BJA

British Journal of Anaesthesia, 124 (5): 594–602 (2020)

doi: 10.1016/j.bja.2020.01.015
Advance Access Publication Date: 12 March 2020
Neuroscience and Neuroanaesthesia

Exposure to surgery with general anaesthesia during adult life is not associated with increased brain amyloid deposition in older adults

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Abstract

Background: Exposure to surgery with general anaesthesia (surgery/GA) is associated with cortical atrophy, but the aetiology remains unknown. Amyloid-β (Aβ) deposition is one of the hallmark pathological characteristics of Alzheimer's disease (AD). We examined brain Aβ burden in study participants exposed to surgery/GA.

Methods: We performed a cross-sectional analysis of residents of Olmsted County, MN, USA, in the Mayo Clinic Study of Aging who were aged 70–97 yr and underwent measurement of (i) brain Aβ with Pittsburgh compound B positron emission tomography (PiB PET), (ii) brain glucose metabolism with 18-fluorodeoxyglucose (FDG) PET, and (iii) temporal cortical thickness with MRI. Separate analyses were performed with exposure to surgery/GA, defined as occurring after age 40 yr, and with exposure to surgery/GA, defined as occurring within 20 yr before neuroimaging. Imaging measurements were compared between participants who were exposed to surgery/GA *vs* not exposed.

Results: Of the 2563 participants, 585 had PET scans. Regardless of the definition used to quantify exposure, no significant associations were detected between exposure and either global PiB PET or FDG PET. In contrast, exposure to surgery/GA was associated with an increased likelihood of abnormal cortical thinning: odds ratio (OR)=1.98 (95% confidence interval [CI]: 1.19–3.31); P=0.010 in those exposed after age 40 yr, and OR=1.64 (95% CI: 1.05–2.55); P=0.029 in those exposed in the prior 20 yr.

Conclusions: Exposure to surgery/GA is not associated with increases in cortical amyloid deposition. This finding suggests that the modest cortical thinning associated with surgery/GA is not related to AD pathology, but rather is caused by other processes.

Keywords: Alzheimer's disease; brain amyloid; general anaesthesia; Mayo Clinic Study of Aging; MRI; neurodegeneration; positron emission tomography; surgery

Editor's key points

- Older adults exposed to surgery with general anaesthesia have increased cortical thinning in cerebral regions associated with early Alzheimer's disease (AD).
- Whether there is a link between exposure to surgery/GA and burden of brain amyloid, a hallmark biomarker of AD, is not known.
- Brain amyloid deposition and metabolism measured by positron emission tomography and cortical thinning measured by MRI were determined in participants from the Mayo Clinic Study of Aging.
- There was no evidence that exposure of older adults to surgery with general anaesthesia is associated with increased brain amyloid deposits.

Received: 26 September 2019 **Accepted:** 27 January 2020

Exposure of rodents to the general anaesthetic drugs isoflurane and sevoflurane promotes cortical deposition of amyloid-β (Aβ) and aggregates of hyperphosphorylated tau protein, both key neuropathological characteristics of Alzheimer's disease (AD).[1–10] Acute inflammation, a result of injury or invasive surgery, may also promote Aβ production in mouse models.[11,12] The clinical relevance of these observations remains unclear, as there is little evidence that exposure of older adults to surgery with general anaesthesia (surgery/GA) is associated with AD. However, we recently showed that surgery in older adults may be associated with a small acceleration in global cognitive decline.[13]

Brain imaging is a powerful tool in the study of AD. The abnormal deposition of both Aβ and tau, molecular markers of AD, differentiates AD from other neuropathological processes that contribute to the burden of dementia.[14,15] As accumulation of Aβ can precede the clinical manifestation of AD by up to three decades,[16,17] imaging for increased burden of Aβ may aid in diagnosing subclinical AD and in predicting who is at risk for developing AD dementia.[14,18] Accumulation of Aβ may be assessed using Pittsburgh compound B positron emission tomography (PiB PET).[19,20] As shown from autopsy studies, retention of PiB closely matches regional fibrillar Aβ plaque distribution in individuals with AD dementia.[21–23] PET studies using 18-fluorodeoxyglucose (FDG) have also shown that AD may be associated with decreased brain glucose metabolism, interpreted as reflecting a significant loss of synaptic activity.

