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Original Article

The cost-effectiveness of an online intervention to prevent dementia: Results from the Maintain Your Brain (MYB) randomised controlled trial

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ABSTRACT

Background: The *Maintain Your Brain* (MYB) randomised controlled trial (RCT) examined the effect of a multi-domain internet-based dementia prevention program against a control group (information only).
Objectives: A cost-effective analysis (CEA) quantified the differences in costs (direct healthcare and program costs) and effectiveness outcomes between the intervention and control groups from a healthcare sector perspective.
Design: An economic evaluation was conducted alongside the MYB RCT over three years.
Setting: Australians aged 55–77 years with at least 2 identified remediable risk factors for cognitive decline/dementia recruited from communities in New South Wales.
Participants: There were 3,025 participants in the intervention group and 3,033 in the control group with available linked healthcare data via the Sax Institute's 45 and Up Study out of the 6104 enrolled in the trial (99.2% of total cohort).
Intervention: The MYB trial comprised a personalised schedule of online coaching in physical activity, nutrition, cognitive activity, and depression or anxiety management.
Measurements: The two effectiveness outcomes were global cognition composite (GCC) scores and the Australian National University-Alzheimer's Disease Risk Index –short form (ANU-ADRI-SF) questionnaire scores. Costs included MYB program costs and the direct healthcare costs incurred by the MYB participants. All costs were reported in Australian dollars (AUD$) during the trial period. The time horizon of this analysis was 3 years after randomisation (2018-2021). Incremental cost-effectiveness ratio (ICERs) between the intervention and the control groups were calculated by comparing the average difference in costs to a mean difference in z score for GCC and ANU-ADRI-SF score using the bootstrapped means and 95% Confidence Intervals.

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Results: The total unadjusted program and healthcare costs over three years were similar between groups (AUD$16,521 per person in the control group and AUD$16,473 in the intervention group). After adjusting for baseline characteristics, the average difference between groups in total cost per person at three years was not statistically different: AUD$467 favouring the control group (95%CI: -$552 - $1585). This was compared to a significant mean difference (improvement) in GCC z score at three years of 0.18 (95%CI: 0.13, 0.23) and -0.57 (95%CI: -0.95, -0.24) point difference in ANU-ADRI-SF for the intervention versus control. The base case ICERs were AUD$2,568 per 1 standard deviation in z score and $823 per reduction of 1 ANU-ADRI-SF point. With 1000 bootstrapped replications, the scatterplots of ICER ellipses suggest that the MYB intervention was more effective than the control group and with no significant difference in overall healthcare costs.
Conclusion: The MYB trial showed cost-effectiveness for preventing cognitive decline and reducing dementia risk. Longer-term follow-up and dissemination to other cohorts is needed to confirm the impact on preventing future cases of dementia and relevance to other socio-economic and cultural/ethnic groups than those enrolled in the original trial.

1. Introduction

It is estimated that over 57 million people globally are living with dementia, and this number is expected to almost triple by 2050 [1]. Diagnosis, treatment, and care for people living with dementia was estimated to cost USD$950 Billion [AUD$1.4Trillion (T)] in 2020 in the United States of America [2]. Currently, no effective curative treatments for most dementias exist. The recently developed monoclonal antibody therapies for Alzheimer's disease produce only modest benefits statistically, with questionable clinical meaningfulness or sustained improvements [3]. However, a significant proportion of dementia cases can potentially be delayed, if not prevented. The Lancet Commission on Dementia Prevention 2024 identified 14 potentially modifiable dementia risk factors, which account for an estimated 45% of the population attributable risk (PAR) of dementia [4]; other research suggests this preventable fraction may be as large as 56% [5].

The *Maintain Your Brain* (MYB) randomised controlled trial (RCT) compared the effect of a multi-domain internet-based dementia prevention program with the primary aim of slowing cognitive decline against an information-only control group [6] . Participants were screened for risk factors related to four modules of the MYB intervention: physical activity, nutrition, cognitive, and depression or anxiety. Depending on their dementia risk profile, participants were allocated two to four modules over three years. Compared to the control group, the intervention group showed improvement in global cognitive performance (with an effect size of 0.18) and a reduction in dementia risk over three years [7]. To date, these results are the largest positive effect on cognition across all published dementia risk reduction trials.

