

Original Article

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Cognitive decline in the elderly after surgery and anaesthesia: results from the Oxford Project to Investigate Memory and Ageing (OPTIMA) cohort

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Summary

Concerns have been raised about the effects on cognition of anaesthesia for surgery, especially in elderly people. We recorded cognitive decline in a cohort of 394 people (198 women) with median (IQR) age at recruitment of 72.6 (66.6–77.8) years, of whom 109 had moderate or major surgery during a median (IQR) follow-up of 4.1 (2.0–7.6) years. Cognitive decline was more rapid in people who on recruitment were: older, $p = 0.0003$; male, $p = 0.027$; had worse cognition, $p < 0.0001$; or carried the $\epsilon 4$ allele of apolipoprotein E ($APOE\epsilon 4$), $p = 0.008$; and after an operation if cognitive impairment was already diagnosed, $p = 0.0001$. Cognitive decline appears to accelerate after surgery in elderly patients diagnosed with cognitive impairment, but not other elderly patients.

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Introduction

A recent editorial in *International Psychogeriatrics* concluded that ‘anaesthesia and surgery induce cognitive dysfunction in susceptible individuals’ [1]. Susceptible people are thought to include the elderly [2]. If true, this is a serious problem. It was recently estimated that

there are annually over 230 million procedures with general anaesthesia worldwide [3]. There are over 880 million people > 60 years old in the world today [4]. The latter figure is predicted to grow rapidly as life expectancy increases, particularly in developing countries.

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Cell and animal studies have gone some way in showing some potentially damaging effects of certain anaesthetics, for example, inhalational anaesthetics such as isoflurane and sevoflurane [5–10]. In contrast, the intravenous anaesthetic, propofol, may have largely protective effects [6, 11–13], mainly shown in animal and cellular models, although it has also been suggested to have some negative actions [14].

However, it has been harder to establish the effects of general anaesthetics on long-term cognitive decline in people. Short-term postoperative cognitive dysfunction is well known. But there have been rather few longitudinal studies of longer term (> 3 months) cognitive decline [15–18]. There have been more studies of the risk of dementia, or specifically of Alzheimer's disease, following surgery with general anaesthesia. But those studies had until recently produced mixed results [19]. However, two very large recent Taiwanese studies [20, 21] both found an increased risk of dementia following surgery with various types of anaesthesia.

The consensus statement of the First International Workshop on Anesthetics and Alzheimer's Disease [22] concluded that 'there is sufficient evidence at multiple levels to warrant further and more definitive investigations of the onset and progression of Alzheimer's disease and neurodegeneration after anaesthesia and surgery'. We therefore undertook a longitudinal cohort study of cognitive function in patients and controls from the Oxford Project to Investigate Memory and Ageing (OPTIMA), who were followed with frequent cognitive assessments and records of episodes of anaesthesia for surgery. Our aim was to assess factors influencing the effects of anaesthesia and surgery on the trajectory of cognitive decline with increasing age. We included the effects of age and gender, and of the apolipoprotein E $\epsilon 4$ variant (*APOE $\epsilon 4$*) on this relationship.

Methods

We interrogated the database of the Oxford Project to Investigate Memory and Ageing (OPTIMA) in order to examine whether the time-course of cognitive decline with age is related to episodes of anaesthesia and surgery. We identified patients with cognitive impairment and normal elderly people recruited by OPTIMA from 1988 until 2008; the follow-up included in this analysis extends from 1988 until 2012.

