

Perspective About Anesthesia Use And Alzheimer's Disease And Dementia

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**ABSTRACT**

There is strong evidence in the literature that various anesthesia play the role of cognitive dysfunction agents in a human body so that the brain is at least temporary impaired after the use of anesthesia. The condition of Post-Operative Cognitive Dysfunction or POCD is a well-recognized condition, and has been linked to the effects of anesthesia on the brain. There have been many animal model studies that show brain cells of rats and other animals adversely affected by various anesthesia chemicals. The accumulation of  $\beta$ -amyloid (linked to Alzheimer's Disease or AD) caused by inhalational anesthetics has also been studied. The current work has shown the perspective that the large incidences of AD and dementia in North America (High Income), Caribbean, Latin America, Western Europe, Asia Pacific (High Income), Southeast Asia, Australasia are probably due to the increased use of anesthesia for C-section childbirths, optional plastic surgeries, optional liposuctions, optional medical tests and procedures, e.g. colonoscopy, MRI's in these regions, as compared to the less developed nations of the sub-Saharan region.

**INTRODUCTION**

It is a scientific fact that humans generate new brain cells. However, if these cells are not used for new connections and activated in different areas, these cells will die within a fortnight<sup>[1,2]</sup>. If these cells are to be kept alive, a need should be created for them with new activities, for example, acquiring a new language or learning a new dance. The nerve cells in the brain act like the computer in the brain. Nerve cells connect to other nerve cells and create these networks. All the connections (synapses) have to be there for a network to work. If some of the cells die off, the networks will not be complete or functional. Thus, prevention efforts stem from building strong, healthy nerve cells, from birth to death.

Five commonly acceptable ways for keeping the minds healthy starts with the first step of eating a healthy diet. Studies have indicated that people who have a heart healthy diet tend to have better brain health. A healthy brain diet is pretty much the same as a healthy heart diet<sup>[3,4]</sup>. Foods rich in cholesterol and bad fats should not be part of a healthy brain diet. In their place should be lots of fruits, vegetables, good fats and antioxidants. Specific substances studied to boost brain health include acetyl-L-carnitine<sup>[5,6]</sup>, huperzine<sup>[7,8,9,10]</sup> and vinpocetine<sup>[11]</sup>.

Second in the list for keeping our minds healthy is to exercise often. The brain is dependent on blood from the body so it is bad if the arteries are not at their best in supplying the brain. The third on the list is to reduce stress. Every time one is under a stressful situation, one produces a lot of hormones that are used in response to threat. It is an accepted fact that these hormones go to the brain

and are very toxic. It has been found that when experimental rats are exposed to discharges of those chemicals, parts of the brain start to die. It is beneficial to reduce stress whenever possible by divorcing oneself from stressful situations, by exercising, listening to music, viewing peaceful photos, practicing breathing techniques or other calming techniques.

The fourth item is sleep. Better sleeping habits result in better sleep. If one's sleep is not restful, one's memory and brain function will be negatively impacted.

