

Online Supplementary Appendix:

A. Studies not showing a significant association between surgery or anesthesia, and persistent (> 6 months) postoperative cognitive decline (POCD) or incident dementia

1. Systematic Reviews

Newman¹, Cormack², Seitz³, Avidan⁴, Scott⁵, Guay⁶, Fink⁷

2. Randomized Controlled Trials

Sauer⁸, Wahrborg⁹, Hlatky¹⁰, Williams-Russo¹¹

3. Controlled Cohort Studies

Simpson¹², Gilberstadt¹³, Goldstein¹⁴, Abildsrom¹⁵, Tyas¹⁶, Avidan¹⁷, Selnes¹⁸, Sweet¹⁹, van Dijk²⁰, Fischer²¹, Ritchie²², Mutch²³, Potter²⁴, Mielke²⁵, Alosco²⁶, Hayden²⁷, Dokkedal²⁸

4. Case Control Studies

Bohnen²⁹, Gasparini³⁰, Yip³¹, Knopman³², French³³, Harmanci³⁴, Sprung³⁵, de Oliveira³⁶, Zuo³⁷, Kokmen³⁸, Kokmen³⁹, CSHA⁴⁰

5. Uncontrolled Cohort Studies

Shroyer⁴¹, van den Goor⁴²

B. Studies showing an association between surgery or anesthesia, and persistent (> 6 months) POCD or incident dementia

1. Systematic Reviews

None found

2. Randomized Controlled Trials

None found

3. Controlled Cohort Studies

Farrag⁴³, Ballard⁴⁴, Zimpfer⁴⁵, Lee⁴⁶, Chen⁴⁷, Liu⁴⁸, Lyketsos⁴⁹, Silbert⁵⁰

4. Case Control Studies

Chen⁵¹

5. Uncontrolled Cohort Studies

Newman⁵², McDonough⁵³, Stockton⁵⁴, Silbert⁵⁵, Bedford⁵⁶

References:

1. Newman S, Stygall J, Hirani S, Shaefi S, Maze M: Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology* 2007; 106: 572-90
2. Cormack F, Shipolini A, Awad WI, Richardson C, McCormack DJ, Colleoni L, Underwood M, Baldeweg T, Hogan AM: A meta-analysis of cognitive outcome following coronary artery bypass graft surgery. *Neurosci Biobehav Rev* 2012; 36(9):2118-29
3. Seitz DP, Shah PS, Herrmann N, Beyene J, Siddiqui N: Exposure to general anesthesia and risk of Alzheimer's disease: a systematic review and meta-analysis. *BMC Geriatr* 2011; 11: 83
4. Avidan MS, Evers AS: Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. *J Alzheimers Dis* 2011; 24: 201-16
5. Scott JE, Mathias JL, Kneebone AC: Postoperative cognitive dysfunction after total joint arthroplasty in the elderly: a meta-analysis. *J Arthroplasty* 2014; 29: 261-7 e1
6. Guay J: General anaesthesia does not contribute to long-term post-operative cognitive dysfunction in adults: A meta-analysis. *Indian J Anaesth.* 2011 Jul;55(4):358-63

7. Fink HA, Hemmy LS, MacDonald R, Carlyle MH, Olson CM, Dysken MW, McCarten JR, Kane RL, Garcia SA, Rutks IR, Ouellette J, Wilt TJ: Intermediate- and Long-Term Cognitive Outcomes After Cardiovascular Procedures in Older Adults: A Systematic Review. *Ann Intern Med* 2015; 163: 107-17
8. Sauer AM, Nathoe HM, Hendrikse J, Peelen LM, Regieli J, Veldhuijzen DS, Kalkman CJ, Grobbee DE, Doevendans PA, van Dijk D, Octopus Study G: Cognitive outcomes 7.5 years after angioplasty compared with off-pump coronary bypass surgery. *Ann Thorac Surg* 2013; 96: 1294-300
9. Wahrborg P, Booth JE, Clayton T, Nugara F, Pepper J, Weintraub WS, Sigwart U, Stables RH: Neuropsychological outcome after percutaneous coronary intervention or coronary artery bypass grafting: results from the Stent or Surgery (SoS) Trial. *Circulation* 2004; 110: 3411-7
10. Hlatky MA, Bacon C, Boothroyd D, Mahanna E, Reves JG, Newman MF, Johnstone I, Winston C, Brooks MM, Rosen AD, Mark DB, Pitt B, Rogers W, Ryan T, Wiens R, Blumenthal JA: Cognitive function 5 years after randomization to coronary angioplasty or coronary artery bypass graft surgery. *Circulation* 1997; 96: II-11-4; discussion II-15
11. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME: Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. *JAMA* 1995; 274: 44-50
12. Simpson BR, Williams M, Scott JF, Smith AC: The effects of anesthesia and elective surgery on old people. *Lancet* 1961; 2: 887-93
13. Gilberstadt H, Aberwald R, Crosbie S, Schuell H, Jimenez E: Effect of surgery on psychological and social functioning in elderly patients. *Arch Intern Med* 1968; 122: 109-15
14. Goldstein MZ, Fogel BS, Young BL: Effect of elective surgery under general anesthesia on mental status variables in elderly women and men: 10-month follow-up. *Int Psychogeriatr* 1996; 8: 135-49
15. Abildstrom H, Rasmussen LS, Rentowl P, Hanning CD, Rasmussen H, Kristensen PA, Moller JT: Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction. *Acta Anaesthesiol Scand* 2000; 44: 1246-51
16. Tyas SL, Manfreda J, Strain LA, Montgomery PR: Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. *Int J Epidemiol* 2001; 30: 590-7

17. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS: Long-term Cognitive Decline in Older Subjects Was Not Attributable to Noncardiac Surgery or Major Illness. *Anesthesiology* 2009; 111: 964-70
18. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM: Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol* 2008; 63: 581-90
19. Sweet JJ, Finnin E, Wolfe PL, Beaumont JL, Hahn E, Marymont J, Sanborn T, Rosengart TK: Absence of cognitive decline one year after coronary bypass surgery: comparison to nonsurgical and healthy controls. *Ann Thorac Surg* 2008; 85: 1571-8
20. van Dijk D, Moons KG, Nathoe HM, van Aarnhem EH, Borst C, Keizer AM, Kalkman CJ, Hijman R: Cognitive outcomes five years after not undergoing coronary artery bypass graft surgery. *Ann Thorac Surg* 2008; 85: 60-4
21. Fischer P, Wallner H, Jungwirth S, Weissgram S, Krampla W, Bauer P, Tragl KH: Cumulative Exposure to General anesthetics and cognitive dysfunction at age 75 in the Vienna Transdanube Aging "VITA" study. *J Neuropsychiatry Clin Neurosci* 2007; 19: 21-6
22. Ritchie K, Carriere I, Ritchie CW, Berr C, Artero S, Ancelin ML: Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *BMJ* 2010; 341: c3885
23. Mutch WA, Fransoo RR, Campbell BI, Chateau DG, Sirski M, Warriar RK: Dementia and depression with ischemic heart disease: a population-based longitudinal study comparing interventional approaches to medical management. *PLoS One* 2011; 6: e17457
24. Potter GG, Plassman BL, Helms MJ, Steffens DC, Welsh-Bohmer KA: Age effects of coronary artery bypass graft on cognitive status change among elderly male twins. *Neurology* 2004; 63: 2245-9
25. Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, Hayden KM, Norton M, Rabins PV, Green RC, Welsh-Bohmer KA, Breitner JC, Munger R, Lyketsos CG: Vascular factors predict rate of progression in Alzheimer disease. *Neurology* 2007; 69: 1850-8
26. Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Paul R, Crosby RD, Mitchell JE, Gunstad J: Improved memory function two years after bariatric surgery. *Obesity (Silver Spring)* 2014; 22: 32-8
27. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, Tschanz JT, Norton MC, Pieper CF, Munger RG, Breitner JC, Welsh-Bohmer KA, Cache County I: Vascular risk factors for incident

- Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Dis Assoc Disord* 2006; 20: 93-100
28. Dokkedal U, Hansen TG, Rasmussen LS, Mengel-From J, Christensen K: Cognitive functioning after surgery in middle-aged and elderly Danish twins. *Anesthesiology* 2015
29. Bohnen NI, Warner MA, Kokmen E, Beard CM, Kurland LT: Alzheimer's disease and cumulative exposure to anesthesia: a case-control study. *J Am Geriatr Soc* 1994; 42: 198-201
30. Gasparini M, Vanacore N, Schiaffini C, Brusa L, Panella M, Talarico G, Bruno G, Mecco G, Lenzi GL: A case-control study on Alzheimer's disease and exposure to anesthesia. *Neurol Sci* 2002; 23: 11-4
31. Yip AG, Brayne C, Matthews FE: Risk factors for incident dementia in England and Wales: The Medical Research Council Cognitive Function and Ageing Study. A population-based nested case-control study. *Age Ageing* 2006; 35: 154-60
32. Knopman DS, Petersen RC, Cha RH, Edland SD, Rocca WA: Coronary artery bypass grafting is not a risk factor for dementia or Alzheimer disease. *Neurology* 2005; 65: 986-90
33. French LR, Schuman LM, Mortimer JA, Hutton JT, Boatman RA, Christians B: A case-control study of dementia of the Alzheimer type. *Am J Epidemiol* 1985; 121: 414-21
34. Harmanci H, Emre M, Gurvit H, Bilgic B, Hanagasi H, Gurol E, Sahin H, Tinaz S: Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey. *Alzheimer Dis Assoc Disord* 2003; 17: 139-45
35. Sprung J, Jankowski CJ, Roberts RO, Weingarten TN, Aguilar AL, Runkle KJ, Tucker AK, McLaren KC, Schroeder DR, Hanson AC, Knopman DS, Gurrieri C, Warner DO: Anesthesia and Incident Dementia: A Population-Based, Nested, Case-Control Study. *Mayo Clin Proc.* 2013; 88(6):552-61
36. de Oliveira FF, Bertolucci PH, Chen ES, Smith MC: Assessment of risk factors for earlier onset of sporadic Alzheimer's disease dementia. *Neurol India* 2014; 62: 625-30
37. Zuo C, Zuo Z: Spine Surgery under general anesthesia may not increase the risk of Alzheimer's disease. *Dement Geriatr Cogn Disord* 2010; 29: 233-9
38. Kokmen E, Beard CM, Chandra V, Offord KP, Schoenberg BS, Ballard DJ: Clinical risk factors for Alzheimer's disease: a population-based case-control study. *Neurology* 1991; 41: 1393-7