Participants were seen at least annually, at many of which visits a Cambridge Cognition Examination (CAMCOG) score (variable termed 'C' below) was obtained [23] and details of episodes of surgery since the preceding assessment recorded. Patients were genotyped with regard to the *APOE $\epsilon 4$* allele, which is known to be associated with a greater risk of cognitive decline [24, 25] and diagnosis of Alzheimer's dementia [26]. We sought participants with at least two measures of CAMCOG who had joined the study as controls, or with mild cognitive impairment [27], who had participated in at least 3 years of follow-up. We identified episodes of surgery that could be regarded as moderate or major in severity, and therefore highly likely to be associated with general or regional anaesthesia, or both. Minor surgical procedures, such as carpal tunnel release, cystoscopy and cataract surgery, were not included. We took account of clinical diagnoses: the presence of mild cognitive impairment possible Alzheimer's dementia or probable Alzheimer's dementia [28] was recorded from diagnosis onwards as a binary variable 'D', and the time of first diagnosis of any one of the three was defined to be TD.

We used mixed-effects modelling with open-source computer software 'R' to model the relationship between CAMCOG score and multiple explanatory variables on which it might be dependent. Although the CAMCOG scores are integers with a maximum of 107, it is not appropriate to model them with a binomial distribution because the answers to the questions which go to make up a CAMCOG score are not independent; a binomial generalised linear model therefore cannot be expected to provide a valid fit, and diagnostics carried out on a mixed-effects binomial generalised linear model indeed confirmed this to be the case. With data concentrated largely towards one end of a scale of fixed length, a folded transformation usually provides acceptable normality. In practice, it turned out that fitting a linear mixed-effects model with a folded transformation (z) of the CAMCOG score (C) of the form

$$z = \log_e \left(\frac{C}{108 - C} \right) \quad (1)$$

produced normally distributed homoscedastic residuals, thereby satisfying the model's diagnostic requirements (Fig. 2).

We modelled z as a linear function of the following variables and all relevant interactions between the variables: baseline age on recruitment (BA); initial, first, CAMCOG score on recruitment (IC); male gender (G); presence of *APOEε4* heterozygosity or homozygosity (AP); time after recruitment (t); first surgery having occurred (S1); second surgery having occurred (S2); time at first surgery (T1); time at second surgery (T2); history of a clinical diagnosis of mild cognitive impairment or possible or probable Alzheimer's disease (D); time at first diagnosis (TD); whether diagnosis was made before or after surgery (A). The initial CAMCOG score was incorporated as an independent variable to allow for a practice effect that could be expected to result from first exposure to the test [29].

Data were fitted to a model in which continuity of C was assumed at episodes of surgery and onset of diagnosis, at first with all of the possible contributing factors allowed, both singly and as interactions. The model was then refined by excluding the least significant factor until parsimony was achieved with all remaining factors showing significance at the level of $p < 0.05$. This procedure was first undertaken excluding the clinical diagnoses, so as to concentrate on the fully objective indices: BA, IC, G, AP, S1, S2, T1 and T2. This then resulted in estimates of the coefficients (β_0 – β_9) that define the linear model:

$$\log_e\left(\frac{C}{108-C}\right) = \beta_0 + \beta_1BA + \beta_2IC + \beta_3G + \beta_4AP + \beta_5t + \beta_6G.IC + \beta_7G.t + \beta_8S1.(t - T1) + \beta_9S2.(t - T2). \quad (2)$$

The procedure was then undertaken including the clinical diagnoses, D. This resulted in estimates of the coefficients (β_0 – β_{13}) that define the linear model:

$$\log_e\left(\frac{C}{108-C}\right) = \beta_0 + \beta_1BA + \beta_2IC + \beta_3G + \beta_4AP + \beta_5t + \beta_6G.IC + \beta_7G.t + \beta_8S1.(t - T1) + \beta_9S2.(t - T2) + \beta_{10}D.(t - TD) + \beta_{11}D.IC.(t - TD) + \beta_{12}D.G.(t - TD) + \beta_{13}D.S1.(t - TD). \quad (3)$$

A final analysis was conducted introducing the binary factor A expressing whether diagnosis was made before or after surgery to examine the possibility of surgery leading to a diagnosis. This explored the possible addition of a variable $\beta_{14}A.D.S1.(t - TD)$ into Eqn. 3 above.

We took the value of $p < 0.05$ to indicate significance throughout.

