Articles

Factors associated with cognitive decline and delirium after transcatheter aortic valve implantation: Preliminary evidence

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Delirium Communications

Background

Transcatheter aortic valve implantation (TAVI) has become the standard for treating severe symptomatic aortic stenosis in those with prohibitive surgical risk. Cognitive complications, including delirium and cognitive decline are common following TAVI, yet an understanding of pre-procedural factors associated with these outcomes is lacking. This prospective observational study set out to identify geriatric pre-procedural factors associated with post-procedural delirium and cognitive decline in patients undergoing TAVI.

Methods

Cognitive outcomes of TAVI patients aged ≥60 years (N=32) were measured over one-year post-TAVI. Pre-procedural measures included frailty, gait, visual symptoms, voice pitch, dysphagia, blink rate, mood, and sleep. Primary outcomes were post-procedural delirium and cognitive decline.

Results

Delirium was present in 25% of patients over two days following TAVI and 26% experienced cognitive decline in the year post-TAVI. Daily physical activity was a protective factor against cognitive decline, and worse baseline visual memory was associated with delirium. While non-significant and with very large confidence intervals, moderate to large effect sizes were found for associations between slowed gait speed, pre-existing atrial fibrillation, and dysphagia for delirium, and slower gait speed, higher blink rate, pre-existing atrial fibrillation for cognitive decline.

Conclusion

Though underpowered, measures of considerable effect size were identified (although non-significant and with large variability). In larger studies, these novel geriatric factors could further be explored for predicting cognitive complications following TAVI. Improvement of risk prediction for cognitive decline and delirium following TAVI could assist with early identification of those at risk, informing clinical decision-making and allowing for targeted intervention to reduce post-procedural incidence of these complications.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become the standard for treating severe symptomatic aortic stenosis in those with prohibitive surgical risk.[1] TAVI is also increasingly recommended for lower-risk patient populations.[2,3] TAVI benefits include procedural success rates exceeding 95% and lower mortality than the surgical alternative.[4] Delirium, an acute disorder of arousal and attention, is experienced by 23% of patients in the days post-TAVI,[5] and approximately 7-14% experience cognitive decline in the following year.[6]

No cognitive decline or delirium risk prediction tools exist specifically for TAVI patients. General surgical and cardiothoracic risk models typically underperform in TAVI patients with specific high-risk characteristics (e.g., advanced age and multiple comorbidities).[7–9] Risk prediction in frailer populations includes many general (e.g., mobility, frailty) and novel (e.g., voice, vision, and dysphagia) factors, yet these have not been applied to delirium and cognitive decline following TAVI.

This exploratory, effect-finding study investigated associations between a wide range of novel pre-procedural factors and post-TAVI delirium and cognitive decline across 12

months post-TAVI as a first step to developing applicable risk prediction models. We investigated measures spanning geriatric and frailty research and included gait, visual symptoms, voice, dysphagia, mood, and sleep.

METHODS

STUDY POPULATION AND PROTOCOL

The study population was derived from TAVI patients enrolled in a clinical trial (ACTRN12618001114235) with pre-published protocol.[10] In brief, consecutive patients ≥60 years undergoing elective TAVI at the Royal Adelaide Hospital between May 2018 and May 2021 were eligible, including individuals with a diagnosed neurodegenerative condition (e.g. dementia). Eligible patients had normal hearing (with or without aid) and lived within one hour of the CBD. Exclusion criteria included current or recent (past year) alcohol or substance dependence, a diagnosed learning disability, or insufficient English language. Procedures were performed under local anaesthetic with sedation (typically propofol or dexmedetomidine). A minority received a general anaesthetic. Patients were usually mobilised 8 hours later and discharged after one night in hospital. COVID-19 restrictions from 2020 onwards severely impacted recruitment, with elective procedures cancelled from the public hospital system multiple times and moved to private hospitals (where we did not have regulatory approval). As such, we could not meet our recruitment target of 60 participants.[10]

We approached eligible participants at their pre-procedural consultation (typically 1-4 weeks pre-TAVI). Consenting participants completed baseline (pre-TAVI) and follow-up assessments on days 1 and 2, 3-, 6-, and 12-months post-TAVI. Trained research staff conducted assessments in participant homes or in hospital. Relevant medical history, risk scores and procedural factors were collected from hospital records. If participants could not be contacted for follow-up, we approached their next of kin.

The study was approved by the human ethics committees of the Central Adelaide Local Health Network (R20170916) and the University of South Australia (200830), and all participants provided written informed consent to participate. Participants were each reimbursed AUD\$80 for the study.

MEASURES

The assessments we collected at which time points are given in [Table 1](#) with details in our published protocol.[10]

PRIMARY OUTCOMES

Participants were assessed for delirium on the two days following their TAVI procedure by research staff trained by expert geriatricians (AB and DD). We used the Confusion Assessment Method (CAM)[12] to ascertain delirium presence or absence, with the Memorial Delirium Assessment Scale (MDAS)[13] informing CAM scoring and as a severity measure. We assigned a motor subtype using a checklist.[21]

We used the Addenbrooke's Cognitive Examination III (ACE-III)[11] to measure global cognition ([Table 1](#)). We classified cognitive decline at each follow-up timepoint as a decline (from baseline) of ≥3 points in ACE-III score. This cut-off was relaxed from that planned in the protocol paper (≥4) to ensure we captured all with cognitive decline and represented 1SD for healthy older adults.[22] To reduce multiple comparisons, we defined cognitive decline (3-, 6- and 12-months) based on the following: (1) if only one cognitive follow-up was available, scores ≥3 points lower than baseline defined decline; (2) if two cognitive follow-ups, one ≥3 points lower and not ≥3 points lower than baseline, no overall decline was recorded (notably, this did not occur), (3) if three cognitive follow-ups, we took the majority change.