MRI is also useful in the study of AD.[24–27] For example, cortical thickness assessed by structural imaging reflects neurodegeneration, and thinning of the cortex can precede cognitive deficits. Our group has identified an 'AD signature' meta-region of interest in the temporal cortex.[28–30] This AD signature region includes cortical subregions that are associated with increased thinning in patients with AD. We recently reported an association between exposure to surgery and anaesthesia and exaggerated cortical thinning on MRI in this region.[31] However, cortical thinning in this region is not specific to AD and may be caused by other pathologies.[32] Finding that exposure is associated with both thinning and other AD markers, such as amyloid accumulation, would support the concept that the thinning may represent AD pathology. However, only one prior study in cardiac surgery patients has examined postoperative amyloid deposition in humans, but did not image a non-surgical reference group.[33]

A series of reports has analysed data from the Mayo Clinic Study of Aging (MCSA), a population-based longitudinal study of cognitive function with ageing, to explore the relationship between exposure to surgery/GA in older adults with various measures of brain function and structure.[13,31,34] Information available from this data set includes both MRI and PET scans in some MCSA participants. The purpose of the present analysis was to test the hypothesis that exposure of older adults to surgery/GA is associated with greater cortical amyloid deposition compared with unexposed individuals. Secondary analyses included determining the association between exposure and brain glucose metabolism, and cortical thickness in the AD signature region.[35,36]

Methods

This study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center, Rochester, MN, USA. At enrolment, all participants provided written informed consent. Exposure to surgery/GA was retrospectively reviewed.

Participants

The MCSA is a population-based study designed to investigate brain ageing amongst residents of Olmsted County, MN, USA.[37] Participants undergo a detailed clinical evaluation of cognition, including MRI scanning, at baseline and at 15 month intervals after enrolment. Details of MCSA evaluations have been described.[13,37] Starting in 2008, MCSA participants were also asked to undergo PET scanning (both PiB and FDG PET). As scanning became more widely available (after 2010), it was offered routinely to participants every 30 months; however, for those who changed diagnosis during follow-up (e.g. mild cognitive impairment [MCI] to dementia) would have a scan at 15 months. The study population for the current analysis includes MCSA participants aged 70–91 yr at enrolment (from October 2004 to November 2009) who had at least one PET scan. The last available PiB and FDG PET scan for each participant was used.

Definitions of exposure to surgery/general anaesthesia

Two definitions of exposure were utilised in separate analyses, both recognising that amyloid accumulation may begin 20–30 yr before the clinical manifestation of cognitive impairment. Consistent with our previous studies,[34,38,39] we first defined exposure as having at least one surgery/GA after age 40 yr, recognising that there could be a long latency between exposure and effect (amyloid accumulation). Our more recent studies suggest that exposure to surgery/GA within 20 yr before enrolment in the MCSA could also be associated with accelerated cognitive decline.[13,38] Therefore, in another set of analyses, exposure was defined as having surgery/GA within 20 yr before PET and MRI scans. Participants with exposure to surgery/GA within 20 yr before imaging represent a subset of the individuals who had exposure to surgery/GA after the age of 40 yr. Of note, for this exposure definition, a participant whose only surgical procedure was performed after the age of 40 yr but more than 20 yr before imaging would be considered unexposed. All surgical exposures were identified through the Rochester Epidemiology Project (REP) medical records linkage system.[40] The REP is a unique research infrastructure, in which medical records are linked for all persons residing in Olmsted County, MN, USA.[41] The REP medical records linkage system can be used to provide an optimal sampling frame for epidemiological studies.[41–43]

Image acquisition and processing

Details of the acquisition, processing, and summary measures for PiB and FDG PET, and MRI for the MCSA participants have been described, and are here briefly summarised.[29,44–46]

Amyloid positron emission tomography

PiB labelled with ^{11}C was administered, and a helical CT image was obtained. The PET acquisition consisted of 5-min dynamic frames from 40 to 60 min post-injection. PiB sinograms were iteratively reconstructed. Individual frames of the PiB dynamic series were realigned if motion was detected, and a mean image was created (late uptake image) as described.[19] Statistical parametric mapping was used to evaluate PiB retention.[47]

The primary amyloid PET variable was the global PiB standardised uptake value ratio (SUVR), which includes prefrontal, orbitofrontal, right and left parietal, temporal,

anterior cingulate, and posterior cingulate/precuneus 'regions of interest' (ROI) scaled by a reference region of cerebellum (Crus I and Crus II) to create the SUVR.[48] Image voxel values were extracted from automatically labelled ROI propagated from an MRI template. Cut point for normal *vs* abnormal amyloid deposition was determined as >1.48.[49,50] Secondary variables included SUVR PiB from posterior cingulate ROI and precuneus ROI, two regions that could provide additional sensitivity to detect early accumulation of amyloid.

