Age Specific Study in Subjects at Risk of Developing Dementia, Anxiety and Depression after Covid-19 Exposure

Jigar Sanjiv Padhiar[a], Uddipak Rai[a*], Parag Rane[b]

[A] Faculty of Pharmacy, DIT University, Dehradun-248009, India
[B] Zydus Lifesciences Limited, Ahmedabad-382213, India
*Corresponding Author: **Dr. Uddipak Rai**

Abstract

Introduction: Dementia, anxiety and depression are brain conditions that affects several upper cortical processes, including memory, thinking, direction, comprehension, calculation, learning capacity, language, and judgement. **Objectives:** The objective of this study is to study the effect of demographic factor on dementia, anxiety and depression in patients recovered from COVID-19 infection. **Methods:** This study is designed to observe subjects at risk of developing dementia, anxiety and depression after Covid-19 exposure patient data were collected from the hospital with help of hospital staff. Eligible patients were involved in the study based on the inclusion and exclusion criteria. Patients who meet the eligibility criteria was required to fill the questionnaire. So based on responses from the subject, the data was analyzed. Clinical Dementia Rating scale (CDL) was used for the study. **Results:** We have performed statistical analyses with the categorization of patient i. e. age and disease condition. The total number of patients (1000, Post Covid-19) enrolled in the study. Based on the response received from post-Covid-19patients, the data were analyzed by SAS Program. The responses, which were resulted in "YES" against each question of the questionnaire, were calculated as proportion. **Conclusion:** while the long-term impact of COVID-19 on dementia, anxiety and depression risk is still uncertain, it is essential to prioritize the health and well-being of older adults, especially those with pre-existing dementia, during and after the pandemic. Maintaining social connections, providing accessible healthcare services, and implementing preventive measures

Keywords: Alzheimer's disease. Cognitive disorder. Diabetes

1. Introduction

Covid-19was firstly identified in Jan-2020. This virus is quickly spreading among humans, resulting in a covid-19 pandemic [1-2]. Patients over the age of 65 and those with cardiovascular disease are more likely to develop acute respiratory syndrome, multiple organ failure, pneumonia and mortality [3-5]. Due to limited availability of vaccine and logistical challenges, the only method to control the outbreak was to enforce isolation, quarantine, and physical separation [6-7]. Vaccines were desperately required to combat the load of mortality and morbidity associated with covid-19 infection [8-10]. A total of 195 vaccine candidates are in line for clinical trial and approval. Currently, 36 vaccines are approved by world health organization (WHO), and 68 candidates are in phase III of the clinical trial. Worldwide 197 countries have approved vaccines available for vaccination [11-13].

Due to cognitive impairment in dementia, the patient's ability to obey with covid-19 infection preventive actions such as, cover face, community distancing and nostrils with mask and frequent sanitizing the hand may be hampered. The loss of one's sense of taste and smell is a warning indication of illness. In addition, the brain can be affected by organ failure in a different place and hypoxia is an assurance of severe infection, leading to malfunction of brain cerebral edema [14-16].

Covid-19 has been shown to complicate dementia in several ways. Firstly, the covid-19 pandemic has led to significant disruptions in routine care for individuals with dementia, including delays in diagnosis and treatment, and reduced access to care. This can lead to a worsening of symptoms and an overall decline in quality of life for

those with dementia. Secondly, individuals with dementia may have difficulty following public health guidelines related to covid-19, such as wearing masks, social distancing, and washing hands regularly[17-19]. This may increase their risk of contracting covid-19, which can have severe and potentially life-threatening consequences, especially for older adults with underlying health conditions like dementia. Thirdly, covid-19 can also directly impact the brain and nervous system, leading to neurological complications such as confusion, delirium, and cognitive impairment. This can further exacerbate the symptoms of dementia and lead to a more rapid decline in cognitive function. Finally, covid-19 has also been associated with long-term neurological effects, such as persistent fatigue, headaches, and cognitive impairment, which can worsen the symptoms of dementia and impact overall quality of life. Anxiety during covid-19 refers to the heightened state of fear, worry, and unease experienced by individuals as they navigate the uncertainties and potential threats associated with the pandemic. The constant barrage of distressing news, the fear of contracting the virus, or witnessing its effects on loved ones can take a toll on mental well-being[20-25].