SECONDARY OUTCOMES

Due to greatly reduced sample size and power, continuous cognitive change over time was not investigated as an outcome. Other secondary outcomes (quality of life, activities of daily living) will be reported in subsequent papers.

STATISTICAL ANALYSIS

De-identified data from this trial are available by open access through the UniSA Research Data Access Portal (https://doi.org/10.25954/f1kj-w151). All data analyses were conducted using R. An F-test for numeric variables and a Chi-square test of independence for categorical variables was used to compare baseline characteristics between study completers and non-completers (those who withdrew their participation or died).

Outliers (z-score <-3 or >3) on baseline measures were removed from analyses (see Table S4 notes). We entered each factor into separate models for each primary outcome (delirium and cognitive decline), using logistic regression (odds ratos) for continuous baseline factors and Fisher's exact tests (Cramer's V) for categorical baseline factors. Fisher's exact tests were not planned in the protocol but were required due to the small number of participants in dichotomous groupings.

As an exploratory, effect-finding study, we did not correct for multiple comparisons. We focused on effect sizes rather than statistical significance to identify factors with potential predictive utility for future studies.

RESULTS

BASELINE DATA

During the recruitment period (May 2018 to May 2021), recruitment was on hold for a total of 15 months due to withdrawal of the Chief Investigator (7 months) and COVID-19 restrictions (8 months). A total of 32 participants (20 men, mean age 82.7 years (SD 5.8)) were enrolled ([Table 2](#)). We identified mild cognitive impairment (ACE-III<89[23]) in 69% of the sample at baseline. Reasons for missing baseline data are provided in Table S1.

Table 1. Details of assessments and timepoints measured throughout the study.

Assessment	Details	Baseline	Day 1 and 2	3-month	6-month	12-month
Primary outcomes						
Global cognition	Addenbrooke's Cognitive Examination III (ACE-III)[11]	X		X	X	X
	Possible scores range from 0 to 100, with higher scores reflecting better cognition.					
	Parallel versions of the ACE-III facilitated longitudinal assessment. High sensitivity and specificity are reported for the two suggested cut-offs, of 88 for mild cognitive impairment (sensitivity = 1.0, specificity = 0.96) and 82 for dementia (sensitivity = 0.93, specificity = 1.0).[11] The ACE-III also demonstrates good internal reliability (α = 0.88).					
Delirium	On the ward and when discharged home, Confusion Assessment Method (CAM)[12] was used to ascertain delirium presence or absence, with the Memorial Delirium Assessment Scale (MDAS)[13] interview informing CAM scoring and as a measure of severity. In the intensive care unit, CAM-ICU was used to assess delirium, with CAM-ICU-7[14] used to ascertain severity.		X			
	Altered level of consciousness was assessed using the Observational Scale of Level of Arousal or the Richmond Agitation and Sedation Scale in the ICU.					
	CAM and CAM-ICU comprise four main features of delirium: (1) acute onset and fluctuating course; (2) inattention; (3) disorganised thinking; and (4) altered level of consciousness. We define a positive diagnosis of delirium as the presence of features 1 and 2 and either 3 or 4 on the CAM or CAM-ICU on days 1 or 2 post-TAVI.					
Baseline factors						
Population characteristics	Age, sex, body mass index, education, Comorbidities (pre-existing) from medical history (renal disease, previous stroke/TIA, atrial fibrillation, coronary artery disease, hypertension, peripheral vascular disease), risk scores (EuroSCORE II and Society of Thoracic Surgery score).	X				
Depression	Geriatric Depression Scale[15]	X				
	Possible scores ranging from 0 to 15 (higher scores indicating a greater likelihood of depression).					
Neuropsychiatric symptoms	Neuropsychiatric Inventory Questionnaire[16]	X				
	Indicates presence or absence of 12 neuropsychiatric symptoms (as reported by a family member or spouse).					
Insomnia	Early, middle, and late insomnia items of the Hamilton Rating Scale for Depression[17]	X				
	Total scores range between 0-6, with higher scores indicating more severe insomnia symptoms.					
Gait	Single- and dual-task gait speed (metres/second), dual-task gait cost and step length (metres).	X				
	Each task completed with participants walking 6 metres at comfortable walking speed.					

Assessment	Details	Baseline	Day 1 and 2	3-month	6-month	12-month
Diplopia	Eye cover test (developed in discussion with a neuro-ophthalmologist).	X				
	Diplopia defined as double vision or blurry vision (by self-report) in addition to any eye movements (in right or left eye) during the eye cover task.					
Blink rate	Blinks per second.	X				
	Based on the conversation task by Fitzpatrick et al.[18]					
Voice pitch	Average voice pitch (Hz) from sustained phonation /a/	X				
	Males and females assessed separately due to expected sex variations in pitch.					
Dysphagia	Visual analogue scale from the Sydney Swallowing Questionnaire[19]	X				
	Dichotomised as presence (>0) or absence (=0) of swallowing problems.					
Frailty	Clinician-administered Edmonton Frail Scale[20]	X				
	Comprises 10 domains (scores from 0 to 17, with higher scores representing more frailty)					
Social engagement	How often participants see a family member or friend. Dichotomised as daily or less than daily (e.g., weekly, monthly, never).	X				
Physical activity	How often participants take part in physical activity. Dichotomised as daily or less than daily (e.g., weekly, monthly, never).	X				
Apolipoprotein E4 (APOE-e4)	Presence or absence of the APOE-e4 allele determined by saliva sample.	X				
	Genotyping of the two single nucleotide polymorphisms (rs439358 and rs7412) determined APOE genotype and were categorised as APOE-e4 carriers or noncarriers.					
Cognitive domains	Cambridge Neuropsychological Test Automated Battery (CANTAB)	X		X	X	X
	Reaction Time (RTI) and Pattern Recognition Memory (PRM) were used, with RTI as a measure of attention and PRM as a measure of visual memory.					
	Each test provides multiple outcome measures and so a composite score for each test, calculated as an average of relevant outcomes (detailed in Table S8), was used.					
Procedure details	TAVI procedure details (procedure time, access type) were obtained from hospital records.		X			

