Re: Error on Page 250 in Acta Arithmetica 148 (2011), 225-256

Acta Arithmetica <actarith@amu.edu.pl>
Thu 10/02/2022 8:24 PM
To:

- John Ting <jycting@hotmail.com>

Cc:

- Timothy Trudgian <t.trudgian@adfa.edu.au>

Dear Professor Ting,

Thank you for your letter. I understand that you are confused by the fact that two research papers contradict each other by giving different values for the same quantity.

If you look at the first three sentences of Section 7.3 in T. Trudgian's paper, it is clear that the author is referring to known previous computations. He has not repeated these computations and he is not pointing to any error therein. Therefore the discrepancy that you mention is clearly due to a typo in T. Trudgian's paper. For your information, I contacted the author and he confirms that.

While it is regrettable that the value in that paper is incorrect, the Editor does not feel that it should lead to misunderstandings, unless someone uses that value for something. However, this should not be done without consulting the source works, precisely because such a typo is quite possible. For this reason we are not going to ask the author for an erratum.

Yours sincerely,
Maciej Radziejewski
Secretary of Acta Arithmetica

--- Original message ---
Dear Editorial Board of Acta Arithmetica,

As per email below, I think there is an error on page 250 in the paper by Timothy Trudgian "On the success and failure of Gram's Law and the Rosser Rule", Acta Arithmetica 148 (2011), 225-256. He wrote [sic] "7.3 The failure of Rosser's Rule. The first exception to the Rosser Rule is at the 13, 999, 825th Gram point. This corresponds to a height t ~ 5, 346, 000 which falls outside the calculations of Rosser et al." This should be "....the 13, 999, 525th Gram point....."

I also have a few other questions as outlined in my email below. It > would be fantastic if you can answer them as well. Many thanks.

Kind regards,
John Ting

From: John Ting
Sent: Friday, 21 January 2022 1:19 PM
To: trudgian@maths.ox.ac.uk <trudgian@maths.ox.ac.uk>; t.trudgian@adfa.edu.au <t.trudgian@adfa.edu.au>; Richard.Brent@rpbrent.com <Richard.Brent@rpbrent.com>
Cc: tom@opertech.com <tom@opertech.com>; rgwv@rgwv.com <rgwv@rgwv.com>; noe@sspectra.com <noe@sspectra.com>; anthony.d.forbes@googlemail.com <anthony.d.forbes@googlemail.com>; njasloane@gmail.com <njasloane@gmail.com>; charles@crg4.com

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Subject: Is 13999525 or 13999825 correct for the first exception to the Rosser Rule, etc?
Dear Richard Brent / Timothy Trudgian (Cc: Neil / Charles, etc from OEIS),

I refer to page 250 of article by Timothy Trudgian "On the success and failure of Gram's Law and the Rosser Rule", Acta Arithmetica 148 (2011), 225-256. He wrote [sic] "*7.3 The failure of Rosser's Rule. *The first exception to the Rosser Rule is at the 13, 999, 825th Gram point. This corresponds to a height t ~ 5, 346, 000 which falls outside the calculations of Rosser /et al/."

Charles R Greathouse IV, Sep 17 2012, author of A216700
https://oeis.org/A216700 <https://oeis.org/A216700> "Violations of Rosser's rule: numbers n such that the Gram block [g(n), g(n+k)) contains fewer than k points t such that Z(t) = 0, where Z(t) is the Riemann-Siegel Z-function." depict 13999525, 30783329, 30930927, 37592215, 40870156, 43628107, 46082042, 46875667, 49624541, 50799238, 55221454, 56948780, 60515663, 61331766, 69784844, 75052114, 79545241, 79652248, 83088043, 83689523, 85348958, 86513820, 87947597...

"On the zeros of the Riemann zeta function in the critical strip" by Author: Richard P. Brent, Journal: Math. Comp. 33 (1979), 1361-1372, DOI: https://doi.org/10.1090/S0025-5718-1979-0537983-2 <https://doi.org/10.1090/S0025-5718-1979-0537983-2> stated in Table 3 (page 1369) this value for the first exception to the Rosser Rule to be 13999525.

Page 253, Trudgian wrote "Theorem 7.7. For sufficiently large T there is a positive proportion of Gram blocks between T and 2T which contain two fewer zeroes of ζ(s) than their length." Here, "zeroes" refer to nontrivial zeros in this article.

Question 1: I seek definite answer on whether13999525 in OEIS by Greathouse IV or13999825 in Acta Arithmetica by Trudgian is correct to represent the first exception to the Rosser Rule?

Question 2: In regards to Gram's Law [for presence of exactly one zero in the interval between two consecutive Gram points] / Weak Gram Law [for presence of an odd zero in the interval between two consecutive Gram points] and Rosser's Rule / Weak Rosser Rule; I wonder whether it is mathematically possible for more SIMULTANEOUSLY existing theorems such as (i) "For sufficiently large T there is a positive proportion of Gram blocks between T and 2T which contain ONE fewer [or ONE greater] zeroes of ζ(s) than their length?" and (ii) "For sufficiently large T there is a positive proportion of Gram blocks between T and 2T which contain TWO greater zeroes of ζ(s) than their length?"

Thanks for your answers.

Kind regards,
John Ting
Author of A228186 (August 15, 2013)

Useful Preliminary Notes from Dr John Ting (Student ID 617104) 14 May 2022:

Case study on Dementia and Older Persons: Mr Paul and Mrs Rita Marshall have lived in a small rural town in New South Wales for all their lives. Paul is 82 years old, and Rita is 78 years old. They are both Aboriginal Australians. They have three children, but their children live in other states of Australia.

Paul is able to undertake most activities of daily living, but has type two diabetes since the age of 32, with comorbidities of kidney disease and cardiovascular disease. In the past, Paul has enjoyed walking for at least an hour a day and lawn bowls (with Rita), although he admits the lawn bowls in the past two years has been basically about going to the club to enjoy other people's company. Recently, he has developed a loss of hearing and fallen down the stairs. Paul hurt his foot, but his wound in his foot doesn't seem to be healing and limits his walking. He finds it increasingly harder to keep up with everyday tasks and his social activities due to the difficulty in walking and his limited hearing. His wife Rita seems able to keep her normal daily life, but she is not social. In the past year or so though she has been experiencing issues with her memory and two months ago was diagnosed with Alzheimer's disease. Up until that point she was engaged in lawn bowls and would drive to the supermarket to shop. Since the diagnosis she has stopped going out and has surrendered her driving licence. She does not want anyone to know she has a diagnosis of dementia. Paul and Rita have not told their children about their health issues. Paul and Rita are struggling with most of the household tasks and grocery shopping. In addition to experiencing some health challenges, the couple are having a lot of trouble maintaining their large house block and the house is in need of a thorough clean. They live in a two-storey house, but Paul finds it really hard to take the stairs. Paul now wonders how he is able to manage the house and look after Rita and himself. Their neighbours notice that Paul and Rita need urgent help and support from services.

1. The term 'Aboriginal and Torres Strait Islander peoples' as Australia's First Nations peoples is hereafter referred to with respect as Aboriginal peoples. Aboriginal peoples could have one of >250 Aboriginal linguistically diverse languages including 800 dialects. Older Australian people and older Aboriginal peoples are, respectively, defined as age over 65 and age over 50. An Aboriginal elder is an identified and respected male or female person of any age within the community who has the trust, knowledge and understanding of Aboriginal culture and has permission to speak about it. Multi-Purpose Services providing combined health and aged care services would be established in small rural towns [classified as remote area] whereby residential aged care service is unlikely to be available. Flexible aged care places allocated to Multi-Purpose Services providers are designated as either home care or residential aged care (high care or low care) including respite care. An Aged Care Assessment Program conducted by My Aged Care Regional Assessment Services [instead of Aged Care Assessment Team] is required for eligible people who needs approval for using Government-funded services of nursing home (aged care home), home care, residential aged care, transition care and/or respite care (Department of Health, 2018). From 1 July 2019, the new Aged Care Quality Standards will apply to all aged care services including residential care, home care and short-term restorative care, as well as services under National Aboriginal and Torres Strait Islander Flexible Aged Care Program and Commonwealth Home Support Programme.
2. Standard One in the Australian aged care quality standards refer to "Consumer dignity and choice" whereby consumers of chosen organizations are provided with various service types. The organisation statements include having a culture of inclusion and respect for consumers; supporting consumers to exercise choice and independence; and respecting consumers' privacy. This foundation standard reflects six requirements to be demonstrated by the organization: (1) Each consumer is treated with dignity and respect, with their identity, culture and diversity valued; (2) Care and services are culturally safe; (3) Each consumer is supported to exercise choice and independence, including to (i) make decisions about their own care and the way care and services are delivered; (ii) make decisions about when family, friends, carers or others should be involved in their care; (iii) communicate their decisions,

and (iv) make connections with others and maintain relationships of choice, including intimate relationships; (4) Each consumer is supported to take risks to enable them to live the best life they can; (5) Information provided to each consumer is current, accurate and timely, and communicated in a way that is clear, easy to understand and enables them to exercise choice; and (6) Each consumer's privacy is respected and personal information kept confidential (Aged Care Quality and Safety Commission, 2019).

3. According to Australian Institute of Health and Welfare (AIHW) in 2018, after adjusting for differences in age structures between the two populations, the incidence rates of Type 1 Diabetes were similar among Aboriginal peoples and non-Indigenous Australians; viz, 12 and 11 cases per 100,000 people respectively. After adjusting for the same; diagnosis of Type 2 Diabetes would be consistent with the finding in 2017–18 that there was a rate of 8,500 per 100,000 population with difference in rates between Aboriginal peoples and non-Indigenous Australians greater for females than males - 5.6 times as high for females and 3.2 times as high for males. Rate of diabetes hospitalisations among Aboriginal peoples was 4.3 times higher than rate for non-Indigenous Australians (AIHW, 2020a). The 2018–19 Health Survey indicated 13% of Aboriginal adults aged 18 and over self-reported as having diabetes or high sugar levels whereby this equates to 2.8 times rate of non-Indigenous adults. Aboriginal adults living in remote areas would report a higher rate of diabetes or high sugar levels (24%) than those in non-remote areas (15%) (AIHW, 2020b). Dementia prevalence rates in Aboriginal peoples are about 3–5 times as high as rates for Australia overall (AIHW, 2021).

Q1: (330 words)

Youth-onset Type 2 Diabetes is defined as diagnosis before age 25. Its prevalence is globally increasing because of higher risks in marginalised, socioeconomically vulnerable (with high unemployment rate, etc), First Nations communities [including Aboriginal peoples in Australia], and foetal exposures from mother's hyperglycaemia and obesity. A new diabetic diagnosis could potentially result in more affected future offspring. Although not provided with 82-year-old-Aboriginal-person Paul's body mass index (BMI) and family history of diabetes [which is likely positive in first or second degree relatives] relevant to early diabetic diagnosis at age 32 [*albeit* not as Youth-onset Type 2 diabetes]; all these elements would increase Paul's chance of developing other comorbidities/cardiometabolic conditions cardiovascular disease and/or overweight/obesity at an even younger age [together with early onset of kidney disease as known complication of diabetes]. Paul's three inter-state children (offspring) as young Aboriginal peoples [defined as age <50 instead <65 for non-Indigenous Australians], if diagnosed with Type 2 Diabetes, will also develop other cardiometabolic conditions at even younger age. Thus, there is high prevalence of Type 2 Diabetes among Aboriginal families as well as in young Aboriginal women reporting at least one pregnancy (Titmuss et al., 2022).

Paul's childhood history and education level are unknown. Low levels of education, ageing population, overweight/obesity as BMI >22kg/m^2 (with poor diet and low physical activity), and psychological distress from forced removal as children are contributing factors that increase risk of Type 2 Diabetes in Aboriginal peoples (Reeve et al., 2014). Genetic inheritance or epigenetic factors are also downstream/proximal determinants of diabetes (Anderson et al., 2015). This relates to metabolism of Aboriginal peoples having been adapted to be efficient hunter-gatherers that is crucial for successful traditional lifestyle. With fewer Aboriginal peoples living traditional lifestyle being exposed to Western diet with low-fibre foods rich in fat and/or sugar, excessive alcohol consumption and smoking cigarettes with adopting sedentary lifestyle; their usually-efficient metabolism is now disadvantaged with high rates of developing obesity, impaired glucose tolerance, hypertension, hyperlipidaemia and elevated blood insulin level.

