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Diabetes and ageing in the Melbourne Collaborative Cohort Study (MCCS)

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ABSTRACT

Aims: To examine the association between diabetes, and ageing 12 years later.
Methods: Subjects reporting angina, cancer, heart attack or stroke at baseline (1990–1994) were excluded. Diabetes at baseline was identified by self-report or elevated plasma glucose (≥7.0 mmol/l fasting or ≥11.1 mmol/l non-fasting). 6431 eligible men and women had survived to age 70 years at follow-up (2003–2007), and 5704 with complete data were included in these analyses. Those without ischemic heart disease, stroke, and cancer, no perceived major difficulty with physical functioning, and no evidence of psychological distress were considered to have aged successfully, irrespective of diabetes at follow-up ($n = 1271$). Logistic regression was used to examine the independent association between baseline diabetes and successful ageing.
Results: At baseline 216 eligible people were identified with diabetes. This was inversely associated with successful ageing at follow-up independent of smoking, physical activity, alcohol use and obesity (OR 0.65, 95% 0.42–0.99), Of the people with diabetes at follow-up, only 12.5% did not have another condition characteristic of usual ageing, compared with 22.7% of people who did not have diabetes.
Conclusions: Diabetes is strongly associated with factors characterising less successful ageing, suggesting that the impact of diabetes may be larger than currently estimated.

1. Introduction

By June 2050, approximately 23% of the Australian population is projected to be aged 65 years and over, an increase from 13.5% in June 2010. The increase in the proportion aged 85 years and over will be even more dramatic; rising from 1.8 to 5.1%. This change will bring economic consequences as the proportion of people in the labour force decreases and the cost of health and other age-related supports increases [1]. One way to minimize the impact of population ageing is to increase the proportion of people enjoying 'successful ageing'; that is

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Abbreviations: BMI, body mass index; WHR, waist to hips ratio; MCCS, Melbourne Collaborative Cohort Study; SEIFA, Socio-Economic Indexes For Areas.
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growing older without the usual age associated health conditions, reductions in mental and physical function, and while maintaining engagement with the community [2].

According to most definitions, the presence of diabetes mellitus precludes healthy ageing. Besides population ageing, there has been a concomitant increase in the prevalence of overweight and obesity, accompanied by an increase in diabetes prevalence, reaching somewhere between 2 and 3 million people in Australia by 2025 [3]. Diabetes may also contribute to other criteria of 'usual' or less healthy ageing, for example, in the 2003 Burden of Disease study, the burden from diabetes increased from 5.5% to 8.3% when the risk of ischaemic heart disease and stroke attributable to diabetes was also included [4]. Diabetes has also been associated with depression, another marker of 'usual' ageing, with some evidence of a bi-directional association [5]. In a recent review, Lu et al. [6] reported prospective associations between diabetes and many of the common syndromes accompanying ageing including cognitive decline, dementia, disability/mobility decline, and in women, falls and urinary incontinence. However, we are not aware of a study looking at diabetes in association with an overall marker of healthy ageing.

Using a large Australian cohort study our objective was to examine the association between diabetes status at baseline and a comprehensive marker of healthy ageing 12 years later [7].

2. Subjects and methods

2.1. Subjects

The MCCS is a prospective cohort study comprising 17,045 men and 24,469 women, aged between 27 and 75 years at baseline (99.3% were aged 40–69 years). Study participants were recruited from the Melbourne metropolitan area between 1990 and 1994 using the Electoral Register, advertisements, and community announcements in local media. Southern European migrants were deliberately over-sampled to extend the range of lifestyle exposures, including dietary factors. In this analysis we have excluded the southern European migrants ($n = 9956$) as they had a poor response to the follow-up survey, especially those in the older age groups. Subjects who self-reported any of the following at baseline (1990–1994) were excluded from these analyses as they had already demonstrated ''usual'' ageing: angina ($n = 1594$), cancer (not including skin cancer) ($n = 3177$), heart attack ($n = 1163$) or stroke ($n = 508$), leaving 26,954 eligible people. Of these 761 died before follow-up started in 2003, 80 of whom were classified as having diabetes. The top causes of death were malignant neoplasm of the colon – 25 deaths, malignant neoplasm of unspecified part of bronchus or lung – 38 deaths, and acute myocardial infarction – 65 deaths. A total of 5704 aged 70 years or older with complete data at follow-up were included in the analyses (Fig. 1). Diabetes at baseline was identified by self-report ($n = 117$) or elevated plasma glucose ($\geq$7.0 mmol/L fasting or $\geq$11.1 mmol/L non-fasting, $n = 99$), and at follow-up by self-report ($n = 466$) or non-fasting plasma glucose $\geq$11.1 mmol/L ($n = 15$). We have based our definition of successful ageing on the 'healthy' or 'successful survival' used by Sun et al. [8,9]. Successful aging was determined by survival