A key strength of MYB was its delivery of a dementia risk reduction program tailored to an individual's risk profile yet delivered in an online setting. The online delivery makes MYB scalable to a large population and in a variety of geographical locations, including rural areas. This potentially lowers program-delivery costs compared to other similar in-person trials ([8,9]). An evaluation of a prior short-term risk reduction online study in Australia showed the potential cost-effectiveness of online interventions [10]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability Program (FINGER) [9] was one of the first trials to successfully demonstrate the effectiveness of a multi-domain lifestyle intervention on cognitive outcomes. Wimo et al. demonstrated the potential long-term future cost-effectiveness of this intervention, despite the fact that there was some face-to-face assessment and delivery of the interventions [11]. The Multidomain Alzheimer Preventative Trial (MAPT) (delivered in person) showed no significant effect of the intervention but an overall trend in improved cognitive scores [12] and a significant improvement in cognition among certain subgroups [13]. Despite these mixed results in effectiveness, when considering health system and program delivery costs, the MAPT interventions were also considered to be cost-effective in delivering shorter-term improvements in cognition based on a three-year time horizon [14].

The impact of the successful MYB intervention, the largest such trial to date, on direct healthcare costs is unknown. It is possible the adoption of preventative health behaviours and improving cognition may reduce healthcare burden due to overall better fitness, mental health, and mobility [15]. Conversely, it is possible increasing exercise and changing diets among an older cohort may result in additional individual burden, health care expenditures, or injuries requiring increased care [16].

The main objective of this study is to conduct a cost-effective analysis (CEA) of the MYB trial by quantifying the differences in costs (direct healthcare and program costs) and effectiveness (cognitive outcomes and dementia risk) between the intervention and the control groups from a healthcare sector perspective.

2. Methods

2.1. Study design

An economic evaluation was conducted alongside the MYB RCT [6]. The reporting of the economic evaluation followed the updated Consolidated Health Economic Evaluation Reporting Standards [17]. The cost-effectiveness analysis was conducted with the time horizon of three years follow-up after randomization. Baseline healthcare utilisation and costs were established based on 1 year period prior to randomization.

2.2. Setting and participants

MYB was a sub-study of the Sax Institute's 45 and Up Study - a prospective cohort study in New South Wales (NSW), Australia [18]. A total of 267,357 joined the 45 and Up Study between 2005-2009 by completing a baseline questionnaire and giving signed consent for follow-up and linkage of their information to health and other databases. Recruitment was through selection from the Services Australia Medicare enrolment database. People 80+ years of age and residents of rural and remote areas were oversampled. This database provided near complete coverage of the target population within NSW. About 19% of those invited participated and participants included ~11% of the NSW population aged 45 years and over [18].

Participants of the 45 and Up Study were invited to the MYB trial if they were alive and aged between 55 and 77 years on 1st January 2018, had agreed to be contacted about further studies, did not have dementia, Parkinson's disease, or multiple sclerosis (based on available 45 and Up Study records), and did not participate in any previous MYB validation or pilot studies. Among those contacted for MYB, the participation rate was 6% [20]. The MYB sample was more highly educated and more likely to be from an English-speaking background compared to the Australian general population, with detailed sample characteristics reported elsewhere [5].

2.3. Intervention modules and control group

The MYB trial comprised web-based materials/tasks and a personalised schedule of online coaching in two to four separate modules depending on their individual risk factor profile. These were: physical

activity which comprised resistance, aerobic and balance exercise prescription and support, Nutrition comprising Mediterranean diet nutritional education and support, Brain training comprising online cognitive training, and Peace of Mind – online depression or anxiety management via cognitive behavioural therapy education. The control group were provided with access to curated but freely available information sheets regarding dementia risk reduction.

2.4. Data linkage

The MYB data were linked by the Sax Institute to 45 and Up Study survey data using a unique project identifier. During this process, names were cross-checked, and individuals were excluded from further analysis if inconsistencies were found or if they had withdrawn consent for linkage (N=46). Medicare claims and Pharmaceutical Benefits Scheme (PBS) data were provided by Services Australia, with linkage to the cohort data undertaken by the Sax Institute using a unique identifier and deterministic matching. The Centre for Health Record Linkage (CHeReL, www.cherel.org.au) linked records from the NSW Admitted Patient Data Collection (APDC) and the NSW Emergency Department Data Collection (EDDC). The CHeReL uses probabilistic linkage procedures, in which records with an uncertain probability of being true matches are checked by hand, with a current estimated false positive rate of 0.5%. Linked data were available for all participants regardless of whether they had completed MYB follow-up or not. See **Figure S0** for cohort selection details. The 45 and Up Study survey data were included for linkage purposes only but was not used in these analyses to ensure consistency with the main trial analysis.

2.5. Costs

The costs analysed in the current study were divided into two categories: [1] MYB program costs; and [2] direct healthcare costs incurred by the MYB participants. All costs were reported on the actual spending in nominal values of Australian dollars (AUD$) during the trial period from 2018 to 2022 and trial set-up costs between 2015 and 2018.