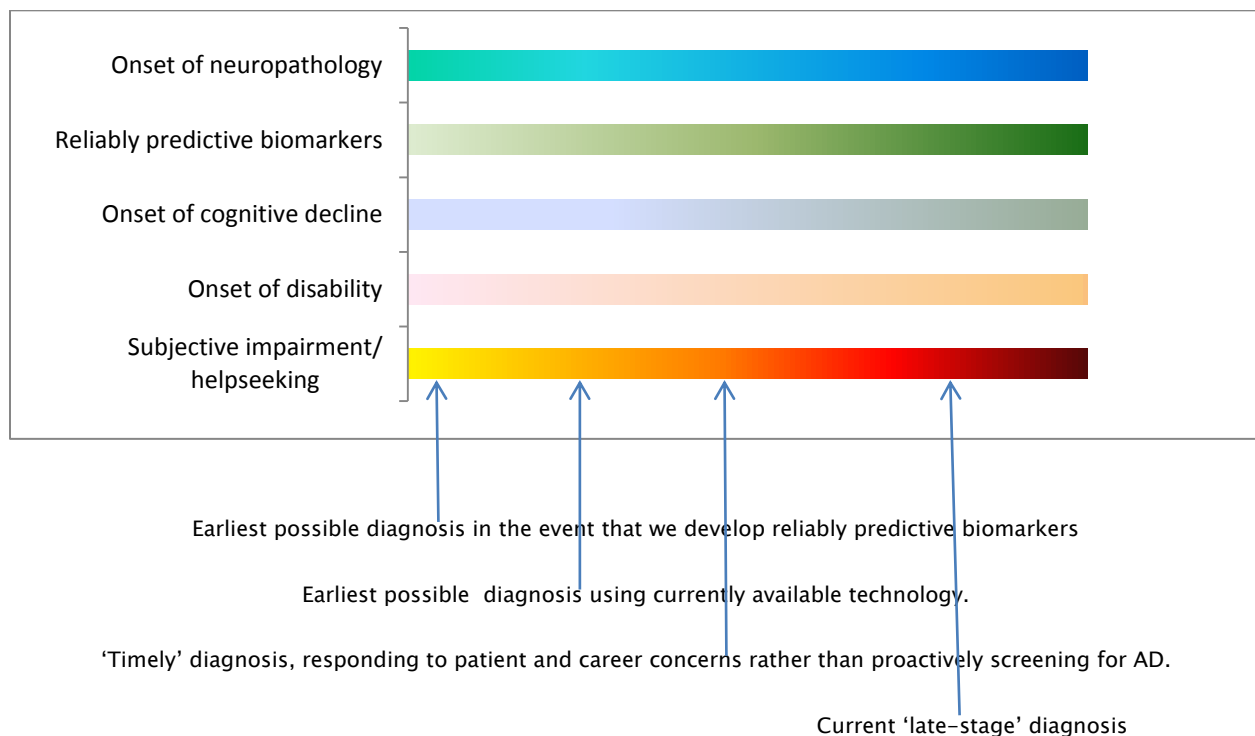
Finally, the brain needs to learn new things to keep it healthy. It is a known fact that when a brain stops learning new items it goes into this mode where it becomes really efficient at the simple activities of daily living but does not make new connections. A brain that has more connections is a more efficient brain and is less prone to Alzheimer's Disease (AD) and dementia. Learning can be acquiring a new skill, doing non-trivial mathematical calculations, playing an instrument, exploring the world or planning things for the future and looking forward by seeing life in the long-term.

At the present time, the aging population has caused the predictions for the year 2050 to be rather bleak. The number of people living into seventies and eighties are increasing, so projections for AD, dementia and strokes are projected to increase. The correct response is to follow the five steps outlined above, as well as to recognize risk factors.

The current work includes a review of the research work done about the impairment of cognitive function, whether temporary or long-term, with the use of anesthesia.

The perspective of the current paper is that with increased use of anesthesia (in more developed western countries, the Caribbean and Southeast Asia in optional procedures that do not require anesthesia but where anesthesia is requested anyway, in C-sections during childbirth, in optional surgeries, etc.) there is an increase in the cases of AD. AD does have a long incubation period and is an affliction of the elderly<sup>[12,13,14]</sup>. See Figure 1. The onset of neuropathology is long before the earliest possible diagnosis using currently available technology.

Fig 1: Timeline of AD progression [14].



The countries of the Caribbean and Southeast Asia were all former colonies of the western powers, and were influenced by western standards of medicine and procedures from prior to the Second World War in the middle of the last century. The fast developing

nations of China (East Asia) and India (South Asia) are just catching up with increased use of optional surgeries and procedures (with concomitant increased use of anesthesia), however, the data of dementia from these nations<sup>[12,13,14]</sup>, have not been altered with modern habits and practices regarding modern widespread use of anesthesia for C-sections for childbirth and optional surgeries because the data is typically for the over 55 or 60 years.

### Hypothesis

The hypothesis is that the more frequent use of anesthesia by people in developed countries contributes to the higher incidence of AD and dementia, as contrasted to the underdeveloped countries of sub-Saharan Africa. The factor of concern is the kind and frequency of anesthesia used, which basically reduces the neuronal pool. The specific anesthetic agents and the cumulative effects of the potent ones are the targets of the current research. This work is expected to improve the understanding of AD and dementia disparities between North America (High Income), Caribbean, Latin America, Western Europe, Asia Pacific (High Income), Southeast Asia, Australasia as compared to the less developed nations of the sub-Saharan region.