Q2: (440 words)

Under 'Closing the Gap' initiative for Aboriginal peoples with chronic medical conditions present ≥ 6 months, Paul would benefit from referral to culturally-competent allied health professionals for 10 [instead of 5 for non-Indigenous Australians] consultations each calendar year [via GP Chronic Disease Management Plan] with

further access to additional group services for diabetes education, exercise physiology and dietetics to educate on diabetic diet and targeted aerobic/anaerobic physical activities which confer optimal diabetic control (Services Australia, 2021).

Progressive disabilities in Paul diminish daily tasks completion and social activities. Over past two years, Paul has reduced his physical activity walking ≥ 1 hour/day plus lawn bowls (with Rita) to just enjoying people's company at club; and recent loss of hearing and fallen down stairs resulting in a hurt foot with a wound [and walking limitation leading to struggles with household tasks, grocery shopping, climbing stairs in two-storey home, house cleaning and large house block maintenance]. Guided by Ride & Burrow (2022) and Titmuss et al. (2022), providing home care with targeted health care could include following four types of services whereby their implementations should reduce morbidity, mortality and health burden stemming from chronic non-communicable disease Type 2 Diabetes in Aboriginal peoples like Paul:

(1) Consulting Allied Health professionals - audiologist [located at out-of-town regional clinics or community shops] for hearing aids to combat Paul's hearing loss (thus improving his social activities); regular podiatrist visits (to treat/check for new diabetic foot ulcers from diabetic neuropathy); regular follow-ups by GP with referrals for annual optometrist/ophthalmologist to supply reading glasses, treat diabetic retinopathy; cardiologist, renal physician to optimally manage cardiovascular disease, chronic kidney disease; diabetic educator, dietitian and endocrinologist to treat diabetes; home visits from occupational therapist to minimize fall risk (e.g. by installing shower grab rails) and physiotherapist to optimize Paul's mobility and balance (e.g. walking aids and assessing safety in climbing stairs with possible need to install suitable home stairlift system funded by National Disability Insurance Scheme); and engaging essential service provided by Meals on Wheels Australia (2021) that delivers meals to Paul and Rita unable to cook or shop for themselves or living with illness or disability thus playing a vital role in early intervention and health prevention enabling them to live longer and happily at home.
(2) Regular Clinical Nursing home visits by professional clinically-trained staffs to supervise his diabetic/cardiac medications, and dress foot wound.
(3) Regular Home and Garden service to maintain Paul's large house block, and Domestic assistance to clean the house.
(4) Social Support provided by social worker that would recruits appropriately-trained Home Care Workers to help household tasks, grocery shopping and keep Paul and Rita socially engaged.

<u>Q3: (440 words)</u>

Home care services provided by Multi-Purpose Services in small rural town include personal care services, social support, continence management, and assistance with activities of daily living. In contrast to Home Care Packages Program, Paul and Rita as clients while living independently at home do not use Consumer-directed care model or need to have individual budget (Department of Health, 2020). Public stigma, self-stigma and/or institutional stigma from dementia could co-exist in society. Two types of dementia-related stigma *that intersect with ageism* Paul and/or Rita face (Richeson & Shelton, 2006; Kim et al., 2019) are:

(1) "People with dementia do not understand their reality as it actually is": Diagnosed with Alzheimer's disease 2 months ago [presenting as memory problems for ~12 months], 78-year-old Rita may assume/***understand*** her realities to be different, making it hard for her as [possible] Aboriginal elder living with dementia to try relate to others. Consequently, although she seems able to keep her normal daily life, she is not social. As [possible] Aboriginal elder and now also as carer for Rita, Paul's own progressive disabilities make this role more challenging and intermittent ***respite care*** provided for her will benefit him. They would both benefit from coordinated care available from Aboriginal Health Service [aided by *Aboriginal Health Worker* using *positive languages for ageing and dementia*] providing, for instance, referral to culturally-sensitive, -safe and -competent allied health professionals

for person-centred care that respect special Aboriginal elder status (Mlcek, McMillan & McMillan, 2016; Claphan & Duncan, 2017).

(2) "If you have dementia your personality will change": Dementia stages are Early Dementia, Moderate Dementia and Advanced Dementia. Rita may ***perceive*** her memory problems as changes that will be misunderstood, regarded only as part of Alzheimer's disease, and not who she is as [possible] Aboriginal elder - an ***attitude*** that is regarded by her as a form of self-stigma possibly resulting in ***discrimination, social exclusion, disempowerment and decreased confidence to seek help which impacts on diagnosis assessment and support***. Thus, despite being in Early Dementia, Rita stopped engaging in lawn bowls, going out, driving to supermarket; surrendered her driving licence; and does not want anyone to know her dementia diagnosis. Health care workers must reduce institutional dementia-related stigma [plus combat discriminations sexism/ageism/elder abuse at micro/meso/macro levels] while respecting Rita's wish for her diagnosis to remain confidential by, example, using National Dementia Helpline and addressing fear (public stigma) surrounding notion of dementia through community awareness and understanding of dementia-related illnesses. Although Paul and Rita have not told their children about their respective health problems, they should be encouraged to do so to elicit family support and family connectedness in accordance with Aboriginal culture and identity.

Q4: (440 words)

Person-centred care [depicted in terms of *family, kinship, community and country* unique to Aboriginal culture and identity (Mlcek, McMillan & McMillan, 2016)] entails forming partnerships with patients and family carers to tailor clinical care according to life circumstances and personal preferences. These are achieved by offering knowledge, skills and access to supports that maximize quality of life through implementation of person-centred rather than disease-centred [relevant] diabetic or dementia cares which are globally recognized as priorities that are viewed through six domains constituting this care model: fostering a healing relationship, exchanging information, addressing emotions, managing uncertainty, sharing decisions, and enabling self-management (Marulappa et al., 2022).

Paul and Rita are ***consumers*** of ***organization/service provider*** Meals on Wheels Australia (M-on-W) providing ***service type*** home meals delivery. Standard One in Australian aged care quality standards reflect six requirements to be demonstrated by M-on-W (Aged Care Quality and Safety Commission, 2019):

1. Employees of M-on-W should communicate respectfully while recognising/respecting individuality in all aspects of dignified/respectful care and services when delivering home meals.
2. M-on-W should deliver responsive, inclusive, culturally-sensitive, -safe and -competent care and services that are inclusive and do not discriminate against them who could also be Aboriginal elders in their community (Nguyen, 2008). Example, referring to them as Uncle and Aunty only when given permission; and using positive languages for ageing and dementia help meet social, cultural, language, religious, spiritual, psychological and/or medical needs.
3. M-on-W should let them (i) make decisions about the way care and services are delivered e.g. days of the week home meals are required; (ii) make decisions when family, friends, carers or others be involved in their care e.g. obtaining input from offspring about home meals; (iii) communicate their decisions about home meals [aided by e.g. *Aboriginal Health Worker*]; (iv) make connections with others and maintain relationships of choice including intimate relationships e.g. deciding to tell offspring about their respective health problems.
4. M-on-W should provide regular/appropriate home meals so they can live independently at home for as long as possible.
5. M-on-W should offer choice of incorporating dietitian-approved traditional *Aboriginal and Torres Strait Islander Foods* into Paul's meals that comply with healthy diabetic diet.
6. Employees of M-on-W should respect Rita's confidentiality in not wanting anyone to know her dementia diagnosis [while complying with Aged Care Charter of Rights, agreement with consumer and

other responsibilities under Aged Care Act 1997 as well as obligations under competition and consumer law]. Privacy Act 1988 and Aged Care Act 1997 both permit disclosure and sharing of health information if this information is necessary to provide health services to Paul and Rita between aged care services and Aboriginal Health Service.

Reference

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CAD119 Discussion board post A

Student: **John Ting (Student ID: 617104)**

Unit Coordinator: Dr. Jenna Ziebell (Email: wicking.CAD119@utas.edu.au)

Dated submitted: 24 July 2021 **AT1A Discussion Board (first post) for CAD 119 Chronicity and Multimorbidity**
Word count: 250 (for Thread), 250 (for Reply)

I certify Assignment 1A (#SEA1) is my own work, based on my personal study and/or research and that I have acknowledged all material and sources used in its preparation, whether they be books, articles, reports, lecture notes, and any other kind of document, electronic or personal communication. I also certify that this assignment/report has not previously been submitted for assessment in any other unit, except where specific permission has been granted from all unit coordinators involved, or at any other time in this unit, and that I have not copied in part or whole or otherwise plagiarised the work of other students and/or persons.

In the textbox below please paste your thread.

Biological ageing can be defined as progressive decline in physical and mental capacity due to cumulative damage at cellular level over time. It is accelerated by environmental factors such as smoking and unhealthy diet; and to a lesser extent by physiological traits or genetic factors such as telomere attrition (Aubert G & Lansdorp PM, 2008), cellular senescence, mitochondrial dysfunction, genomic instability, stem cell exhaustion, and epigenetic alterations. Physical ageing is physiological ageing occurring across all body systems resulting in decreased ability to maintain homeostasis in response to stress. Examples: Cardiovascular system – Diastolic heart failure from left ventricle hypertrophy caused by hypertension; Musculoskeletal system – skeletal muscle atrophy and osteoporosis related height loss with ageing; Gastrointestinal tract – reduced ability to chew food with ageing due to losing teeth; Genitourinary system – aged related decline in renal function; Central Nervous System – aged related brain atrophy of around 20% brain volume by age 85 years. World Health Organization (2020) defines healthy ageing as 'the process of developing and maintaining the functional ability that enables wellbeing in older age'. Functional ability is the capabilities that allow people to meet biopsychosocial needs such as learn, grow and make decisions; be mobile; build and maintain relationships; and contribute to society. Functional ability consists of intrinsic capacity (mental and physical) of a person, relevant environmental characteristics and the interaction between them. Biomedical standards compare an individual to an expected path of decline. If a person does better or last longer than expected, he or she is ageing well (successfully).

Reference

Aubert G & Lansdorp PM, 2008, 'Telomeres and Aging', *Physiol Rev* 88: 557–579. Retrieved from doi:10.1152/physrev.00026.2007

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In the textbox below please paste your reply to another student which details the similarities and differences in your ideas.

Dear Masami,

Regarding your posting on "What is ageing?" on 20 July 2021, it gave me a good sense of understanding on this question and various aspects of ageing well. You have provided four good references to support your posting. Usefully discussed using biopsychosocial modelling, ageing is a dynamic progressive decline in physical and mental capacity over time (Morrison J, et al., 2018). You have provided the healthy ageing definition by World Health Organization (2015) as the ability to maintain and improve level of functional ability in the face of adversity – this definition is conceptually similar to that provided by me whereby healthy ageing could also be usefully visualized as biological or physiological age being less than chronological age. Regarding ageing well, you mentioned its physiological, social, and well-being facets. This is intuitively akin to biopsychosocial facets which can generally be achieved with healthy diet, regular physical and cognitive exercise in healthy ageing. There are increased individual, community and society health costs involved with pathological (as opposed to normal) ageing with increased incidence of injuries, physical or neurological illnesses. Definitions and theoretical understanding on ageing can vary widely. As useful illustration, you mentioned the approximate 20% of brain volume loss by the age of 85 years old with uniform white matter loss but variable gray matter loss. You quoted the four elements of cellular damages that involve mitochondrial changes, the accumulation of aberrant protein in the cytosol, oxidative stress caused by free radical and somatic mutation (Adam JM & White M, 2004).

Reference:

Morrison J, et al. (eds), 2018, Chapter 8 'Adult & Aging Brain', in *Brain Facts: A primer on the brain and nervous system*, 8th ed, 53 – 58, Society for Neuroscience

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Kind regards,

John Ting

Assignment 2: Short answers on Cardiovascular Disease for CAD119 by John Ting (Student ID 617104). Unit Coordinator: Dr. Jenna Ziebell (Email: wicking.CAD119@utas.edu.au)

Word counts = 991. Date of submission: Friday 20 August 2021

Q1: What is the disease? Describe the disease and the normal function of system(s) of the body affected by the disease. Q2 What body system(s) does it affect? Describe how chronic illness changes the body's systems. Q3 What affect chronic disease has on the individual and ageing? Explanation of risk and the impact of chronic disease on the individual.