(1) Program costs

Program costs included program staff, staff training, and IT infrastructure, and they were estimated based on the University of New South Wales financial and MYB program management records. Costs were categorised as either related to the online platform (platform costs) or module-specific with the module-specific costs further allocated to four sub-categories: (A) Nutrition and Physical Activity (PA); (B) Brain Training; (C) Peace of Mind (targeting anxiety and depression); (D) Module non-specific. The Nutrition and PA targeted distinct risk factors and were delivered as separate modules within the MYB trial. For the PA and nutrition modules, there were instructional and behavioural change elements delivered as needed (by phone, email, or internet) throughout the 3 years by allied health staff with expertise in geriatric medicine, exercise physiology and/or dietetics. However, their costs could not be separated as the development and operation of the modules occurred in combination using the same resources. A small proportion of IT development costs related to the intervention but could not be separated across the modules were classified into the non-specific category (D). In terms of allocating program costs to an individual participant, cost was calculated as:

$$P_{COST_i} = \frac{Platform-related\ COST}{N\ Total} + \frac{e_i \times Module\ (A)\ COST}{N\ eligible} + \frac{e_i \times Module\ (B)\ COST}{N\ eligible} + \frac{e_i \times Module\ (C)\ COST}{N\ eligible} + \frac{e_i \times Module\ non-specific\ (D)\ COST}{N\ eligible}$$

where cost for an individual i is related to the individual's eligibility e_i for each cost component (either not eligible = 0 or eligible =1). Both intervention and control participants in MYB were eligible for platform-related costs as this included generic costs such as the infrastructure to host the system, IT support to log in and access content and the general design of the website. All participants in the intervention group were eligible for module non-specific costs, which included for example, the extra IT development required to develop the scheduling and reminders for modules (D). Further details are provided in the **supplementary section S1**.

(2) Healthcare costs

Direct healthcare costs for each individual were identified from the four linked administrative datasets (Medicare claims, PBS, ADPC, EDDC). Collectively these sources cover most of the hospital care and primary care costs, approximately 75% of healthcare expenditures in Australia [19]. Medicare is Australia's universal health insurance scheme that provides free or subsidised health services including primary and specialist care consultations, allied health (for managing chronic conditions), diagnostic testing and imaging services. An additional cost estimation approach was required for private hospitalisations. The process of assigning national weighted activity unit (NWAU) approximations to each episode to estimate costs is described in the **supplementary section S2**.

2.6. Outcomes

MYB's primary outcome was the global cognitive composite (GCC) score, a validated standardised z score used to measure cognitive function [20]. Dementia risk was examined as a secondary outcome for effectiveness and measured using the Australian-National University Alzheimer's Disease Risk Index – Short Form (ANU-ADRI-SF) questionnaire, and was reported as the raw score [21].

2.7. Statistical analysis

The analysis approach followed that of Costa et al. [14] in modelling the intervention effect on program cost, healthcare cost, and total costs per person for the three-year study period. Healthcare costs were estimated separately within each of the four domains (inpatient hospitalisations, ED, MBS, PBS) and within MBS further categorised by GP-related, specialist, or other (includes diagnostic testing and pathology). Differences in cost between control and intervention groups were calculated and compared using bootstrapped means and bias corrected and accelerated 95% confidence intervals (BCA CIs).

Differences in total costs were modelled using a generalised linear model (GLM) with a gamma log-link function, including baseline cost as a covariate. A fully adjusted model was also fitted with additional baseline covariates: age, sex, years of education, number of eligible modules, number of MBS claims, PBS claims, hospitalisations, and ED visits. This modelling approach was repeated for all sub-categories of cost. For hospitalisation and ED costs, which had a high proportion of zero costs, a hurdle model was used, modelling first the likelihood of a non-zero cost and then modelling the cost using a gamma GLM.

Linear models were fitted separately to model three-year change in GCC and ANU-ADRI-SF scores including the same additional covariates as the fully adjusted cost model. Missing data for both GCC and ANU-ADRI-SF outcomes were imputed using the mice package in R (R Project for Statistical Computing, Vienna, Austria) based on 10 iterations, 25 imputations and including all covariates [22]. This was consistent with Brodaty et al [7] but focused just on the overall change from baseline to three years to be in line with the cost models. Additionally, baseline health service use was included (number of: ED visits, inpatient hospitalisations, MBS claims, PBS claims at baseline – defined as the 12-month period prior to the trial).

Table 1
MYB cohort characteristics at baseline.