FDG positron emission tomography

FDG PET images were preprocessed using our in-house automated image processing pipeline.[19] FDG PET scans were scaled by the signal in the pons to create SUVR images, and spatially normalised using SPM12 to the in-house template via their co-registered MRI scan. The methodological approach that uses the ROI-based data analysis involves the preselection of five specific brain regions.[51,52] This global FDG PET was computed for each participant by calculating the median uptake over voxels in the right and left angular, right and left temporal, and posterior cingulate regions divided by the median uptake over voxels in the pons.[52–54] FDG values were classified as normal *vs* abnormal (>1.47 *vs* ≤1.47 SUVR).[29] Secondary FDG variables included SUVR from regions that could provide additional sensitivity to detect brain metabolic changes: (i) posterior cingulate and precuneus region (early AD sensitive regions); (ii) anterior cingulate region (region associated with greater cognitive resilience)[55]; and (iii) inferior temporal/medial temporal region, which is considered to be a biomarker for hippocampal sclerosis.[56,57]

Magnetic resonance imaging

All images were acquired on 3T MRI scanners (SIGNA™; GE Healthcare, Waukesha, WI, USA). Cortical thickness from magnetisation-prepared rapid acquisition gradient echo image sequences was estimated using FreeSurfer version 5.3 (http://surfer.nmr.mgh.harvard.edu/). Cortical thickness in the AD signature region was the primary MRI outcome of interest, calculated as the surface-area weighted average of the

Table 1 Participant characteristics and co-morbidities according to exposure to general anaesthesia and procedures since age 40 yr. Data are presented as *n* (%) with *P*-values from χ^2 tests for categorical variables and median (inter-quartile range) with *P*-values from rank-sum tests for continuous variables. When data were not available for all participants, the number of participants with available data are indicated. APOE, apolipoprotein E.

Characteristic	Exposure to surgery with general anaesthesia		
	No exposures (n=92)	One or more exposures (n=493)	P-values
Age (yr)	82 (79, 87)	83 (79, 86)	0.15
Sex			0.33
Male	47 (51)	279 (57)	
Female	45 (49)	214 (43)	
Education			0.10
<12 yr	3 (3)	39 (8)	
12 yr	23 (25)	150 (30)	
13–15 yr	21 (23)	123 (25)	
≥16 yr	45 (49)	181 (37)	
Smoking status			0.45
Never	57 (62)	273 (55)	
Former	32 (35)	206 (42)	
Current	3 (3)	14 (3)	
Marital status			0.12
Single	13 (14)	40 (8)	
Married	58 (63)	355 (72)	
Widowed	21 (23)	98 (20)	
APOE ε-4	25 (27)	131 (27)	0.90
Allele frequency			0.99
Zero	67 (73)	362 (73)	
One copy (heterozygotes)	23 (25)	120 (24)	
Two copies (homozygotes)	2 (2)	11 (2)	
Ever-diagnosed alcohol problem	3 (3)	21 (4)	0.66
Charlson Comorbidity Index	2 (1, 4)	3 (2, 5)	<0.001
Midlife diabetes mellitus	6 (7)	24 (5)	0.51
Midlife hypertension	15 (16)	183 (37)	<0.001
Midlife dyslipidaemia	40 (43)	238 (48)	0.40
Atrial fibrillation	5 (5)	66 (13)	0.032
Congestive heart failure	3 (3)	26 (5)	0.41
Stroke	2 (2)	16 (3)	0.58
Coronary artery disease	18 (20)	192 (39)	<0.001
Cardio-metabolic conditions	2 (1, 3)	2 (1, 3)	0.002
Cognitive status			0.86
Cognitively unimpaired	65 (71)	362 (73)	
Mild cognitive impairment	23 (25)	112 (23)	
Dementia	4 (4)	19 (4)	

Table 2 Imaging metrics according to exposure to surgery with general anaesthesia since age 40 yr. Continuous measurements are summarised as median (inter-quartile range) and categorical measurements are summarised as *n* (%). *Global cortical PiB PET includes prefrontal, orbitofrontal, right and left parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions. †Global cortical FDG-PET is composite of right and left angular, right and left temporal, and posterior cingulate cortical regions divided by the median uptake in the pons. ‡AD signature region includes the surface-area weighted average of the mean global thickness in the entorhinal, inferior temporal, middle temporal, and fusiform regions. FDG, 18-fluorodeoxyglucose; PiB PET, Pittsburgh compound B positron emission tomography; SUVR, standardised uptake value ratio.