Note: ACE-III = Addenbrooke's Cognitive Examination III; APOE = Apolipoprotein E; CAM = Confusion Assessment Method; CAM-ICU = Confusion Assessment Method – Intensive Care Unit; CANTAB = Cambridge Neuropsychological Test Automated Battery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MDAS = Memorial Delirium Assessment Scale; PRM = Pattern Recognition Memory; RTI = Reaction Time; TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack.

FOLLOW-UP DATA

Post-TAVI follow-ups were completed by 28, 27, 25, and 23 participants at delirium assessment, 3-, 6-, and 12-month timepoints, respectively. Two participants died, and one could not be contacted. Participants also withdrew due to lack of interest (N=5) or feeling unable to continue following a stroke (N=1) (Figure 1). Non-completers had higher baseline Society of Thoracic Surgery scores, lower BMI, and fewer neuropsychiatric symptoms (Table S2).

FACTORS ASSOCIATED WITH DELIRIUM

Delirium was present in seven participants (25% of those assessed) (Table S3). Of these, three were hypoactive, three were hypoactive, and one had mixed delirium. The average maximum MDAS score in delirium patients was 7.4 (SD 1.5, range 5-9).

Worse baseline visual memory (Table 1) was significantly associated with delirium (OR=0.89, 95%CI 0.77 to 0.99). We found non-significant but notable associations with slower *dual-task gait speed* (large effect, OR=0.08, 95%CI 0.00 to 3.88), and a small effect for lower *blink rate* (OR=0.54, 95%CI 0.04 to 5.65) (Figure 2 and Table S4). Importantly, there was large variability around these estimates. Large but non-significant associations were found for *atrial fibrillation* and *non-transfemoral access* (both Cramer's V=0.5). *Dysphagia* showed a medium effect (Cramer's V=0.4), and weak associations were found for *no renal disease*, *no hypertension*, *peripheral vascular disease*, *coronary artery disease*, *APOE-e4 allele*, *male gender*, and more *daily physical activity* (Cramer's V=0.1 to 0.3) (Figure 3, Table S5).

FACTORS ASSOCIATED WITH COGNITIVE DECLINE

We observed cognitive decline in seven participants (26% of 27 assessed, Table S6, S7). Logistic regressions did not show any significant predictors (Figure 2 and Table S4). We found non-significant associations with a large effect for slower *single-task gait speed* (OR=0.08, 95%CI 0.00 to 11.82), medium effects for higher *blink rate* (OR=2.52, 95%CI 0.19 to 35.42) and slower *dual-task gait speed* (OR=0.25, 95%CI 0.00 to 10.78), and small effects for lower *voice pitch average* (women only) (OR=0.68, 95%CI 0.27 to 0.95). Once again noting large variability around estimates indicates less confidence in these results.

Fisher's exact tests of dichotomous predictors showed that undertaking *physical activity less than daily* (e.g., weekly) was significantly related to cognitive decline (strong association, Cramer's V=0.5). Non-significant associations were found for *no atrial fibrillation* (medium association, Cramer's V=0.4) and small associations for *non-transfemoral access*, *dysphagia*, *no peripheral vascular disease*, *less daily social activity*, *non-APOE-e4 allele*, *no renal disease*, *no previous stroke*, and *coronary artery disease* (Cramer's V=0.1 to 0.3) (Figure 3 and Table S5).

Of those with delirium, only four were assessed for cognitive decline, which was positive in one case. The other three had withdrawn (N=1 had a stroke and did not wish to continue, N=2 withdrew for other reasons).

DISCUSSION

In this prospective cohort study, 25% of TAVI patients experienced delirium and 26% cognitive decline in the year following TAVI. We identified several possible effects (although non-significant and with wide confidence intervals) for incident delirium and cognitive decline post-TAVI. Gait, dysphagia, pre-existing atrial fibrillation, and visual memory could be further investigated for *delirium prediction*, and physical inactivity, gait, blink rate, and atrial fibrillation for *cognitive decline*.

TAVI patients who partook in less than daily physical activity (pre-TAVI) were more likely to develop cognitive decline following TAVI. The recent Lancet commission identified physical inactivity as a risk factor for demenia.[24] Exercise interventions can enhance cognitive function, but TAVI patients may be limited in their capacity to increase physical activity due to frailty and comorbidities.[25] Even if intervention is not feasible in all cases, physical inactivity is an important risk marker which is simple to address within pre-operative risk assessment.