Results

From 982 participants recruited by OPTIMA at the start of this study, we identified 394 (198 women, 196 men) satisfying the criteria of having at least two measures of CAMCOG score who had joined the study as controls, or with mild cognitive impairment, and who had participated in at least 3 years of follow-up. The median age at recruitment was 72.6 years (IQR 66.6–77.8 years). One-thousand nine-hundred and twenty-two observations of CAMCOG were made during a median follow-up time of 4.1 years (IQR 2.0–7.6 years) up to a maximum of 23 years. *APOEε4* allele heterozygosity was present in 117 and homozygosity in 14 participants. A first episode of surgery occurred in 109 participants and this was at a median (IQR) time of 3.0 (2.0–6.1) years from recruitment. A second episode of surgery occurred in 37 of these and this was at a median (IQR) time of 5.1 (2.6–7.1) years from recruitment. Third and subsequent episodes of surgery were too few to warrant specific identification in the analysis. Initial CAMCOG score on recruitment had a median (IQR) value of 98.0 (93.0–101.0). Mild cognitive impairment was diagnosed in 79 participants at some stage of their follow-up. In many of these, the clinical diagnosis progressed to possible or probable Alzheimer's disease. A total of 150 patients were diagnosed with one or more of these three categories. Of these 36 had surgery, 16 of them receiving their diagnosis before (usually shortly before) their first surgery. A few other clinical diagnoses were recorded on patients, which were not separately included in the analysis.

Figure 1 provides an overview of the dataset, showing the time-course of mean values of CAMCOG over the first 10 years from recruitment for participants. Data have been collected into bins of 1-year periods for this visual summary. Ten participants received their surgery after the 10-year period depicted in Fig. 1 and are therefore not included in this graph. It is important to note that these data cannot be regarded as trajectories for individual participants; they are included to provide an overview of the ranges of CAMCOG and follow-up times. In relation to the range of CAMCOG seen here, it may be

helpful to note that a cut-off score of 79 is traditionally used to indicate dementia.

The results of the modelling associated with Eqn. 2 are shown in Table 1. Recall that the coefficients and p

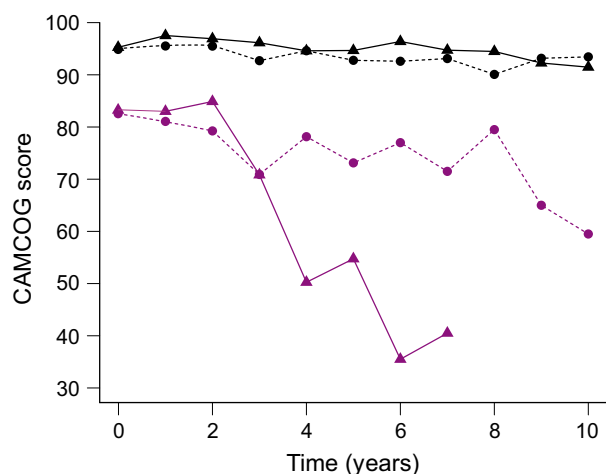


Figure 1 Summary overview of Cambridge Cognition Examination (CAMCOG) scores for the participants in the study, showing the time-course of mean values of CAMCOG over the first 10 years from recruitment for participants divided into four groups. Black lines depict participants with a CAMCOG of 86 or higher at recruitment; purple lines depict those with a CAMCOG of 85 or lower at recruitment. Dashed lines show data for participants who received no surgery within the 10-year period; solid lines show data for those who receive an episode of surgery within the 10-year period. Ten of 394 participants received their surgery after the 10-year period depicted in this figure and are therefore not included in this graph.

values here are obtained without reference to clinical diagnoses. The low p values for the negative coefficients β_1 , β_3 and β_4 , respectively for BA, G and AP, indicate that the absolute level of CAMCOG score is significantly lowered by increasing age at recruitment, male gender and the presence of the *APOEε4* allele. The significance of the negative co-efficient β_5 shows the anticipated decrease in CAMCOG score with increasing age during the follow-up. The significance of the co-efficient β_6 for the interaction term G.IC shows that there is a positive component to the CAMCOG score, throughout the follow-up period, that depends upon IC but is enhanced by the male gender; this will tend to offset the deleterious influence of male gender alone expressed in the negative co-efficient β_3 , but the degree of offset is dependent upon IC. The significance of the co-efficient β_7 for the interaction term G.t shows a greater rate of decline in CAMCOG with time in men. The effect of gender is therefore complex, acting via three coefficients in the model, two of which are interactive terms.