	Intervention n=3,025	Control n=3,033
Demographics		
Age at baseline, yr (mean (SD))	64.94 (5.77)	64.84 (5.87)
Gender = female (%)	1926 (63.7)	1930 (63.6)
Education, yr (mean (SD))	12.92 (3.06)	12.94 (3.06)
ANU-ADRI-SF score, (mean (SD))	-2.01 (8.10)	-2.07 (8.05)
GCC z score (mean (SD))	-0.02 (1.00)	0.02 (1.00)
Module eligibility		
Number of modules (%)		
Two	942 (31.1)	955 (31.5)
Three	1590 (52.6)	1588 (52.4)
Four	493 (16.3)	490 (16.2)
	3009 (99.5)	3019 (99.5)
Physical activity module = yes (%)	2870 (94.9)	2897 (95.5)
Peace of mind module = yes (%)	815 (26.9)	838 (27.6)
Brain training module = yes (%)	1932 (63.9)	1880 (62.0)
Healthcare use (1 year period prior to randomisation)		
Total healthcare costs (AUD$) (mean (95% CI))	4185 (3909-4561)	3953 (3733-4203)
MBS claims per year, n (%)		
0-9 claims	686 (22.7)	685 (22.6)
10-19	930 (30.7)	950 (31.3)
20-39	970 (32.1)	897 (29.6)
40+	439 (14.5)	501 (16.5)
PBS claims per year, n (mean (SD))		
0-1 claim	787 (26.0)	806 (26.6)
2-11	779 (25.8)	746 (24.6)
12-24	695 (23.0)	717 (23.6)
25+	764 (25.3)	764 (25.2)
At least one hospitalisation = yes (%)	702 (23.2)	728 (24.0)
At least one ED visit = yes (%)	357 (11.8)	359 (11.8)

SD: Standard Deviation, ANU-ADRI-SF: Australian National University Alzheimer's Disease Risk Index – Short Form, higher scores indicate greater risk; GCC: Global Cognitive Composite, higher scores indicate better cognition; MBS: Medicare Benefits Schedule, PBS: Pharmaceutical Benefits Scheme, ED: Emergency Department.

The incremental cost-effectiveness ratio (ICER) was calculated separately for GCC and ANU-ADRI-SF by dividing the effectiveness difference between groups by the cost difference between groups at three years. Means from the fully adjusted total cost and effectiveness models were used to estimate group differences. We conducted a bootstrapping analysis with 1000 replications of ICERs to account for uncertainty in the distribution of ICERs. The bootstrap procedure was used to run multiple imputations and fit each model 1000 times to produce 95% confidence ellipses for the ICERs.

Sensitivity tests were conducted by: (i) restricting the analyses to complete data only where follow-up scores were available at year 3; (ii) assuming a missing not at random (MNAR) pattern for the GCC and ANU-ADRI-SF missing data whereby the imputed data were adjusted to be 0.4 standard deviations lower for GCC and 0.25 of an ANU-ADRI-SF point higher (as per Brodaty et al [7]); (iii) stratifying the base case ICER analyses by age group (55-64 years for the middle-aged and 65-77 years for seniors).

All analyses were undertaken within the Sax Institute's "Secure Unified Research Environment (SURE)".

2.8. Ethics approval and trial registration

The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee. The MYB trial protocol was approved by the University of New South Wales Human Research ethics committee (HC 16252) and data linkage by the New South Wales (NSW) Population and Health Services research ethics committee (2016/03/636). The MYB trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12618000851268). Details on how MYB participants provided informed consent for trial participation and data linkage have been published [23].

3. Results

3.1. Participant characteristics

Among the 6,104 participants in the MYB trial, 6,058 (99.2%) participants had available linked healthcare cost data and were included in these analyses. In total, 3,033 participants were in the control group and 3,025 in the intervention group (See **Supplementary Figure S0**). Table 1 shows that there were no differences observed between the two groups across socio-demographic, module eligibility, health service utilisation or healthcare costs at baseline. A more complete comparison of participant characteristics and comorbidities can also be found in the MYB main outcome paper by Brodaty et al [7].

3.2. Costs analysis

The program cost per person participating in the MYB trial was AUD$538 for the control group and for the intervention group, it ranged between AUD$1,179 if eligible for 2 modules and AUD$2,065 if eligible for four, with a mean cost of AUD$1,572 per person (See **Supplementary Table S1** for more detail).

The unadjusted direct healthcare costs in the three-year study period were AUD$14,901 per person in the intervention group and AUD$15,983 in the control group. However, the cost difference of AUD$1,082 was not statistically significant at the 95% confidence level (95% CI: - AUD$2,386, AUD$51) (Table 2). When combining the program and healthcare costs, the total costs between the two groups were comparable, with an average of AUD$16,521 per person in the control group and AUD$16,473 in the intervention group. Results revealed a negligible and non-significant difference of AUD$48 less in the intervention group (95% CI: -AUD$1,295, AUD$1,104). The intervention group

Table 2
Healthcare utilisation and costs in three-year trial period.