Poor baseline visual memory was significantly associated with post-TAVI delirium. It is unclear why the small association between poor baseline visual memory and post-TAVI delirium did not extend to global cognition or attention scores, as the overall relationship between baseline cognition and incident delirium is well-established.[26-30]

While not statistically significant and with wide confidence intervals, gait and dysphagia had consistent and substantial (mostly medium-large) effects for both delirium and cognitive decline. Previous research has implicated slower gait as a risk factor for dementia,[31] with slowing gait shown to precede declines in cognitive function and diagnosis of mild cognitive impairment by a decade.[32] Gait speed has also been implicated in TAVI, as a predictor of mortality and other clinical outcomes.[33-35] Dysphagia has been overlooked in the context of TAVI, except for post-procedurally, with an incidence rate of 3%.[36] Dysphagia is associated with the development of malnutrition, dehydration, and aspiration pneumonia,[37] all of which can precipitate delirium.[38-40] If replicated and extended in larger studies, dysphagia could be useful in preoperative risk prediction modelling for TAVI as it can be measured quickly using a single visual analogue scale.

The potential benefit of improving risk prediction in the context of TAVI would come from early intervention, detection, and diagnosis of these clinical factors. It could enable proactive decision-making by the patient and care partners or substitute decision-makers. Effective identification of those at risk is vital for delirium, considering that up to 30-40% is preventable.[27,41] Furthermore, the factors we identified require minimal time, equipment, and training if found useful.

There are some important limitations to highlight. Most notably, COVID-19 restrictions impacted recruitment and sample size. Consequently, we had greatly reduced power and could not conduct all planned analyses[10] or evaluate factors using multivariate modelling. We also had high attrition rates (31% by 12-month follow-up) and hence re-

Table 2. Baseline characteristics of participants (N=32).

Variable	N	Mean/%	SD
Age (years)	32	82.48	5.79
Sex	32		
Male	20	62%	
Female	12	38%	
BMI	29	28.17	5.75
Education (years)	32	10.8	3.68
Social engagement	32		
Daily	17	53%	
Less than daily	15	47%	
Physical activity	32		
Daily	24	75%	
Less than daily	8	25%	
Cognition (ACE-III score)	32	81.22	10.9
Cognitive impairment (ACE-III < 89)	32		
No	10	31%	
Yes	22	69%	
Dementia (ACE-III < 83)	32		
No	13	41%	
Yes	19	59%	
PRM composite score (%)	31	76.08	8.74
RTI composite score (ms)	31	423.58	60.25
Depression (GDS score)	32	2.56	1.7
Neuropsychiatric symptoms (N)	26	2.92	2.51
Insomnia symptoms	32	2.22	1.66
Single-task gait speed (m/s)	30	0.87	0.28
Dual-task gait speed (m/s)	30	0.79	0.25
Dual-task gait cost (%)	30	9.39	12.73
Diplopia	25		
No	25	100%	
Yes	0	0%	
Blink rate (blinks/sec)	32	0.73	0.45
Average pitch (male)	20	147.35	50.17
Average pitch (female)	12	195.24	33.21
Dysphagia	32		
No	20	62%	
Yes	12	38%	
Edmonton Frail Scale (score)	32	5.28	2.59
APOE-e4 carrier	31		
No	22	71%	
Yes	9	29%	
Renal disease	30		
No	19	63%	
Yes	7	23%	
Unknown	4	13%	
Previous stroke/TIA	30		
No	26	87%	
Yes	4	13%	

Variable	N	Mean/%	SD
Unknown	0	0%	
Pre-existing atrial fibrillation	30		
No	15	50%	
Yes	6	20%	
Unknown	9	30%	
Coronary artery disease	30		
No	14	47%	
Yes	13	43%	
Unknown	3	10%	
Hypertension	30		
No	4	13%	
Yes	23	77%	
Unknown	3	10%	
Peripheral vascular disease	30		
No	21	70%	
Yes	4	13%	
Unknown	5	17%	
EuroSCORE II	18	4.45	2.91
Society of Thoracic Surgery	24	4.87	3.94
Access type	20		
Subclavian	2	10%	
Transfemoral	18	90%	
Procedure time (min)	7	50.29	10.95
Delirium	28		
No	21	75%	
Yes	7	25%	

Note: ACE-III = Addenbrooke's Cognitive Examination III; APOE = Apolipoprotein E; BMI = body mass index; EuroSCORE = European System for Cardiac Operative Risk Evaluation; GDS = Geriatric Depression Scale; PRM = Pattern Recognition Memory; RTI = Reaction Time; TIA = transient ischemic attack.

duced ability to measure cognitive decline at later time points (6- and 12-months post-TAVI). Without a comparison group, we could not account for cognitive decline related to factors other than TAVI (e.g., age-related decline). We also acknowledge the limits of our relaxed criteria for cognitive decline (decline of ⩾ 3 points on ACE-III). While ensuring all with decline are captured, our risk of Type 1 error increased. Based on our (albeit relaxed) criteria, we also saw 30% cognitive improvement in our sample. Improvements in cognition following TAVI should be considered in future research. Due to logistical difficulties in accessing participants, we could not confirm they were delirium-free immediately before their procedure. Delirium was also only assessed once daily, potentially limiting our ability to capture delirium presence. Including participants from only one public hospital site makes our sample biased towards patients within the public healthcare system, which may represent a higher-risk group.