I certify Assignment 2 is my own work, based on my personal study and/or research and that I have acknowledged all material and sources used in its preparation, whether they be books, articles, reports, lecture notes, and any other kind of document, electronic or personal communication. I also certify that this assignment/report has not previously been submitted for assessment in any other unit, except where specific permission has been granted from all unit coordinators involved, or at any other time in this unit, and that I have not copied in part or whole or otherwise plagiarised the work of other students and/or persons.

Q1-Answers

Cardiovascular system (CVS) consists of heart as cardiac muscle pump containing heart valves and cardiac conduction system, and cardiac (coronary) and extracardiac blood vessels [arteries, capillaries and veins]. CVS combines with respiratory system (RS) as [1]cardiorespiratory system.

Functions of CVS:

• oxygen (O2) and nutrients delivery to / carbon dioxide (CO2) and metabolites removal from tissues

• blood supply to organs of excretion of waste product urea by kidneys and faeces by large intestine; and organs of absorption, digestion and metabolism of food/nutrients by stomach, small intestine, liver and pancreas.

• transport white blood cells to combat infection, inflammation, and injury

Cardiovascular diseases (CVD) are a group of disorders of CVS:

• ischemic heart disease (IHD)

• cerebrovascular disease

• peripheral arterial disease (PVD)

• valvular heart disease

• thrombo-embolic (TE) disease

• Heart failure (HF)

• cardiac conduction disease

• congenital heart disease in newborns such as Atrial Septal Defect and Ventricular Septal Defect.

Q2-Answers

Depicted with clinical symptoms and signs (S&S); CVD affect CVS itself, RS, nervous system (NS), and all other body systems to various degree:

• IHD (coronary heart disease) caused by atherosclerosis of coronary artery resulting in angina and myocardial infarct with common S&S chest pain radiating to arms and neck.

• cerebrovascular disease caused by atherosclerotic arteries supplying brain causing transient ischemic attacks, cerebrovascular accident (ischemic stroke due to emboli from atrial thrombus associated with atrial fibrillation and haemorrhagic stroke due to hypertension and/or rupture of brain aneurysm), vascular dementia consisting mainly Multi-infarct dementia and Binswanger's disease due to stroke (caused by hypertension in 50% of cases), small vessel disease, or a mixture of the two. Arising neurological disabilities include S&S hemiplegia and deficits in cognitive functions (memory, language, thinking or judgment).

• PVD due to atherosclerotic arteries supplying arms or legs commonly causing leg claudication with S&S pallor, pain, paraesthesia and pulselessness.

• valvular heart disease e.g. rheumatic heart disease from streptococcal rheumatic fever resulting in mitral and aortic stenosis or regurgitation. More common in indigenous Australian population, S&S consist of heart murmurs and HF with severe disease.

• TE disease - deep vein thrombosis in legs that could dislodge and move to lungs as pulmonary embolus with S&S calf swelling, pleuritic chest pain and breathlessness.

• HF as Right HF (RHF) and left HF (LHF). Cor Pulmonale is pulmonary CVD causing RHF usually secondary to chronic pulmonary artery hypertension. Two types of LHF are HF with reduced [2]ejection fraction (HFrEF) termed systolic failure; and HF with preserved ejection fraction (HFpEF) termed diastolic failure or diastolic dysfunction. S&S of HF include peripheral oedema, fatigue, orthopnoea, paroxysmal nocturnal dyspnoea, raised jugular venous pressure, and breathlessness from pulmonary oedema. Excessive alcohol intake could result in alcohol-related dementia and alcohol cardiomyopathy causing HF.

• cardiac conduction disease as bradycardia, tachycardia and irregular types of arrhythmias. Clinical S&S fast palpitations, chest pain, fainting or slow pulse.

Q3-Answers

'Ageing is the predominant risk factor for most diseases and conditions that limit health span' (Franceschi et al., 2018, p.2) including most chronic [non-communicable] diseases (MacNee, Rabinovich, & Choudhury, 2014, p. 1333). Franceschi et al. advocate accelerated ageing [in diseases] to be discussed in terms of frailty, sarcopenia, chronic obstructive pulmonary disease, cancer, neurodegenerative diseases of Alzheimer and Parkinson, and Down syndrome. *Normal healthy (physiological) ageing and abnormal accelerated (pathophysiological) ageing in diseases cause a spectrum of increasing (physical/structural) gross anatomical and cellular changes, and (pathophysiological) functional changes in all body systems*. These changes in CVS predispose an individual to develop CVD. Changes in structure and function of CVS with ageing include:

• atherosclerosis caused by generalized endothelial dysfunction of arteries.

• Age associated vascular defects from slower/incomplete vascular repair.

• Increased thickness/stiffness of arterial walls causing LV hypertrophy/diastolic HF with greater demands on coronary circulation.

• Loss of Windkessel effect (elastic recoil) in arteries.

• Heart valves calcification/stiffening.

• Fibre and fat deposits around cardiac myocytes potentially causing systolic HF.

• Conduction system degeneration with decrease in (maximum) heart rate and/or arrhythmias.

Clinical indicators of age-related changes in CVS include increased systolic blood pressure (BP) due to the heart pumping harder to push blood through stiffened arterial walls and decreased diastolic BP due to loss of elastic recoil in arteries.

CVD is leading global cause of approximately 17.9 million premature death each year (WHO, 2021). In 2015–16, an estimated 8.9% [$10.4 billion] of total disease expenditure in Australia was attributed to CVD

(AIHW, 2019). The 'disease burden' can be measured in disability-adjusted life years (DALYs) where a DALY reflects one year of 'healthy' life lost. In 2018, coronary heart disease contributed 6.3% out of 13% of total disease burden (DALYs) caused by CVD that occurs mainly in the ≥75-year-old (AIHW, 2021).

Age, gender, ethnicity, and (genetic) family history are non-modifiable cardiac risk factors. Obesity, hypertension, hyperlipidaemia, smoking, diabetes, unhealthy diet and sedentary lifestyles (physical inactivity) are modifiable cardiac risk factors. We can conveniently discuss risk and impacts of CVD on individual using Biopsychosocial framework: Biology – pathophysiology of CVD with S&S; Psychology – anxiety and stress associated with CVD to individual; Social – health cost of managing CVD for individual, relatives and society.

Livingston et al. (2020) outline 12 modifiable risk factors accounting for ~40% of worldwide dementias: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution. Grouped together with **Body health** and **Mind health; Heart health** include treating hypertension, high cholesterol, Type 2 diabetes, obesity through regular check-ups for blood pressure, blood glucose levels and cholesterol, eating a healthy diet and stopping smoking (Dementia Australia, 2020). Adopting these three concepts could theoretically prevent/delay dementia as well as CVD since this action include **Heart health** which forms an essential tool in managing CVD.

Brief synopsis on Management: Key treatments for CVD include cardiac rehabilitation, adopting healthy life-style choices, prescribing appropriate medications as well as heart valve surgery, pacemaker, coronary angioplasty, coronary artery bypass graft surgery and carotid endarterectomy. COVID-19, pneumococcal and influenza vaccinations to prevent communicable diseases are crucial in elderly. Yearly flu shot reduce risk of dying from serious heart-related complications.

Footnotes

1. Right ventricle (RV) as part of pulmonary circuit pumps deoxygenated-with-higher-CO2-level blood to lungs which becomes oxygenated-with-lower-CO2-level blood [external respiration]. Left ventricle (LV) as part of systemic circuit pumps oxygenated-with-lower-CO2-level blood to rest of body whereby O2 diffuses from blood in systemic capillary to tissues and CO2 diffuses in opposite direction [internal respiration], thus enabling cellular respiration to happen.
2. In adult: Cardiac output (CO, 5 to 6 L/min) = Heart Rate (HR, 60 to 100 beats/min) X Stroke volume (SV, 50 to 100 ml). SV = end-diastolic volume (EDV, about 120 ml) minus end-systolic volume (ESV, about 50 ml). EF = SV/EDV X 100%. Normal LVEF = 50% to 70%. Borderline LVEF = 41% to 49%, HF = LVEF ≤ 40%.

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CAD119 Assignment 1B (Discussion board – second post)

Student: **John Ting (Student ID: 617104)** Unit Coordinator: Dr. Jenna Ziebell

Monday 4 October 2021 [REVISED on Friday 8/10/2021 after 4/10/2021 dateline for Attention: CAD119 Marking Team]. Word count: 250.

AT1B Discussion Board (second post - Reflection on ageing concepts) for CAD 119 Chronicity and Multimorbidity.

Criterion 1: Theoretical perspectives of ageing and the ageing process that incorporate **biological / sociological theories / concepts.**

Criterion 2: Translation of ageing concepts to the individual/society that demonstrates how **theory can be integrated at an individual or societal level.**

Criterion 1

'Ageing is the predominant risk factor for most diseases and conditions that limit health span' (Franceschi et al., 2018, p.2) including most chronic [non-communicable] diseases (MacNee, Rabinovich & Choudhury, 2014, p. 1333). Franceschi et al. advocate accelerated ageing [in chronic diseases] be discussed in terms of frailty, sarcopenia, chronic obstructive pulmonary disease, cancer[1], neurodegenerative diseases of Alzheimer and Parkinson, and Down syndrome. *Normal healthy (physiological) ageing[2] and abnormal accelerated (pathophysiological) ageing in diseases cause a spectrum of increasing (physical/structural) gross anatomical and (biological) cellular changes, and functional changes in all body systems*[3] *[to various degree]*. Changes in [example] cardiovascular system (CVS) predispose an individual to develop cardiovascular diseases (CVD). Common changes in structure/function of CVS with ageing include arterioslerosis (increased thickness/stiffness of arterial walls). Clinically, age-related changes manifest as increased systolic blood pressure (BP), decreased diastolic BP, and decrease in (maximum) heart rate and/or arrhythmias.

Criterion 2

Age, gender, ethnicity, and (genetic) family history are non-modifiable cardiac risk factors.

Obesity, hypertension, hyperlipidaemia, smoking, diabetes, unhealthy diet and sedentary lifestyles (physical inactivity) are modifiable cardiac risk factors.

Livingston et al. (2020) outline 12 modifiable risk factors accounting for ~40% of worldwide dementias: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution.

Treating hypertension, hyperlipidaemia, Type 2 diabetes, obesity, stopping smoking, being physically active, avoid excessive alcohol and adopting a healthy diet will result in *healthy heart*[4] and *healthy mind*[4] with beneficial impacts on individual, society and health care systems.

Footnotes

1 Cancer is a chronic [genetic] disease caused by certain [somatic or germline] changes to our genes [constituting our "Genetic system" – usefully regarded here as the "13th human physiological system"] that

control the way cells function, especially how they grow and divide. Lynn & Adamson (2006) have previously outlined the three typical trajectories followed by chronic progressive and eventually fatal illness in the elderly: (i) "Short period of evident decline" caused by mostly cancer; (ii) "Long term limitations with intermittent serious episodes" caused by mostly heart and lung failure; and (iii) "Prolonged dwindling" caused by mostly frailty and dementia.

