

INTRODUCTION

- Parkinson's disease (PD) is the second most prevalent neurodegenerative condition after Alzheimer's disease
- There are few laboratory tests to track PD's progress due to its unknown pathophysiology
- Homocysteine, though its mechanism is unknown, may be a reliable predictor of cognitive decline
- Several aspects of homocysteine could lead to cognitive decline including (as seen in figure 1):

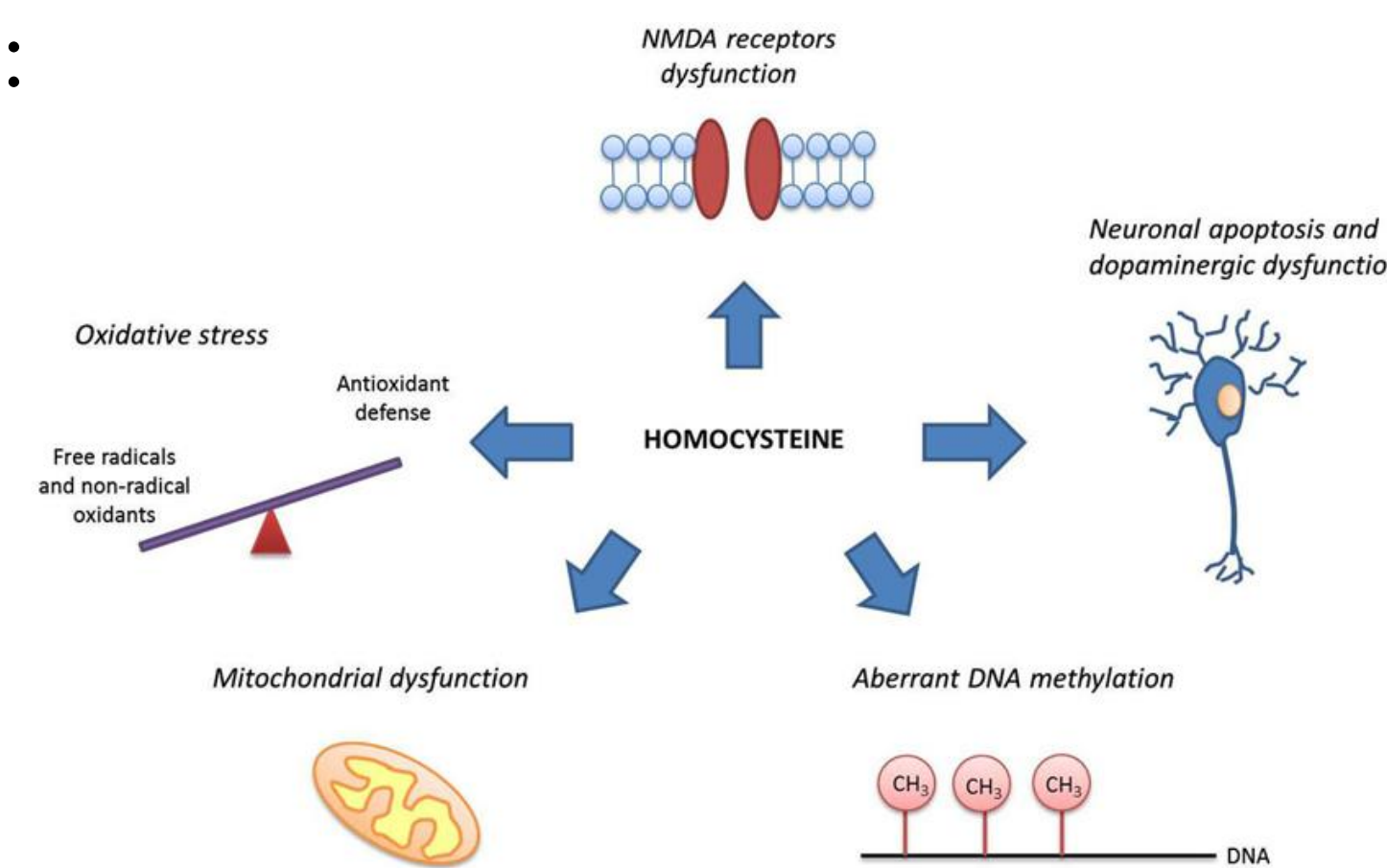


Figure 1. Homocysteine's effects on neurons².

- Interrupts DNA methylation¹
- Stimulates NMDA to an excitotoxic response¹
- Triggers neuronal apoptosis¹
- Increases free radicals¹
- Interrupts mitochondrial function¹
- Hyperhomocysteinemia is linked to vitamin B and folate deficiencies, as well as taking L-dopa
- The goal of this research is to analyze research articles for a relationship between homocysteine serum levels and cognitive decline in PD

CLINICAL QUESTION

Can hyperhomocysteinemia be linked as a causative agent in the progression of cognitive decline in PD?