Imaging metrics	Exposure to surgery with general anaesthesia			
	No exposure (*n*=92)		One or more exposures (*n*=493)	
Primary outcome				
Global cortical PiB PET*				
Global cortical PIB (SUVR)	1.51	(1.40, 1.97)	1.53	(1.38, 2.05)
Abnormal global cortical PiB, *n* (%)	47	(51)	274	(56)
Secondary outcomes				
Global cortical FDG PET†				
Global cortical FDG (SUVR)	1.48	(1.35, 1.58)	1.46	(1.36, 1.55)
Abnormal global cortical FDG, *n* (%)	44	(48)	261	(53)
AD signature region‡				
Cortical thickness (mm)	2.79	(2.65, 2.90)	2.73	(2.62, 2.83)
Abnormal cortical thickness, *n* (%)	58	(63)	388	(80)
PET in specific regions of interest (SUVR)				
PiB region of the posterior cingulate and precuneus	1.55	(1.40, 2.22)	1.57	(1.40, 2.29)
FDG region of the posterior cingulate and precuneus	1.58	(1.49, 1.70)	1.60	(1.49, 1.69)
FDG ratio of the inferior temporal/medial temporal	1.24	(1.19, 1.28)	1.24	(1.20, 1.29)
FDG region of the anterior cingulate	1.22	(1.17, 1.31)	1.24	(1.18, 1.31)

mean global thickness in the entorhinal, inferior temporal, middle temporal, and fusiform ROI.[28] Thickness in this region was analysed as both a continuous variable and also dichotomised in the AD signature region using binary approach (normal ≤2.86 mm or abnormal >2.86 mm).

Statistical analysis

Exposure to surgery/GA was defined using two time periods: (i) exposure after the age of 40 yr and before PiB PET, FDG PET, or MRI; and (ii) exposure in the 20 yr period before imaging. For both definitions, the primary exposure variable was a

Table 3 Association between exposure to surgery with general anaesthesia and global PiB PET. Results are from generalised linear regression for global cortical PiB treated as continuous variable and logistic regression for abnormal global cortical PiB treated as a binary variable. Prior anaesthesia was assessed both according to exposures since age 40 yr and in the 20 yr before imaging. *Because of highly skewed residuals, the natural log of global cortical PiB was modelled. Estimates are for the multiplicative increase in global cortical PiB associated with the given exposure. †Estimates are odds ratios associated with the given exposure. Global cortical PiB PET includes prefrontal, orbitofrontal, right and left parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions. CI, confidence interval; PiB PET, Pittsburgh compound B positron emission tomography.

Imaging metrics	Exposure to surgery with general anaesthesia			
	Since age 40 yr		In the prior 20 yr	
	Estimate (95% CI)	*P*-values	Estimate (95% CI)	*P*-values
Global cortical PiB PET*				
Any anaesthetic	1.01 (0.96, 1.06)	0.733	0.99 (0.94, 1.03)	0.547
Count of anaesthetics		0.975		0.852
0	Reference		Reference	
1	1.01 (0.95, 1.08)		1.00 (0.94, 1.05)	
2	1.01 (0.94, 1.07)		0.98 (0.92, 1.03)	
3 or more	1.01 (0.95, 1.07)		0.99 (0.93, 1.04)	
Duration of anaesthesia (per 5 h)	1.00 (0.98, 1.02)	0.983	1.00 (0.98, 1.01)	0.709
Abnormal global cortical PiB PET†				
Any anaesthetic	1.20 (0.73, 1.97)	0.465	1.04 (0.69, 1.55)	0.862
Count of anaesthetics		0.734		0.988
0	Reference		Reference	
1	1.04 (0.57, 1.89)		1.08 (0.67, 1.75)	
2	1.32 (0.73, 2.39)		1.02 (0.61, 1.69)	
3 or more	1.24 (0.72, 2.11)		1.00 (0.60, 1.66)	
Duration of anaesthesia (per 5 h)	1.06 (0.92, 1.23)	0.410	1.03 (0.87, 1.22)	0.738