While underpowered, our study provides some indication of novel geriatric and age-related factors that may predict delirium and cognitive decline following TAVI. TAVI patients are a unique, high-risk population who need specific risk assessment. Within this homogeneous population, negligible associations were found with typical risk factors for delirium and cognitive decline, such as increased age and depression. More importantly for TAVI patients, gait, dysphagia, pre-existing atrial fibrillation, and visual memory should be further investigated for delirium prediction and physical inactivity, gait, and blink rate for cognitive decline. With further research, incorporating these quick and simple measures could improve risk prediction for cognitive decline and delirium following TAVI and enhance targeted intervention.
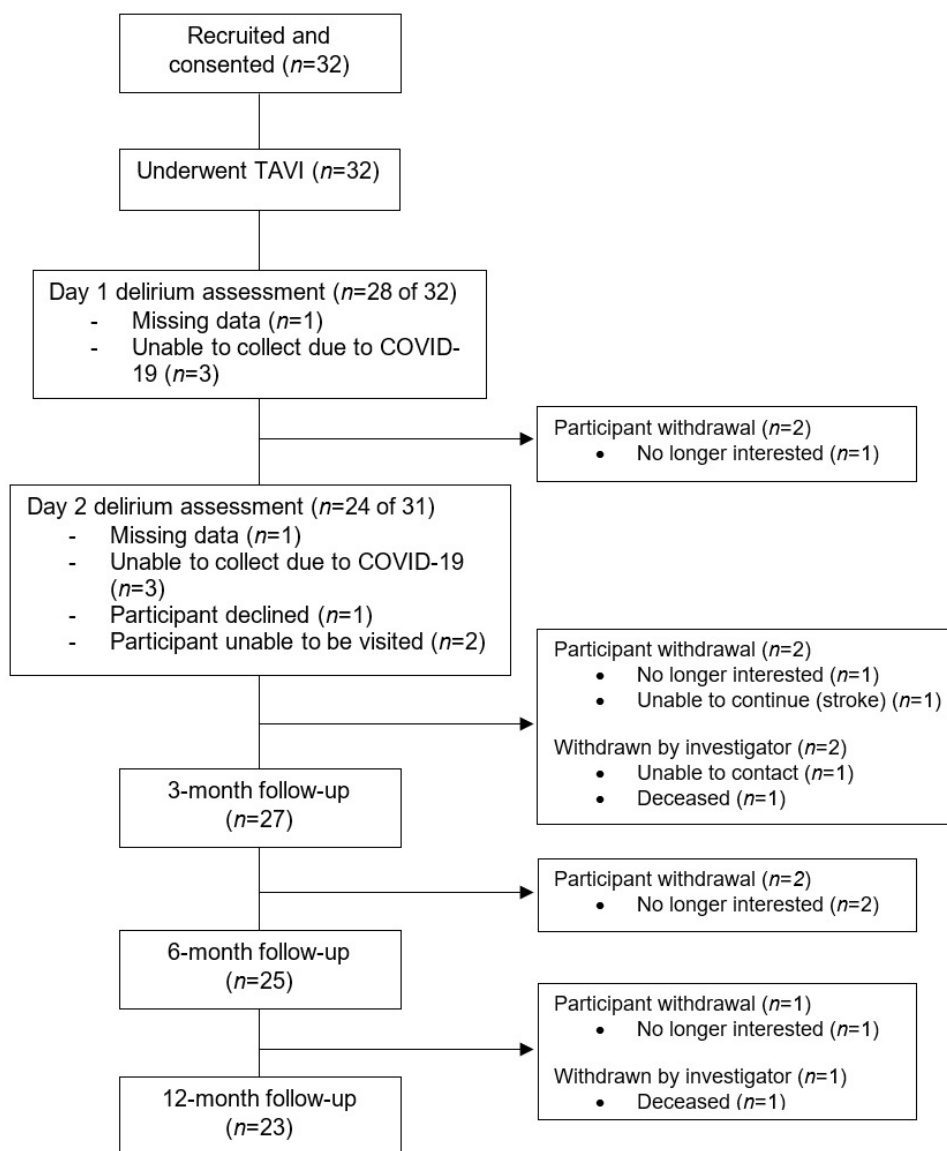
Figure 1. Participant flow diagram.

COVID-19 = Coronavirus Disease 2019; TAVI = transcatheter aortic valve implantation.

AUTHOR CONTRIBUTIONS

Erica S. Ghezzi: Formal analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Visualisation, Project administration. *Peter J. Psaltis*: Conceptualisation, Methodology, Writing – Review & Editing. *Tobias Loetscher*: Conceptualisation, Methodology, Writing – Review & Editing. *Daniel Davis*: Conceptualisation, Methodology, Resources, Writing – Review & Editing. *Monique S. Boord*: Software, Investigation, Resources, Writing – Review & Editing. *Danielle Greaves*: Investigation, Resources, Writing – Review & Editing. *Joseph Montarello*: Methodology, Resources, Writing – Review & Editing. *Jerrett K. Lau*: Methodology, Resources, Writing – Review & Editing, *Sinny Delacroix*: Methodology, Resources, Writing – Review & Editing. *Alice Bourke*: Methodology, Resources, Writing – Review & Editing. *James McLoughlin*: Methodology, Resources, Writing – Review & Editing. *Megan Keage*: Methodology, Resources, Writing – Review & Editing. *Han-nah A.D. Keage*: Conceptualisation, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