	Intervention		Control		
	Mean Frequency (95% CI)	Mean Cost in AUD$ (95% CI)	Mean Frequency (95% CI)	Mean Cost in AUD$ (95% CI)	Cost difference: intervention – control (95% CI)
Inpatient Hospitalisation	1.39 (1.28, 1.50)	4379 (4038-4839)	1.51 (1.38-1.65)	5020 (4543-5627)	-640 (-1369, -15)
ED visits	0.59 (0.54, 0.63)	369 (340-399)	0.58 (0.53-0.62)	366 (338-397)	3 (-39, 44)
MBS claims	87.95 (85.53, 90.48)	7650 (7386-7932)	89.66 (87.05-92.43)	8002 (7698-8324)	-352 (-773, 53)
Primary Care	24.91 (24.36, 25.45)	1510 (1473, 1547)	24.67 (24.13, 25.24)	1494 (1459, 1531)	15 (-37, 70)
Specialist visits	7.44 (7.11, 7.78)	1065 (1021, 1111)	7.88 (7.49, 8.34)	1145 (1086, 1233)	-80 (-178, -5)
Other	55.6 (53.78, 57.55)	5075 (4860, 5306)	57.1 (55.15, 59.24)	5363 (5113, 5632)	-287 (-634, 44)
PBS claims	58.12 (55.92, 60.29)	2504 (2215, 2907)	57.48 (55.44, 59.69)	2596 (2281, 3299)	-92 (-767, 402)
Direct healthcare costs		14901 (14219, 15654)		15983 (15132, 17065)	-1082 (-2386, 51)
MYB program costs		1572		538	
TOTAL costs		16473 (15792, 17224)		16521 (15670 – 17602)	-48 (-1354, 1082)

ED: Emergency Department, MBS: Medicare Benefits Schedule, PBS: Pharmaceutical Benefits Scheme, MYB: *Maintain Your Brain*. Means calculated via 6500 bootstrapped replications with bias corrected and accelerated (BCA) 95% confidence intervals.

incurred slightly reduced hospital costs and MBS claims in follow-up compared to the control group. Notably, the differences in hospitalization costs and specialist visits were statistically significantly lower at the 95% confidence level. **Supplementary Table S2** shows that the diagnostic codes related to the highest hospitalisation costs in both groups were M17 (Knee arthropathies), H26 (Cataracts) and M16 (Hip arthropathies) with costs higher for categories M17 and M16 in the control group compared to the intervention group but this was not significantly different.

Table 3 presents the results of the fully adjusted GLM for the total healthcare costs over three years. Group allocation was not significantly associated with healthcare costs (RR=1.03, p = 0.407). Age, baseline healthcare costs, and number of MBS and PBS claims at baseline were significant predictors of healthcare costs in the follow-up period. The fully adjusted GLM showed an average incremental cost difference of AUD$467 per person for the intervention vs control groups (95% CI: AUD-$552, AUD$1585).

3.3. Cost-effectiveness analysis

Incremental effectiveness was estimated over three years with a between-group mean difference of z score 0.18 (95%CI: 0.13, 0.23) in GCC and -0.57 (95%CI: -0.95, -0.24) in ANU-ADRI-SF points (Table 4). The base case ICERs calculated were AUD$2568 per 1 standard deviation increase in z score and AUD$823 per 1 ANU-ADRI-SF point reduction. Results from subgroup analysis in **Supplementary Table S4** demonstrated higher ICERs for younger participants aged 55-64 years (AUD$3517 per 1 standard deviation increase in z score and AUD$1141 per 1 ANU ADRI-SF point reduction) and lower ICERs for older participants aged 65-77 years (AUD$183 and AUD$823 respectively). Effectiveness was higher in younger participants, but this was offset by cost differences being smaller in older participants.

Fig. 1 presents the confidence ellipses for the between group changes in z score and reduction in dementia risk (ANU-ADRI-SF score) on an ICER plane including all sensitivity test scenarios. In all cases, the results of the ICER scatterplots are concentrated within the two right-hand quadrants, suggesting that the intervention was effective in improving dementia-related scores. The bootstrapped ICER ellipses cross the x-axis suggests the MYB intervention was relatively cost-neutral. **Supplementary Figure S5** based on similar analyses stratified by age groups also showed that the older (65-77 years) groups had more ICER scatterplots located within the fourth quadrants which showed dominance of the MYB intervention than those of the younger (55-64 years) group.

Table 3
Multivariable analysis of total costs over the three-year follow-up period.

