]			
Underweight (BMI < 18.5)		1.78 (1.55–2.03)	1.77 (1.53–2.04)
Overweight (25 ≤ BMI < 30)		0.92 (0.86–0.98)	0.91 (0.85–0.98)
Obese (BMI ≥ 30)		0.97 (0.89–1.05)	0.98 (0.90–1.08)
Demographics			
Age			1.16 (1.13–1.18)
Education (ref = Year 12 or below)			
Trade certificate/ diploma			0.94 (0.85–1.02)
University degree or above			0.94 (0.81–1.09)
Marital status (ref = Not partnered)			
Partnered			0.91 (0.86–0.97)
Residence area (ref = Major cities)			
Inner regional			1.12 (1.05–1.20)
Outer regional/remote/very remote			1.10 (1.01–1.20)
Duke Social Support Scale (for a 1 unit increase)			0.97 (0.95–0.98)
Health care use			
Number of GP visits (ref = low)*			
High			1.23 (1.15–1.32)
Specialist visit (ref = no)			
Yes			1.12 (1.05–1.19)

Model 1: Diabetes.
Model 2: Diabetes + comorbidities + health related characteristics.
Model 3: Diabetes + comorbidities + health related characteristics + demographic factors + social support + health care use.
* Low: 0–4 times/ year, high: ≥5 times/year.

level of health care use, were included for examination. Third, our study allowed examination of the impact of both incident and prevalent diabetes on survival. A possible limitation of the study would be the potential for misunderstanding and misreporting of diabetes diagnosis. However, this was reported to be unlikely for diseases such as diabetes, which has a clear diagnostic criteria and requires patients to have a frequent interaction with the health care system [32]. Moreover, the ALSWH survey had a good level of agreement and corroboration with other sources such as hospital data in identifying patients with chronic diseases including diabetes [33–35]. Another limitation of this study is the absence of data on clinical findings such as measures of glucose level (HbA1c), lipids or blood pressure.

Our findings show that older women with either incident or prevalent diabetes have consistently lower survival probabilities compared to those with no diabetes. The study found that having comorbidities, smoking, and being underweight were all independently associated with increased risk of all-cause mortality. However, the long lead-time between reporting diabetes and death can be used to modify the risk factors contributing to increased mortality risk. This underscores the importance of integrating these mortality risk predictors in guidelines aimed at management of diabetes even at older age. This may include, for instance, ways for the prevention or early treatment of the commonest complications and comorbidities of diabetes, smoking cessation and weight management.

5. Conclusion

The survival probabilities of women with prevalent diabetes was significantly lower than that of women with incident diabetes throughout the follow-up period, which were in turn lower than that of women without diabetes. Heart diseases, cancer, cerebrovascular diseases, dementia and Alzheimer's disease and COPD are the top leading causes of death for the entire deceased women in the study. Diabetes is the second and third leading primary cause of death for women with prevalent and incident diabetes, respectively. Smoking, being underweight and comorbidities were associated with significantly increased all-cause mortality risks. These findings suggest that diabetes management guidelines for older women need to integrate factors such as comorbidities, smoking and being underweight to reduce the risk of mortality.

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Conflict of interest

The authors have no conflicts of interest to report.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.02.016.

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