The significance of the negative co-efficient β_8 for the interaction term S1.(t - T1) indicates that first surgery significantly increases the rate of decline in CAMCOG (p = 0.025). Interestingly, the borderline significance of the positive co-efficient β_9 for the interaction term S2.(t - T2) indicates that second surgery may slow the rate of decline in CAMCOG score to a similar extent to which it had been worsened by first surgery (p = 0.05). A further possibility is that patients receiving second surgery were selected in part because they had shown less cognitive decline following first

Table 1 Co-efficients obtained by mixed-effects modelling associated with Eqn. 2. Central to the question addressed by this paper is the finding that the co-efficient β_8 is significant, suggesting that surgery with anaesthesia increases the rate of cognitive decline in this cohort as a whole.

Variable	Co-efficient	Value	95% CI	Std. Error	p value
Intercept	β_0	1.143	0.635–1.650	0.259	0.0000
BA, baseline age	β_1	-0.010	-0.016 to -0.004	0.003	0.0006
IC, initial CAMCOG	β_2	0.890	0.786–0.994	0.053	0.0000
G, male gender	β_3	-0.106	-0.198 to -0.014	0.047	0.0253
AP, <i>APOEε4</i> *	β_4	-0.637	-1.003 to -0.241	0.202	0.0017
t, time	β_5	-0.038	-0.058 to -0.018	0.010	0.0001
G.IC	β_6	0.289	0.116–0.461	0.088	0.0011
G.t	β_7	-0.068	-0.099 to -0.037	0.016	0.0000
S1.(t - T1)	β_8	-0.043	-0.080 to -0.006	0.019	0.0251
S2.(t - T2)	β_9	0.059	0.000–0.118	0.030	0.0498

*Heterozygous or homozygous for gene allele. S1 and S2 refer to first and second surgery having occurred, respectively, at times T1 and T2.

surgery, and cannot therefore be regarded as randomly selected from those having first surgery.

The results of the modelling associated with Eqn. 3 are shown in Table 2. Here we note similar co-efficients β_1 – β_7 , together with similar associated p values, expressing similar dependence of CAMCOG score on BA, IC, G, AP, t and the interactive terms G.IC and G.t. The model resolves the effect of surgery, however, by examining the influence of diagnosis, D. Co-efficient β_{10} indicates that a diagnosis is followed by a significantly more rapid rate of decline in CAMCOG score. Co-efficients β_{11} and β_{12} indicate that this rate of decline is lessened by having a higher IC but worsened by being of male gender. The highly significant co-efficient β_{13} associated with variable D.S1 (t – T1) suggests that it is those patients with a diagnosis who are susceptible to the effects of first surgery; for the cohort as a whole, the non-significant co-efficient β_8 for the variable S1.(t – T1) indicates that individuals without a diagnosis may be exempted from the risk of surgery. The effects of second surgery remain poorly defined in the second model, as in the first.

We finally examined the model expressed in Eqn. 3 by introducing a further factor A expressing the timing of diagnosis with regard to the timing of S1.

Co-efficient β_{14} associated with the variable $\beta_{14}A.D.S1.(t - TD)$ received the value -0.009 with p value 0.743, indicating that the surgery appeared not to be related to the subsequent making of a diagnosis. All other co-efficients were largely unaffected by this additional term in the model.