	Fully adjusted model	
Baseline covariates	RR (95% CI)	p value
Intervention vs Control	1.03 (0.96-1.10)	0.407
Age at baseline (ref = <60 years)		
60-64 years	**1.16 (1.06-1.26)**	**0.002**
65-69 years	**1.19 (1.08-1.31)**	**0.001**
70 years +	**1.40 (1.26-1.56)**	**<0.001**
Female vs male	0.95 (0.89-1.02)	0.180
Years of education (per year)	1.00 (0.99-1.01)	0.568
Baseline GCC z score	0.97 (0.94-1.01)	0.119
Number of modules		
Three modules vs two	0.97 (0.90-1.05)	0.492
Four modules vs two	1.07 (0.97-1.19)	0.186
Direct healthcare costs at baseline (per baseline costs $)	**1.02 (1.01-1.02)**	**<0.001**
MBS claims at baseline (ref = 0-9)		
10-19	**1.30 (1.19-1.43)**	**<0.001**
20-39	**1.54 (1.39-1.71)**	**<0.001**
40+	**2.06 (1.79-2.37)**	**<0.001**
PBS claims at baseline (ref = <2)		
2-11	1.05 (0.95-1.15)	0.335
12-24	**1.29 (1.17-1.43)**	**<0.001**
25+	**1.59 (1.43-1.77)**	**<0.001**
At least one hospital visit at baseline vs none	0.94 (0.85-1.03)	0.159
At least one ED visit at baseline vs none	1.05 (0.94-1.17)	0.385
Average incremental costs; Intervention vs Control	$467 (-$552 - $1585)	

Based on a Gamma GLM. GCC: Global Cognition Composite, MBS: Medicare Benefits Schedule, PBS: Pharmaceutical Benefits Scheme, ED: Emergency Department.

4. Discussion

This study provides new evidence regarding cost-effectiveness of the MYB online intervention for dementia prevention. MYB targeted people aged 55–77 years without dementia who carried major dementia risk