The rationale behind the study on the effect of covid-19 on dementia, anxiety and depression is that there is a growing concern that the covid-19 pandemic may have significant impacts on the health and well-being of individuals with dementia. The covid-19 pandemic has disrupted healthcare systems around the world and has led to significant changes in the way that care is provided to patients, including those with dementia. Additionally, covid-19 can directly impact the brain and nervous system, potentially exacerbating the symptoms of dementia. Anxiety during covid-19 refers to the heightened state of fear, worry, and unease experienced by individuals as they navigate the uncertainties and potential threats associated with the pandemic. The constant barrage of distressing news, the fear of contracting the virus, or witnessing its effects on loved ones can take a toll on mental well-being[26-28].

We hypothesized that pre-existing dementia predisposes individuals to increased risks of morbidity and mortality from covid-19 as a result of these common brain problems and autopsy findings. Once infected, dementia sufferers are more likely to suffer negative consequences [11]. Alzheimer's disease is challenging not just for people who have it, but also for those who care for them and their families. It is leading causes of disability and dependency among the elderly across the world. Dementia can no longer be ignored; it must now be included in all countries' public health agendas[29-31].

The objective of the study is to identify the specific impacts of the covid-19 pandemic on individuals with dementia, including changes in access to care, worsening of symptoms, and increased risk of infection. To examine the potential direct impact of covid-19 on the brain and nervous system in individuals with dementia, and to understand the potential long-term neurological effects of covid-19 on this population[32-34]. To investigate the factors that may exacerbate the impact of covid-19 on individuals with dementia, such as social isolation, comorbidities, and access to resources and support. To identify strategies for mitigating the negative impacts of covid-19 on individuals with dementia, including interventions to address social isolation, access to care and support, and management of comorbidities. To understand the broader societal impacts of the covid-19 pandemic on individuals with dementia and their caregivers, including changes in healthcare systems, social policies, and economic factors. Anxiety, as a natural response to perceived threats, can serve as a protective mechanism, enabling individuals to stay alert and focused during uncertain situations[35-37]. However, the prolonged and intense nature of the pandemic has pushed many people into chronic anxiety, disrupting their daily lives and overall well-being. The multifaceted impact of COVID-19 on mental health calls for a comprehensive understanding of the factors contributing to anxiety and the various coping mechanisms that can help individuals navigate these challenging times[38-40]. Anxiety, as a natural response to perceived threats, can serve as a protective mechanism, enabling individuals to stay alert and focused during uncertain situations. However, the prolonged and intense nature of the pandemic has pushed many people into chronic anxiety, disrupting their daily lives and overall well-being[41-45].

2. Material and Method

This study is design to observe Subjects at Risk of Developing Dementia, Anxiety and Depression after Covid-19 exposure theCovid patient data are collected from the covid hospital (Unique hospital multispecialty & research institute, Surat, India). Patients who meet the eligible criteria was required to fill the questionnaire. So based on

responses from the subject, the data was analyzed. Clinical dementia rating scale (CDL) was used for the study so data as per CDL scale was collected[46].

2.1. Enrollment: Patient those who were considered to have severe illness and required prolonged hospitalization (≥ 4 days or transferred to ICU) was enrolled in the study.

2.2. Study design and procedure

This was an observational study to analysis subjects at risk of developing dementia, anxiety and depression after covid-19 exposure. This study included total 1000 patients. The covid patient data were collected from the covid hospital with help of hospital staff. Eligible patients wereenrolled in the study based on the inclusion and exclusion criteria. Those patients admitted in intense care unit (ICU) in the hospital with more ≥ 4 days. Patients with no history of dementia in past but have any neurological problem or any other condition were involved in study. Patients with mild severity or asymptomatic covid-19 but admitted to hospital for ≥ 4 days or transferred to ICU will be enrolled. Patients who meet the eligible criteria was required to fill the questionnaire (Figure 1). Questionnaire contain total 11 questions these questions will be fill by the patients. So based on responses from the subject, the data will be analyzed.CDL will be used for the study so data as per CDL scale will be collected.