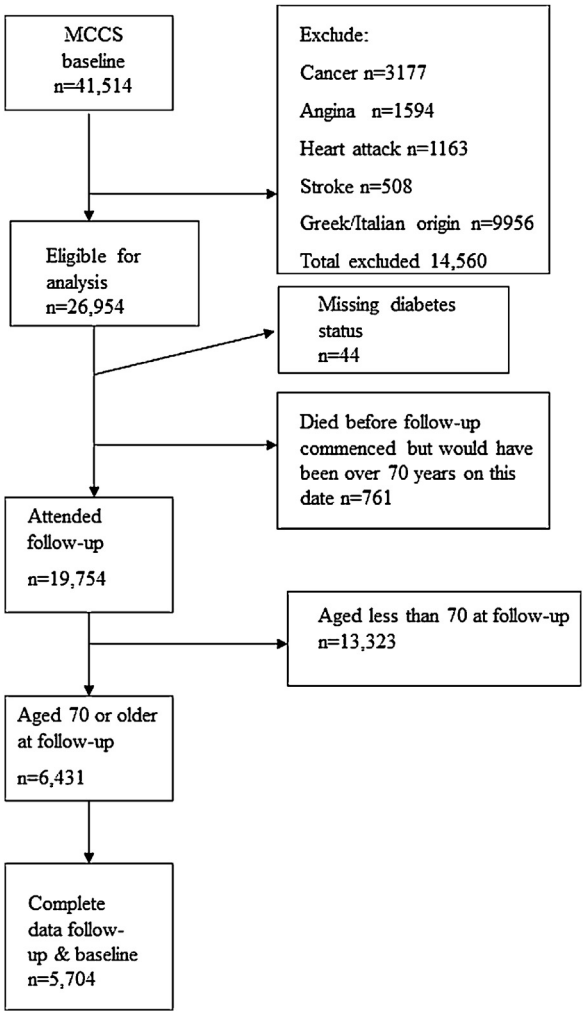

Fig. 1 – Flow chart showing exclusions and final numbers for analysis.

to age 70 years at follow-up (2003–2007), plus the absence of ischemic heart disease, stroke, and cancer, no perceived major difficulty with physical functioning, and a score of less than 20 for the Kessler scale of psychological distress [10]. Those who did not meet all criteria for successful ageing were classified as 'usual' ageing.

The Cancer Council Victoria's Human Research Ethics Committee approved the study protocol. Further details of the study have been published elsewhere [11].

2.2. Assessment of physical functioning

Those subjects who reported having any limitation in moderate activities (such as moving a table, pushing a vacuum cleaner, bowling, or playing golf), or having a lot of limitation in climbing several flights of stairs on the SF-12 [12,13] were not considered to have aged successfully. We also classified as usual ageing those subjects who reported some or more difficulty in personal activities of daily living, which included bathing, dressing, eating, standing up and toileting; and those subjects who reported some or more difficulty in using a telephone or who had a lot of difficulty or could not perform

Table 1 – Baseline characteristics of participants aged 70 or more at follow-up, according to baseline diabetes status.

Variable	Diabetes, $n = 216$	No diabetes, $n = 5488$	p
Age at baseline (years)[a]	64.0 ± 3.1	64.0 ± 3.0	0.9671
Period of follow-up (years)[a]	12.0 ± 1.3	11.6 ± 1.3	0.0004
Proportion female (%)	50.9	63.4	<0.0001
Country of birth (%)			0.854
Australia/New Zealand	91.2	90.8	
UK	8.8	9.2	
Education level (%)			<0.0001
Primary	11.6	5.8	
Secondary	75.0	70.7	
Tertiary	13.4	23.5	
SEIFA quintiles (%)			<0.0001
1 (Most disadvantaged)	22.2	12.7	
2	24.1	17.7	
3	16.2	17.7	
4	23.1	22.2	
5 (Least disadvantaged)	13.9	29.6	
BMI (kg/m^2) (%)			<0.0001
<18.5	0	0.7	
18.5–25	18.5	39.1	
25–30	53.7	44.3	
30+	27.8	15.9	
WHR (men/women) (%)			<0.0001
<0.90/0.80	25.5	51.9	
0.90–1.00/0.80–0.85	43.1	35.2	
>1.0/0.85	31.5	12.9	
Physically active (%)	28.7	35.5	0.039
Current smoker (%)	8.3	5.7	0.060
Self reported conditions (%)			
Asthma	12.5	11.3	0.573
Hypertension	47.7	28.3	<0.001
Arthritis	47.2	42.6	0.180
Kidney stones	6.5	5.4	0.513
Gallstones	13.9	9.9	0.053
Social connectedness			
Marital status (%)			0.634
Single	30.1	28.6	
Married/defacto	66.7	69.0	
Not given	3.2	2.4	
Live alone (%)	22.2	21.4	0.851
No reported social activity (%)	14.8	11.2	0.383
Number of relatives visited without invite (%)			0.115
None	7.4	6.1	
1–2	15.3	18.4	
3–4	13.9	19.6	
5–9	31.0	27.8	
10+	32.4	28.1	
Number of friends visited without invite (%)			0.083
None	9.3	6.1	
1–2	13.9	13.0	
3–4	25.9	22.0	
5–9	22.2	28.8	
10+	28.7	30.2	
Alcohol intake (%)			0.083
None	33.8	33.3	
1–20 g/d	47.7	46.3	
21–40 g/day	7.9	13.2	
41–60 g/day	6.5	4.7	
60 + g/d	4.2	2.5	

