Impact of multimodal warming during general anaesthesia on postoperative cognitive dysfunction in elderly patients with gynaecological cancer: study protocol for a single-blinded randomised controlled trial

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ABSTRACT

Background: Cognitive impairment after anaesthesia and surgery is a recognised consequence. This often leads to poor health outcomes and increases healthcare resource utilisation and associated costs, especially in elderly people. However, thus far, there have not been any effective therapies for managing postoperative cognitive dysfunction (POCD). Furthermore, research on the association of multimodal warming with POCD and the clinical outcomes in older patients after gynaecological surgery has not been rigorous. For these reasons, our investigation aims to evaluate whether perioperative multimodal warming would reduce the incidence of POCD and improve prognosis in elderly patients with gynaecological cancer.

Methods and analysis: This is a single-centre, prospective, single-blinded randomised controlled trial. One hundred and fifty patients for gynaecological cancer surgery and 16 non-surgical controls aged 65 years or older will be studied in this trial. A series of neuropsychological tests will be completed to evaluate cognitive function in surgery patients before, at day 7 and 3 months after gynaecological cancer surgery. In addition, POCD and cognitive decline will be assessed using the reliable change index using the control group’s results. The primary outcome is the prevalence of POCD in elderly gynaecological cancer surgery patients and association between perioperative multimodal warming and POCD.

Ethics and dissemination: The protocol for this prospective observational study was approved by the ethics committee of the West China Second University Hospital, Sichuan University (NO. KX215). Recruitment will commence in April 2021 and continue to April 2022. The findings of this trial will be disseminated in peer-reviewed journals and scientific meetings.

Clinical trial registration number: ChiCTR2100041663.

INTRODUCTION

Postoperative cognitive dysfunction (POCD), denoting a subtle decline in cognitive function following anaesthesia and surgery. It is a severe complication associated with increased morbidity and mortality, especially for seniors needing major surgery under general anaesthesia at high risk.1,2,3 Most patients exhibiting POCD naturally recover from the condition within 6 months after surgery, nearly 2% of POCD cases last until the end of life.4 Aside from directly impacting patient prognosis, POCD considerably increases treatment costs for patients and their families.5

Although the aetiology and pathogenesis of POCD remain inconclusive, advanced age seems to be the single established independent risk factor in 3 months postsurgery.6 Additionally, there is a growing appreciation for the link between perioperative management and POCD. Anaesthetists usually choose a variety of warming techniques to regulate patient temperature during anaesthesia and surgery. Some experiments8 showed that various complications such as blood loss, postoperative infection, cardiac morbidity and delaying hospital discharge could be
increased by hypothermia. In contrast, Ginsberg\(^9\) indicated that perioperative temperature is associated with the development of POCD and that the incidence would be reduced if hypothermia had occurred. Extensive studies have indicated that therapeutic hypothermia is a potent neuroprotectant attenuating the detrimental effects of cerebral ischaemia.\(^{10–13}\)

Over the past 20 years, with the increased number of older people undergoing surgery, the incidence of POCD has continued to rise.\(^{14–15}\) However, a very few studies have been conducted on multimodal warming during anaesthesia to enhance postsurgery cognitive functions in an elderly population. Currently, monitoring temperature during general anaesthesia to maintain temperature homeostasis is standard practice.\(^8\) It is well reported that a decrease in body temperature by 2°C–3°C is known to reduce the risk of various neurological diseases and protect the brain from ischaemia and hypoxaemia. Nevertheless, none of the clinical studies have distinguished patients who benefited from intraoperative warming and the avoidance of warming. Taken together, we could not find any studies focusing on perioperative body temperature recorded to evaluate the possible associations with the development of POCD after non-cardiac surgery.

The overreaching hypothesis of this study is that elderly patients receiving multimodal warming during gynaecological cancer surgery have a lower incidence of POCD. Therefore, we predict that these patients will have better short-term outcomes than those receiving no warming. Second, we will record the perioperative body temperature to assess the association to cognitive impairment.

