

Chronic Type 2 Diabetes and Future Risks of Alzheimer’s Disease: An Outlook from the Tale of two Population

Somiranjan Ghosh^{1,2}, Tanmoy Mondal¹, Zarish Noreen⁴, Abhay Maghekar³, Gail Nunlee-Bland², Vijay Chandra⁵

¹Department of Biology, Howard University, Washington, DC 20059, USA. ²Department of Pediatrics & Child Health, College of Medicine, Howard University, USA.; ³ Johns Hopkins University School of Medicine, Johns Hopkins Bayview Hospital, USA. ⁴ Department of Biological Sciences, International Islamic University, Islamabad, Pakistan; 5. Department of Neurology, Primus Hospital, New Delhi 110021, India.

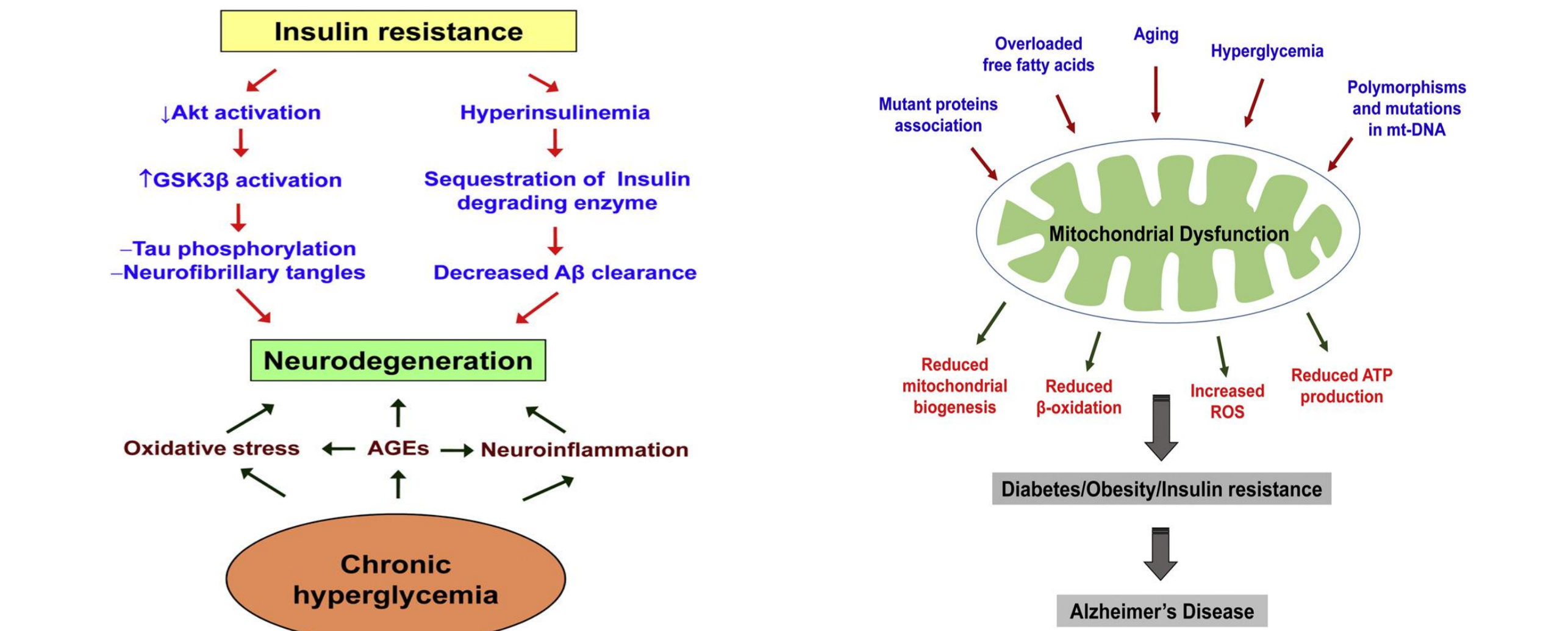
LEARNING OBJECTIVE

- Relate the pathobiology in the etiology of T2DM risking AD.
- Translate the information in developing non-invasive markers for early risk assessment of AD.