2 *Healthy ageing* versus *ageing well*: Healthy ageing is defined as 'the process of developing and maintaining functional ability that enables wellbeing in older age' (World Health Organization, 2015, p. 28). Functional ability is the capabilities that allow people to meet biopsychosocial needs such as learn, grow and make decisions; be mobile; build and maintain relationships; and contribute to society. Functional ability consists of [intrinsic] mental and physical capacity of a person, relevant environmental characteristics and the interaction between them. Ageing well, successful ageing, positive ageing and ageing productively are concepts associated with healthy ageing (Sims, 2017). The concept of frailty is defined as accumulation of age- and health-related deficits across physical, psychological and social systems. The self-reported frailty index consists of 42 deficits including 19 comorbidities and 23 deficits related to independence and self-care. Frailty index is calculated as the proportion of items present divided by total number of surveyed items, expressed as a continuous variable between 0 and 1. Frailty is defined as frailty index >0.21. In patients with fibrotic interstitial lung disease, functional ageing was determined by frailty index and biological ageing by measurement of absolute telomere length (aTL) from peripheral blood leucocytes. The frailty index was strongly associated with quality of life, rate of hospitalisation, time to hospital discharge and mortality whereas aTL was not associated with most adverse health outcomes (Guler et al., 2020). 'Disability can be related to genetic disorders, illnesses, accidents, ageing, injuries or a combination of these factors' (AIHW, 2020, p. 9) resulting in different degrees of impairment, activity limitation and participation restriction. All kinds of impairment arise from birth or acquired through illness, accident, or ageing process, and includes cognitive impairment as well as physical, sensory and psychosocial disability. Thus, as social ageing [referring to ways by which society shape the meanings and experiences of ageing], an amputee due to accident or an elderly person with lots of age-related skin wrinkles [more than that expected for same chronological age] is often incorrectly deemed by the layperson to not be undergoing healthy ageing. However, based on multi-dimensional approach (Urtamo, Jyväkorpi & Strandberg, 2019), this person will likely be ageing well or undergo successful ageing when he or she adopts healthy lifestyle choices. Franceschi et al (2018) further differentiate (a) *successful ageing* to indicate slow-ageing trajectory without developing or postponing geriatric syndromes (GSs or initial clinical symptoms) / age-related diseases (ARDs) that occur in centenarians; (b) *normal ageing* with developing GSs; and (c) *accelerated ageing* with developing ARDs. Kuh (2019, p.2) regards health at any stage of life to depend on our ability to respond - to resist, compensate, adapt to, and recover from environmental challenges with these responses taking place over different time scales: homeostasis acting over a short time scale, developmental plasticity across life, and natural selection over generations. The nine hallmark denominators (López-Otín et al., 2013) of ageing purportedly occurring in all cell types are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Research suggest we could slow down or partially reverse healthy ageing in all body systems from cellular senescence using senolytic therapy (Sikora et al., 2021). Neuronal plasticity, defined

as morphological and functional changes at the level of neurons and dendritic spines [mainly as reduced dendrite diameter, reduced spine volume and loss of synapses], can be the hallmark of neuronal senescence occurring in healthy brain ageing. Recall of memories and learning is also enhanced if there is an increase in the strength of synaptic connections between neurons [termed as *long-term potentiation*]. On the gross anatomical level, the ageing brain shows minor regional atrophy manifested as shrinkage of cerebral cortex, hippocampus and entorhinal cortex with moderately enlarged ventricles. In particular, the cerebral cortex shows volume declines from 20 years of age approximately 0.1% per year; and the hippocampus volume remains stable until around 60 years after which there is a steep trajectory of volume loss approximately 0.3% per year (Fjell et al., 2014). In principle, these phenomena occurring in the brain should potentially be directly or indirectly susceptible to the effects of senolytic therapy and/or other anti-ageing agents.

3 We provide an alternative/innovative view of the ageing process [and diseases] for the layperson: Common knowledge definition of isolated system is either: (1) a physical system far removed from other systems such that it does not interact with them, or (2) a thermodynamic system enclosed by rigid immovable walls in which neither mass nor energy can pass through. Common terminology used in thermodynamics: (1) a closed system is enclosed by selective walls which energy can pass through as heat or work, but not matter; and (2) an open system has both matter and energy entering or exiting its walls [although it may have various kinds of impermeable walls in parts of its boundaries]. Entropy can be usefully interpreted as *degree of disorder or randomness* in the system. The three laws of thermodynamics:

The first law [also called Law of Conservation of Energy] states that energy cannot be created or destroyed in an isolated system.

The second law of thermodynamics states that entropy of an isolated system always increases.

The third law of thermodynamics states that entropy of a system approaches a constant value as temperature approaches absolute zero.

The concept of an open system was formalized within a framework that enable us to connect nonliving and living things on theory of organism, thermodynamics, and evolutionary theory. Living things can be usefully divided into (1) simple asexual acellular organisms such as viruses, viroids, and prions to (2) simple asexual (and unicellular) prokaryotic cells organisms such as Archaea and Bacteria to (3) complex sexual but can be asexual (usually multicellular but can be unicellular that all contain nucleus) organisms such as animals, plants, protists, fungi, algae, and protozoa. Then, open systems such as living human body (or any living organisms) will obey the second law of thermodynamics implying the inevitable temporal consequences of life and death: being born, mature while undergoing the ageing process, and dying.

There are six levels of organization in human body as living organism of increasing complexity: chemical (involving atoms, inorganic molecules and organic molecules such as amino acids, protein, sugar, lipids, DNA, etc) → cellular (contains organelles which are subcellular structures having one or more specific jobs to perform in the cell e.g. the nucleus is a membrane-bound organelle that contains the cell's chromosomes) → 4 tissue types (composed of groups of cells and materials to perform a particular function) → [generally taken to consist of about] 78 organs (structure composed of 2 or more types of tissues to perform specific functions) → system (composed of related organs with a common function whereby some organs e.g. pancreas with endocrine and exocrine functions can be part of more than 1 system) → organismal level of organization (all the different parts

of body functioning together as total organism). Telomere is a compound structure at the end of a chromosome [located in the nucleus] in which its length shortens with age. Lifestyle factors such as smoking, little or no physical activity, obesity, stress and exposure to pollution are likely to increase rate of telomere shortening, cancer risk, and speed of ageing. Ageing process [and diseases] will occur in all six levels of organization on the microscopic scale (cells) to macroscopic scale (tissues, organs and systems). Example, autoimmune destruction of endocrine function in pancreas will result in Type 1 Diabetes. Four types of tissue:

(I) Epithelial tissue, which covers body surfaces, lines hollow organs and cavities, and form glands.
(II) Connective tissue connects, support and protect body organs while distributing blood vessels to other tissues.
(III) Muscle tissue that contracts to produce movement and generate heat.
(IV) Nervous tissue that conducts nerve impulses (information) from one part of body to another.

Tissues group together to form many body organs including the vital body organs of brain, heart, lungs, kidney and liver. These vital organs together with other body organs such as stomach, gallbladder, appendix, small intestine, large intestine, spleen, thyroid, parathyroid, adrenal, ovaries and testicles together form the conveniently assigned 12 physiological systems which help keep our bodies function normally within homeostasis: (1) Integumentary [Skin] system, (2) Musculo-skeletal system, (3) Haematological-Biochemical blood system, (4) Immune-Lymphatic System, (5) Gastrointestinal system, (6) Nervous system [Central nervous system + Peripheral nervous system], (7) Endocrine system, (8) Cardiovascular system, (9) Renal [Kidney] system, (10) Genito-urinary [Reproductive] system, and (12) Special organs system [*vision* by the eye, *hearing and balance* by the ear which includes the auditory system and vestibular system, *smell* by the nose, *taste* by the tongue, and *touch*].

4 Type 2 Diabetes causing diabetic retinopathy with poor vision in an individual results in *decreased Quality of Life*, *decreased safety* (increased falls) and *increased chance of developing other conditions* such as CVD. *Biopsychosocial impacts* of dementia and CVD on individual: Biology – pathophysiology of dementia as "brain failure" [associated with structural, chemical, functional and neurocognitive changes in the brain] and CVD affecting heart, blood and blood vessels; Psychology – varying severity and deficits in *cognitive functions* (= thinking, moving, speaking [language], and memories) PLUS *higher order functions* (= personality, memories, reasoning, decision making skills [judgement] and problem-solving ability) AS WELL AS *physical functions* (mobility, bowel and bladder control essentially mediated by spinal cord through to brain) in a person living with [for instance] mild, moderate or severe stage of Alzheimer's disease, anxiety and stress associated with CVD to the individual person; and Social – health cost of managing dementia and CVD for individual, relatives and society e.g., in 2015–16, an estimated 8.9% [$10.4 billion] of total disease expenditure in Australia was attributed to CVD (AIHW, 2019) [such as atherosclerosis developing in coronary arteries causing angina and heart attack]. Dementia, often associated with coexisting multi-morbidities such as diabetes, is a progressive and terminal illness whereby there will be impacts not just on *individual* [e.g. growing number of individuals age > 65 requiring *rehabilitation (reablement or restorative care)* and *palliative care (including palliative approach and end-of-life care)*] but also on *society* [e.g. in dementia as *Years of life with disability* > *Years of life lost*] and *health care system* [e.g. disproportionate high health cost incurred by individuals age > 65 in managing complex health conditions and multimorbidity but which will ultimately lower overall health cost through reduction of "expensive" *potentially preventable hospitalizations*]. In its most prevalent form as Alzheimer's disease: (I) Pathological features ("cause and effect") involve (microscopic) *changes at cellular level* [that cause neurons to degenerate/die] will result in (macroscopic) *changes at systemic level* [that cause atrophy in various brain

regions]; and (II) Clinical features ("signs and symptoms") include *behavioural changes*, *cognitive changes and motor changes*.

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Student: **John Ting (Student ID: 617104)** Unit Coordinator: Dr. Jacqueline Leung

CAD101 Assessment Task 3: Discussion Board Part A [current posting]: Major clinical features (signs and symptoms) that occur in a person living with Alzheimer's disease

Date: Friday 8 October 2021 [Due date for resubmission is Thursday 14 Oct, 23:59 pm]. Word Count = 525.

CAD101 Assessment Task 3: Discussion Board Part B [separate posting]: Major clinical features' relationship to Major pathological changes that occur in the brain of a person with Alzheimer's disease

I certify Assessment Task 3: Discussion Board Part A and Part B are my own work, based on my personal study and/or research and that I have acknowledged all material and sources used in their preparation, whether they be books, articles, reports, lecture notes, and any other kind of document, electronic or personal communication. I also certify that these assignments/reports have not previously been submitted for assessment in any other unit, except where specific permission has been granted from all unit coordinators involved, or at any other time in this unit, and that I have not copied in part or whole or otherwise plagiarised the work of other students and/or persons.

Part A Major clinical features (signs and symptoms) that occur in a person living Alzheimer's disease

Estimated annual global incidence of sporadic [late-adult onset] Alzheimer's disease (AD) is ~1 - 3% of population resulting in ~10 million new cases/year and global prevalence of ~55 million cases (World Health Organization, 2021). Stage 1/mild dementia, Stage 2/moderate dementia and Stage 3/severe dementia describe "staged" progression of AD (General Practice Supervisors Australia, 2018) but they actually involve gradual progression[#] of underlying pathology as terminal disease that inevitably increase in severity and spread to more parts/regions of brain. Not all **features/symptoms [*with functional correlation to different parts/regions of brain being affected*]** from each stage are present in every person, nor will every person go through every stage. These features/symptoms are not unique to AD and pure AD are likely rare (Emrani et al., 2020).

Table 2 (Hodges, 2006, p. 2815) depicts AD and mild cognitive impairment (MCI) against cognition domain with following implications: Episodic memory involves recollection of everyday events. Changes in anterograde episodic memory, whereby new learning is compromised causing difficulty with a range of everyday tasks, is hallmark/earliest cognitive dysfunction occurring with AD. There is temporally graded impairment manifested as relative preservation of old memories but with impaired ability to form new memories. Semantic memory refers to general knowledge accumulated throughout our lives. It is affected later in AD impairing performances on tests for "category fluency" and confrontational naming. Attention and executive abilities are more subtly impaired in early stages of AD than episodic memory. They underlie difficulties with activities of daily living.

Disorder of fine motor movements [apraxia] is caused by visuospatial, memory and executive functioning deficits occurring close to 40% AD manifesting as difficulties locating arm/leg holes to dress and knowing how/why to use a fork (Mandell & Green, 2011; Lesourd et al., 2013). Various executive functioning e.g. reasoning, planning, problem-solving, paying attention and multi-tasking are additionally impaired. Involving higher order processes, these are manifested as troubles to independently perform simple tasks e.g. making tea and bathing (Ladera et al., 2018); and will impair e.g. neuropsychological Stroop Colour and Word test.

Language function involves reading, writing and speaking. Fluency is maintained in early stages of AD. Word finding difficulties are common. Naming of objects is impaired by mid stage. Later, fluency is impaired; and echolalia, palilalia (repetition of others/self) and mutism can also occur (Mandell & Green, 2011).

Visuospatial and perceptual functions refer to capacity to visually judge stimuli, perceive stimuli and see change in spatial landscape. These impairments are subtle in early stage but worsen as AD progress with manifestations in orientation, contrast and figure-ground discrimination, and constructional difficulties (Harbi et al., 2015) e.g. drawing and judgements of lines.

Behaviours associated with dementia can be described as 'behavioural and psychological symptoms of dementia'. *Noncognitive* or neuropsychiatric symptoms of dementia such as depression and apathy are common. Depression is a risk factor for AD; considered an early sign or prodrome of dementia in AD; and occur at the State of dementia in AD (Dasfari & Jessen, 2020). Personality changes and social behaviour remain intact in early stage of AD. Agitation, sleep disturbances, wandering and other behavioural disturbances occur in almost all cases at some stage of AD (Budson & Kowall, 2011).