### Literature Review

Alzheimer's disease (AD) is characterized by progressive deterioration of cognitive function. Many nonmodifiable (e.g., gender, age, genotype, head circumference) and modifiable (e.g., education, smoking, alcohol use, head trauma, stroke, cardiovascular disease, possible non-steroidal anti-inflammatory drug, NSAID, or statin use) risk factors have been identified or suggested to have a role in either the delay (prevention) or onset of AD<sup>[15,16,17]</sup>. Many of the etiologic factors implicated in the development of AD relate to a reduced neuronal reserve: older age, traumatic and ischemic brain injury and smaller head circumference are all scenarios where there is a primary or secondary reduction in the neuronal pool.

The development of mild forms of cognitive impairment, most often defined as Post-Operative Cognitive Dysfunction or POCD, is well documented after cardiac surgery in short and long-term studies<sup>[18,19,20,21,22,23]</sup>. Studies on the adverse cognitive effects of anesthesia include<sup>[24,25,26]</sup>. In fact<sup>[27]</sup>, is a review on the subject of POCD and neuroinflammation associated with cardiac surgery and anesthesia. Increasing evidence shows that inhalational anesthetics may cause or increase the risk of developing POCD, especially in the elderly population. POCD may exist as a transient or long-term complication of surgery and anesthesia and is associated with reduced quality of life. There still is discrepancy between clinical studies investigating the prevalence of POCD and inhalational anesthetics as many studies do not show an association. "However, numerous animal studies have suggested that inhalational anesthetics may change cognitive function via amyloid  $\beta$  accumulation, modified neurotransmission, synaptic changes and dysregulated calcium homeostasis. Other factors like neuroinflammation and pro-inflammatory cytokines may also play a role"<sup>[28]</sup>, is a review of the role of inhalational anesthetics in the etiology and underlying mechanisms that cause POCD.

As reported in the journal Science, rising brain levels of beta-amyloid do not mean that patients are making more of it but that they can no longer clear it from their brains as efficiently [29]. In the study, the researchers tested 24 people, average age 74, and divided them into a cohort composed of people with minor AD and another whose members were cognitively normal. Special testing revealed that both groups produced  $\beta$ -amyloid at the same average rate within the brain. From<sup>[29]</sup>, "This suggests that AD is associated with disruption of the brain's ability to normally handle the beta-amyloid. They found that those with AD had decreased clearance of  $\beta$ -amyloid from the brain to the cerebrospinal fluid – about 30 percent less than those who were cognitively normal. This suggests that AD is linked with disruption of the brain's ability to normally handle the  $\beta$ -amyloid."

Early diagnosis of AD has not been achieved. However, since researchers have uncovered a possible mechanism of early disease development, it is possible that this discovery could lead to both a test for early detection and the development of effective therapies to stop or reverse AD's memory disruption. They compute that it would take an adult 10 years to accumulate enough amyloid in his or her brain to reach the amount typically present in someone with AD. Hence, the incubation period before the onset of AD is long, as indicated in Figure 1.

In<sup>[30,31]</sup>, there were some similar observations regarding foods with low nutrients. In<sup>[31]</sup>, it was concluded that "recent increases in consumption of more energy-dense, nutrient-poor foods with high levels of sugar and saturated fats, combined with reduced physical activity, have led to obesity rates that have risen threefold or more since 1980 in some areas of North America and Europe". Obesity poses a major risk for serious diet-related chronic diseases, including hypertension, stroke, and dementia.