INTRODUCTION

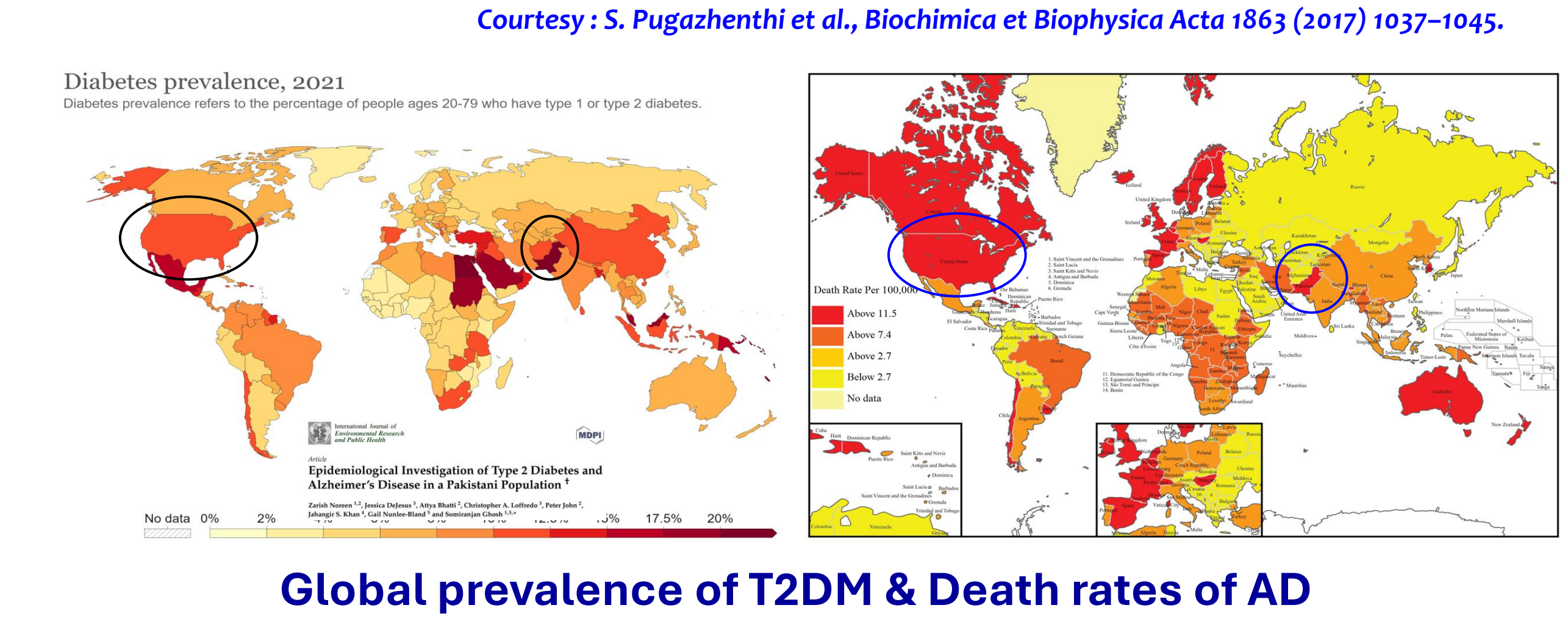
Metabolic diseases like chronic Type 2 Diabetes Mellitus (T2DM) are now a serious global health concern In the United States. African Americans (AA) are being affected at a disproportionate rate with the condition compared to other ethnic groups, yet there are relatively few studies that have specifically focused on this group. Our previous findings have suggested that AA and Pakistani patients with T2DM had gene expression signals associated with Alzheimer’s Disease (AD). The current pilot study aimed to examine the *amyloidogenic processing pathways* (APP) and *cholesterol biosynthesis-related* marker genes in the blood circulation of clinically identified T2DM AA patients in the Washington DC area and Pakistani Population.