[#]Gradual progression is often described in term of five domains consisting of psychiatric, cognition, function, behaviour and physical with decline in cognition and function domains starting early in Stage 1/mild dementia and tending to parallel each other; psychiatric illnesses coming and going out of that domain across whole course of dementia (e.g. hallucinations and delusions occurring at various stages); and behaviour and physical domains developing in Stage 3/severe dementia. Three phases of AD progression [as outlined by National Institute on Aging/Alzheimer's Association diagnostic guidelines for Alzheimer's disease] are *preclinical AD* (where disease is present in brain but there are no symptoms), *mild cognitive impairment due to AD* (also called prodromal AD), and *dementia caused by AD* (Dementia Australia, 2020). The ABC-DS further classified AD patients into subgroups characterized by activities of daily living (ADL), behavioural and psychological symptoms of dementia (BPSD), and cognitive function (CF) states. It can precisely monitor dynamic changes in the symptoms of individuals with conditions ranging from probable MCI to severe AD (Wada-Isoe et al., 2020).

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CAD101 Assessment Task 3: Discussion Board Part B [current posting]: Major clinical features' relationship to Major pathological changes that occur in the brain of a person with Alzheimer's disease [29 September 2021 collaborate session on assessment task 3B]

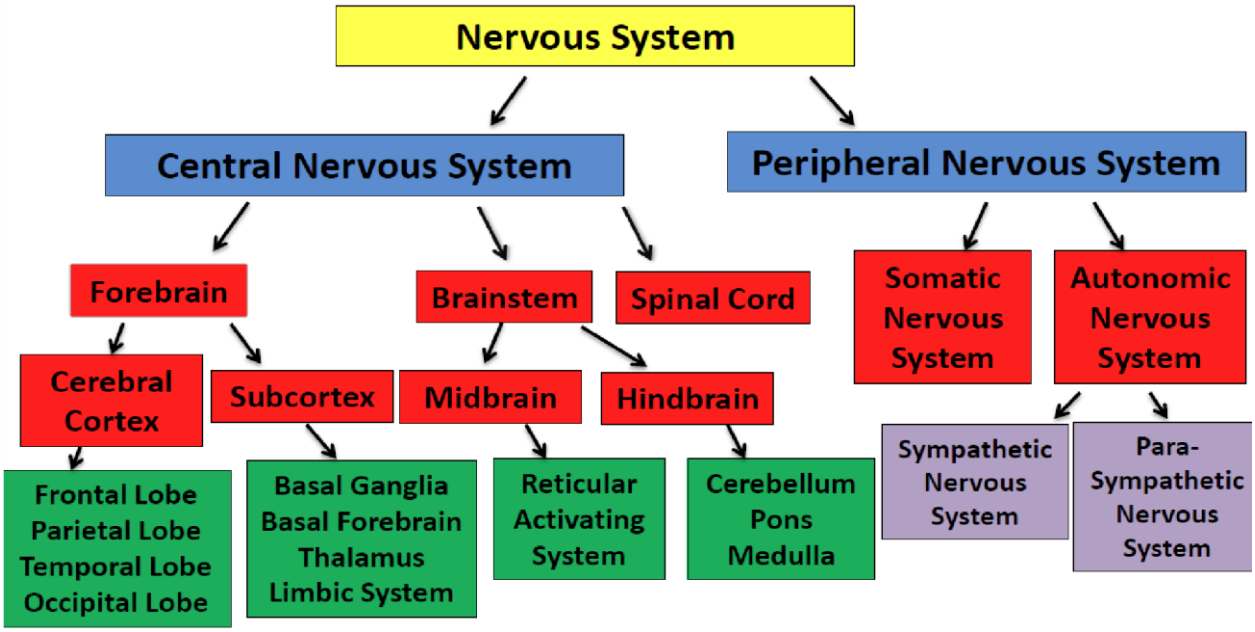
Date: Thursday 30 September 2021. Word Count = 500. Footnotes used to ensure optimal understand of this posting.

CAD101 Assessment Task 3: Discussion Board Part A posting]:

Major clinical features (signs and symptoms) that occur in a person living with Alzheimer's disease

I certify Assessment Task 3: Discussion Board Part A and Part B are my own work, based on my personal study and/or research and that I have acknowledged all material and sources used in their preparation, whether they be books, articles, reports, lecture notes, and any other kind of document, electronic or personal communication. I also certify that these assignments/reports have not previously been submitted for assessment in any other unit, except where specific permission has been granted from all unit coordinators involved, or at any other time in this unit, and that I have not copied in part or whole or otherwise plagiarised the work of other students and/or persons.

General Introduction [valid for both Assessment Task 3: Discussion Board Part A and Part B]



Broad overview based on above diagramatic representation of human nervous system: Spinal cord is the pathway for messages sent by brain to body and from body to brain. The brainstem is composed of midbrain, pons, and medulla oblongata; and is the connection central between brain and spinal cord. It regulates sleep cycle, cardiac and respiratory function [helping to control heart rate and breathing rate]; provides main motor and sensory nerve supply to face and neck via cranial nerves [whereby ten pairs of cranial nerves come from the brainstem].

The hindbrain includes most of brainstem and cerebellum. It consists of pons, cerebellum, and medulla oblongata. Most of the 12 cranial nerves are found in hindbrain. The midbrain is the topmost part of brainstem acting as vital connection point between forebrain and hindbrain. It is associated with vision, hearing, motor control, sleep and wakefulness, arousal (alertness), and temperature regulation. There are three main parts of midbrain - colliculi, tegmentum, and cerebral peduncles. Of the 12 cranial nerves, two thread directly from midbrain - oculomotor and trochlear nerves, responsible for

eye and eyelid movement. The forebrain with its main role to carry out movement, sensory perception and higher order functions (e.g. thinking, decision making, and reasoning) include cerebrum, thalamus, hypothalamus, pineal gland, pituitary gland, limbic system, and olfactory bulb.

The four lobes of cerebral cortex are frontal lobe, parietal lobe, temporal lobe and occipital lobe. The three important cortical regions of frontal lobe include Primary motor cortex which directs and plans movement; Broca's area for speech production; and Prefrontal cortex for personality and higher order functions. An important cortical region of parietal lobe is Somatosensory cortex which perceives sensory information. The entorhinal cortex is a major part of hippocampal formation of the brain and is reciprocally connected with hippocampus. Three important cortical regions of temporal lobe include hippocampus (and entorhinal cortex) - responsible for learning, memory consolidation [of information from short-term memory to long-term memory] and in spatial memory that enables navigation; Wernicke's area for language comprehension; and Primary auditory cortex for processing sound. The two important cortical regions of occipital lobe are Primary visual cortex – processing light, interpreting and perceiving our visual environment; and Secondary visual cortex – support primary visual cortex to perceive visual environment.

Limbic system, located within the sub-cortical area of forebrain, is a collective term for a group of structures that are broadly concerned with emotions and memory as these two brain functions are intimately linked. It includes Amygdala, Hypothalamus, Cingulate Gyrus, Thalamus, Hippocampus, Fornix, Cingulum, Corpus callosum and Septal area. The amygdala assists in interpretation of emotional response.

The thalamus serves as gateway to cerebral cortex and takes input from many of our senses. The hypothalamus regulates the internal state of our body [via endocrine and autonomic nervous systems] including body temperature, hunger, thirst, sleep-wake cycles, blood pressure, and carbohydrate and fat metabolism.

The basal ganglia as defined functionally are the striatum, consisting of both dorsal striatum (caudate nucleus and putamen) and ventral striatum (nucleus accumbens and olfactory tubercle), globus pallidus, ventral pallidum, substantia nigra, and subthalamic nucleus. The basal ganglia involve control of voluntary motor movements, procedural learning, habit learning, conditional learning, eye movements, cognition, and emotion. In particular, the basal ganglia interact with the cortex to ensure appropriate movements are carried out and unwanted movements are stopped; viz, basal ganglia act to ensure movements are smooth and coordinated.

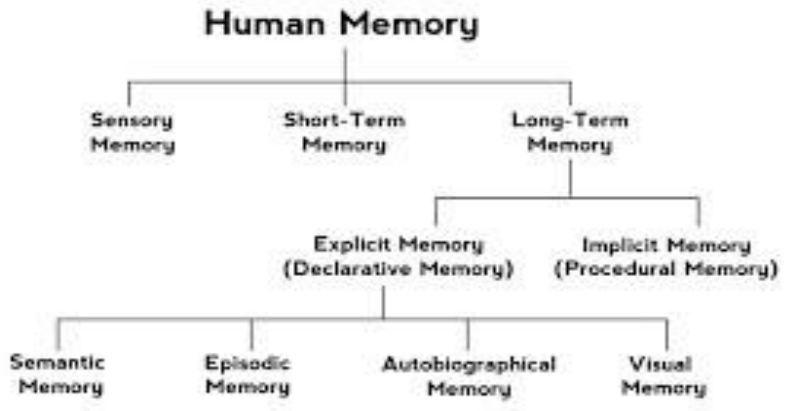
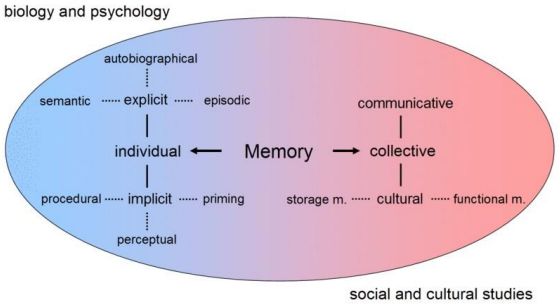


Figure 1. Memory classification

In all my presentations, I will concentrate on the most common Amnestic type of Alzheimer's disease. As depicted in Figure 1 on memory classification of relevance to memory physiology, memory is a function of the brain by which data or information is encoded, stored, and retrieved when needed. It is the retention of information over time for purpose of influencing future action. Figure 2 is courtesy of Bernhard Wenzl (Creative Commons CC0 License, 28 September 2020) giving a detailed overview of memory as used in various branches of academia. Figure 3 on parts of brain involved in anatomy of memory is courtesy of University of Queensland (Queensland Brain Institute, 2018) whereby (1) Explicit (conscious) memory refers to events that happened to us (episodic memory) as well as general facts and information

(semantic memory) involving three important areas of brain: hippocampus, neocortex and amygdala; (2) Implicit (unconscious) memory such as procedural (motor) memory relies on basal ganglia and cerebellum; and (3) Short-term (working) memory relies most heavily on prefrontal cortex.



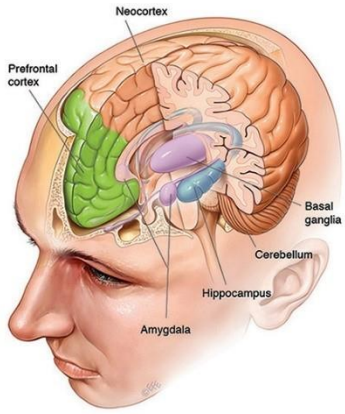


Figure 2. Overview of forms and functions of memory **Figure 3.** Parts of brain involved in memory

Dementia is a progressive and terminal syndrome caused by over 100 neurodegenerative diseases whereby Alzheimer's disease (AD) is the commonest cause in people either above or below age 65. With prevalence[1] of 1 - 2% of people in normal population (currently affecting around 55 million people globally in 2021), dementia is essentially brain organ failure[2] with ongoing and irreversible death/degeneration of nerve cells and their connections manifesting as progressive loss of [initially] *mental functions* and [ultimately] *physical functions* in affected individuals.

Diagnosis[3] of dementia is predominantly determined by clinical signs and symptoms including a clinically significant decline in one or more areas of cognitive function e.g. memory, language, behaviour, personality or emotional function. This decline must be significantly different from where the person was previously, and it usually occurs gradually over time. It usually spreads from one function to involve more and more functions. Organic mental disorder (organic brain syndrome) consists of three categories: delirium, dementia and amnestic (encephalopathy). Functional psychiatric conditions such as depression, anxiety and schizophrenia are often termed pseudo-dementia as they can mimic dementia. However, depression or anxiety are also extremely common in dementia and mild cognitive impairment (MCI). Vitamin B12, folate and thiamine deficiency, and hypo/hyperthyroidism often cause neuropsychiatric symptoms that are easily reversible with treatment. Delirium in the elderly, with reduced neuroplasticity (ability to form and reorganize synaptic connections), cognitive and brain reserve, usually emerges quickly and can resolve quickly e.g. it could be caused by an infection that can be treated with antibiotics. In Part A presentation, I will outline the major clinical features (signs and symptoms) occurring in a person living with AD that usually manifest as memory, thinking and behavioural symptoms. In Part B presentation, I will outline how these major clinical features relate to microscopic (neuronal/cellular) and macroscopic pathological changes in the brain of a person with AD[4].