ETHICS STATEMENT

The Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee (Reference number: R20170916) and the University of South Australia Human Ethics Committee (Reference number: 200830) approved the research with original approval obtained on 13 December 2017 and 3 April 2018, respectively. Informed consent is signed by all participants or appropriate caregiver before inclusion. Consent is continually monitored during the study by asking participants if they want to continue at the start and end of each session.
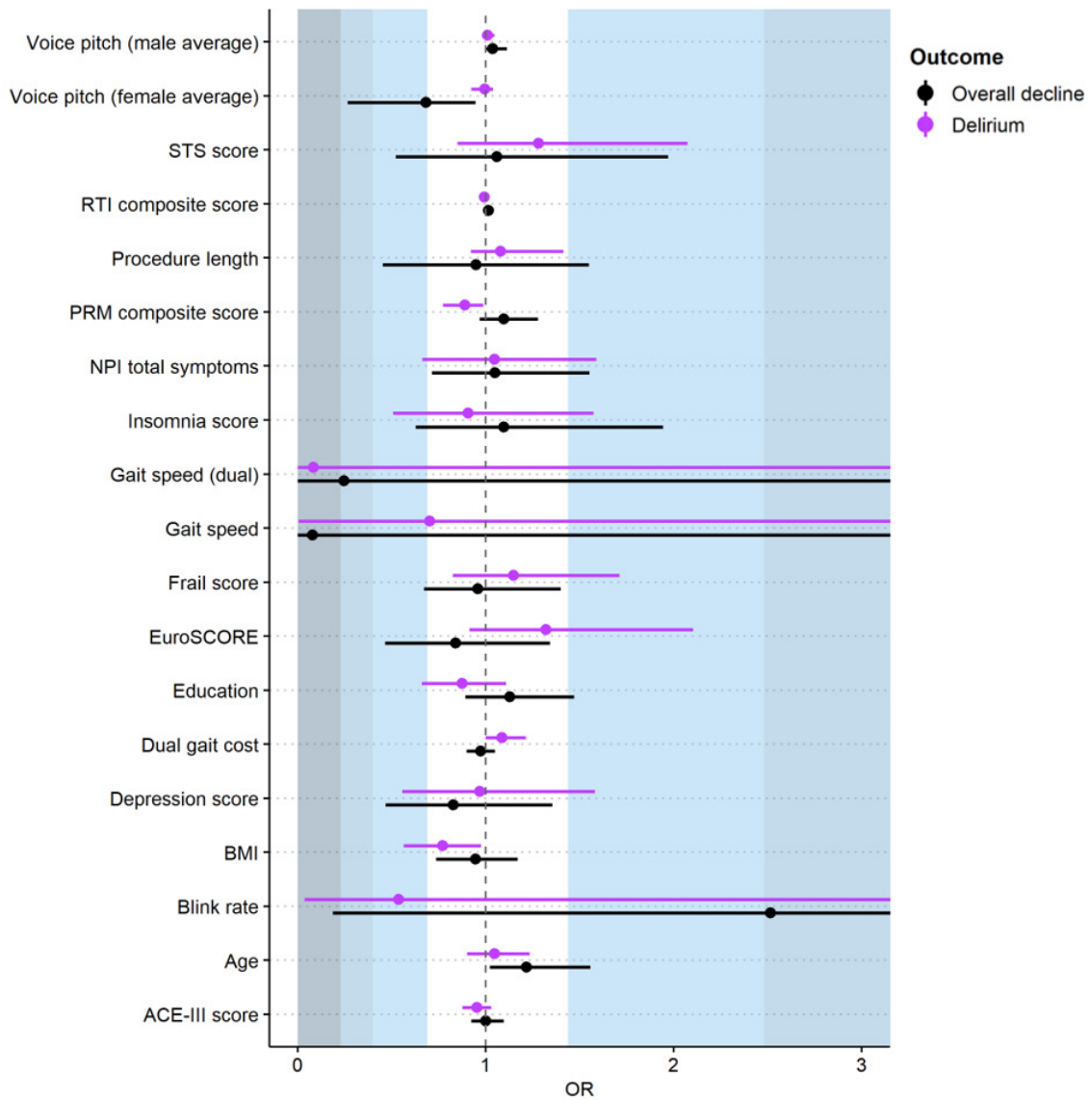
Figure 2. Odds ratios for logistic regressions with delirium or cognitive decline as the outcome.