T2DM: A Major Risk Factor for Alzheimer’s Disease



Pathways of neurodegeneration in the diabetic brain: Neurodegeneration in *Alzheimer's disease* is caused by the formation of *neurofibrillary tangles* and the deposition of *extracellular β amyloid plaques*. Both pathways are facilitated by insulin resistance, the major cause of type 2 diabetes. Chronic hyperglycemia-generated advanced glycation end products (AGEs), oxidative stress and neuroinflammation are also important causes of neurodegeneration, thus providing critical links between diabetes and AD.

Causes and consequences of mitochondrial dysfunction: Multiple factors are known to cause mitochondrial dysfunction. These factors include aging, increased free fatty acids, hyperglycemia, **polymorphisms and DNA mutations in mitochondrial genome** and mutant protein(s) association with mitochondria. Dysfunctional mitochondria produce reduced ATP, decreased biogenesis, impaired β-oxidation and increased reactive oxygen species. These events may contribute to diabetes, obesity and insulin resistance ultimately causing Alzheimer's disease in elderly individuals.



METHODS

We analyzed previously published datasets from South Asian individuals (Pakistani; T2DM, n = 18; AD, n = 4) and African American participants (n = 12) from Washington, DC, USA. Socioeconomic and demographic variables were recorded. Gene expression profiling was performed using TaqMan Low-Density Array (TLDA) qRT-PCR targeting 96 transcripts associated with amyloid precursor protein (APP) processing pathways. Differentially expressed genes were analyzed using Ingenuity Pathway Analysis (IPA) to construct molecular networks and identify enriched signaling pathways and disease functions. We recruited healthy participants without diabetes, frequency-matched in age to the cases. The exclusion criteria included participants with HIV/AIDS, cancer, severe chronic illness, and major surgical procedure(s) in the last 5 years.