Prior Conduct of Study below listed approvals were taken:

1. University Research Ethics Committee from Dehradun Institute of Technology University, Dehradun, India (DITU/UREC/2022/04/6)
2. Ethics Committee Approval from hospital (Ethics Committee-Unique Hospital, Surat, India)

Fig 1: Questionnaire for the post COVID treatment

DIT UNIVERSITY IMAGINE ASPIRE ACHIEVE	**Questionnaire**	Strictly confidential Page 969 of 1

Questionnaire for the post COVID treatment

Patient Name:
DOB: Age:
Last day of Discharge:
Responded Name: Relationship:

Please answer following questions by circling the appropriate response

Sr .no	Questionnaire of subject	Yes	No
1	He/she talks and asks about the same thing repeatedly	Yes	No
2	He/she has become unable to understand the context of facts	Yes	No
3	He/she has become indifferent about clothing and other personal concerns	Yes	No
4	He/she has begun to forget to turn off the faucet and/or close the door and/or has become unable to clean up properly	Yes	No
5	When doing two thing at the same time he/she forget one of them	Yes	No
6	He/she has become unable to take medication under proper management	Yes	No
7	He/ she has begun to take a longer time to do work (e.g. Household chores), which could be done quickly before	Yes	No
8	He/ She has become unable to make plan	Yes	No
9	He /She cannot understand complex topic	Yes	No
10	He/ she become less interested and willing and stopped hobbies etc.	Yes	No
11	He/She has become more irrotable and suspicious than before	Yes	No
Totoal SED – 11Q Score			

Patient with Depression: Yes / No Patient with Anxiety: Yes / No

Declaration by Participant		Subject Initial
1	I confirm that I have read and understood the information Sheet dated TBD for the above study and have had the opportunity to ask questions.	[ ]
2	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
3	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes	[ ]
4	I agree to take part in the above study without seeking any financial benefits considering academic nature off this study.	[ ]

Following activities will be performed during Study Research.

1. Informed consent.
2. Demographic details including sex, height, weight and BMI
3. Medical history, Vital signs and Clinical examination

All subjects will be strictly required to follow the instructions given to them as per protocol**.**

2.3. Method of administration of study tools:

Objective 1: Patient data was obtained from hospital database (unique hospital, Surat, India) which were used to identify patient based on I/E criteria.

Objective 2: Quantitative- ICF; CRF and questionnaires was given to patients by research assistants and was filled by patient.

Qualitative: The Principal investigator (PI) will take the ICF and questionnaire will be filled in the presence of patient and based on the Questionnaire data will be analyzed and translated for analysis

2.4. Data Collection and Management:

Data was collected using paper-based forms and entered into Microsoft excel. Analysis of data will involve statistical software as appropriate.

1. ANOVA
2. Inclusion/Exclusion Checklist
3. Paper based crfs
4. Paper Based icfs
5. CDL Questionnaire

2.5. Statistical Analysis:

Analysis and statistics Data was extracted from the source database and was analyze using ANOVA test. The socio-demographic features was tabulated. Mean and standard deviations (SD) will be calculated.

2.6. Qualitative Statistical Analysis

Based on the response received from post-covid-19 patients, the data were analyzed by SAS Program. The responses which were resulted in "YES" against each question of the questionnaire were calculated as proportion. We have performed the statistical analysis in 1000 post-Covid-19 patients.

3. Results:

We have performed comparison of agegroup with diseases condition among covid-19 survivors developing dementia/anxiety/depression by SAS program. The total number of patients (1000, post covid-19) enrolled in the study.

Based on the response received from post-covid-19patients, the data were analyzed by SAS Program.Data were collected, each with a different number of observations for younger and older. The means procedure was employed to calculate descriptive statistics for each study. The results from each study were aggregated and analyzed collectively to observe common patterns and trends across the samples.

Table 1: Dementia Age Statistical Analysis

Age	N Obs	Mean	Median	Std Dev	Pr > |t|
19	**8**	4.1250000	3.5000000	3.7201190	0.0165
20	**16**	3.5000000	4.0000000	2.1291626	<.0001
25	**23**	5.1304348	5.0000000	3.2516338	<.0001
28	**8**	5.5000000	4.5000000	1.8516402	<.0001
29	**6**	3.6666667	3.5000000	1.2110601	0.0007
30	**42**	4.1428571	4.0000000	2.3013403	<.0001
31	**5**	4.2000000	4.0000000	1.9235384	0.0081
32	**7**	5.0000000	4.0000000	1.5275252	0.0001
33	**7**	5.5714286	5.0000000	2.8199966	0.0020
34	**15**	5.8000000	5.0000000	3.2557641	<.0001
35	**17**	4.0588235	3.0000000	2.2491829	<.0001
38	**10**	5.1000000	4.5000000	2.8848262	0.0003
39	**12**	4.8333333	5.0000000	2.6227443	<.0001
40	**25**	4.8800000	4.0000000	2.3860707	<.0001
42	**9**	3.8888889	4.0000000	2.0883273	0.0005
43	**9**	5.3333333	6.0000000	2.7838822	0.0004
44	**6**	4.8333333	4.0000000	2.2286020	0.0032
45	**13**	5.3076923	5.0000000	1.7974341	<.0001
47	**8**	3.8750000	4.0000000	1.8850919	0.0007
48	**7**	4.2857143	4.0000000	1.6035675	0.0004
50	**5**	5.0000000	6.0000000	2.8284271	0.0168
55	**20**	5.2500000	5.5000000	2.5930068	<.0001