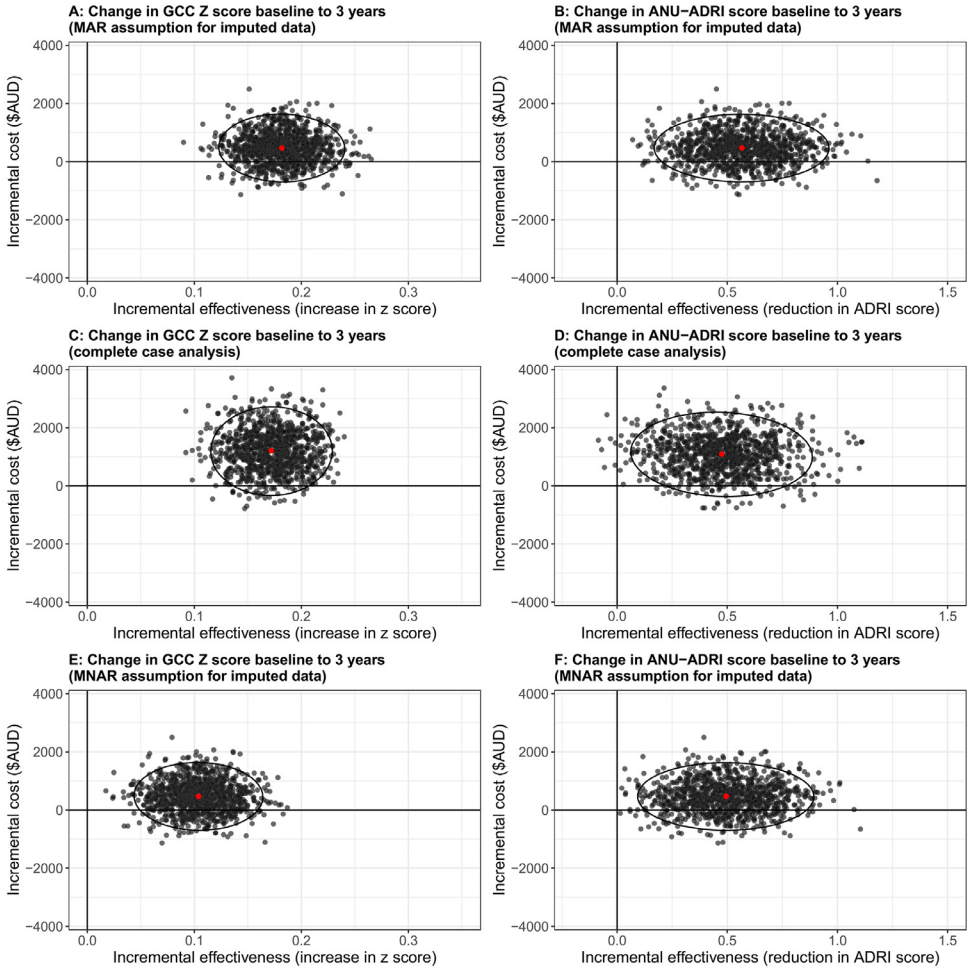

Figure 1. Bootstrapped incremental cost effectiveness modelling cost difference versus difference in cognition and dementia risk over three years. Showing the change in cost versus change in global cognitive composite z score (panel A) and in ADRI score (panel B) for the full sample, separately for complete cases (panels C and D respectively), and when missing not at random assumptions are made for any imputed outcome data (panels E and F respectively). The dots represent each of the 1000 bootstrapped replications.

factors. The primary outcomes of the trial demonstrated that the delivery of MYB online and remotely-supported modules that targeted physical inactivity, non-Mediterranean diet patterns, depression and anxiety, and cognitive inactivity, were effective in improving cognitive outcomes and in reducing dementia risk [7]. These substantive benefits of the MYB intervention are further extended by the current analysis which compares program costs with healthcare costs.

The current study shows that over three years of follow-up, the average MYB program cost was AUD$1,572 per person. However, items solely related to trial delivery (e.g., trial recruitment costs) would not be required for future implementation. Therefore, program costs are estimated to be slightly lower for any future implementation at around AUD$1,257, after excluding research and development (R&D) costs. This amount is lower than the program costs of the Multidomain Alzheimer Preventive Trial (MAPT) [14], but slightly higher than the costs reported by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial [15]. The per person costs for participating in the MAPT intervention plus taking two capsules of polyunsaturated fatty acids per day was €1,469 in 2018 [14] (equivalent of AUD$2,938 according to the purchasing power parity (PPP) conversion factors for the two currencies published by the World Bank) [24]. On the other hand, the net costs of the FINGER program per person were estimated to be $5,490 SEK in 2016 [15] (equivalent to AUD$965 after PPP conversion and adjustment in 2018 value).

A major point of difference between MYB costs and those required to deliver an in-person intervention, such as in FINGER, is that the majority of MYB costs were incurred in the development of the online platform and modules, rather than through ongoing participant visits. Consequently, if the intervention is scaled up to a larger population, the average MYB per person costs could potentially be reduced considerably whereas the per person costs in the in-person FINGER trial would be likely to remain static.

Within the MYB participants, there were no significant differences in total direct healthcare costs over the three-year trial period, nor in total costs when healthcare and program costs were combined. Despite this cost equivalence at an overall level, our findings suggest the intervention group had slightly lower hospitalisation costs over the follow-up period, with both fewer inpatient stays and an average reduction of $A640 in hospitalisation costs. While our study was not able to determine the reason for these differences, we identified that one of the biggest costs in the two groups was for hospitalisations related to arthropathies including common procedures such as knee and hip replacement surgery, and this cost was reduced in the intervention group but not significantly so. It is plausible engagement in modules such as physical activity, which included aerobic exercise and strength training, may confer a protective effect on knee and hip function within the intervention group [25]. However, further investigation in a larger sample or over a longer time horizon would be required to establish this link.

The MYB intervention compared to control achieved both a higher cognition z score of 0.18 and a lower ANU-ADRI-SF absolute risk score of 0.57. The average cost difference between groups was non-significant at AUD$467 resulted in ICERs of AUD$2,568 per improved z score point and AUD$823 per ANU-ADRI-SF score point compared to the control group with confidence ellipses that crossed the X-axis, showing relative cost-neutrality. Our ICER per improved cognitive z score point was much lower than the lowest ICER of €21,443 (equivalent of AUD$42,886 after

Table 4
Incremental cost effectiveness ratios (ICER) comparing cost versus z score increase and dementia risk reduction.

Scenario	Group	N	Cost difference* per person over 3 years, AUD$ (95% CI)	z score difference* at 3 years (95% CI)	ANU-ADRI-SF difference* at 3 years (95% CI)	ICER for increase in z score by 1 point, AUD$	ICER for reduction in ANU-ADRI-SF score by 1 point, AUD$
Base case (imputation for missing data assuming MAR)	Control	3033	$467	0.182	-0.567	$2568	$823
	Intervention	3025	(-$552, $1585)	(0.126, 0.234)	(-0.949, -0.236)	(-$3418, $9000)	(-$1011, $3837)
Sensitivity test 1A: Complete case (z score)	Control	1985	$1163	0.171	–	$6801	–
	Intervention	1392	(-$109, $2676)	(0.118, 0.220)		(-$823, $17072)	
Sensitivity test 1B: Complete case (ANU-ADRI-SF)	Control	2027	$1076	–	-0.466	–	$2308
	Intervention	1408	(-$223, $2440)		(-0.882, -0.092)		(-$577, $13716)
Sensitivity test 2: MNAR assumption (imputation for missing data assuming missing not at random pattern)	Control	3033	$467	0.104	-0.495	$4493	$944
	Intervention	3025	(-$552, $1585)	(0.028, 0.160)	(-0.866, -0.140)	(-$6177, $18321)	(-$1334, $5088)