OR > 1 indicates that higher scores on the predictor factor relate to presence of the outcome, OR < 1 indicates that lower scores on the predictor factor relate to presence of the outcome. Light, medium, and dark blue indicate small, medium, and large effect sizes, respectively. Error bars represent 95%CI. ACE-III = Addenbrooke's Cognitive Examination III; BMI = body mass index; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NPI = Neuropsychiatric Inventory; OR = odds ratio; PRM = Pattern Recognition Memory; RTI = Reaction Time; STS = Society of Thoracic Surgery.
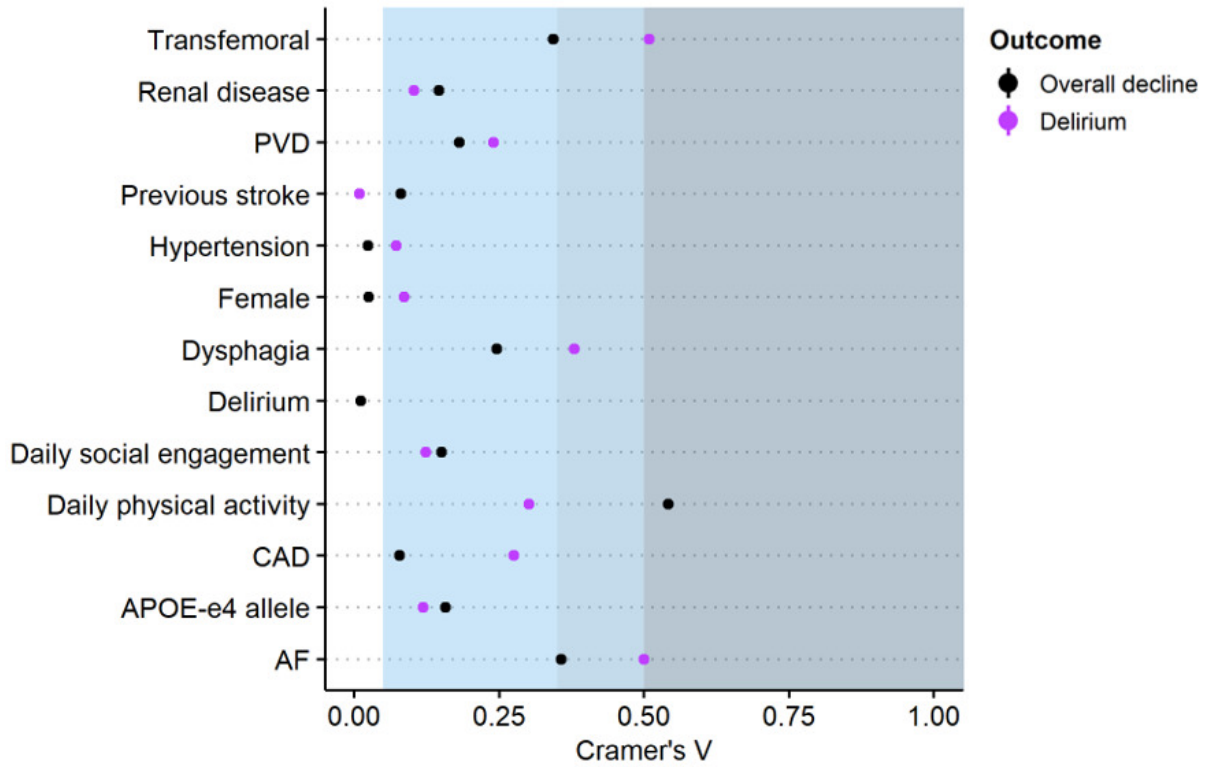
Figure 3. Cramer's V for association of dichotomous predictors with delirium and cognitive decline from Fisher's exact tests.

Delirium = purple; Overall cognitive decline = black. Light, medium, and dark blue indicate small, medium, and large effect sizes, respectively. AF = pre-existing atrial fibrillation; APOE = Apolipoprotein E; CAD = coronary artery disease; PVD = peripheral vascular disease

REFERENCES

1. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ*. 2016;354:i5085. doi:10.1136/bmj.i5085

2. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med*. 2019;380(18):1706-1715. doi:10.1056/nejmoa1816885

3. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med*. 2019;380(18):1695-1705. doi:10.1056/nejmoa1814052

4. Holmes DR Jr, Brennan JM, Rumsfeld JS, et al. Clinical Outcomes at 1 Year Following Transcatheter Aortic Valve Replacement. *JAMA*. 2015;313(10):1019-1028. doi:10.1001/jama.2015.1474

5. Tilley E, Psaltis PJ, Loetscher T, et al. Meta-analysis of Prevalence and Risk Factors for Delirium After Transcatheter Aortic Valve Implantation. *The American Journal of Cardiology*. 2018;122(11):1917-1923. doi:10.1016/j.amjcard.2018.08.037

6. Ghezzi ES, Ross TJ, Davis D, Psaltis PJ, Loetscher T, Keage HAD. Meta-Analysis of Prevalence and Risk Factors for Cognitive Decline and Improvement After Transcatheter Aortic Valve Implantation. *The American Journal of Cardiology*. 2020;127:105-112. doi:10.1016/j.amjcard.2020.04.023

7. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *N Engl J Med*. 2011;364(23):2187-2198. doi:10.1056/nejmoa1103510

8. Durand E, Borz B, Godin M, et al. Performance Analysis of EuroSCORE II Compared to the Original Logistic EuroSCORE and STS Scores for Predicting 30-Day Mortality After Transcatheter Aortic Valve Replacement. *The American Journal of Cardiology*. 2013;111(6):891-897. doi:10.1016/j.amjcard.2012.11.056

9. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and Validation of a Preoperative Prediction Rule for Delirium After Cardiac Surgery. *Circulation*. 2009;119(2):229-236. doi:10.1161/circulationaha.108.795260

10. Ghezzi ES, Psaltis PJ, Loetscher T, et al. Identifying New Factors Associated With Cognitive Decline and Delirium After Transcatheter Aortic Valve Implantation: A Study Protocol. *Front Cardiovasc Med*. 2021;8:657057-657057. doi:10.3389/fcvm.2021.657057

11. Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. *Dement Geriatr Cogn Disord*. 2013;36(3-4):242-250. doi:10.1159/000351671

12. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948. doi:10.7326/0003-4819-113-12-941

13. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The memorial delirium assessment scale. *Journal of Pain and Symptom Management*. 1997;13(3):128-137. doi:10.1016/s0885-3924(96)00316-8

14. Khan MM, Lanctôt KL, Fremes SE, et al. The value of screening for cognition, depression, and frailty in patients referred for TAVI. *Clin Interv Aging*. 2019;14:841-848. doi:10.2147/cia.s201615

15. Kurlowicz L, Greenberg SA. The Geriatric Depression Scale (GDS). *The American Journal of Nursing*. 2007;107(10).

16. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *Journal of neuropsychiatry and clinical neurosciences*. 2000;12(2):233-239. doi:10.1176/jnp.12.2.233

17. Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 1960;23(1):56-62. doi:10.1136/jnnp.23.1.56