Table 4 Association between exposure to surgery with general anaesthesia and global FDG PET. Results are from generalised linear regression for global cortical FDG treated as a continuous variable and logistic regression for abnormal global cortical FDG treated as a binary variable. Prior anaesthesia was assessed both according to exposures since age 40 yr and in the 20 yr before imaging. *Estimates are for the difference in global cortical FDG associated with the given exposure. †Estimates are odds ratios associated with the given exposure. Global cortical FDG PET is composite of right and left angular, right and left temporal, and posterior cingulate cortical regions divided by the median uptake in the pons. CI, confidence interval; FDG, 18-fluorodeoxyglucose; PET, positron emission tomography.

Imaging metrics	Exposure to surgery with general anaesthesia			
	Since age 40 yr		In the prior 20 yr	
	Estimate (95% CI)	P-values	Estimate (95% CI)	P-values
Global cortical FDG PET*				
Any anaesthetic	−0.001 (−0.032, 0.030)	0.947	−0.001 (−0.027, 0.024)	0.917
Count of anaesthetics		0.794		0.861
0	Reference		Reference	
1	0.008 (−0.030, 0.046)		0.005 (−0.026, 0.035)	
2	0.001 (−0.036, 0.039)		−0.001 (−0.034, 0.031)	
3 or more	−0.007 (−0.041, 0.027)		−0.009 (−0.041, 0.023)	
Duration of anaesthesia (per 5 h)	−0.006 (−0.015, 0.003)	0.188	−0.009 (−0.020, 0.002)	0.104
Abnormal global cortical FDG PET†				
Any anaesthetic	1.14 (0.70, 1.83)	0.601	1.00 (0.68, 1.47)	0.990
Count of anaesthetics		0.612		0.848
0	Reference		Reference	
1	1.06 (0.60, 1.90)		0.90 (0.57, 1.44)	
2	0.98 (0.55, 1.74)		1.00 (0.61, 1.64)	
3 or more	1.29 (0.76, 2.16)		1.13 (0.69, 1.84)	
Duration of anaesthesia (per 5 h)	1.14 (0.99, 1.31)	0.074	1.15 (0.98, 1.37)	0.093

dichotomous indicator of exposure (any *vs* none). The categorical number of exposures (0 [no exposure], 1, 2, 3, or more) and cumulative duration of exposure were considered in secondary analyses for each definition. The primary outcome was the global cortical PiB PET analysed as a continuous and binary variable (abnormal/normal). The secondary outcomes of interest included (i) global cortical FDG PET, (ii) region-specific PiB and FDG PET, and (iii) cortical thickness in AD signature regions as assessed using MRI.

Continuous outcomes were analysed using multivariable linear regression, and binary outcomes were analysed using multivariable logistic regression. Log transformations of PiB PET values were performed to satisfy distributional assumptions.[58] The multivariable models adjusted for 'risk factors' are age; sex; education; marital status; smoking status; apolipoprotein E ε-4 genotype; and midlife diabetes mellitus, hypertension, and dyslipidaemia (midlife defined as before age 65 yr). These participant characteristics and co-morbidities were

Table 5 Association between exposure to surgery with general anaesthesia and PiB PET and FDG PET in cortical regions of interest, and cortical thickness of AD signature regions from structural MRI. Individuals were categorised based on exposure to surgery with general anaesthesia after the age of 40 yr or in the 20 yr before date of imaging. Results are from generalised linear regression for the continuous end points and logistic regression for the abnormal status outcome. All values are comparison to participants who were not exposed to anaesthesia in respective time periods (i.e. after age 40 yr and 20 yr before imaging). In all analyses, anaesthesia was modelled as any anaesthetic in the given time frame compared with none. *Because of skewed residuals, the natural log of the PIB region of the posterior cingulate and precuneus was modelled. Estimates are for the multiplicative increase in end point associated with exposure to anaesthesia in the given time frame compared with no exposure. †Estimates are for the increase in end point associated with exposure to anaesthesia in the given time frame. ‡Estimates are odds ratios associated with exposure to anaesthesia in the given time frame compared with no exposure. AD signature region includes the surface-area weighted average of the mean global thickness in the entorhinal, inferior temporal, middle temporal, and fusiform regions. CI, confidence interval; FDG, 18-fluorodeoxyglucose; PiB PET, Pittsburgh compound B positron emission tomography.