The validity of the modelling requirement of normality in the response can be assessed by plotting the residuals of measured values of z (sample quantiles) against the standardised theoretical quantiles (units of standard deviation) taken from the model in Eqn. 3. This plot is shown in Fig. 2, and its approximate linearity confirms that there is no reason to reject the normality assumption. A measure of the success of the model in representing the data is R^2 , the proportion of the variance that is explained by the model. This was a remarkable 73% for the model of Eqn. 3.

We present sample predictions from the model to illustrate the time course of CAMCOG in hypothetical individuals with characteristics that are typical for our data set. Figure 3 shows the model predictions from Eqn. 2 for women and men, without diagnoses, incorporating four different scenarios for each of two starting values of CAMCOG score: high and low. The scenarios are as follows: no *APOEε4* allele gene, black lines; *APOEε4* hetero- or homozygosity, blue lines; no

Table 2 Co-efficients obtained by mixed-effects modelling associated with Eqn. 3. Central to the question addressed by this paper is the finding that the co-efficient β_8 is here insignificant, while the co-efficient β_{13} is highly significant, suggesting that the patients who are susceptible to experiencing an increased rate of cognitive decline after first surgery with anaesthesia are those who have had a clinical diagnosis of mild cognitive impairment, or possible or probable Alzheimer's disease.

Variable	Co-efficient	Value	95% CI	Std. Error	p value
Intercept	β_0	1.164	0.658–1.670	0.258	0.0000
BA, baseline age	β_1	–0.010	–0.016 to –0.004	0.003	0.0003
IC, initial CAMCOG	β_2	0.890	0.786–0.994	0.053	0.0000
G, male gender	β_3	–0.105	–0.197 to –0.013	0.047	0.0267
AP, <i>APOEε4</i> *	β_4	–0.538	–0.934 to –0.142	0.202	0.0079
t, time	β_5	–0.032	–0.050 to –0.014	0.009	0.0003
G.IC	β_6	0.227	0.054–0.399	0.088	0.0101
G.t	β_7	–0.038	–0.067 to –0.009	0.015	0.0133
S1.(t – T1)	β_8	–0.029	–0.064 to 0.006	0.018	0.1151
S2.(t – T2)	β_9	0.055	0.000–0.110	0.028	0.0500
D.(t – TD)	β_{10}	–0.129	–0.223 to –0.035	0.048	0.0076
D.IC.(t – TD)	β_{11}	0.055	0.006–0.104	0.025	0.0264
D.G.(t – TD)	β_{12}	–0.085	–0.130 to –0.040	0.023	0.0002
D.S1.(t – T1)	β_{13}	–0.050	–0.073 to –0.026	0.012	0.0001

*Heterozygous or homozygous for gene allele. S1 and S2 refer to first and second surgery having occurred, respectively, at times T1 and T2. D refers to the presence of a clinical diagnosis of cognitive impairment having been made at time TD.

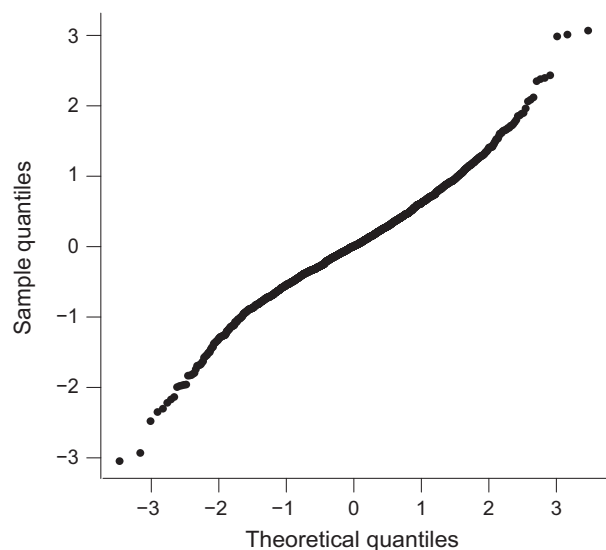


Figure 2 The commonly termed ‘QQ-Plot’ assessing the normality assumptions of the statistical model. Residuals of the measured values of the folded transformation variable z representing the Cambridge Cognition Examination (CAMCOG) score (sample quantiles) are plotted against the standardised theoretical quantiles taken from the model expressed in Eqn. 3. The degree to which the assumption of Normality of the distribution of residuals is appropriate can be judged by the linearity of this plot, which in this case is entirely satisfactory.