*N Obs: Number of age; Std Dev: Standard Deviation

Table 1 presents the age groups 20, 25, 28, 30, 32, 33, 34, 35, 38, 39, 40, 43, 45, and 55 all have p-values less than 0.05, which suggests that the mean for these age groups is significantly different from the other age group In other words, there are statistically significant differences in the means of these age groups.Age group 20 has the lowest mean (3.5) and a very low p-value, indicating that it is significantly different from the reference group.Age group 33 has the highest mean (5.57) among the groups with significant differences, but it also has a relatively high standard deviation (2.82), indicating greater variability.Age group 50 has a mean of 5, which is higher than the reference group, but it has a p-value of 0.0168, which is still less than 0.05, indicating a significant difference.Age

groups 19, 29, 31, 42, 44, 47, and 48 have p-values greater than 0.05, suggesting that there is no significant difference between their means and the reference group

Table 2: Anxiety Age Statistical Analysis

Age	N Obs	Mean	Median	Std Dev	Pr > |t|
19	**8**	4.1250000	3.5000000	3.7201190	0.0165
20	**16**	3.5000000	4.0000000	2.1291626	<.0001
25	**23**	5.1304348	5.0000000	3.2516338	<.0001
28	**8**	5.5000000	4.5000000	1.8516402	<.0001
29	**6**	3.6666667	3.5000000	1.2110601	0.0007
30	**42**	4.1428571	4.0000000	2.3013403	<.0001
31	**5**	4.2000000	4.0000000	1.9235384	0.0081
32	**7**	5.0000000	4.0000000	1.5275252	0.0001
33	**7**	5.5714286	5.0000000	2.8199966	0.0020
34	**15**	5.8000000	5.0000000	3.2557641	<.0001
35	**17**	4.0588235	3.0000000	2.2491829	<.0001
38	**10**	5.1000000	4.5000000	2.8848262	0.0003
39	**12**	4.8333333	5.0000000	2.6227443	<.0001
40	**25**	4.8800000	4.0000000	2.3860707	<.0001
42	**9**	3.8888889	4.0000000	2.0883273	0.0005
43	**9**	5.3333333	6.0000000	2.7838822	0.0004
44	**6**	4.8333333	4.0000000	2.2286020	0.0032
45	**13**	5.3076923	5.0000000	1.7974341	<.0001
47	**8**	3.8750000	4.0000000	1.8850919	0.0007
48	**7**	4.2857143	4.0000000	1.6035675	0.0004
50	**5**	5.0000000	6.0000000	2.8284271	0.0168
55	**20**	5.2500000	5.5000000	2.5930068	<.0001

*N Obs: Number of age; Std Dev: Standard Deviation

Table 2 presents the Age 20: This group has a relatively low mean (3.5) and median (4), suggesting that the data may not be normally distributed. The p-value is extremely low, indicating a significant difference from the reference group.Age 25: This group has a mean of 5.13 and a median of 5, indicating that it's relatively normally distributed. The p-value is very low, indicating a significant difference from the reference group.Age 30: This group has a mean of 4.14 and a median of 4, indicating a relatively normal distribution. The p-value is extremely low, suggesting a significant difference from the reference group.Age 34: This group has a high mean (5.8) and a median of 5, indicating potential skewness in the data. The p-value is very low, showing a significant difference from the reference group.Age 35: This group has a mean of 4.06 and a median of 3, indicating potential skewness.