39. Kokmen E, Beard CM, O'Brien PC, Kurland LT: Epidemiology of dementia in Rochester, Minnesota. *Mayo Clin Proc* 1996; 71: 275-82
40. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. *Neurology* 1994; 44: 2073-80
41. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D: On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med* 2009; 361: 1827-37
42. van den Goor J, Saxby B, Tijssen J, Wesnes K, de Mol B, Nieuwland R: Improvement of cognitive test performance in patients undergoing primary CABG and other CPB-assisted cardiac procedures. *Perfusion* 2008; 23: 267-73
43. Farrag AK, Khedr EM, Abdel-Aleem H, Rageh TA: Effect of surgical menopause on cognitive functions. *Dement Geriatr Cogn Disord* 2002; 13: 193-8
44. Ballard C, Jones E, Gauge N, Aarsland D, Nilsen OB, Saxby BK, Lowery D, Corbett A, Wesnes K, Katsaiti E, Arden J, Amaoko D, Prophet N, Purushothaman B, Green D: Optimised Anaesthesia to Reduce Post Operative Cognitive Decline (POCD) in Older Patients Undergoing Elective Surgery, a Randomised Controlled Trial. *PloS one* 2012; 7: e37410
45. Zimpfer D, Czerny M, Vogt F, Schuch P, Kramer L, Wolner E, Grimm M: Neurocognitive deficit following coronary artery bypass grafting: a prospective study of surgical patients and nonsurgical controls. *Ann Thorac Surg* 2004; 78: 513-8; discussion 518-9
46. Lee TA, Wolozin B, Weiss KB, Bednar MM: Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. *J Alzheimers Dis* 2005; 7: 319-24
47. Chen PL, Yang CW, Tseng YK, Sun WZ, Wang JL, Wang SJ, Oyang YJ, Fuh JL: Risk of dementia after anaesthesia and surgery. *Br J Psychiatry* 2014; 204: 188-93
48. Liu Y, Pan N, Ma Y, Zhang S, Guo W, Li H, Zhou J, Liu G, Gao M: Inhaled sevoflurane may promote progression of amnesic mild cognitive impairment: a prospective, randomized parallel-group study. *Am J Med Sci* 2013; 345: 355-60
49. Lyketsos CG, Toone L, Tschanz J, Corcoran C, Norton M, Zandi P, Munger R, Breitner JC, Welsh-Bohmer K, Cache County Study G: A population-based study of the association between coronary artery

bypass graft surgery (CABG) and cognitive decline: the Cache County study. *Int J Geriatr Psychiatry* 2006; 21: 509-18

50. Silbert B, Evered L, Scott DA, McMahon S, Choong P, Ames D, Maruff P, Jamrozik K: Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. *Anesthesiology* 2015; 122: 1224-34

51. Chen CW, Lin CC, Chen KB, Kuo YC, Li CY, Chung CJ: Increased risk of dementia in people with previous exposure to general anesthesia: a nationwide population-based case-control study. *Alzheimers Dement* 2014; 10: 196-204

52. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001; 344: 395-402

53. McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, Newman MF: Cognitive Function after Major Noncardiac Surgery, Apolipoprotein E4 Genotype, and Biomarkers of Brain Injury. *Anesthesiology* 2010; 112: 852-9

54. Stockton P, Cohen-Mansfield J, Billig N: Mental status change in older surgical patients. Cognition, depression, and other comorbidity. *Am J Geriatr Psychiatry* 2000; 8: 40-6

55. Silbert BS, Scott DA, Evered LA, Lewis MS, Kalpokas M, Maruff P, Myles PS, Jamrozik K: A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. *Anesthesiology* 2006; 104: 1137-45

56. Bedford PD: Adverse cerebral effects of anaesthesia on old people. *Lancet* 1955; 269: 259-63