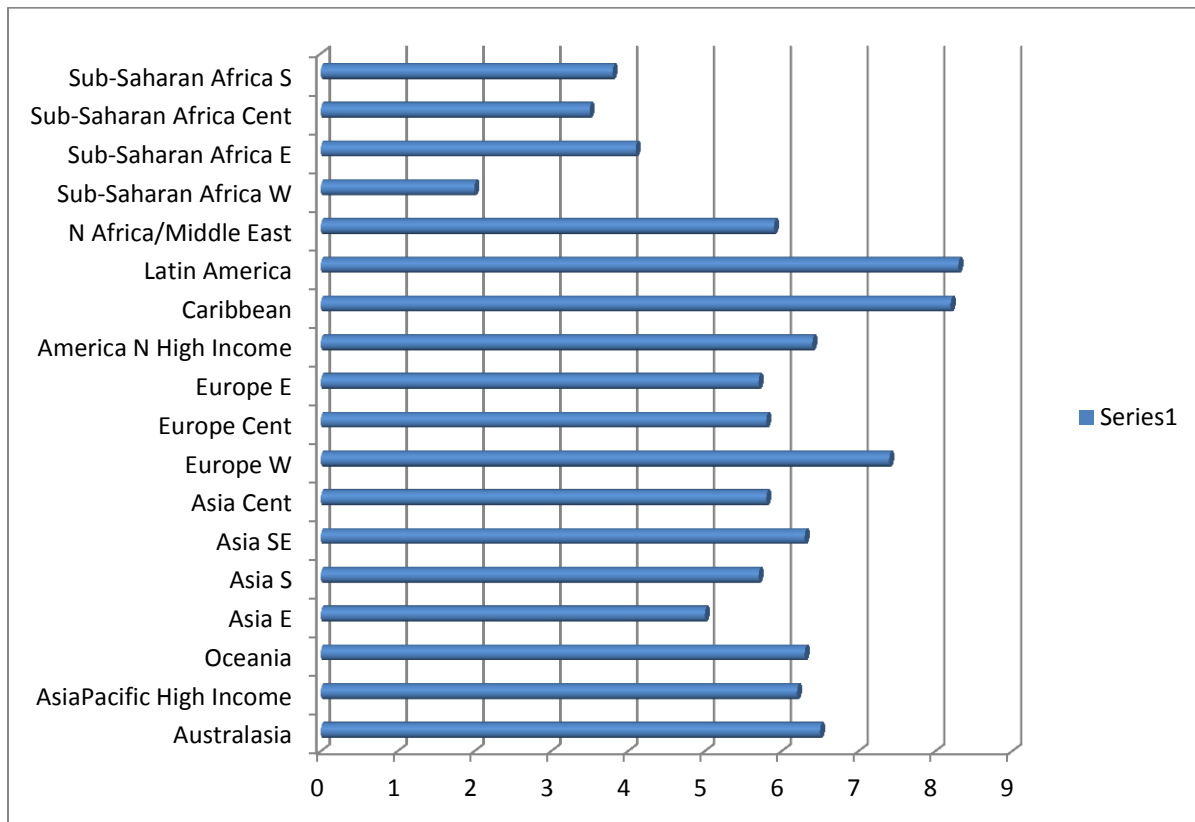
Research papers regarding gender as a risk factor in AD include<sup>[32,33,34]</sup>. In<sup>[33]</sup>, the work was done to try to answer the question whether the risk of developing AD is greater for women than for men. The findings suggest that the excess of women with AD (in the USA) is due to the longer life expectancy of women rather than sex-specific risk factors for the disease. It does not preclude the fact that women might go through childbirths (including C-sections) which requires anesthesia, whereas many men will go from cradle to grave without being administered any anesthesia. The Alzheimer's Association claims that 16 percent of women age 71 and over (in the USA) have AD or other types of dementia; 11 percent of men do<sup>[35]</sup>.

**Perspective**

From Table 1, it is evident for the total population over 60, the crude estimated prevalence of dementia (2010), that there is a disparity in dementia between the high income countries of the West and Asia, and the low income sub-Saharan countries <sup>[13]</sup>.

These estimates of numbers of people with dementia worldwide, published in 2005 <sup>[36]</sup>, were based on expert consensus. A large number of newer studies unearthed in the systematic review, particularly from low and middle income countries, enabled meta-analyses in 11 of the 21 Global Burden of Disease (GBD) world regions<sup>[13]</sup>. The new estimates, Figure 2, showed that age standardized prevalence (for those aged 60 years and over) varied between 5% and 7% in most regions, the exceptions were the four sub-Saharan African regions where between 2% and 4% were affected. In this figure, Australasia, Asia Pacific High Income, Southeast Asia, Western Europe, America North High Income, Caribbean, and Latin America are the highest, with more than 6% standardized prevalence. Latin America is apparently the highest with 8.3% standardized prevalence.