MAR: Missing at random, MNAR: Missing not at random, ANU-ADRI-SF: Australian National University Alzheimer's Disease Risk Index-Short Form, CI: Confidence Interval, *Difference is calculated as the average marginal difference (Intervention – Control).

PPP conversion) per cognitive z score reported in the MAPT study, which included costs of daily medicine of polyunsaturated fatty acids [14].

We found that the ICERs were even lower in the older age group of 65–77-year-olds compared to 55–64-year-olds. In line with the primary trial findings [7], effectiveness was slightly higher among younger participants, but overall cost differences between groups over three years were very small for older participants who utilise health services more. This demonstrates better value for money of this preventive intervention among people aged over 65 years.

This current study reflects the real-world evidence of a dementia prevention program. Unlike previous cost-effectiveness studies for dementia prevention programs (including the FINGER trial) which used decision modelling to estimate ICERs ([15,26]), this study considered short-term measures of effectiveness only. It cannot be compared directly with studies that have estimated longer-term outcomes such as change in quality-adjusted life-years (QALYs) through extrapolation and modelling [15]. Although this is a limitation, our study provides more robust findings to support further extrapolation of short-term surrogate outcome measures to longer-term health gains estimations in the future. This evaluation makes no assumptions about the potential future impact of the intervention but provides the basis for establishing the costs and effectiveness in the short-term and lays the groundwork for future investigation of measured reduction in dementia cases once longer follow-up data, such as health-related quality-of-life (HRQoL) measurement, is available [27].

Since this was a cost-effectiveness analysis for an RCT, one strength of our study lies in using individual data of healthcare utilisations and costs obtained through administrative data linkage rather than self-report questionnaires. Our study also provided robust results by employing advanced statistical methods. Bootstrapping analyses were conducted to account for uncertainty in the distribution of ICERs, and the issue of missing data was also addressed through multiple imputations (including sensitivity testing to address the potential of MNAR scenarios assumptions). However, the true long-term cost savings will only be known if the sample is followed long enough to identify whether cases of incident dementia are prevented. We estimate that the lifetime dementia-related cost in Australia per person due to dementia is approximately $A442,360, based on a previous study on the societal cost of dementia due to Alzheimer's disease (AD) in Australia [28]. This means that if more than 1 dementia case is prevented for every 282 MYB participants the intervention will become cost-saving (**supplementary section S6**).

Despite the strengths listed above, our findings are limited in guiding resource allocation in a broader decision-making context due to the lack of a common matrix in QALYs. While there is no explicit cost-effectiveness threshold adopted by Australian decision-making authorities, the literature suggests that new health technologies with ICER between AUD$45,000 and AUD$75,000 for QALYs were more likely to be considered by the Australian Pharmaceutical Benefits Advisory Committee [29]. However, since our study did not have measures of QALYs, the results of our ICERs could not be compared to existing ICERs measured by costs per QALY. Furthermore, we did not include informal and formal aged care costs in our analysis. Instead, we focused on direct healthcare costs. As our sample included only older adults without dementia, previous research has indicated that informal and formal aged care costs should be very low ([30,31]) in this population over a three-year time-horizon, and so exclusion of social aged care costs is unlikely to affect the results. It should also be noted that the MYB cohort had higher than average education and better socioeconomic status than the general Australian population and were primarily Caucasian [23]. This implies the intervention itself may be limited in generalisability as it is an online program requiring participants have a certain level of technology capability, resources and literacy. But it also means the cost-effectiveness estimate reported in our study may have been conservative, since the potential benefit of risk reduction in higher risk populations may be

greater. We did not subsidise internet costs which may have been a barrier to enrolment or use of the platform in lower socio-economic areas.

The MYB online multi-domain lifestyle intervention is relatively cost-neutral in the context of health system costs and shows cost-effectiveness for improving cognition and reducing dementia risk over three years. This provides promising support that it may be cost-effective in the longer-term in preventing dementia. Further investigations are needed to quantify the longer-term cost-effectiveness of these interventions for dementia prevention.

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Declaration of competing interest

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Supplementary materials

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