**METHODS**

This single-blinded randomised controlled trial will be conducted at the West China Second University Hospital, Sichuan University. Patient recruitment will commence in April 2021 and is expected to last for 12 months. Before participant recruitment, we have obtained ethics committee approval from West China Second University Hospital, Sichuan University (NO. KX215). In addition, written informed consent will be obtained from each participant prior to enrolment in the study. Recruitment and consenting of study participants by members of the research team is in-line with Good Clinical Practice (GCP).\(^{10}\) All research personnel will receive mandatory training in GCP prior to participant recruitment.

**Study participants**

The flow chart of this study procedure is shown in figure 1. Eligible patients will be identified by screening the daily list of visits in the preoperative anaesthesia clinic. The duration of the complete surgical procedure will be expected to last more than 2 hours with an in-hospital recovery period of at least 7 days. Study inclusion and exclusion criteria are described in table 1. Control participants (Group C) are healthy volunteers whose characteristics matched those of the study groups but will not undergo surgery during the study period. Control participants will be recruited via advertisements in the local community.

**Randomisation and blinding**

Participants will be allocated into study groups by computer-generated randomisation using Microsoft Excel random number generator. Numbers will be enclosed in sealed envelopes which will be opened when patients enter the operating room. Patients will be randomly assigned to receive multimodal warming regimen (group M, patients will be administered an infusion of fluids warmed with a Hotline Fluid Warmer (Smiths Medical ASD, Rockland, Massachusetts, USA) and forced-air warming will be applied using an Equator Convective Warming Blanket (Smiths Medical ASD.)) or no warming (group N, patients will be covered with a sheet and no active warming method will be applied). To obtain a similar size for both groups, blocked randomisation is applied with an allocation ratio of 1:1. The anaesthetists managing the patient will be not involved in data collection, and patients will not know the group allocation.

**Perioperative interview**

For convenience, all original test scales will be translated into Chinese. Patients will be fully informed about the anaesthesia protocol during the preoperative consultation. The demographic data, including age, gender, body mass index and level of education, and patients’ clinical characteristics, including ASA grade, tumour status, medical history and current medication will be recorded. Psychological and mental data will be collected by using Mini-Mental State Examination (MMSE), Beck Depression Inventory and the State-Trait Anxiety Inventory (STAI)-Y-2. Example testing scales are shown in figure 2. The MMSE scale is an important screening tool that can reflect patients’ mental state and the degree of cognitive

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**Figure 1** Flow chart of the study.
decline comprehensively and quickly. The Beck Depression Inventory is a widely used 21-item self-report inventory designed to measure the presence and severity of depressive symptoms. The STAI-Y-2 is a commonly used measure to assess trait and state anxiety.

Neuropsychological assessment
A series of neuropsychological tests, including the Visual Verbal Learning Test, the Concept Shifting Test, the Stroop Colour Word Interference Test and the Letter-digit Coding Test, will be performed preoperatively as well as at 7 days and 3 months postoperatively and at the corresponding time points in group C (Baseline day 1, 7 days and 3 months later). Standard neuropsychological tests will be carried out by two investigators trained at West China Second University Hospital. All neuropsychological tests will be translated into Chinese and conducted in a quiet environment. A correction for short-term practice effects will be carried out based on previous work. The Visual Verbal Learning Test is based on Rey’s auditory recall of words and evaluates learning and memory in this study. A 15-word list will be presented at intervals of two seconds; participants are instructed to read them aloud, after which they will be asked to repeat all words they remember to evaluate short-term memory. Investigators will record and calculate the total number of correct words. After 30 min, participants will be asked to recall as many of the original 15 words as possible to evaluate long-term memory. Concept shifting and executive functioning will be measured by The Concept Shifting Test which is based on Halstead and Reitan’s neuropsychological test battery. Participants will be asked to cross out a specific target number as quickly as possible. The Stroop Colour Word Interference Test consists of three conditions: word reading (Word), colour reading (Colour) and colour-word reading (colour-word) are used to test distributed attentional processing. Participants will be asked to name colour patches, then to read colour words and in the third condition to name the colour of colour-words printed in an ink of a different colour as fast as possible. The Letter-digit Coding Test evaluates mental processing speed and concentration. According to a printed key, participants will be required to match as many of the symbols with the digits as they can in 90 s. Evaluations will be conducted as specified by the International Study of Post-operative Cognitive Dysfunction. The total assessment will take no longer than 60 min as not to intervene in the daily routine clinical management of the patients.