[a] Mean ± SD.

the following instrumental activities of daily living: shopping, walking 200 m, getting out by car or public transport by themselves, going up stairs or doing heavy work round the house such as shoveling dirt or washing walls [14].

2.3. *Possible confounders*

Possible confounders identified *A priori* were: age, length of follow-up, country of birth (Australia and New Zealand,or the

United Kingdom); physical activity (low/high [15]); body mass index (BMI), alcohol intake (g/d); education (primary school, secondary, tertiary); Socio-Economic Indexes For Areas (SEIFA) index of relative disadvantage in quintile groups; smoking status (never, past, current); previous history of arthritis, asthma, kidney stones or gallstones, information on social support was collected with questions on marital status (single, married/defacto, not given); the number of people in the household (1, 2, 3–4, 5+), the number of relatives visited each month, the number of friends that could be visited without an invitation (0, 1–2, 3–4, 5–9, 10+), and the number of hours of social activity per week (0, 1–2, 3–4, 5–9, 10+).

2.4. *Statistical analysis*

Logistic regression was used to examine the association between baseline diabetes and successful ageing at follow-up, adjusting for other risk factors associated with baseline diabetes status ($p < 0.1$ in Table 1). Because it was expected that people with diabetes at baseline would still have diabetes at follow-up we did not use the absence of diabetes in our definition of successful ageing. An interaction term for baseline diabetes and gender was tested by running the model both with and without the interaction term and comparing the likelihood ratios. Cross sectional associations between diabetes and individual components of 'usual' ageing at follow-up, adjusting for age at follow-up and gender were determined using logistic regression.

3. Results

Table 1 shows the baseline characteristics of people with and without diabetes at baseline. Participants with diabetes were more obese by both BMI and WHR, less physically active, less likely to be female, more likely to have hypertension, less likely to be in the least disadvantaged SEIFA group and had a slightly longer follow-up period on average than those without diabetes. There was no difference between people with and without diabetes with regard to proportion of current smokers, age, country of birth or social connectedness measures.

Of the 216 people identified with diabetes at baseline, 78% still met the criteria for diabetes at follow-up; 67% of those no longer meeting the criteria had been identified by blood glucose measurement at baseline. Of the 481 with diabetes at follow-up, only 35% had diabetes at baseline. Of the people with diabetes at follow-up, only 12.5% were classified as successful ageing compared with 22.7% of those not having diabetes In bivariate analyses baseline diabetes was inversely associated with successful ageing at follow-up (OR 0.49 95% CI 0.32–0.73). Similarly in multivariate analyses, baseline diabetes was inversely associated with successful ageing at follow-up after adjustment for potential confounders including age, gender, BMI, WHR, physical activity, smoking status, alcohol intake, education, SEIFA, medical history and aspects of social engagement (OR 0.65, 95% 0.43–0.98). There was no evidence for any interaction between baseline diabetes status and gender so men and women were analysed together (p *int* = 0.73)

Table 2 – Odds ratios and 95% confidence intervals for associations between diabetes at follow-up and individual components of 'usual' rather than 'successful' ageing adjusting for gender and age at follow-up.

Component of ageing status	OR	95% CI	n[a]
Heart attack	1.75	1.27–2.40	5671
Heart bypass	1.59	1.08–2.35	5699
Angioplasty	2.10	1.54–2.86	2692
Stroke	1.18	0.79–1.76	5685
Angina	2.01	1.49–2.71	5010
Incident cancer	1.46	1.15–1.84	5704
Distress (K10 > 20)	1.35	0.97–1.88	5704
Health limits moderate activity SF12	1.39	1.14–1.69	5694
Health limits climbing stairs SF12	1.54	1.24–1.90	5687
Difficulty bathing	1.65	1.18–2.31	5704
Difficulty dressing	1.29	0.96–1.74	5703
Difficulty eating	1.68	1.12–2.51	5702
Difficulty standing up from chair	1.41	1.15–1.72	5702
Difficulty with toilet	1.46	1.02–2.10	5704
Difficulty with phone	0.74	0.47–1.16	5704
Difficulty shopping	1.39	0.87–2.22	5699
Difficulty walking 200–300 m	1.73	1.27–2.34	5697
Difficulty with transport	1.57	1.05–2.34	5682
Difficulty climbing 2–3 steps	1.45	0.97–2.17	5703
Difficulty with heavy housework	1.68	1.36–2.07	5680

[a] People who refused to answer or answered 'Do not know' were excluded from these analyses.