The p-value is very low, indicating a significant difference from the reference group.Age 39: This group has a mean of 4.83 and a median of 5, suggesting some skewness. The p-value is very low, indicating a significant difference from the reference group.Age 40: This group has a mean of 4.88 and a median of 4, indicating a relatively normal distribution. The p-value is very low, suggesting a significant difference from the reference group.Age 43: This group has a high mean (5.33) and a median of 6, indicating potential skewness. The p-value is very low, showing a significant difference from the reference group.Age 45: This group has a mean of 5.31 and a median of 5, indicating a relatively normal distribution. The p-value is very low, indicating a significant difference from the reference group.Age 50: This group has a mean of 5 and a median of 6, suggesting potential skewness. The p-value is significant but relatively higher (0.0168), indicating a less significant difference from the reference group compared to some other age groups.Age 55: This group has a mean of 5.25 and a median of 5.5. The p-value is very low, indicating a significant difference from the reference group

Table 3: Depression Age Statistical Analysis

Age	N Obs	Mean	Median	Std Dev	Pr > |t|
19	**8**	4.5000000	4.0000000	1.6903085	0.0001
20	**15**	5.0000000	4.0000000	2.4494897	<.0001
25	**23**	5.3913043	5.0000000	2.7259549	<.0001
28	**7**	5.2857143	4.0000000	2.2886885	0.0009
29	**9**	6.1111111	6.0000000	3.0184617	0.0003
30	**46**	4.5000000	4.0000000	2.2973415	<.0001
31	**8**	4.3750000	4.0000000	2.2638463	0.0009
32	**8**	4.8750000	4.0000000	2.1671245	0.0004
33	**8**	3.1250000	4.0000000	2.2320714	0.0055
34	**15**	5.6000000	4.0000000	2.8735245	<.0001
35	**23**	4.5652174	4.0000000	2.0186874	<.0001
38	**16**	3.6250000	3.0000000	2.5000000	<.0001
39	**16**	4.2500000	4.0000000	2.1447611	<.0001
40	**33**	5.3333333	5.0000000	2.6887110	<.0001
42	**7**	3.5714286	3.0000000	2.6367368	0.0116
43	**8**	5.0000000	4.5000000	2.1380899	0.0003
44	**8**	5.2500000	4.5000000	1.9086270	0.0001
45	**16**	4.2500000	4.0000000	2.3237900	<.0001
47	**8**	2.7500000	3.5000000	1.5811388	0.0017
48	**7**	5.5714286	6.0000000	3.2586880	0.0040
50	**8**	5.0000000	4.0000000	3.3380918	0.0039
55	**24**	5.4583333	5.0000000	2.8586888	<.0001

*N Obs: Number of age; Std Dev: Standard Deviation

Table 3presents the, Age 20: This group has a mean of 5 and a median of 4, indicating potential skewness in the data. The p-value is extremely low, indicating a significant difference from the reference group.Age 29: This group has a relatively high mean (6.11) and a median of 6, suggesting potentialskewness. The p-value is significant (0.0003), indicating a significant difference from the reference group.Age 32: This group has a mean of 4.88 and a median of 4, indicating potential skewness. The p-value is significant (0.0004), suggesting a significantdifference from the reference group.Age 33: This group has a relatively low mean (3.13) and a median of 4, indicating potential skewness. The p-value is significant (0.0055), indicating a significant difference from the reference group.Age 38: This group has a mean of 3.63 and a median of 3, suggesting potential skewness. The p-value is very low, indicating a significant difference from the reference group.Age 47: This group has a relatively low mean (2.75) and a median of 3.5. The p-value is significant (0.0017), suggesting a significant difference from the reference group.Age 48: This group has a high mean (5.57) and a median of 6, indicating potential skewness. The p-value is significant (0.004), suggesting a significant difference from the reference group.Age 50: This group has a mean of 5 and a median of 4, indicating potential skewness. The p-value is significant (0.0039), suggesting a significant difference from the reference group.Age 55: This group has a mean of 5.46 and a median of 5, indicating a relatively normal distribution. The p-value is very low, indicating a significant difference from the reference group

4. Discussion:

Age is a critical factor in the development and progression of dementia. Dementia is not a normal part of aging, but it is more common among older individuals.

The observed differences in standard deviations between ages suggested that the score distributions may vary in spread. However, further research is needed to understand the underlying factors contributing to these disparities, as the small sample sizes in some studies may limit the generalizability of the results.The study's large sample size enhances the reliability of the findings and increases the generalizability of the results to the broader population. The highly significant p-values indicate that the observed age differences are unlikely to occur by chance alone.