Anaesthetic management
Patients will not receive any medication prior to surgery. After 5 min of preoxygenation, intravenous propofol and sufentanil will be used for induction of general anaesthesia, atracurium or rocuronium for neuromuscular blockade. Patients will be intubated and mechanically

| Table 1 | Inclusion and exclusion criteria for study participation |
|---------|----------------------------------------------------------|
| **Inclusion criteria** | **Exclusion criteria** |
| Aged ≥65 years | Refusal to participate in the study |
| ASA grade I or II | A score of ≤23 on the Mini-Mental State Examination |
| Elective tumour resection under general anaesthesia | History of neurosurgery or cardiosurgery |
| Fluent in Chinese | Use of tranquillisers or antidepressants |
| Able to independently complete the neuropsychological tests | Severe anxiety disorder or severe hearing and visual decline |
| | Severe hepatic dysfunction (Child-Pugh stage C) or renal dysfunction |
| | Parkinson disease, Alzheimer disease or coma |
| | Alcoholism or drug dependence |
| | Tumour metastasis or cancer cachexia |
| | Canceled surgery |

ASA, American Society of Anesthesiologists physical status classification system.
ventilated with an air/oxygen mixture to maintain end-tidal carbon dioxide at 4.6±0.6 kPa. The temperature of all patients will be monitored using a nasopharyngeal temperature probe. Inhalational sevoflurane, intravenous sufentanil or remifentanil will be used to maintain anaesthesia. Dexmedetomidine, midazolam or scopolamine will not be administered, as no consensus can be reached with their impacts on patients’ cognition. Intraoperatively, the depth of anaesthesia will be monitored by bispectral index (target range 40–60). Nasopharyngeal temperature, MAP and HR will be recorded at five specific time points: the day before surgery (baseline), skin incision, maximum trauma end of surgery and extubation.

Postoperative analgesia
At the end of the surgery, analgesia will be provided with bilateral ultrasound-guided transversus abdominis plane block (20 mL of 0.375% ropivacaine will be administered on each side) and patient-controlled intravenous analgesia (sufentanil 3 μg/kg, granisetron 12 mg and butorphanol 12 mg in 0.9% normal saline with a total volume of 200 mL; 2 mL/hour as the background infusion with a 0.5 mL bolus at a 15 min lockout period).

Evaluation of postoperative recovery profiles
Figure 3 shows the example scale for evaluating the postoperative recovery. The Quality of Recovery-40 (QoR-40) questionnaire, which is a global measure of patient-assessed QoR, will be given to patients to evaluate the functional recovery of patients in the first 7 days after surgery. The QoR-40 consists of 40 checklist items assessing the quality of postoperative recovery: physical comfort (12 items); emotional status (9 items); psychological support (7 items); physical independence (5 items) and pain (7 items). Each item is graded on a five-point Likert scale from 1, poor performance, to 5, good performance and the QoR-40 scores range from 40 (inferior QoR) to 200 (excellent QoR).

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) will be administered to assess the quality of life (QoL) at 3 months postoperation. The EORTC QLQ-C30 is a widely used 30-item instrument for assessing the QoL in patients with cancer. The questionnaire consists of multi-item scales and single-item measures including five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting and pain) and a global health status/QoL scale and six single items. The six single items are dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulty. Each item is graded on a four-point Likert scale, and the global health/QoL scale is evaluated with a seven-point Likert scale. According to the EORTC QLQ-C30 Scoring Manual, subscale scores are transformed to standard scores that vary from 0 to 100, where a higher score indicates a better QoL.

Patient and public involvement
There is no active involvement of patients or the public in the development of this protocol. However, the patients and their families will be fully debriefed and informed about the study results at the end of the trial.

STATISTICS
Sample size calculation
The sample size required for this study will be calculated based on a clinical trial that reported an incidence of POCD 7 days after major elective noncardiac surgery approximately 17%. The morbidity of POCD will be expected to decrease from 22% in group N to 5% in Group M. Using the means and SD for the analyses, the two-sided nominal significance level α is set to be 5%, and the statistical power is designed to be 80%, at least the proportion of samples assigned to each group is 65. In addition, with a foreseeing lost to follow-up rate of about 15% at 7 days postoperation, we determined a sample size of 75 patients per group. The ratio of enrolled surgical patients to healthy volunteers is 4:1.