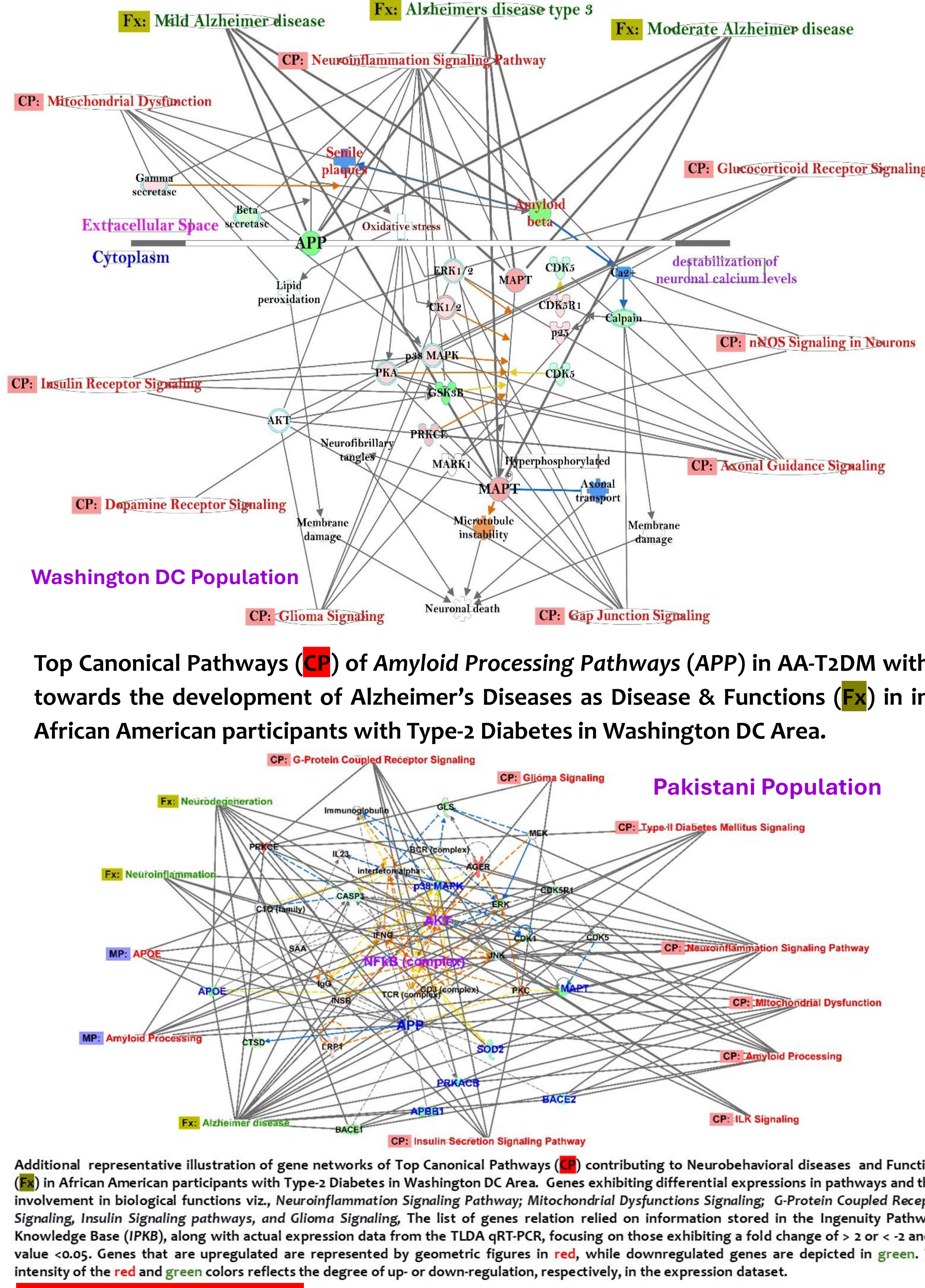
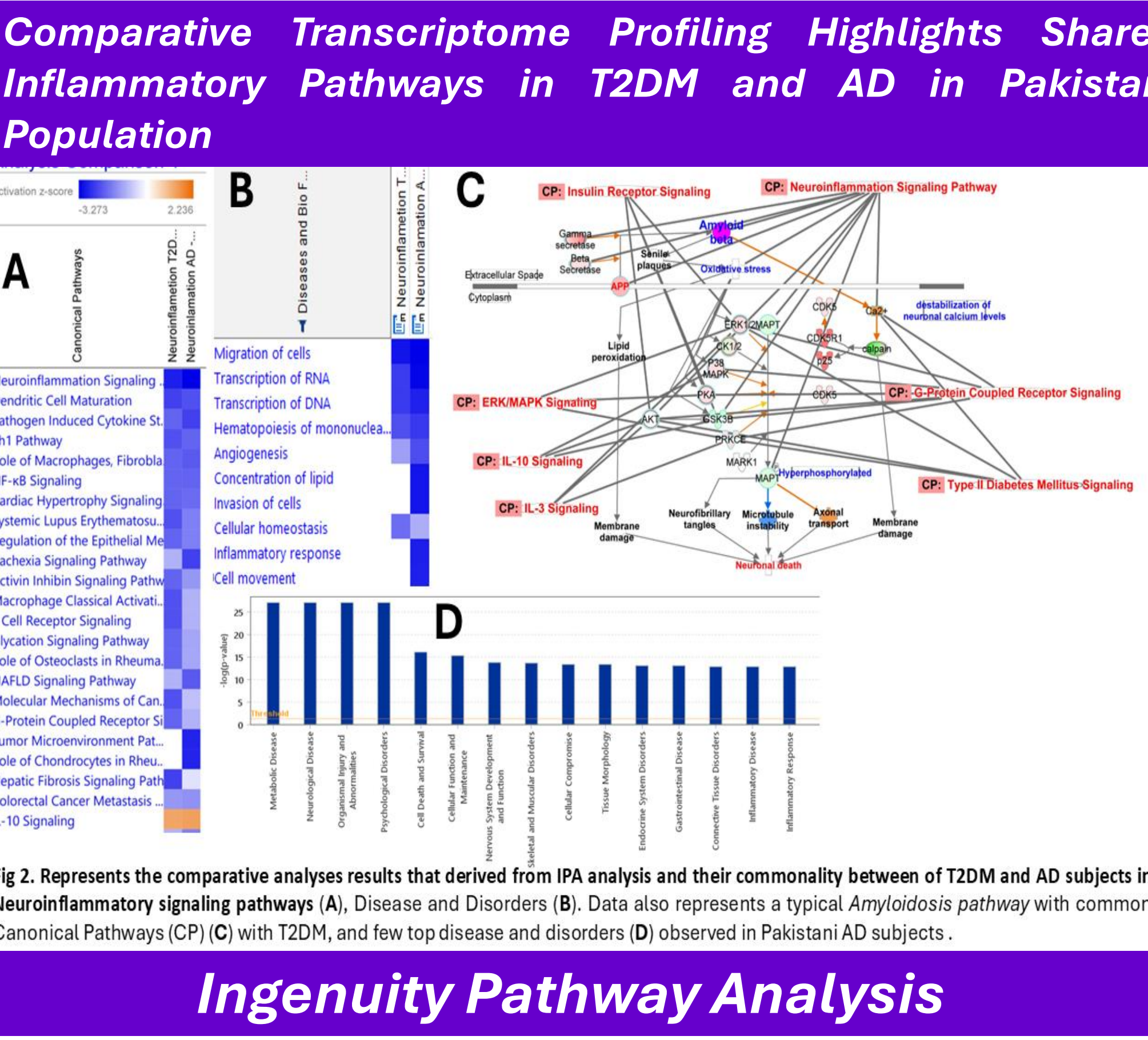
RESULTS