surgery is indicated by short dashes; a single episode of surgery at 3 years, is indicated by solid lines. Initial CAMCOG scores are 98 and 84 for women; the (lower) male initial CAMCOG values are those for all variables being identical other than gender.

Figure 4 examines the effect of diagnoses. It shows the model predictions for women and men, without *APOEε4* alleles, incorporating four different scenarios for each of two starting values of CAMCOG score: high and low. The scenarios are as follows: no diagnoses, black lines; diagnoses made at 2.5 years, red lines; no surgery is indicated by short dashes; a single episode of surgery at 3 years, is indicated by solid lines. Initial CAMCOG scores are 98 and 85 for women; the (lower) male initial CAMCOG values are those for all variables being identical other than gender. In Fig. 4, the solid red lines illustrate the substantial significant increase in the rate of decline in CAMCOG score occurring at first surgery in patients with a diagnostic category.

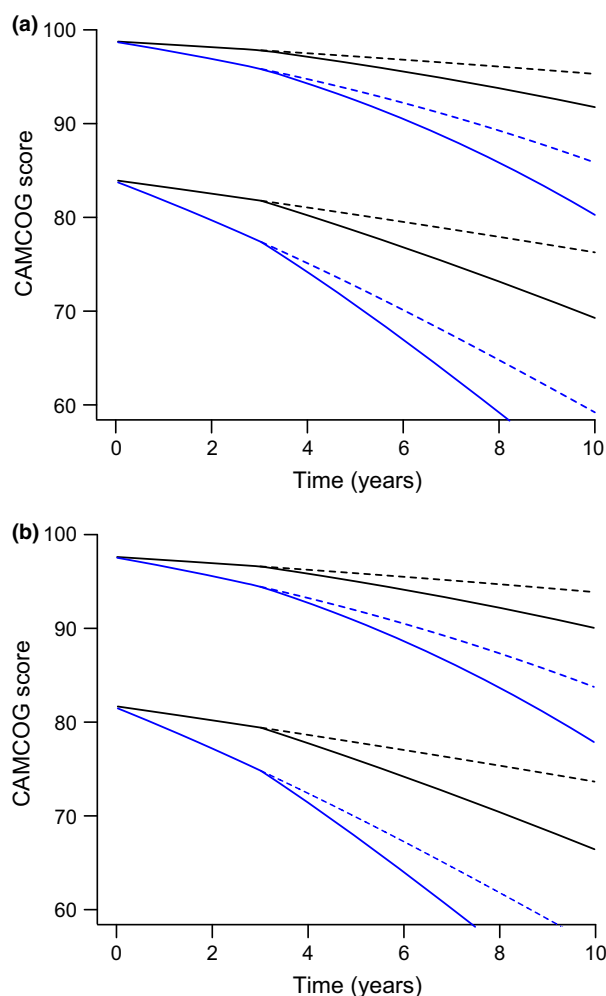


Figure 3 Sample predictions from the model of Eqn. 2 and Table 1 to illustrate the trajectory of Cambridge Cognition Examination (CAMCOG) in hypothetical individuals with characteristics that are typical for the data set used in the analysis. (a) women; (b) men, both without diagnoses. Four different scenarios are depicted for each of two starting values of CAMCOG score: high and low. The scenarios are as follows: no *APOEε4* allele, black lines; *APOEε4* hetero- or homozygosity, blue lines; no surgery is indicated by dashes; a single episode of surgery at 3 years is indicated by solid lines. Initial CAMCOG scores are 98 and 84 for women; the (lower) male initial CAMCOG values are those for all variables being identical other than gender.