METHODS

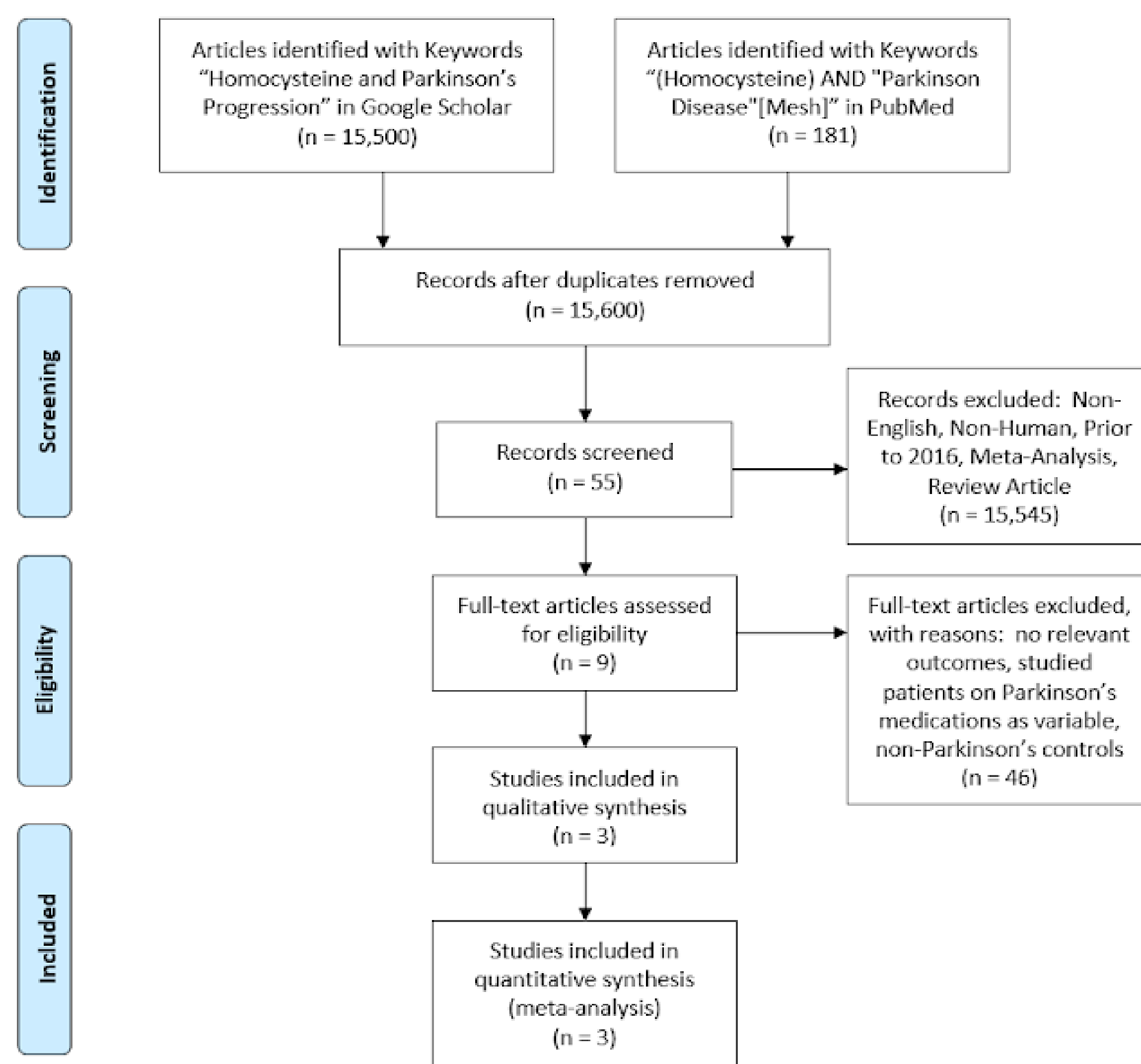


Figure 2. PRISMA flow diagram depicting the literature review resulting in the three studies evaluated.