Fig 2: Estimated prevalence of dementia for those aged 60 and over, standardized to Western Europe population, by GBD region (%), [13].



Several sources of information suggest that man evolved on a diet with a ratio of omega 6 to omega 3 fatty acids of approximately 1 whereas today this ratio is about 10:1 to 20-25:1, indicating that "Western diets" (Canada, USA, Australia, New Zealand, Western Europe minus the Mediterranean Countries) are deficient in omega 3 fatty acids compared with the diet on which humans evolved and their genetic patterns were established<sup>[37]</sup>. If this decrease of omega 3 is the major cause of dementia in the human population, the Asia Pacific High Income region (Japan, Taiwan and South Korea) and Southeast Asia (Singapore, Malaysia, Indonesia) will not be a high Global Burden of Disease (GBD) region, nor will Latin America. These countries do not have a prevalence of Western diets which are

deficient in omega-3 fatty acids. Hence, the lack of omega 3 fatty acids in the diet may not be a major contributor of dementia and AD, as may be suggested by model studies using omega 3 fatty acids, such as<sup>[38]</sup>.

Table 1. Total population over 60, crude estimated prevalence of dementia (2010), by GBD world region, [14].

GBD Region	Over 60 population (millions)	Crude estimated prevalence (%)
	2010	2010
Australasia	4.82	6.4
Asia Pacific High Income	46.63	6.1
Oceania	0.49	4.0
Asia, Central	7.16	4.6
Asia, East	171.61	3.2
Asia, South	124.61	3.6
Asia, Southeast	51.22	4.8
Europe, Western	97.27	7.2
Europe, Central	23.61	4.7
Europe, East	39.30	4.8
North America High Income	63.67	6.9
Caribbean	5.06	6.5
Latin America, Andean	4.51	5.6
Latin America, Central	19.54	6.1
Latin America, Southern	8.74	7.0
Latin America, Tropical	19.23	5.5
North Africa / Middle East	31.11	3.7
Sub-Saharan Africa, Central	3.93	1.8
Sub-Saharan Africa, East	16.03	2.3
Sub-Saharan Africa, Southern	4.66	2.1
Sub-Saharan Africa, West	15.33	1.2

The foregoing has been a build-up for the following review of the various studies involving different types of anesthesia in use for operations and procedures, and their effects on the brain to substantiate the hypothesis. In many cases, their findings have been quoted for accuracy. There is an assumption that anesthesia used for required surgeries have been used equally (based on statistics) throughout the various GBD regions.

In<sup>[24]</sup>, POCD was discovered in elderly patients (over 60 years) who underwent elective surgery for distal or gastrectomy under general anesthesia. The patients were arbitrarily divided into two groups, one given intravenous remifentanyl, and second with epidural ropivacaine.

In<sup>[25]</sup>, changes of learning and memory was studied in aged rats after isoflurane inhalational anesthesia correlated with hippocampal acetylcholine level. The results showed that isoflurane inhalational anesthesia may interfere with learning and memory in aged rats.

In<sup>[26]</sup>, an assessment study was made of the emergence of AD following coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA). "These results suggest that patients undergoing CABG surgery were at increased risk for the emergence of AD than those undergoing PTCA. These data support the hypothesis that CABG surgery is associated with a reduced neuronal reserve in an aging population." CABG surgery requires general anesthesia, whereas PTCA usually does not.

Intravenous and inhalation anesthesia are often used in the operations and medical procedures. Recovery of cognitive function in elderly patients after surgery has received increased attention. In<sup>[39]</sup>, the authors compared recovery of cognitive function in patients after different anesthesia techniques, and researched into which technique is safer. The authors also explored association between apolipoprotein E4 and postoperative cognitive dysfunction in patients undergoing general anesthesia. "There was a strong association between the apolipoprotein E  $\epsilon$ 4 and postoperative cognitive dysfunction in elderly patients undergoing inhalation anesthetics"<sup>[39]</sup>. The epsilon4 allele of the apolipoprotein E gene has been shown as a risk factor for AD, poor consequence after cerebral injury, and accelerated cognitive deterioration with normal aging, as stated in the background literature of<sup>[40]</sup>.