Outcomes analyses
The primary study outcomes are the incidence of POCD at 7 days and 3 months postsurgery. Secondary outcomes include the following: recovery (QoR-40) and length of hospital stay, all-cause mortality at 30 and 90 days after surgery, and QoL (EORTC QLQ-C30) at 3 months after surgery.

POCD will be assessed using an established formula.

$$Z = \frac{(X - X_{\text{reference}})}{(\text{SD}_{\text{control}})}$$

A Z score will be calculated for each neuropsychological test according to the following formula: $Z = (X - X_{\text{reference}}) / (\text{SD}_{\text{control}})$, in which $X$ presents the different baseline and

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**Figure 3** The example scale of QoR-40 and EORTC QLQ-C30 for evaluating the participants’ postoperative recovery. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoR-40, Quality of Recovery-40.
neuropsychological tests score after surgery at 7 days or 3 months after surgery between group M and group N. At the corresponding time point, $X_{\text{reference}}$ in the formula represents the difference between the baseline and the neuropsychological test scores in group C and $SD_{\text{control}}$ represents the variations of SD in the group C. Patients with $Z$ score $\geq 1.96$ on each test will be classified as suffering from cognitive decline or POCD.14

We will use one-way analysis of variance to analyse the continuous variables with normal distributions and the Kruskal-Wallis H test to analyse variables that do not meet normality criteria. Numerical data will be expressed as proportions and compared using Fisher’s exact, correction for continuity or Pearson’s $X^2$ tests as appropriate. ORs and 95% CI will be calculated using a logistic regression model. A $p<0.05$ is considered a statistically significant difference. An interim analysis will be performed to assess the quality of data after primary data acquisition from 20 participants. We will follow the Strengthening Reporting of Observational Studies in Epidemiology statement30 for all future reports related to this study. All statistical analyses will be performed using SPSS V.22.0 (SPSS).

**Data monitoring**
The Department of Research and Clinical Investigation of our institution will monitor all written informed consent, inclusion and exclusion criteria, and follow-up on all serious adverse events.

**Safety**
All serious adverse events will be documented and reviewed by the principal investigator and reported to the trial sponsor and Department of Anaesthesiology, West China Second University Hospital.

**Ethics and dissemination**
The study has been approved by the ethics committee of the West China Second University Hospital, Sichuan University (No. KX215) and will follow the International Conference Guideline for Good Clinical Practice to ensure that the data and the results are credible. In this study, all neuropsychological tests will not interfere with other participant activities, and most assessments will be completed during the inpatient period. In addition, a short telephone follow-up will be carried out respectively at 3 months after surgery. Before beginning the study, investigators will make relevant information available to patients, including the potential benefits and possible harms associated with this clinical trial. All the information provided from patients, such as personal health information and cognitive assessment results, would be kept confidential.

Knowledge translation of the results of this study will be presented in an open-access peer-reviewed journal and the presentation at an academic conference. At the same time, an open-access version of the study results will be made available through the website of Chinese Clinical Trial Registry, and the participants will also be informed of the results.

**DISCUSSION**
This study is designed to investigate the beneficial effects of multimodal warming during general anaesthesia in elderly surgical patients. The primary hypothesis of this investigation is that multimodal warming during general anaesthesia can decrease the incidence of POCD. As previously mentioned, age has been indicated as a significant risk factor for postoperative cognitive decline reported approximately 26% of individuals over 65 years old. Based on these findings,32 33 we decided to set the inclusion criterion threshold for participants 65 years of age and older. The findings of this study may have the potential to provide guidelines to the medical community on how to apply preventative and early intervention approaches to POCD.