Table 1: Population Demography

	Control Group (n=12)	T2DM Group (n=12)
Male/Female	6/6	6/6
Age (Years)	59 ± 1.41	57.7 ± 5.61
BMI (Kg/m²)	26.2 ± 0.56	32.67 ± 5.37
HbA1C (mmol/mol)	5.6 ± 0.56	8.3 ± 2.83
Hypertension (%)	10	80
Heart Problem (%)	-	30

TaqMan Low Density Array Analysis

Across both populations, significant overlap ($p < 0.05$) was observed in dysregulated genes associated with key pathways, including *Neuroinflammation Signaling*, *Mitochondrial Dysfunction*, *G-Protein–Coupled Receptor Signaling*, *Insulin Signaling*, and *Glioma Signaling*. Key APP-related molecules identified included upregulation of APBB1, APBB3, LRPAP1, MAPK3, INSR, and GSK3B, with the downregulation of APBB2, CASP6, APOE, and PRKACB



This study demonstrates shared molecular and pathogenic mechanisms linking T2DM and AD across ethnically and geographically distinct populations. These findings highlight convergent neuroinflammatory and metabolic signaling pathways that may underline increased AD risk in individuals with T2DM and support the potential for early biomarker development and targeted prevention strategies. Notably, similarities in socioeconomic status and dietary patterns, including high cholesterol diet, were observed across populations and warrant further investigation in ongoing studies.

1.Mondal T, Noreen Z, Loffredo CA, et al. Transcriptomic Analysis of Alzheimer's Disease Pathways in a Pakistani Population. J Alzheimer Dis Rep. 2024;8(1):479-493., International Diabetes Federation. IDF Diabetes Atlas, 10th Ed. Brussels, Belgium: 2021. Available at: <https://www.diabetesatlas.org>; Alzheimer’s Association. 2021 Alzheimer’s Disease Facts and Figures. Alzheimer’s Dement 2021;17(3).; Marciani, D. J. (2017). Facing Alzheimer’s disease in the developing countries. Revista de Neuro-Psiquiatria, 80(2), 105-110.; World Health Organization, 2018, <https://www.who.int/news-room/fact-sheets>