18. Fitzpatrick E, Hohl N, Silburn P, O'Gorman C, Broadley SA. Case–control study of blink rate in Parkinson's disease under different conditions. *J Neurol*. 2012;259(4):739-744. doi:10.1007/s00415-011-6261-0

19. Wallace KL, Middleton S, Cook IJ. Development and validation of a self-report symptom inventory to assess the severity of oral-pharyngeal dysphagia. *Gastroenterology*. 2000;118(4):678-687. doi:10.1016/s0016-5085(00)70137-5

20. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. *Age and Ageing*. 2006;35(5):526-529. doi:10.1093/ageing/afl041

21. Meagher D. Motor subtypes of delirium: past, present and future. *International Review of Psychiatry*. 2009;21(1):59-73. [doi:10.1080/09540260802675460](doi:10.1080/09540260802675460)

22. So M, Foxe D, Kumfor F, et al. Addenbrooke's Cognitive Examination III: Psychometric Characteristics and Relations to Functional Ability in Dementia. *J Int Neuropsychol Soc*. 2018;24(8):854-863. [doi:10.1017/s1355617718000541](doi:10.1017/s1355617718000541)

23. Noone P. Addenbrooke's Cognitive Examination-III. *Occupational Medicine*. 2015;65(5):418-420. doi:10.1093/occmed/kqv041

24. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*. 2020;396(10248):413-446. [doi:10.1016/s0140-6736(20)30367-6](doi:10.1016/s0140-6736(20)30367-6)

25. Sáez de Asteasu ML, Cuevas-Lara C, García-Hermoso A, et al. Effects of Physical Exercise on the Incidence of Delirium and Cognitive Function in Acutely Hospitalized Older Adults: A Systematic Review with Meta-Analysis. *Journal of Alzheimer's Disease*. 2022;87(2):503-517. [doi:10.3233/jad-220103](doi:10.3233/jad-220103)

26. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers*. 2020;6(1):90. [doi:10.1038/s41572-020-00223-4](doi:10.1038/s41572-020-00223-4)

27. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *The Lancet*. 2014;383(9920):911-922. [doi:10.1016/s0140-6736(13)60688-1](doi:10.1016/s0140-6736(13)60688-1)

28. Jones RN, Marcantonio ER, Saczynski JS, et al. Preoperative Cognitive Performance Dominates Risk for Delirium Among Older Adults. *J Geriatr Psychiatry Neurol*. 2016;29(6):320-327. [doi:10.1177/0891988716666380](doi:10.1177/0891988716666380)

29. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. *Ann Intern Med*. 1990;113(12):941-948. [doi:10.7326/0003-4819-113-12-941](doi:10.7326/0003-4819-113-12-941)

30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596

31. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buschke H. Abnormality of Gait as a Predictor of Non-Alzheimer's Dementia. *N Engl J Med*. 2002;347(22):1761-1768. doi:10.1056/nejmoa020441

32. Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J. The Trajectory of Gait Speed Preceding Mild Cognitive Impairment. *Arch Neurol*. 2010;67(8):980-986. doi:10.1001/archneurol.2010.159

33. Bo M, Bergamo D, Calvi E, et al. Role of comprehensive geriatric assessment in low surgical risk older patients with aortic stenosis. *Aging Clin Exp Res*. 2020;32(3):381-388. [doi:10.1007/s40520-019-01228-0](doi:10.1007/s40520-019-01228-0)

34. Kano S, Yamamoto M, Shimura T, et al. Gait Speed Can Predict Advanced Clinical Outcomes in Patients Who Undergo Transcatheter Aortic Valve Replacement: Insights From a Japanese Multicenter Registry. *Circ Cardiovasc Interv*. 2017;10(9). doi:10.1161/circinterventions.117.005088

35. Alfredsson J, Stebbins A, Brennan JM, et al. Gait Speed Predicts 30-Day Mortality After Transcatheter Aortic Valve Replacement. *Circulation*. 2016;133(14):1351-1359. doi:10.1161/circulationaha.115.020279

36. Nakamura T, Kawakami M, Fukui S, et al. Incidence and Risk Factors of Postoperative Dysphagia in Severe Aortic Stenosis. *Topics in Geriatric Rehabilitation*. 2021;37(2):58-63. [doi:10.1097/tgr.0000000000000318](doi:10.1097/tgr.0000000000000318)

37. Love AL, Cornwell PL, Whitehouse SL. Oropharyngeal dysphagia in an elderly post-operative hip fracture population: a prospective cohort study. *Age and Ageing*. 2013;42(6):782-785. doi:10.1093/ageing/aft037

38. Dharmarajan K, Swami S, Gou RY, Jones RN, Inouye SK. Pathway from Delirium to Death: Potential In-Hospital Mediators of Excess Mortality. *J Am Geriatr Soc*. 2017;65(5):1026-1033. [doi:10.1111/jgs.14743](doi:10.1111/jgs.14743)

39. George J, Rockwood K. Dehydration and Delirium—Not a Simple Relationship. *The Journals of Gerontology Series A*. 2004;59(8):M811-M812. doi:10.1093/gerona/59.8.m811

40. Rosted E, Prokofieva T, Sanders S, Schultz M. Serious Consequences of Malnutrition and Delirium in Frail Older Patients. *J Nutr Gerontol Geriatr*. 2018;37(2):105-116. [doi:10.1080/21551197.2018.1470055](doi:10.1080/21551197.2018.1470055)

41. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database of Systematic Reviews*. 2016;(3). doi:10.1002/14651858.cd005563.pub3

SUPPLEMENTARY MATERIALS

Supplementary Materials

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