Understanding age-based disparities in mental health conditions is essential for developing targeted interventions and support systems. This research contributes valuable insights that may aid healthcare professionals, policymakers, and researchers in tailoring strategies to address mental health challenges based on age-specific needs. However, further research is necessary to explore the underlying factors contributing to these age differences in dementia, anxiety, and depression prevalence.

The data might be part of a research study or survey that investigates the co-occurrence of mental health conditions and other medical conditions among survivors[46-47]. Such data can be useful for understanding potential associations or comorbidities between these conditions, which can help healthcare professionals in providing better care and support for patients with multiple health concerns[48-50].

5. Conclusion:

The comprehensive statistical analysis of age differences in the prevalence of dementia, anxiety, and depression has yielded significant insights. The study found that older agetend to have slightly higher mean scores and a higher prevalence of dementia and anxiety, while younger age exhibit a slightly higher mean score and a higher prevalence of depression.

This study provides valuable insights into age differences in dementia, anxiety, and depression. To advance our understanding, future research should investigate causal factors, conduct longitudinal studies, explore intersectionality's influence, develop age-specific interventions, consider cultural influences, and examine risk factors and resilience. Addressing these research gaps will contribute to more effective and equitable mental health policies and interventions, promoting better mental health outcomes for all, regardless of age.

Acknowledgement: We would like to thanks to all authors, co-authors, and supportive staff to provide intimate support for this work.

6. References:

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. New England Journal of Medicine. 2020;382(8):727-733.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine. 2020;382(13):1199-1207.
3. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. New England Journal of Medicine. 2020;382(24):2327-2336.
4. Weiss P, Murdoch D. Clinical course and mortality risk of severe COVID-19. The Lancet. 2020;395(10229):1014-1015.
5. Cowling B, Ali S, Ng T, Tsang T, Li J, Fong M et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. The Lancet Public Health. 2020;5(5):e279-e288.
6. Gudbjartsson D, Helgason A, Jonsson H, Magnusson O, Melsted P, Norddahl G et al. Spread of SARS-cov-2 in the Icelandic Population. New England Journal of Medicine. 2020;382(24):2302-2315.
7. Wang Q, Davis P, Gurney M, Xu R. COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US. Alzheimer's & Dementia. 2021;17(8):1297-1306.
8. Dr. Christopher M Clark, Alzheimer's Disease Core Center Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
9. Arden KE, Nissen MD, Sloots TP, Mackay IM. New human coronavirus, hcov-NL63, associated with severe lower respiratory tract disease in Australia. Journal of Medical Virology. 2005;75(3):455–62.
10. Woo PC, Lau SK, Chu C-ming, Chan K-hung, T soi H-wah, Huang Y, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. Journal of Virology. 2005;79(2):884–95.
11. Woo PCY, Lau SKP, Tsoi H, Huang Y, Poon RWS, Chu C, et al. Clinical and molecular epidemiological features of Coronavirus HKU1–associated community-acquired pneumonia. The Journal of Infectious Diseases. 2005;192(11):1898–907.
12. Lee N, Sung JJY. Severe acute respiratory syndrome outbreak in a University Hospital in Hong Kong. Imaging in SARS. 2001:29–32.
13. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA. 2014;311(2):183.
14. Schreiber S, Bueche CZ, Garz C, Braun H. Blood brain barrier breakdown as the starting point of cerebral small vessel disease new insights from a rat model. Experimental & Translational Stroke Medicine. 2012; 32:278-290.
15. Farkas E, De Jong GI, de Vos RA, Jansen Steur EN, Luiten PG. Pathological features of cerebral cortical capillaries are doubled in Alzheimer's disease and Parkinson's disease. Acta Neuropathologica. 2000;100(4):395–402.
16. Stefani A, Sancesario G, Pierantozzi M, Leone G, Galati S, Hainsworth AH, et al. CSF biomarkers, impairment of cerebral hemodynamic and degree of cognitive decline in Alzheimer's and mixed dementia. Journal of the Neurological Sciences. 2009;283(1-2):109–15.
17. Tyas SL, White LR, Petrovitch H, Webster Ross G, Foley DJ, Heimovitz HK, et al. Mid-life smoking and late-life dementia: The honolulu-asia aging study. Neurobiology of Aging. 2003;24(4):589–96.
18. Batty G, Russ T, Starr J, Stamatakis E, Kivimäki M. Modifiable cardiovascular disease risk factors as predictors of dementia death: pooling of ten general population-based cohort studies. Journal of Negative Results in biomedicine. 2014;13(1)
19. Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatrics. 2008; 8(1).
20. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: A meta-analysis of prospective studies.American Journal of Epidemiology. 2007;166(4):367–78.
21. Cataldo JK, Prochaska JJ, Glantz SA. Cigarette smoking is a risk factor for Alzheimer's disease: An analysis controlling for tobacco industry affiliation. Journal of Alzheimer's Disease. 2010;19(2):465–80.

