Estimating the number of cases of dementia that might be prevented by preventing delirium

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Editor—Patients who experience delirium are at increased risk for developing dementia in both medical and surgical patients.[1–3] Recent attention has focused on preventing dementia through addressing modifiable risk factors.[4] Evidence of the strong inter-relationship between delirium and dementia is accumulating, supported by proposed pathophysiologic pathways.[5] Reducing the incidence of delirium in non-ICU hospital settings, in both medical and surgical wards, has been shown possible by implementing the Hospital Elder Life Program (HELP).[6] Similar multicomponent, non-pharmacologic approaches to delirium prevention based on HELP have been recommended in multiple Cochrane reviews,[7,8] and the evidence for HELP effectiveness is well established.[6] For this reason, we focused our analysis on this intervention. Understanding how many cases of dementia might be prevented with multicomponent, non-pharmacologic delirium prevention (MNDP) approaches would contribute to the existing literature by making explicit predictions in clinically relevant terms about the possible long-term public health benefits of MNDP. We used a decision analysis approach to estimate the number of cases of new-onset Alzheimer's disease and related dementias (ADRD) expected to be preventable per 1000 patients via implementing MNDP.

We constructed a decision tree to link the risks of delirium and subsequent ADRD (Supplementary Fig. S1). A simulated patient is randomised into the 'Intervention' (MNDP) or 'Usual Care' group at a decision node as if the patient were in a clinical trial. Chance nodes occur through the remainder of the tree, where the outcomes, for example 'Delirium' or 'No ADRD', occur according to published probabilities. We implemented our decision tree using commercially available software (TreeAgePro Healthcare, Williamstown, MA, USA). We assumed a baseline probability of delirium in an older population (that includes our base case patient outlined in Supplementary materials) of ~15% (Table 1). The reduction in the risk of delirium attributable to participation in the MNDP programme in this population is given by the odds ratio (OR) of 0.47 (95% confidence interval [CI], 0.37–0.59) from Hshieh and colleagues[6] in a meta-analysis combining results from 14 studies with a total of 1942 subjects. The baseline probability of developing ADRD was taken to be 8% based on data from Witlox and colleagues.[2] The relative risk of developing ADRD in patients who experienced delirium was taken from Goldberg and colleagues[1] in an analysis of data from 24 studies totalling 10 549 subjects that found that delirium increases the risk of ADRD with an OR of 2.30 (95% CI, 1.85–2.86).

Estimating the impact that MNDP might have on the development of ADRD requires combining data from multiple studies[1,2,6] into a single model (Supplementary Table S1). No single study to date has directly measured this impact. Combining results from the above studies appears well

Table 1 Data used in base case and sensitivity analyses. *Cells marked in grey indicate values same as the base case. Italicised numbers differ from the base case values. ADRD, Alzheimer's disease and related dementias; HELP, Hospital Elder Life Program.

Analysis	Baseline probability of delirium[6]	Baseline probability of ADRD[2]	Relative risk of delirium given use of HELP[6]	Relative risk of ADRD given occurrence of delirium[1,2]	Cases of dementia prevented per 1000 patients
Base case analysis	0.15	0.08	0.51	2.08	6
Relative risk of delirium: lower bound	*	*	*0.41*	*	8
Relative risk of delirium: upper bound	*	*	*0.63*	*	5
Relative risk of dementia: lower bound	*	*	*	*1.73*	4
Relative risk of dementia: upper bound	*	*	*	*2.49*	9

justified as all studies involve individuals of similar ages in similar settings, that is patients hospitalised or residing in post-acute care facilities. The relative risks above were converted from ORs reported in the cited studies[1,6] using the formula: RR=OR/((1−PO)+(PO×OR)), where RR denotes relative risk, OR is odds ratio, and PO is the proportion with the outcome in the control group. The expected number of incident ADRD cases per 1000 patients was calculated by multiplying the proportion of patients under each arm by 1000. The total number of incident cases of ADRD was compared between the two decision arms to find the number of cases prevented by intervention per 1000 patients. Sensitivity analyses were performed to estimate the effects of varying key parameters in the model to quantify how variation in published values across populations affects the results by varying over the 95% CI for the relative risk of delirium given the use of MNDP and of dementia given the occurrence of delirium.

Our model estimates that MNDP could prevent six new cases of ADRD per 1000 patients over a 2.4-yr period after hospital discharge (the mean follow-up duration in the meta-analysis by Goldberg and colleagues[1]). To examine the variability across settings or services, we performed sensitivity analyses, which are outlined in Table 1. If the relative risk of delirium given the use of MNDP was 0.41 (lower bound of the 95% CI for an OR of 0.37, converted to relative risk), about eight new cases of ADRD per 1000 patients would be prevented by MNDP over the ~2.5-yr follow-up period. The upper bound of the OR (0.59) translates to a 0.63 relative risk, which in turn predicts that about five new cases of ADRD per 1000 patients would be prevented.

We also varied the relative risk of dementia conferred by delirium by replacing the relative risk (2.08) with the bounds of the 95% CI, from 1.73 to 2.49 (Goldberg and colleagues[1]). Over this range, the number of ADRD cases per 1000 patients preventable by MNDP over a ~2.5-yr follow-up period ranged from 4 to 9. Our analysis suggests that widespread implementation of MNDP, like HELP, might be able to prevent 6 patients per 1000 from developing new-onset ADRD over the 2.4 yr after hospital discharge, meaning this delirium-mitigating intervention could prevent around 33 000 cases of dementia per year after delirium.[9]

It is important to acknowledge that the relationship between delirium and accelerated onset of ADRD is supported, but not proven, by data from several prior studies.[1–3] Nevertheless, the possibility of a link between delirium and ADRD is further supported by recent studies highlighting potential pathophysiologic pathways, including delirium leading to direct neuronal injury.[5] Several trials also suggest that preventing delirium prevents subsequent cognitive decline.[10] Our analysis shows how HELP or similar multicomponent programmes may provide meaningful reductions in the number of patients who develop ADRD after hospitalisation, with limitations in such preventative strategies in populations such as those who undergo emergency surgery. If this prediction is borne out by clinical trials, the reduction in incident dementia would provide yet another powerful justification for the importance of delirium prevention programmes.

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Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.03.001.

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