Table 1. Stages of cognitive breakdown in typical Alzheimer's disease[#] as adapted from (Hodges, 2006)

	MCI	Mild	Moderate	Severe
Memory				
Working	–	–/+	++	+++
Anterograde episodic[(a)]	++	+++	+++	+++
Remote	–/+	–/+	++	+++
Semantic[(b)]	–/+	+	+++	+++

	MCI	Mild	Moderate	Severe
Attention and executive abilities[c]	−/+	++	++	+++
Language (syntax and phonology)[d]	−	−	+	++
Visuospatial and perceptual[e]	−	−/+	++	++
Praxis	−	−	++	++

Key: − absent, + present, −/+ variable. ***Clinical-Pathology correlation:*** (a) Anterograde episodic memory loss is linked to pathology in medial temporal lobes (hippocampus) resulting in their disconnection from the cortex. (b) Semantic memory loss is linked to pathology spreading to anterior and lateral regions of temporal lobes. (c) Loss in attention and executive abilities are linked to pathology in frontal lobes including prefrontal cortex and other subcortical areas. (d) Loss in language function is linked to later-on pathology progression that compromise frontal and temporal lobes. (e) Loss in visuospatial and perceptual function are linked to plaque and tangle formation within the visual cortex.

Three main pathological hallmarks of Alzheimer's disease further outlined by ***Part B presentation*** include (1) [microscopic] Beta-amyloid plaques occurring in extracellular space associated with dystrophic neurites and synapse loss, (2) [microscopic] Neurofibrillary tangles (occurring in cell body) and neuropil threads (occurring in neurites). Beta-amyloid plaques deposition generally precede neurofibrillary tangles accumulation. These two processes of progressively greater severity in affected brain regions result in subset of pyramidal excitatory neurons degeneration from neurite loss and synapse loss leading to their death and eventually ending in (3) [macroscopic] Atrophy process (with enlarged ventricles). Of increasing severity, there are **three stages of beta amyloid plaque pathology** (Masters et al., 2015) and **six Braak stages of neurofibrillary tangle (NFT) pathology** (Braak & Braak, 1991). Atrophy closely follows pattern of NFT pathology spread: **first in entorhinal cortex/hippocampus; basal cortical region; remainder of cortex; and motor areas spared until late in disease**. Atrophy can also be variable e.g. limbic predominant and hippocampal sparing. Patterns[5] of amyloid plaque and NFT pathologies, and atrophy can vary from person to person, again with ***Clinical-Pathology correlation.***

Table 2. STAGES OF CARE FOR PEOPLE WITH DEMENTIA

Stage	Goal of care	Signs and symptoms
First stage (Stage 1 dementia): Still at Home	Dignity through ***maintaining independence*** and enjoyment	• Short-term memory loss • Repetitive questions • Hobbies, interests lost • Impaired instrumental functions
Second stage (Stage 2 dementia): Now needing 24-hour care	Dignity through ***keeping safe*** and maximising any quality	• Progression of cognitive deficits • Declining function

Third stage (Stage 3 dementia): Diminished quality of life	Dignity through ***providing comfort***	• Increasing loss of independence; dressing, feeding, bathing • May have behaviours of concern e.g. from apathy to sundowner [becoming increasingly irritable or difficult as the day progresses in early or late afternoon] • Usually physical decline [in mobility and swallowing with associated bowel/bladder incontinence]

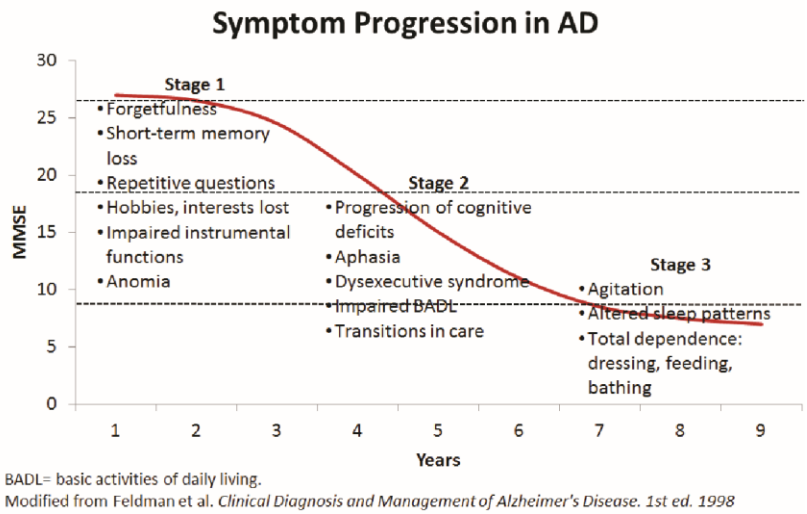


Figure 4. Symptom progression in Alzheimer's disease

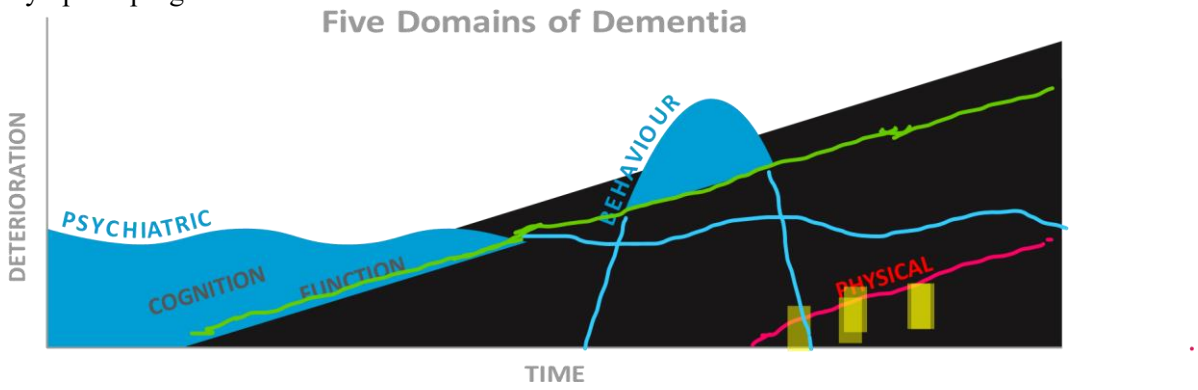


Figure 5. Five domains in dementia consisting of psychiatric, cognition, function, behaviour and physical

Progression in the three dementia stages and five domains of dementia are practically summarized in Table 2, Figure 4 and Figure 5 (General Practice Supervisors Australia, 2018).

The decline[6] in cognition and function domains start early in dementia and tend to parallel each other. Psychiatric illnesses come and go out of that domain across the course of dementia (for example, hallucinations and delusions at various stages). Behaviour and physical domains develop at Stage 3 or end-stage dementia whereby this is often when the patient and a distressed or concerned carer will increasingly consult medical practitioners. For example, the patient may be wandering, aggressive, shouting out or questioning repetitively.

Part B Major clinical features' relationship to Major pathological changes that occur in the brain of a person with Alzheimer's disease

Three pathological hallmarks of Alzheimer's disease (AD) are (i) [microscopic] amyloid plaques, (ii) [microscopic] neurofibrillary tangles (NFT) [plus neuropil threads] and (iii) [macroscopic] atrophy [with enlarged ventricles]. With increasing anatomical severity are Stage A, B and C of beta amyloid plaque pathology (Masters et al., 2015) and Braak Stage I, II, III, IV, V and VI of neurofibrillary tangle (NFT) pathology (Braak & Braak, 1991) – these are succinctly summarized below (adapted from 2021 video lecture 'Alzheimer's disease pathological progression' by Dr Adele Woodhouse). There are some 'complex' correlation/relationship between [gradual worsening of] clinical signs/symptoms in Stage 1 'early/mild' dementia to Stage 2 'moderate' dementia to Stage 3 'advanced/severe' dementia progression and the [increasing severity and progression of various stages in] amyloid plaques and NFT pathologies, and brain atrophy. This correlation/relationship is illustrated in *General Introduction* (Tables 1 and 2, and Figures 4 and 5) including description on relevant anatomical brain areas affected by Clinical-Pathology at bottom of Table 1 (Hodges, 2006)[7,8] for (a) Anterograde episodic memory loss, (b) Semantic memory loss, (c) Loss in attention and executive abilities, (d) Loss in language function, and (e) Loss in visuospatial and perceptual function. A common model of AD is Hyperphosphorylated tau protein and amyloidbeta hypothesis (Thakur, K. et al, 2018)[9].

Beta-amyloid plaque pathology: Three stages: A, B and C. Overall begins in basal cortical regions; Spreads 'bottom up' (ventral to dorsal) and 'inside to out' (medial to lateral). Stage A: low density in basal frontal, temporal and occipital cortices; some in entorhinal cortex. Stage B: Medium density in frontal, temporal, occipital and parietal cortex; mild density in hippocampus. Stage C: High density in frontal, temporal, occipital and parietal cortex; moderate density in primary somatosensory and motor cortex. Caveats: Beta-amyloid plaque deposition is variable between individuals e.g. plaque deposition can occur first in parietal and occipital lobes with sparing of hippocampus. Stage C may also include plaques in sub-cortical structures including striatum, thalamus and hypothalamus.

Neurofibrillary tangle pathology: Six Braak stages: I-VI. Overall starts at hippocampus/entorhinal cortex (medial), basal cortical and limbic regions; Spreads upwards across all cortical regions. Stage I-II: Mild density in trans-entorhinal cortex and hippocampus. Stage III-IV: Mild density in entorhinal cortex and basal frontal, temporal and occipital lobes; moderate density in cingulate gyrus. Stage V-VI: Spread throughout all lobes; high density in hippocampus and entorhinal cortex. Caveats: NFT accumulation can be variable between individuals (although less variable than plaques). Sub-cortical structures involvement: Thalamus (Stage II onwards), Striatum (Stage III onwards) and Hypothalamus (Stage IV onwards).

Brain atrophy (with progressive ventricles enlargement) closely follows pattern of NFT pathology spread but can be variable: First in entorhinal cortex/hippocampus, Basal cortical regions, Remainder of cortex, Motor areas spared until late in disease.

Noncognitive (neuropsychiatric) symptoms of dementia include depression, apathy and sleep disturbances. Psychiatric illnesses such as aggression, agitation, delusions, hallucinations and psychosis occur across course of dementia. Behaviour and physical domains develop at Stage 3 dementia. Patterns of amyloid plaques and NFT pathologies, and atrophy can vary from person to person.

Footnotes

1 More than 90% of all dementia occurs in people above age 65 [late onset dementia]. Approximately 10% of all dementia consist of *younger onset dementia* (also known as early onset dementia), which is any form of dementia in people under age 65. The most common types of dementia are Alzheimer's disease [60-70% of all dementia cases], Vascular dementia [10-15% of all dementia cases], Dementia with Lewy bodies, Frontotemporal dementia, Huntington's disease, Alcohol related dementia (Korsakoff's syndrome) and Creutzfeldt-Jakob disease. Mixed dementia e.g. Alzheimer's disease with vascular dementia is dementia from more than one cause. Alzheimer's disease is also the commonest cause of younger onset dementia [about 33% of all dementia below the age of 65, most commonly between the ages of 45 – 64 although it can rarely occur much earlier than this]. Vascular dementia is the second most common type in people above age 65 but in younger onset dementia, this is replaced by frontotemporal dementia. Younger onset dementia has the following features: A wider range of diseases cause younger onset dementia. A younger person is much more likely to have a rarer form of dementia. Younger people with dementia are less likely to have memory loss as one of their first symptoms. Younger onset dementia is more likely to cause problems with movement, walking, coordination or balance. Younger onset dementia is more likely to be inherited – this affects up to 10% of younger people with dementia. Many younger people with dementia do not have any other serious or long-term health conditions. Livingston et al. (2020) outline 12 modifiable risk factors accounting for approximately 40% of worldwide dementias: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution. Age and genetics/family history are non-modifiable risk factors for developing dementia with approximately *10% of all people age > 65 and 50% of all people age > 95 having dementia*. The average time *from onset of dementia to death is 4 - 5 years with enormous range of 6 months in Creutzfeldt–Jakob disease up to 20 years in Alzheimer's disease*. Globally, dementia has a disproportionate impact on women (WHO, 2021). About 65% of total deaths due to dementia are women, and disability adjusted life years due to dementia are roughly 60% higher in women than in men. Additionally, women provide majority of informal care for people living with dementia, accounting for 70% of carer hours. Lynn & Adamson (2006) have previously outlined three typical trajectories followed by chronic progressive and eventually fatal illness in the elderly: (i) "Short period of evident decline" caused by mostly cancer; (ii) "Long term limitations with intermittent serious episodes" caused by mostly heart and lung failure; and (iii) "Prolonged dwindling" caused by mostly frailty and dementia. Thus, early involvement of palliative approach (consisting of palliative care and end-of-life care) will greatly benefit the person living with dementia that has poorly predictable time-line trajectory.