Table 2 shows the association of diabetes with the individual components of 'usual' ageing, adjusting for age and gender. Diabetes was positively associated with all the components other than difficulty phoning, although confidence intervals for some included unity.

4. Discussion

Diabetes at baseline predicted a cluster of conditions and disabilities, which we have defined as characteristic of 'usual' rather than 'successful' ageing. This association was independent of common risk factors such as smoking, physical activity, alcohol use and obesity. Diabetes at follow-up was positively associated with individual components of 'usual' ageing except the ability to use the telephone.

Although the study questionnaires were comprehensive we did not measured all possible usual ageing components at baseline, notably psychological distress. Also we did not measure cognitive function on either occasion. This is an important criterion for successful ageing [2], and has been shown to decline more quickly in middle-aged people with diabetes [16].

The analysis includes a large number of participants, despite exclusion from the original cohort of those who had already aged unsuccessfully or were originally from southern Europe. In our study we were able to assess diabetes mellitus by both blood glucose measurement and self-report, and we have adjusted for several important behavioural confounders. We did not differentiate between type 1 and type 2 diabetes; in Australia around 90% of diabetes is type 2 [17], and this is likely to be similar to our cohort.

We have used a comprehensive definition of successful ageing including freedom from major disease and psychological

distress, and no major limitations in physical function. While this is similar to definitions used in other studies, it is not the only way to view successful ageing; older adults rate themselves as ageing successfully even in the presence of disease and disability [18–20]. We were not able to assess this aspect.

Lu et al. [6] in a review and meta-analysis, reported prospective associations between diabetes and a number of individual 'aging phenotypes'-cognitive decline, mobility decline, falls and urinary incontinence, but not depression. They proposed possible mechanisms including hyperglycemia, accumulation of advanced glycation end products (AGEs), systemic inflammation, and traditional diabetic vascular complications, all of which could contribute to other components of usual ageing [6].

Other studies assessing individual components of usual ageing have noted associations between diabetes and depressive symptoms [5,21–23]. In our data there was no association between baseline diabetes and K10 score at follow-up as a marker of depression and anxiety. There was however, a non-significant positive association between diabetes at follow-up and K10 defined distress.

A recent review of cross-sectional studies exploring the association of diabetes with physical impairment concluded that diabetes was associated with a variety of outcomes, largely relating to mobility or lower extremity function [24]. Among Canadian men and women aged 70 years and over, people with diabetes were on average 2 years younger than those without (survival bias), but had more co-morbidities and similar levels of frailty, suggesting that the presence of diabetes was equivalent to 2 years of biological ageing [25]. A study from the Netherlands evaluated the contribution of various conditions, including diabetes, to the prevalence of disability in activities of daily living [26]. Diabetes had a greater disabling impact among women than men, contributing to between 5% and 8% of disability in women, but a long way behind musculoskeletal disease (40–50%) and cardiovascular disease (around 15%) [26]. Volpato et al. [24] also reviewed 4 prospective studies which consistently found that diabetes at baseline was associated with incident disability.

While other studies have tended to consider diabetes associated conditions such as cardiovascular disease or depression as mediators of the association between diabetes and physical disability or functional limitation, we have considered a single outcome including these conditions. This latter approach may be a better measure of the potential impact of diabetes, as adjusting for intermediate variables does not necessarily estimate the direct effect, and may introduce other biases [27].

The possibility of common lifestyle factors being associated with both diabetes and adverse ageing outcomes cannot be overlooked, for example a longitudinal association between depression and diabetes incidence reported from the Multiethnic Cohort Study was partly explained by lifestyle factors [5]. We did adjust for several lifestyle factors: smoking, physical activity, alcohol use and obesity, which were all significantly associated with the outcome. However, changes could have occurred in these time-dependent measures as a consequence of diabetes diagnosis, either before or since the baseline measures.

Diabetes mellitus is a potent contributor to usual ageing and this may be a major burden associated with diabetes. The burden of disease previously associated with diabetes mellitus may be a major underestimate if causal associations between diabetes and ageing can be demonstrated. Even if this is not the case, strategies to prevent or delay the onset of diabetes and to limit the known adverse consequences may have wider significance than has been previously recognized.

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Conflict of interest

The authors declare that they have no conflict of interest.

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