Imaging metrics	Exposure to surgery with general anaesthesia			
	Since age 40 yr		In the prior 20 yr	
	Estimate (95% CI)	P-values	Estimate (95% CI)	P-values
PIB PET region of the posterior cingulate and precuneus*	1.00 (0.95, 1.07)	0.885	0.98 (0.93, 1.03)	0.402
FDG PET region of the posterior cingulate and precuneus†	0.004 (−0.029, 0.036)	0.812	−0.003 (−0.029, 0.024)	0.836
FDG PET ratio of the inferior temporal/medial temporal†	0.006 (−0.011, 0.023)	0.463	0.008 (−0.006, 0.022)	0.259
FDG PET region of the anterior cingulate†	0.016 (−0.004, 0.036)	0.129	0.010 (−0.007, 0.026)	0.250
AD signature region				
Abnormal cortical thickness‡	1.98 (1.18, 3.31)	0.010	1.64 (1.05, 2.55)	0.029
Cortical thickness (mm)†	−0.037 (−0.078, 0.003)	0.070	−0.029 (−0.062, 0.004)	0.088

described in earlier MCSA reports.[37,59] In addition, we used 'cardiac and metabolic conditions'[60] to adjust for vascular health. All co-variables were obtained at MCSA enrolment, except age and cardio-metabolic conditions, which were obtained at the time of PET/MRI. Analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC, USA).

Results

Of the 2563 individuals who were enrolled in the MCSA between 2004 and 2009, 585 had at least one PET scan available at the time of last follow-up (Supplementary Fig 1). The characteristics of those with PET scans available (n=585) and those without PET scans but still participating in MCSA when amyloid imaging was initiated (n=1182) are shown in Supplementary Table 1. Those with PET scans were younger, more educated, and healthier, but did not differ on prior exposure to surgery/GA.

Of the 585 participants with PET scans, 493 (84.3%) had at least one exposure to surgery/GA after the age of 40 yr, and 92 (16%) had no exposure. If exposure was limited to the 20-yr period before imaging, 422 (72%) had at least one exposure and 163 (28%) did not. Of 493 with at least one exposure to surgery/GA since age 40 yr, the median (inter-quartile range) time between first exposure and PET scans was 25.9 (14.6, 35.6) yr, and the time between the most recent surgery/GA and PET scanning was 7.2 (3.0, 13.8) yr.

All surgeries and procedures requiring general anaesthesia since age 40 yr are provided in Supplementary Table 2. Table 1 shows the participant characteristics and co-morbidities in those exposed and unexposed to surgery/GA since age 40 yr. Participants exposed to surgery/GA had higher frequency of co-morbidities (Table 1).

Table 2 summarises the global PiB PET and FDG PET data along with ROI-specific values for those exposed since age 40 yr and those with no exposure to surgery/GA. Cortical thickness in the AD signature region assessed in the MRI scan closest to the PET scan was also summarised.

For the primary variables of interest (global PiB PET), the results of adjusted analyses assessing the potential association with surgery/GA are summarised in Table 3. For the secondary variables of interest (global FDG PET), the results of adjusted analyses assessing the potential association with surgery/GA are summarised in Table 4. Regardless of the definition used to quantify anaesthesia exposure (any anaesthetic, count of anaesthetics, and cumulative duration of anaesthesia) or the time period used to assess exposure (since age 40 yr and in the past 20 yr before scanning), no significant associations were detected between anaesthesia exposure and global PiB PET or FDG PET values (Tables 3 and 4). No significant effects were detected in secondary analyses assessing the association of surgery/GA exposure since age 40 yr or in the prior 20 yr with region-specific PiB PET and FDG PET (Table 5). Although not statistically significant, there was some evidence suggesting that exposure to surgery/GA was associated with reduced cortical thickness in the AD signature region obtained from MRI (−0.037 mm [95% confidence interval {CI}: −0.078 to 0.003]; P=0.070 for exposure since age 40 yr; and −0.029 mm [95% CI: −0.062 to 0.004]; P=0.088, for exposure in the prior 20 yr) (Table 5). When assessed as a binary outcome, exposure to surgery/GA was significantly associated with an increased likelihood of abnormal cortical thickness (odds ratio [OR]=1.98 [95% CI: 1.19−3.31]; P=0.010 in those exposed since age 40 yr, and OR=1.64 [95% CI: 1.05−2.55]; P=0.029 in those exposed to surgery/GA in the prior 20 yr) (Table 5).