Discussion

We found that elderly people were at risk of more rapid cognitive decline after an episode of moderate or major surgery with general or regional anaesthesia

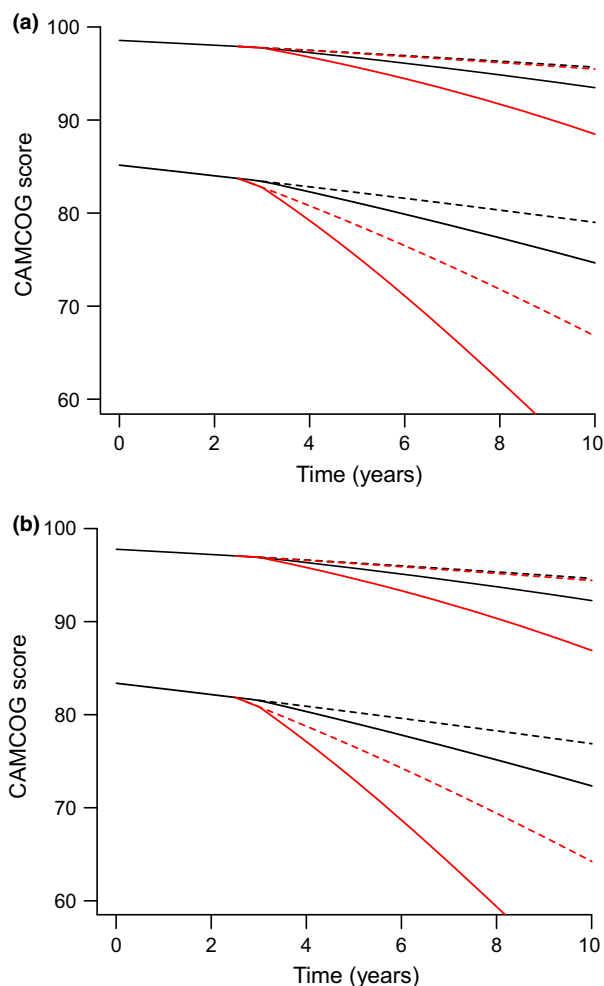


Figure 4 Sample predictions from the model of Eqn. 3 and Table 2 to illustrate the trajectory of Cambridge Cognition Examination (CAMCOG) in hypothetical individuals with characteristics that are typical for the data set used in the analysis. (a) women; (b) men, both without *APOEε4* allele. Four different scenarios are depicted for each of two starting values of CAMCOG score: high and low. The scenarios are as follows: no diagnoses (mild cognitive impairment or possible or probable Alzheimer's dementia), black lines; diagnoses made at 2.5 years, red lines; no surgery is indicated by dashes; a single episode of surgery at 3 years is indicated by solid lines. Initial CAMCOG scores are 98 and 85 for women; the (lower) male initial CAMCOG values are those for all variables being identical other than gender.

(Fig. 3). On further analysis, we discovered that in our cohort this effect was limited to those who had already suffered cognitive impairment (Fig. 4), that is, either mild cognitive impairment or possible or probable

Alzheimer's disease. A second episode of such surgery reversed that decline at borderline significance (Tables 1 and 2). We found no difference between men and women. We found no independent influence of the *APOEε4* allele on the effects of surgery.

A few longitudinal studies have examined cognitive [15–18] or functional decline [16, 30] after surgery. An early study [15], with a wide age-range (24–86 years), found no association of cognitive performance with a history of general anaesthesia, nor any interaction with age. However, two recent studies [16, 18] have found effects of surgery on cognitive decline in the elderly. One of those studies [18], of 1731 cognitively normal participants, with a mean age of 79 years at recruitment, found no association of surgery after the age of 40 years with incident mild cognitive impairment during a median follow-up of 4.8 years, but did find a risk of mild cognitive impairment associated with surgery after the age of 60 years or during the 10 years or 20 years before diagnosis of mild cognitive impairment. They did not find any increased risk associated with multiple (≥ 4) episodes of surgery, however. Our findings, including the apparently beneficial effect of a second surgery, were consistent with those of their results relating to the elderly. Some reports have suggested [17], as we have shown above, that pre-existing cognitive impairment may contribute to greater postoperative cognitive dysfunction. One study [31] replicated, in elderly people with mild cognitive impairment, the pre-clinical findings [6, 13] of relatively benign actions of propofol, compared with inhalational anaesthetics.