22. De Reuck J, Deramecourt V, Cordonnier C, Leys D, Pasquier F, Maurage C-A. Prevalence of cerebrovascular lesions in patients with lewy body dementia: A neuropathological study. Clinical Neurology and Neurosurgery. 2013;115(7):1094–7.
23. Thal DR, von Arnim CA, Griffin WS, Mrak RE, Walker L, Attems J, et al. Frontotemporal lobar degeneration FTLD-Tau: Preclinical lesions, vascular, and alzheimer-related co-pathologies. Journal of Neural Transmission. 2015;122(7):1007–18.
24. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiology and Molecular Biology Reviews. 2005;69(4):635–64.
25. Fisher D, Heymann D. Q&A: The novel coronavirus outbreak   causing covid-19. BMC Medicine. 2020;18(1).
26. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory diseasein China. Nature 2020; 579:265–9.
27. El Zowalaty ME, Järhult JD. From sars to COVID-19: A previously unknown SARS- related coronavirus (SARS-COV-2) of pandemic potential infecting humans – call for a one health approach. One Health. 2020;9:100124.
28. Sahu P. Closure of universities due to coronavirus disease 2019 (covid-19): Impact on education and mental health of students and academic staff. Cureus. 2020;
29. JOAO BELMIRON. Geographic information systems and covid-19: The Johns Hopkins University dashboard. 2020;
30. Farkas E, De Jong GI, de Vos RA, Jansen Steur EN, Luiten PG. Pathological features of cerebral cortical capillaries are doubled in alzheimer's disease and parkinson's disease. Acta Neuropathologica. 2000;100(4):395–402.
31. Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: Systematic review and meta-analysis. BMC Public Health. 2014;14(1).
32. Hershey LA, Modic MT, Jaffe DF, Greenough PG. Natural history of the vascular dementias: A prospective study of seven cases. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 1986;13(S4):559–65.
33. Loeb C. The history of Vascular dementia. Journal of the History of the Neurosciences. 1994;3(2):109–14.
34. HACHINSKI V. Multi-infarct dementia a cause of mental deterioration in the elderly. The Lancet. 1974;304(7874):207–9.
35. Suri S, Topiwala A, Mackay CE, Ebmeier KP, Filippini N. Using structural and diffusion magnetic resonance imaging to differentiate the Dementias. Current Neurology and Neuroscience Reports. 2014;14(9).
36. Villeneuve S, Reed BR, Madison CM, Wirth M, Marchant NL, Kriger S, et al. Vascular risk and a interact to reduce cortical thickness in AD vulnerable brain regions. Neurology. 2014;83(1):40–7.
37. Honjo K, Black SE, Verhoeff NP. Alzheimer's disease, cerebrovascular disease, and the β-amyloid cascade. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 2012;39(6):712–28.
38. Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, et al. Ad lesions and infarcts in demented and non-demented Japanese-American men. Annals of Neurology. 2004;57(1):98–103.
39. Stefani A, Sancesario G, Pierantozzi M, Leone G, Galati S, Hainsworth AH, et al. CSF biomarkers, impairment of cerebral hemodynamics and degree of cognitive decline in alzheimer's and mixed dementia. Journal of the Neurological Sciences. 2009;283(1-2):109–15.
40. De Reuck J, Deramecourt V, Cordonnier C, Leys D, Pasquier F and Maurage CA. Prevalence of cerebrovascular lesions in patients with Lewy body dementia: a neuropathological study. Clin Neurol Neurosurg 2013;115: 1094–1097.
41. Itzhaki RF, Golde TE, Heneka MT, Readhead B. Do infections have a role in the pathogenesis of Alzheimer disease?. Nat Rev Neurol. 2020; 16(4): 193- 197.

42. Wu Z, mcgooganJM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in China. JAMA. 2020;323(13):1239.
43. Robinson CP, Busl KM. Neurologic manifestations of severe respiratory viral contagions. Critical Care Explorations. 2020;2(4).