2 We must differentiate between normal ageing process versus dementia pathology that occurs in the brain. The nine hallmark denominators (López-Otín et al., 2013) of ageing purportedly occurring in all cell types are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Research suggest we could slow down or [partially] reverse healthy ageing in all body systems from cellular senescence using senolytic therapy (Sikora et al., 2021). Neuronal plasticity, defined as morphological and functional changes at level of neurons and dendritic spines [mainly as reduced dendrite diameter, reduced spine volume and loss of synapses], can be the hallmark of neuronal senescence occurring in healthy brain ageing. Recall of memories and learning is also enhanced if there is an increase in the strength of synaptic connections between neurons [also known as long-term potentiation]. On gross anatomical level, the ageing brain shows minor regional atrophy manifested as shrinkage of cerebral cortex, hippocampus and entorhinal cortex with moderately enlarged ventricles. In particular, the cerebral cortex shows volume declines from 20 years of age approximately 0.1% per year; and the hippocampus volume remains stable until around 60 years after which there is a steep trajectory of

volume loss approximately 0.3% per year (Fjell et al., 2014). In principle, these phenomena occurring in the brain should potentially be directly or indirectly susceptible to the effects of senolytic therapy or other anti-ageing agents. Our brain is protected by the skull, meninges, cerebrospinal fluid and blood brain barrier (BBB). Each cell within neurovascular unit of BBB can be impacted by ageing contributing to neuronal dysfunction, neuroinflammation and neurodegeneration. The ten warning signs of Alzheimer's disease (Alzheimer's Association, 2019) that are clinically contrasted with ageing changes are listed below: 1. MEMORY LOSS THAT DISRUPTS DAILY LIFE. One of the most common signs of Alzheimer's disease, especially in the early stage, is forgetting recently learned information. Others include forgetting important dates or events, asking the same question over and over again, or increasingly needing to rely on memory aids (e.g., reminder notes or electronic devices) or family members for things the person used to handle on their own. *What's a typical age-related change?* Sometimes forgetting names or appointments but remembering them later.

2. CHALLENGES IN PLANNING OR SOLVING PROBLEMS. Some people living with dementia may experience changes in their ability to develop and follow a plan or work with numbers. They may have trouble following a familiar recipe or keeping track of monthly bills. They may have difficulty concentrating and take much longer to do things than they did before. *What's a typical age-related change?* Making occasional errors when managing finances or household bills.

3. DIFFICULTY COMPLETING FAMILIAR TASKS. People living with Alzheimer's disease often find it hard to complete routine tasks. Sometimes they may have trouble driving to a familiar location, organizing a grocery list or remembering the rules of a favourite game. *What's a typical age-related change?* Occasionally needing help to use microwave settings or to record a TV show.

4. CONFUSION WITH TIME OR PLACE. People living with Alzheimer's can lose track of dates, seasons and the passage of time. They may have trouble understanding something if it is not happening immediately. Sometimes they may forget where they are or how they got there. *What's a typical age-related change?* Getting confused about the day of the week but figuring it out later.

5. TROUBLE UNDERSTANDING VISUAL IMAGES AND SPATIAL RELATIONSHIPS. For some people, vision problems are a sign of Alzheimer's. They may also have problems judging distance and determining colour or contrast, causing issues with driving. *What's a typical age-related change?* Vision changes related to cataracts.

6. NEW PROBLEMS WITH WORDS IN SPEAKING OR WRITING. People living with Alzheimer's may have trouble following or joining a conversation. They may stop in the middle of a conversation and have no idea how to continue or repeat themselves. They may struggle with vocabulary, have trouble naming a familiar object or use the wrong name. *What's a typical age-related change?* Sometimes having trouble finding the right word.

7. MISPLACING THINGS AND LOSING THE ABILITY TO RETRACE STEPS. A person living with Alzheimer's may put things in unusual places. They may lose things and be unable to go back over their steps to find them again. He or she may accuse others of stealing, especially as the disease progresses. *What's a typical age-related change?* Misplacing things from time to time and retracing steps to find them.

8. DECREASED OR POOR JUDGMENT. Individuals may experience changes in judgment or decision-making. For example, they may use poor judgment when dealing with money, or pay less attention to grooming or keeping themselves clean. *What's a typical age-related change?* Making a bad decision once in a while, like neglecting to change oil in the car.

9. WITHDRAWAL FROM WORK OR SOCIAL ACTIVITIES. A person living with Alzheimer's may experience changes in the ability to hold or follow a conversation. As a result, he or she may withdraw from hobbies, social activities or other engagements. They may have trouble keeping up with a favourite team or activity. *What's a typical age-related change?* Sometimes feeling uninterested in family or social obligations.

10. CHANGES IN MOOD AND PERSONALITY. Individuals living with Alzheimer's may experience mood and personality changes. They may be easily upset at home, at work, with friends or when out of their comfort zone. *What's a typical age-related change?* Developing very specific ways of doing things and becoming irritable when a routine is disrupted.

Researchers and clinicians have identified different phenotypes (clinical presentations) of Alzheimer's disease:

(1) Amnestic type of Alzheimer's disease: the most common variant, characterised by early significant impairment to memory

(2) Logopenic aphasia: where changes to language function are most prominent in the early stages

(3) Posterior cortical atrophy: characterised by initial impairment to visuospatial function

(4) Frontal variant (behavioural/dysexecutive Alzheimer's disease): where early behavioural changes are most prominent, due to more frontal lobe degeneration in the initial stages.

The [first] amnestic phenotype is the commonest (typical) form of Alzheimer's disease. Up to 1 in 3 younger people with Alzheimer's disease have one of the [last three] atypical forms, but only 1 in 20 older people with Alzheimer's disease have an atypical form. Familial Alzheimer's disease is a very rare form of Alzheimer's disease. It is caused by genetic mutations (changes in genes) that run-in families manifesting as autosomal dominant inheritance pattern. Three genes have been found to have these rare mutations – PSEN1 (presenilin 1 on chromosome 14), PSEN2 (presenilin 2 on chromosome 1) and APP (amyloid precursor protein on chromosome 21). Other variants in genes that increase or decrease susceptibility to Alzheimer's disease but do not cause the disease include the apolipoprotein (APOE) gene whereby APOE 2 form decreases risk, APOE 3 form is neutral and APOE 4 form increases risk.

There is a 50% risk of a parent passing on the familial Alzheimer's disease mutation to their children. People with the condition usually have a strong family history of the disease and will know a range of family members who were affected at a similar age, along with one of their parents. Symptoms of familial Alzheimer's disease usually start in person in their 30s, 40s or 50s. The earlier the symptoms start, the more likely it is that the disease is genetic. Familial Alzheimer's disease is very rare and probably accounts for fewer than 1 in 100 people with Alzheimer's disease.

As extra side notes, there are also different phenotypes (clinical presentations) of frontotemporal dementia (FTD): Behavioural variant FTD (also known as Pick's disease), Primary progressive aphasia which consists of semantic dementia and progressive non fluent aphasia, Familial FTD which is an inherited form of the condition, the movement disorders Progressive supranuclear palsy and Corticobasal degeneration. Most familial FTD is caused by mutations in three genes. These are a recently discovered gene called C9ORF72, and genes for the proteins tau (MAPT) and progranulin (GRN). The particular mutation that a person has tends to influence their symptoms. For example, C9ORF72 is linked to both FTD and motor neurone disease and some affected families have a history of both conditions.

3 Dementia was renamed 'major neurocognitive disorder' (major NCD) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). International Classification of Diseases (ICD) published by the World Health Organisation as ICD-11 in June 2018 adopted the terminology 'neurodevelopmental disorders' for dementia with very similar diagnostic criteria to those of the DSM-5. Mild cognitive impairment (MCI) or prodromal dementia as earlier stages of cognitive decline were renamed 'mild neurocognitive disorder' (mild NCD) in DSM-5. NCDs are characterised by acquired deficits, which represent a decline from previous functioning, rather than neurodevelopmental deficits present from birth or early life. DSM-5 provides diagnostic criteria for both major NCD and mild NCD, followed by diagnostic criteria for the different subtypes or causes of NCD. DSM-5 details six cognitive domains below which may be affected in both mild and major NCD [– we should contrast these six cognitive domains against the

five domains of dementia viz. psychiatric, cognition, function, behaviour and physical; and against the three dementia stages and trajectory viz. Stage 1 'early' dementia, Stage 2 'moderate' dementia and Stage 3 'advanced' dementia]:

- **Complex attention**, which includes sustained attention, divided attention, selective attention and information processing speed
- **Executive function**, which includes planning, decision making, working memory, responding to feedback, inhibition and mental flexibility
- **Learning and memory**, which includes free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, and implicit learning
- **Language**, which includes object naming, word finding, fluency, grammar and syntax, and receptive language
- **Perceptual-motor function**, which includes visual perception, visuo-constructional reasoning and perceptual-motor coordination
- **Social cognition**, which includes recognition of emotions, theory of mind and insight

Mild NCD or MCI causes modest cognitive decline from a previous level of performance in one or more of the cognitive domains outlined above that are serious enough to be noticed by the person affected and by family members and friends but do not interfere with independence in daily activities, although greater effort and compensatory strategies may be required to maintain the level of independence. Further, the cognitive deficits must not be due to another mental disorder (such as depression). Approximately 12-18% of people aged 60 or older are living with MCI. MCI is best seen as a risk factor for developing dementia with a 3 to 5 times increased risk of developing dementia, about 15% of individuals with MCI go on to develop dementia each year. a substantial proportion of people with MCI have remained stable or even improved. MCI can also be further classified based on the thinking skills affected:

Amnestic MCI: MCI that primarily affects memory. A person may start to forget important information that he or she would previously have recalled easily, such as appointments, conversations or recent events.

Non-amnestic MCI: MCI that affects thinking skills other than memory, including the ability to make sound decisions, judge the time or sequence of steps needed to complete a complex task, or visual perception.

It is believed that many MCI cases — but not all — result from brain changes occurring in the very early stages of Alzheimer's disease or other neurodegenerative diseases that cause dementia. The risk factors most strongly linked to MCI when the underlying cause is neurodegenerative disease and not another cause are advancing age, family history of Alzheimer's or another dementia, and conditions that elevate risk for cardiovascular disease.

Diagnosis of major NCD (dementia) requires evidence of significant cognitive decline from a previous level of performance in one or more of the cognitive domains outlined above. Additionally, the cognitive deficits must be sufficient to interfere with independence in activities of daily living. The cognitive deficits must not be attributable to another mental disorder. The criterion of maintenance or loss of independent functioning represents key distinction between mild and major NCD.

4 The National Institute on Aging and the Alzheimer's Association (NIA/AA, 2011a, 2011b, 2011c & 2011d) in United States published new diagnostic guidelines specifically and only for Alzheimer's disease (AD). Three phases of AD progression are outlined – *preclinical AD* (where the disease is present in the brain but there are no symptoms), *mild cognitive impairment due to AD* (also called prodromal AD), and *dementia caused by AD*. The guidelines include test for two biomarker categories that measure biological changes in the brain associated with AD: biomarkers which indicate level of beta-amyloid accumulation in the brain and biomarkers which indicate injured or degenerating nerve cells in the brain. Research areas to establish biomarkers for dementia include brain imaging, cerebrospinal fluid proteins and substances in blood. Shrinkage in specific brain regions such as the hippocampus may be an early sign of AD. Patterns of shrinkage in

other brain regions may help identify other forms of dementia. For example, frontotemporal dementia is often associated with reduced volume in the frontal and/or temporal lobes. AD is often associated with reduced use of glucose in brain areas important for memory, learning and problem solving. Other forms of dementia may be associated with patterns of reduced glucose metabolism in other brain regions. Deposits of beta-amyloid (one pathological hallmark of AD) could be used to delineate development and progression of AD.