For the primary exposure variable (any exposure after the age of 40 yr), no significant age-by-exposure interactions were detected from supplemental analyses assessing whether the effect of exposure was dependent upon age. Furthermore, no significant associations were detected from sensitivity analyses assessing the association of anaesthetic exposure in the past 10 and 5 yr before scanning with global cortical PiB PET and FDG PET (Supplementary Table 3). Finally, 26/92 (28%) and 45/163 (28%) participants with no exposure to general anaesthesia since age 40 yr or in the 20 yr before imaging, respectively, had at least one exposure to regional anaesthesia in that same time frame. If these participants are excluded from the analysis, the findings were unchanged (Supplementary Table 4).

Discussion

The main finding of the present analysis was that exposure of older adults to surgery/GA was not associated with increases in a PET marker of cortical amyloid deposition. This suggests that the accelerated cortical thinning observed in MCSA participants exposed to surgery/GA in our prior analysis is likely unrelated to AD pathway.[31]

This report is the latest in a series analysing data from the MCSA, which assesses factors related to cognition in older adults.[13,31] These analyses address concerns arising from preclinical non-human and human studies, suggesting that exposure to surgery/GA may cause, or be associated with, permanent cognitive impairment.[1–4,12,13] Previous studies found that exposure to surgery/GA is not associated with the incidence or prevalence of MCI or AD.[34,39,61] However, in longitudinal analyses, exposure to surgery/GA was associated with a small acceleration in global cognitive decline, primarily in domains of memory and attention/executive function.[13] In a prior analysis of 1410 participants in the MCSA cohort, surgery/GA was associated with increased temporal cortical thinning (including in AD signature regions) as measured by MRI, but for the most part not in other regions typically involved in normal ageing.[31] Subjects in the current analysis (n=585) are a subset of those included in the prior analysis, so it is not surprising that the present study observed certain similar results.

Studies in rodent models suggest that anaesthetic drugs can produce pathological changes consistent with AD, including effects on Aβ, tau, and neuroinflammation.[1,8] However, two findings suggest that the associations observed in our cohort are not caused by the anaesthetics themselves. First, accelerated global cognitive decline is also observed in participants receiving surgery with regional anaesthesia.[62] Second, accelerated decline and cortical thinning are not associated with a dose−response relationship for exposure (i.e. those with multiple exposures are not more affected).[13,31] These findings imply that factors, such as confounding by indication (i.e. individuals requiring surgery are more likely to experience cognitive decline caused by the conditions necessitating surgery) or effects accompanying surgical experience itself (e.g. inflammation from surgical trauma), may be responsible for the observed associations. Nonetheless, if anaesthetic drugs cause pathology consistent with AD in humans, as it was shown in some animal models, evidence of such pathology might be associated with anaesthesia exposure, a possibility motivating the current analysis.

Cortical deposition of Aβ is a hallmark of AD.[14,18] Because Aβ accumulation precedes neurodegeneration, PiB imaging can serve as a tool for early diagnosis of AD.[27,35,36,63–65] Few studies have examined postoperative Aβ burden after exposure to surgery/GA.[33,66] In one study of cardiac surgery patients, amyloid deposition measured with the PET tracer ^{18}F-florbetapir at 6 weeks after operation was greater than expected compared with age- and sex-matched individuals who were cognitively normal in the Alzheimer's Disease Neuroimaging Initiative database.[33] Amongst the cardiac surgery patients, amyloid deposition was not associated with cognitive dysfunction up to 3 yr after operation. Another small study (n=11) found acute perioperative changes in CSF indicating neuroinflammation that are consistent with AD pathology, although concentrations of Aβ remained unchanged.[66] We found no evidence that surgery/GA is associated with increased Aβ deposition. This finding suggests that the modest acceleration in cognitive decline and cortical thinning observed in this cohort[13,31] is not accompanied with changes characteristic of AD pathology. This does not exclude a causative role of anaesthesia, but does not support the potential clinical relevance of animal model finding that anaesthesia causes increased brain deposition of Aβ. The pattern of brain pathology seen with exposure to surgery/GA in older age may be related to accelerated normative ageing, cerebrovascular pathology, and other non-amyloid degenerative diseases (such as the more recently recognised disease entity limbic-predominant age-related TDP-43 encephalopathy).[67]