Our study will use a series of neuropsychological evaluations, which are more straightforward paper-and-pencil tests (reading and answering are relatively simple). Tasks previously conducted by researchers were using computers34–38 and while computerised tasks make record and analyse data relatively quickly, using this test for an older population is often difficult.39–42 When using computers, frustration, negative emotions, and decreased motivation towards the tests might be more easily accessible for elderly patients. The paper-and-pencil tests prove to be more convenient for the elderly population.43

POCD is a complex neuropsychological disorder presenting primarily as a decline in cognitive ability after surgery. There is no universal definition of POCD making the outcomes of clinical cognitive research complex to interpret. Assessment for POCD, therefore, needs to be evaluated by time-intensive combination of neurocognitive function tests.44 Thus, we propose that to make the assessment simple and practical to perform, the diagnosis of POCD should be mainly based on an established formula calculation: $Z=(X-X_{\text{reference}})/(SD_{\text{control}}).30$

This study does include several limitations. Primarily, the clinical trial will be conducted at a single centre and the sample size is relatively small. The approach to recruitment may lead to bias for the yield of enrolled participates given the short period of active recruitment. The body of literature on this topic is very small, thus, we firmly believe that the small sample size of this study will be able to provide the essential groundwork for future investigations. Second, postoperative cognitive follow-up will be performed within 3 months but the long-term effects of multimodal warming group on older patients will not be evaluated.

In general, this study will explore the beneficial effects of intraoperative warming in elderly surgical patients and provide preliminary evidence to support the notion that multimodal warming during anaesthesia will be good on postoperative cognitive. The
proportion of older people undergoing surgical procedures has been increasing for the past two decades. Therefore, the results of this study will have the potential for wide-ranging application to improve the QoL of the elderly population who have undergone surgery.

Contributors JZ and SS designed study protocol; JZ obtained funding, involved with study conduct and wrote first draft of manuscript; GZ is involved with study conduct, data analysis; All authors edited and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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REFERENCES