Dementia caused by AD involves memory, thinking and behavioural symptoms that impair a person's ability to function in daily life. Dementia caused by AD can be further classified as:

1. **Probable Alzheimer's disease dementia**, to be diagnosed when the person meets all the core clinical criteria
2. **Possible Alzheimer's disease dementia**, to be diagnosed when there is an atypical or mixed presentation
3. **Probable or possible Alzheimer's disease dementia with evidence of the Alzheimer's disease pathological process**, to be diagnosed when there is biomarker evidence to increase the certainty that the dementia is due to Alzheimer's disease

Mild cognitive impairment due to Alzheimer's disease

MCI due to AD involves mild changes in memory or thinking abilities, which are noticeable to the person and/or to others but are not severe enough to significantly compromise activities of daily living. MCI can be further classified as:

1. **MCI – core clinical criteria**, to be diagnosed when the person meets all the core clinical criteria
2. **MCI due to Alzheimer's disease – intermediate likelihood**, to be diagnosed when the person meets all the core clinical criteria in addition to some biomarker evidence in one of the two biomarker categories (beta-amyloid accumulation or neurodegeneration)
3. **MCI due to Alzheimer's disease – high likelihood**, to be diagnosed when the person meets all the core clinical criteria in addition to biomarker evidence in both of the categories
4. **MCI – unlikely due to Alzheimer's disease**, to be diagnosed when biomarker tests indicate that there is the lowest likelihood of underlying AD pathology

Preclinical Alzheimer's disease

Preclinical AD involves the detection of changes in biomarkers that indicate the very earliest signs of AD in the brain, before any cognitive or behavioural symptoms are noticeable. A three-stage framework for preclinical AD includes:

Stage 1 – when there is biomarker evidence of beta-amyloid accumulation in the brain, but no biomarker evidence of degenerating nerve cells in the brain and no cognitive or behavioural symptoms

Stage 2 – when there is biomarker evidence of both beta-amyloid accumulation in the brain and degeneration of nerve cells in the brain, but no cognitive or behavioural symptoms

Stage 3 – when there is biomarker evidence of both beta-amyloid accumulation in the brain and degeneration of nerve cells in the brain, and evidence of subtle cognitive decline

5 There are two existing primary hypotheses that describe how Alzheimer's disease (AD) occurs: Beta-Amyloid Cascade Hypothesis and Tau Hypothesis. There is evidence to support both hypotheses. Beta-amyloid forms Type 1 oligomers [affect normal synaptic function] and Type 2 oligomers [causes plaques]; and tau forms tau oligomers that could impact the functioning of neurons. Enzymatic cleavage of amyloid precursor proteins (APP) gives rise to beta-amyloid and sAPP (Zhang et al., 2019). Normal roles for beta-amyloid include (i) Regulate synaptic transmission; (ii) Neuron survival/injury recovery; and (iii) Repair leaks in blood brain barrier. Normal roles for sAPP include (i) Modulate synaptic

transmission; (ii) Neuroprotective; and (iii) Neurogenesis. The [extra-cellular] beta-amyloid plaques are made up of [insoluble] beta-amyloid peptides which are associated with dystrophic neurites and synapse loss. Increased production of beta-amyloid usually occurs in inherited AD and decreased clearance of beta-amyloid usually occurs in sporadic AD.
The [intra-cellular] neurofibrillary tangles (NFT) are made up of insoluble accumulation of peptides made from tau proteins. *NOTE: Tombstone or ghost tangles are tangles that mark where the neuron has died*. Normal roles for tau proteins include (i) Stabilises microtubules; (ii) Regulates DNA integrity; (iii) Regulates transport; and (iv) Regulates synaptic plasticity. Abnormally phosphorylated tau dissociates from microtubules in AD leading to abnormal tau aggregates. Tau accumulation is called NFT in cell body and neuropil threads in neurites.
National Institute on Aging-Alzheimer Association guidelines define post-mortem AD neuropathologic changes as a composite score based on three elements. These elements are the extent of involvement (spread) by cerebral Aβ based on the progression model defined by the Thal Aβ phases, the extent of involvement (spread) by neurofibrillary tangles (composed of hyperphosphorylated tau proteins) based on the progression model defined by Braak (Braak & Braak, 1991), and the Consortium to Establish a Registry for Alzheimer's Disease score, which describes the density of neuritic plaques based on certain key locations in the neocortex. A revised post-mortem classification system (ABC, for amyloid, Braak, and CERAD) based on these 3 components has emerged. Depending on level of each component, pathologic findings are scored as indicating *no likelihood of AD* or indicating *a low, intermediate, or high likelihood* (Koychev, Hofer & Friedman, 2020).

6 The ABC-DS classified Alzheimer's disease (AD) patients into subgroups characterized by activities of daily living (ADL), behavioural and psychological symptoms of dementia (BPSD), and cognitive function (CF) states. It can precisely monitor dynamic changes in the symptoms of individuals with conditions *ranging from probable MCI to severe AD* (WadaIsoe et al., 2020).

7 Visuospatial impairments signs include getting lost in familiar environments and being unable to find the way home (Mandell & Green, 2011); trouble with contrast and object differentiation resulting in shadows being misconstrued as holes or being unable to see a white toilet amongst white tiles (Mandell & Green, 2011). Apraxia (disorder of fine motor movements) is the result of visuospatial, memory and executive functioning deficits occurring in up to 40% of cases of Alzheimer's disease; and manifest as difficulties finding arm and leg holes to dress, and knowing how, or even why, to use a fork (Mandell & Green, 2011; Lesourd et al., 2013). Other executive functioning skills, such as ability to reason, plan, problem-solve, pay attention and multi-task, are also impaired in Alzheimer's disease. This is manifested as difficulties in independently accomplishing simple tasks like bathing or making tea (Ladera et al., 2018).

8 Pathology occurring at Broca's area [in frontal lobe] for speech production and Wernicke's area [in temporal lobe] for language comprehension will result in loss in language function. This affects most levels of language processing encompassing production of speech and writing, and comprehension of speech and reading (Mandell & Green, 2011) which increase through the middle stages of Alzheimer's disease and include difficulties in finding the correct word or using it correctly, in understanding spoken information, and in writing or speaking coherently (Ortiz et al., 2021). In the later stages of Alzheimer's disease, disturbances to speech production can also include repeating the words of others (echolalia) or themselves (palilalia) or being unable to speak at all (Mandell & Green, 2011). Note: *Autobiographical memory* is often described in terms of two types of long-term memory: semantic (knowledge about the self) memory and episodic (event specific knowledge related to past personal experiences) memory. *Anterograde episodic memory*, whereby new memories linked with a particular time and place [personal to the individual] cannot be retained in Alzheimer's disease. Memories for general knowledge, and those from the past, remain longer and can lead to a noticeable preoccupation with past events. As Alzheimer's disease progresses, *retrograde episodic memory* (that of past personal events) also declines.

9 It is postulated that overproduction of amyloid beta protein causes [extracellular] amyloid plaques and interferes with neuron-to-neuron communication at neural synapses, which then causes problems for cell axon. Amyloid beta causes hyperphosphorylation of tau in cell axons. The microtubule stabilizing tau protein changes shape by joining together with other tau and becomes tangled forming [intracellular] NFT. The transport of nutrients inside the cell then becomes blocked ultimately leading to neuronal death.

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How does culture impact on ageing, and how can cultural awareness and sensitivity be expressed towards older adults living in Australia who are from a culturally and linguistically diverse background? [By John Ting, Wednesday 20 April 2022]

Introduction

Australian Bureau of Statistics (ABS) defines culturally and linguistically diverse (CALD) population predominantly by country of birth, spoken language at home, English proficiency, and other characteristics such as year of arrival in Australia, parents' country of birth and religious affiliation (ABS, 1999). Australia is a multi-cultural/culturally-diverse developed country whose economy depend substantially on migrant intake under skilled migration program (Department of Home Affairs, 2022). Department of Home Affairs has recently granted thousands of visas to Ukrainians in Ukraine and elsewhere due to Russia-Ukraine war commencing on 24 February 2022. As recent new migrants in Australia, we have a unique CALD population of children, young and older Ukrainian war refugees of non-English speaking background (NESB).

Coming to Australia

We selectively look at older Ukrainian war refugees aged over 65 in disadvantaged socio-economic position with special needs as our CALD subgroup with distinct Ukrainian culture displaced from their local society/communities in Ukraine. Being psychologically traumatized by the conflict in Ukraine, they will likely develop mental health conditions such as post-traumatic stress disorder and perhaps sustain physical disability such as amputated limbs from war injuries. In addition to common underlying multiple morbidities of chronic non-communicable diseases such as diabetes and hypertension that may be present in this cohort needing ongoing medical health care, these people will also require mental health support. Service accessibility is dependent on many factors whereby some Australian people with disability below age 65 experience difficulties in accessing health services with unacceptable or lengthy waiting times, cost, inaccessibility of buildings and discrimination by health professionals (Australian Institute of Health and Welfare, 2017). These same difficulties could be experienced by older Ukrainian people.

Ensuring English language proficiency in older NESB Ukrainian people as extrapolated from the study by Temple (2021) would likely improve their ability to better access Australian health care services and find new jobs. Just as adult Indian people in India of all age groups [which included older adult aged over 65 with disability and associated multiple morbidities such as diabetes and hypertension] are reported to have higher adverse health outcomes and face major challenges in accessing health services (Gudlavalleti, 2018); the older Ukrainian people in Australia will likely encounter these same

problems which are caused by health provider prejudices and attitudes, and inadequacies in skills and infrastructure to care for people with disabilities. Thus, we need to find locally affordable, contextually specific interventions to improve the quality of health of these people with disabilities. In addition to reliance on family/friends to interpret, competent bilingual English-Ukrainian interpreters/translators are required at health appointments, accessing social services such as Centrelink support, and navigating health care systems.

Older Ukrainian people who can still work will face challenges in finding work due to poor English proficiency. Some with physical disability may have to move from living in the community into residential aged-care facilities if they are unable to live independently despite Home Care Packages support which should be provided by culturally competent home care workers in a culturally sensitive manner. Providing culturally different food and respecting unique religious requirements are likely required (Radermacher & Feldman, 2017).

Accepting the challenge of getting older

Cultural beliefs shape social norms and values surrounding the ageing process and influence the role of older people in Ukrainian society. Cultural awareness, sensitivity, and competence for Ukrainian people are analogous to, for instance, the indigenous Australians (Claphan & Duncan, 2017) but there are differences such as: Firstly, indigenous Australians are not regarded as CALD people; and Secondly, cultural sensitivity warning regarding deceased persons "Aboriginal and Torres Strait Islander people should be aware that this website contains images, voices and names of deceased persons" (The Australian Institute of Aboriginal and Torres Strait Islander Studies, n.d.) do not [analogically] apply to Ukrainian people. We must focus on offering beneficial information regarding Ukrainian culture with aim of enhancing integration, diversity and communication. In developed country Ukraine, Third Age refer to a time after retirement age of personal fulfilment for older Ukrainian adults who are "well off" and can access and afford resources/services with a "new stage of life" involving a "positive attitude" whereas Fourth Age refer to a time of dependency, ill-health (physical/cognitive), frailty and death as an example of "unsuccessful" or "unhealthy" ageing (Laslett, 1991). In Australia, their smooth journey through Third Age could be curtailed with "unsuccessful" or "unhealthy" ageing tending to be more prevalent in the Fourth Age. Combatting ageism is a supremely important step to improve successful or healthy ageing. Ageism, being an important social determinant of health, intersect with other forms of discrimination and negatively impacts all non-indigenous individuals aged over 65 [and aged over 50 for individual indigenous Australians]; and ageism is expensive not to be dealt with, and we can all benefit from its extermination (Curryer & Cook, 2021).

Conclusion

English language proficiency is a key determinant of positive health, social and economic outcomes for Australian migrants. Apart from increasing family connectedness, it is important to alleviate social exclusion and loneliness through reduction in language barriers. A need for interventions that acknowledge value of cultural awareness-based approaches while also exploring utility of comprehensive cultural competence and safety approaches is required (Shepherd et al., 2019). Health workers must be willing to respect and learn about Ukrainian culture, and have their thoughts and beliefs challenged and changed.

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