FDG PET measurements, which assess metabolic activity, were also available in our cohort.[14,53] Reductions in brain metabolic activity have been interpreted as decreased synaptic activity associated with neurodegenerative processes.[45,68,69] These reductions are not limited to specific pathologies, such as AD, and are rather a non-specific marker related to a variety of pathologies.[53] The lack of association between exposure to surgery/GA and FDG PET shows that any acceleration of cortical thinning associated with anaesthetic exposure is insufficient to produce detectable changes in this parameter.

Potential limitations of this study include selection bias regarding individuals with available PET images, who differed in some respects from those who did not have imaging. In studies of the elderly, there is frequently a participation bias towards individuals who are healthier, younger, and more educated. This has been studied earlier in the context of participation in the MCSA. Although prevalent dementia cases were under-recruited in the MCSA cohort, this participation bias did not affect estimates of dementia incidence.[70] Importantly, for the present study, prior exposure to anaesthesia did not differ significantly between MCSA participants who had PET scans available or not. Amyloid PET is an important biomarker for AD, but PET evidence of Aβ deposition is insufficient by itself to assign the diagnosis of AD.[14] Evidence from other biomarkers, such as tau (measured in CSF or by PET), is required for diagnosis, which was not available in this cohort over this time period. Therefore, we cannot exclude that exposure to surgery/GA could have effects on these other biomarkers. Given the cross-sectional design of the present study, we cannot assess the changes in amyloid accumulation before and after exposure to anaesthesia and surgery. Finally, a number of studies have reported associations between non-surgical hospitalisation and subsequent cognitive decline or incident dementia. Our data set does not have information for non-surgical hospitalisations; therefore, the potential influence of this risk factor was not accounted for in our study.

In conclusion, exposure of older adults to surgery/GA is not associated with increases in a PET marker of global cortical amyloid deposition. This suggests that the modest acceleration of cognitive decline and cortical thinning observed in prior analyses of this cohort is not associated with pathological changes characteristic of AD, but rather is caused by other processes.

Authors' contributions

Study conception/design: JS, DOW, PV; Data acquisition: PV, VJL; Data analysis: JS, DOW, PV, PJS, ACH, SAP, DRS; Data interpretation: JS, DOW, PV, VJL; Statistical work: PV, PJS, ACH, SAP, DRS; Drafting of the article: JS, DOW, PV; Critical revisions for important intellectual content: all authors; Final approval: all authors.

Declarations of interest

DSK previously served as deputy editor for the journal *Neurology*, and serves on a Data Safety Monitoring Board for Lundbeck and for the Dominantly Inherited Alzheimer Network Trials Unit. He is an investigator in clinical trials sponsored by Biogen, Eli Lilly and Company, University of Southern California, and TauRx Therapeutics Limited, and receives research support from the National Institutes of Health. RCP is chair of the Data Monitoring Committees for Pfizer, GE Healthcare, and Janssen Alzheimer Immunotherapy, and has served as a consultant for F. Hoffmann-La Roche, Biogen, Eisai, Merck and Co., and Genentech. He receives royalties from the sales of the book Mild Cognitive Impairment (Oxford University Press). The other authors declare that they have no conflicts of interest.

Funding

National Institutes of Health (U01 AG006786) to RCP; (P50 AG016574) to RCP; (RF1 AG055151) to MMM; (R01 AG041851) to CRJ and DSK; (R37 AG011378) to CRJ; (R01 NS097495) to PV; (R01 AG056366) to PV; Robert H. and Clarice Smith and Abigail van Buren Alzheimer's Disease Research Program; Elsie & Marvin Dekelboum Family Foundation; Liston Family Foundation; Rochester Epidemiology Project (R01 AG034676); Mayo Clinic Center for Translational Sciences Activities; National Center for Advancing Translational Sciences (UL1 TR000135).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.01.015.

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Handling editor: Hugh C Hemmings Jr