Schenning et al. [16] reported an interaction between surgery and *APOEε4* contributing to cognitive decline. But neither we nor Sprung et al. [18] found any such effect. Further, a meta-analysis of 1063 *APOEε4* carriers and 2983 non-carriers [32] found no association of *APOEε4* with increased cognitive decline at 1 year after surgery (OR 1.15, 95% CI 0.71–1.86). However, *APOEε4* has been shown to accelerate cognitive decline in elderly people, whether non-demented [25] or with Alzheimer's disease [24], regardless of surgery. Thus, elderly cognitively impaired, *APOEε4* carriers who experience moderate or major surgery may be in danger of suffering particularly rapid cognitive decline.

More studies have investigated associations of surgery or anaesthesia with either dementia [20, 21, 33–

36] or Alzheimer's disease [33, 37–40]. Several [20, 21, 38, 40] have reported increased risks for these outcomes, but several have not [33–36, 39]. Two very large Taiwanese studies [20, 21], both based on medical records, found an increased risk of dementia following surgery with anaesthesia, of various types [20]. A large US study [40] found an increased risk of Alzheimer's disease for coronary artery bypass graft surgery compared with percutaneous transluminal coronary angioplasty. In contrast, a recent large US study [33] reported a reduced risk of dementia or of Alzheimer's disease associated with previous surgery with general anaesthesia. But their method, based on the elderly participants' reports of lifetime exposures, is very likely to be subject to recall bias, as the authors accept. However, a meta-analysis of 15 case-control, mostly general epidemiological, studies [19] found no evidence of an association between general anaesthesia and risk of Alzheimer's disease: pooled OR 1.05 (0.93–1.19). But the authors commented on the few high-quality studies and found no valid cohort studies. Also, some large studies, for example, the two Taiwanese studies [20, 21], have been reported since that meta-analysis. Generally, it appears unreliable to base primary data on the recollections of elderly participants, especially those shortly to be diagnosed with mild cognitive impairment or dementia. This is likely to bias the result against a positive association with such risk.

To improve the definition(s) of the vulnerable, population(s) will require the study of elements such as age, sex and genetic and environmental factors. Although we found no effects of age or sex, we studied a rather narrow age range (IQR 66.6–77.8 years). A younger cohort would be unlikely to show any effect, since very few would already be cognitively impaired pre-surgery. But the study of a sufficiently large cohort, including cognitively impaired people, with a broad interquartile range extending beyond the age of 80 years, could be valuable. We note that several of the studies that failed to find a relevant association [15, 33, 35, 39], but not all [34, 36], had a substantial proportion of participants who had surgery when < 70 years old. As the definition of the vulnerable population(s) is refined, some of the apparent contradictions above may be explained.

The balance of current evidence suggests that anaesthesia and surgery may provoke long-term

cognitive damage in certain vulnerable elderly people, which may lead to dementia. These effects may be limited to those who are already cognitively impaired, even if only mildly. Carriage of the *APOEε4* allele exacerbates cognitive decline, even if there is no direct independent interaction with the effects of surgery and anaesthesia. It also appears that certain anaesthetics, including some that are widely used, may be the harmful agents, while others may be relatively benign. Moreover, current options for preventing or even moderating these effects are somewhat limited. If this is so, then it becomes of considerable importance to define the susceptible population(s), to specify the harmful agents, to understand the damaging mechanisms and to discover appropriate solutions. That is because there will always be elderly people who will need major surgery, despite the risks to their cognitive powers.

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Competing interests

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