In<sup>[41]</sup>, "patients with silent brain infarction (SBI) were ranked at moderate risk of neurological complications after coronaryartery bypass grafting (CABG) between control and symptomatic brain infarction (BI). Increased age, renal dysfunction, and preoperative cognitive impairment appeared to be strongly associated with SBI." CABG is normally performed with the administration of general anesthesia.

In<sup>[42]</sup>, "when subjected to isoflurane/nitrous oxide anesthesia, aged rats demonstrated anesthesia-induced spatial learning impairments". A potential therapeutic intervention for anesthesia associated cognitive deficits is discussed.

In<sup>[43]</sup>, "the results suggest to the investigators that isoflurane increases inflammatory cytokine expression and causes cell injury in the hippocampus, which may contribute to isoflurane-induced cognitive impairment in rats".

In<sup>[44]</sup>, the study suggested that the serum levels of pro-inflammatory markers IL-6 and S-100b protein increase after general anaesthesia in total hip-replacement, and such increases may be associated with the occurrence of POCD.

In<sup>[45]</sup>, the researchers found that "surgical patients, during the first follow-up interval (5-9 months), but not subsequently, had increased rates of atrophy for cortical gray matter and hippocampus, and lateral ventricle enlargement, as compared with nonsurgical controls. A composite score of five cognitive tests during this interval showed reduced performance for surgical patients with mild cognitive impairment".

## DISCUSSION AND CONCLUSION

Most published literature on the subject show that elderly patients after surgery experienced an increased rate of brain atrophy during the initial evaluation interval, a time associated with enhanced risk for POCD.

Numerous animal studies have suggested that inhalational anesthetics may change cognitive function via  $\beta$ -amyloid accumulation, modified neurotransmission, synaptic changes and dysregulated calcium homeostasis. Other factors like neuroinflammation and pro-inflammatory cytokines may also play a role. Furthermore, isoflurane inhalational anesthesia may impede learning and memory in aged rats. Additionally, others have found that AD is linked with disruption of the brain's ability to normally handle the  $\beta$ -amyloid.

Research support the hypothesis that CABG surgery is associated with a reduced neuronal reserve in an aging population. CABG surgery requires general anesthesia whereas PTCA usually does not.

There was a significant link between the apolipoprotein E  $\epsilon$ 4 and POCD in elderly patients using inhalation anesthetics. The epsilon4 allele of the apolipoprotein E gene has been shown as a risk factor for AD, poor consequence after cerebral injury, and accelerated cognitive deterioration with normal aging.

The popularity of plastic surgery (hence use of anesthesia) is well known in many Latin American countries. Because plastic surgery is so prevalent in Latin America (up to 70% of middle/upper-class women in some Latin American cities have had at least one cosmetic procedure<sup>[46]</sup>), multiple exposures to anesthesia is a given fact. The cumulative effects of the potent anesthesia used could contribute to the reduction of the neuronal reserve, hence becoming a risk factor for dementia.

Egg yolk is a leading source for choline, which has been proven to boost brainpower by speeding up the sending of signals to nerve cells in the brain<sup>[47]</sup>. Deficiencies of folate and vitamin B<sub>12</sub> are of interest given their consequences: anaemia, raised homocysteine levels, increased risk of stroke and ischaemic heart disease<sup>[11]</sup>. Vitamin B<sub>12</sub> deficiency is common in Venezuela and Cuba (Latin America)<sup>[48,49,50]</sup>. However, dementia associated with deficiencies is treatable.

The use of anesthesia for optional medical operations, tests and procedures has been in place for a long time in the Caribbean and Southeast Asia. It is assumed that anesthesia used for required surgeries have been used equally (based on statistics) throughout the whole world.

The sub-Saharan countries of Africa, the use of optional plastic surgeries, optional liposuctions, optional medical tests and procedures, e.g. colonoscopy, MRI's, is not common.

The current paper has shown the perspective that the larger incidences of AD and dementia in North America (High Income), Caribbean, Latin America, Western Europe, Asia Pacific (High Income), Southeast Asia, Australasia as compared to the less developed nations of the sub-Saharan region, are probably due to the increased use of anesthesia for C-section childbirths, optional plastic surgeries, optional liposuctions, optional medical tests and procedures, e.g. colonoscopy, MRI's in the former.

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