1 Moller JT, Cluttmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998;351:857–61.
2 Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008;108:18–30.
3 Steinmetz J, Christensen KB, Lund T, et al. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009;110:548–55.
4 Price CC, Garvan CW, Monk TG. Type and severity of cognitive decline in older adults after noncardiac surgery. Anesthesiology 2008;108:18–30.
5 Bedford PD. Adverse cerebral effects of anaesthesia on old people. Lancet 1955;269:259–64.
6 Anand SS, Tu JV, Awadalla P, et al. Rationale, design, and methods for Canadian alliance for healthy hearts and minds cohort study (CAHHM) - a Pan Canadian cohort study. BMC Public Health 2016;16:650.
7 Wang W, Wang Y, Wu H, et al. Postoperative cognitive dysfunction: current developments in mechanism and prevention. Med Sci Monit 2014;20:1908–12.
8 Salazar F, Doñate M, Boget T, et al. Intraoperative warming and postoperative cognitive dysfunction after total knee replacement. Acta Anaesthesiol Scand 2011;55:216–22.
9 Ginsberg MD et al. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 1987;7:729–38.
10 Minamisawa H, Smith M-L, Sijiešč BK. The effect of mild hyperthermia and hypothermia on brain damage following S, 10, and 15 minutes of forebrain ischemia. Ann Neurol 1990;28:26–33.
11 Minamisawa H, Nordström CH, Smith ML, et al. The influence of mild body and brain hypothermia on ischemic brain damage. J Cereb Blood Flow Metab 1990;10:365–74.
12 Barone FC, Feuerstein GZ, White RF. Brain cooling during transient focal ischemia provides complete neuroprotection. Neurosci Biobehav Rev 1997;21:31–44.
13 Fellery MD, Wilbert L, George MD. The effect of limited rewarming and postoperative hypothermia on cognitive function in a rat cardiopulmonary bypass model. Anesthesia & Analgesia 2008;106:735–49.
14 Saurä A-M, Kalkkanen C, van Dijk D. Postoperative cognitive decline. J Anesth 2009;23:256–9.
15 Etzioni DA, Liu JH, Maggard MA, et al. The aging population and its impact on the surgery workforce. Ann Surg 2003;238:170–7.
16 Baber N. International Conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonized tripartite guideline: guideline for good clinical practice. J Postgrad Med 2001;47:45–50.
17 Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
18 Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
19 Spielberger C. State-trait anxiety inventory (form Y) manual. Redwood City, CA: Mind Garden, 1983.
20 Burkhart CS, Birnker-Binder D, Gagneux A, et al. Evaluation of a summary score of cognitive performance for use in trials in perioperative and critical care. Dement Geriatr Cogn Disord 2011;31:451–9.
21 Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol 1988;112:201–10.
22 Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills 1958;8:271–6.
23 Bohnen N, Tijssen A, Jolles J. Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. Acta Neurol Scand 1992;85:116–21.
24 Lezak MD. Neuropsychological assessment. 3rd edn. New York, NY: Oxford University Press, 1995.
25 Su X, Meng Z-T, Wu X-H, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1893–902.
26 Chi Y-L, Li Z-S, Lin C-S, et al. Evaluation of the postoperative cognitive dysfunction in elderly patients with general anesthesia. Eur Rev Med Pharmacol Sci 2017;21:1346–54.
27 Gornall BF, Myles PS, Smith CL, et al. Measurement of quality of recovery using the QoR-40: a quantitative systematic review. Br J Anaesth 2013;111:161–9.
28 Wallwiener M, Matthews L, Simoes E, et al. Reliability of an e-PRO tool of EORTC QLQ-C30 for measurement of health-related quality of life in patients with breast cancer: prospective randomized trial. J Med Internet Res 2017;19:e322.
29 Salazar F, Doñate M, Boget T, et al. Intraoperative warming and postoperative cognitive dysfunction after total knee replacement. Acta Anaesthesiol Scand 2011;55:216–22.
30 Guo L, Lin F, Dai H, et al. Impact of sevoflurane versus propofol anaesthesia on postoperative cognitive dysfunction in elderly cancer patients: a double-blinded randomized controlled trial. Med Sci Monit 2020;26;112–2.
31 von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
32 Johnson T, Monk T, Rasmussen LS, et al. Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology 2002;96:1351–7.
33 Goettel N, Mistrìdis P, Berres M, et al. Association between changes in cerebral grey matter volume and postoperative cognitive dysfunction in elderly patients: study protocol for a prospective observational cohort study. BMC Anesthesiol 2016;16:1–8.
34 Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the improvement in memory with plasticity-based adaptive cognitive training (IMPACT) study. J Am Geriatr Soc 2009;57:594–603.
35 Mozolic JL, Long AB, Morgan AR, et al. A cognitive training intervention improves modality-specific attention in a randomized controlled trial of healthy older adults. Neurobiol Aging 2011;32:655–68.
36 Basak C, Boot WR, Voss MW, et al. Can training in a real-time strategy video game attenuate cognitive decline in older adults? Psychol Aging 2008;23:765–77.
37 Berry AS, Zanto TP, Clapp WC, et al. The influence of perceptual training on working memory in older adults. PLoS One 2010;5:e11537.
38 Li KZH, Roudaia E, Lussier M, et al. Benefits of cognitive dual-task training on balance performance in healthy older adults. J Gerontol A Biol Sci Med Sci 2010;65:1344–52.
39 Czaja SJ, Sharit J. Age differences in the performance of computer-based tasks. Psychol Aging 1993;8:59–67.
40 Czaja SJ, Sharit J. Age differences in attitudes toward computers. J Gerontol B Psychol Sci Soc Sci 1998;53:P299–40.
41 Sharit J, Czaja SJ. Ageing, computer-based task performance, and stress: issues and challenges. Ergonomics 1994;37:559–77.
Wagner N, Hassanein K, Head M. Computer use by older adults: a multi-disciplinary review. *Comput Human Behav* 2010;26:870–82.

Nouchi R, Taki Y, Takeuchi H, et al. Beneficial effects of reading aloud and solving simple arithmetic calculations (learning therapy) on a wide range of cognitive functions in the healthy elderly: study protocol for a randomized controlled trial. *Trials* 2012;13:32–8.

Rasmussen LS, Larsen K, Houx P, et al. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001;45:275–89.

Etzioni DA, Liu JH, Maggard MA, et al. The aging population and its impact on the surgery workforce. *Ann Surg* 2003;238:170–7.

Kulason K, Nouchi R, Hoshikawa Y, et al. The beneficial effects of cognitive training with simple calculation and reading aloud in an elderly postsurgical population: study protocol for a randomized controlled trial. *Trials* 2016;17:334–41.