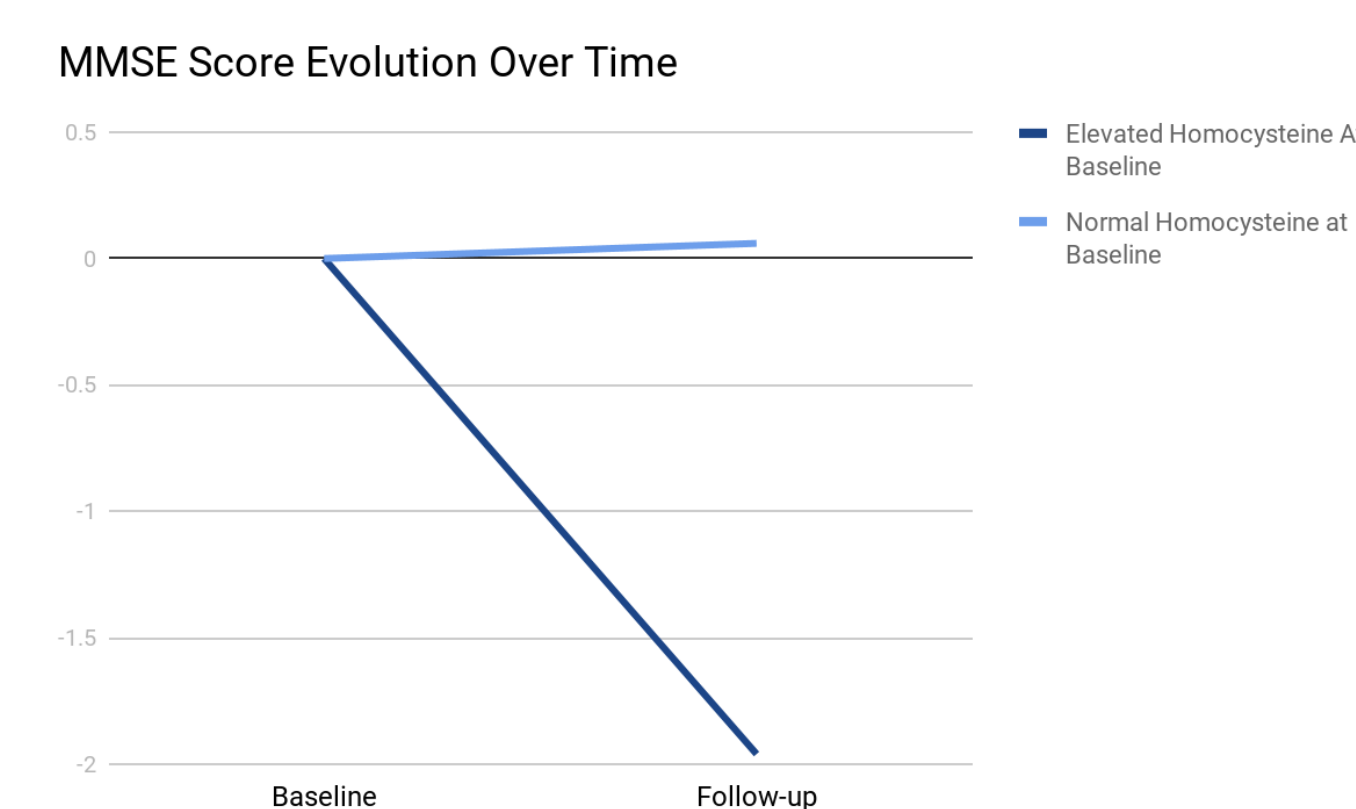
RESULTS

Study Comparison

Title & Author	Homocysteine and Cognitive Function in Parkinson's Disease, Licking et al. ⁴	Vitamin B12 and Homocysteine Levels Predict Different Outcomes in Early Parkinson's Disease, Christine et al. ⁵	Elevated Serum Homocysteine Levels Have Differential Gender-Specific Associations with Motor and Cognitive States in Parkinson's Disease, Bakeberg et al. ⁶
Year Published	2017	2018	2019
Sample Size	294	680 (456 follow up)	205
Journal	<i>Parkinsonism & Related Disorders</i>	<i>Movement Disorders</i>	<i>Parkinson's Disease</i>
Cognitive Measurement	Neurocognitive testing of memory, visuospatial, executive functioning, and language	UPDRS, ambulatory capacity score (sum of UPDRS items 13-15, 29&30), and MMSE, calculated as annualized rates of change.	MDS-UPDRS III and H&Y scale (physical), Clinical psychologist and Neuropsychological assessments, and ACE-R (cognitive)
Homocysteine Measurement	Homocysteine chromatography, Serum	Fasting total homocysteine (tHcy), Serum	Fasting total homocysteine (tHcy) Serum, collected prior to clinical or psychological assessments
Elevated Homocysteine Level Cut off	14 $\mu\text{mol/L}$	15 $\mu\text{mol/L}$	N/A
Outcomes	Elevated homocysteine was linked with verbal memory function and semantic fluency memory, but an overall causal relationship between homocysteine and cognitive function was unclear.	Elevated homocysteine predicted greater cognitive decline with decreased MMSE scores.	Elevated serum homocysteine levels are associated with a greater motor impairment in males with Parkinson's disease and poorer cognitive performance in females with Parkinson's disease.
Critique	Study had limited exclusion criteria for treatment. Treatments, like L-dopa, are known for altering homocysteine levels. But they corrected for several confounding variables.	Study was sponsored by the Michael J. Fox Foundation, potentially introducing bias. 224 patients lost to follow up. But there is a large sample size and only included patients without treatment.	Study didn't include patients with advanced PD and the ACE-R does not assess for executive function. But they controlled for medications, age, and gender.

Table 1: Table comparing the demographics of three articles^{4,5,6} analyzed in this review.

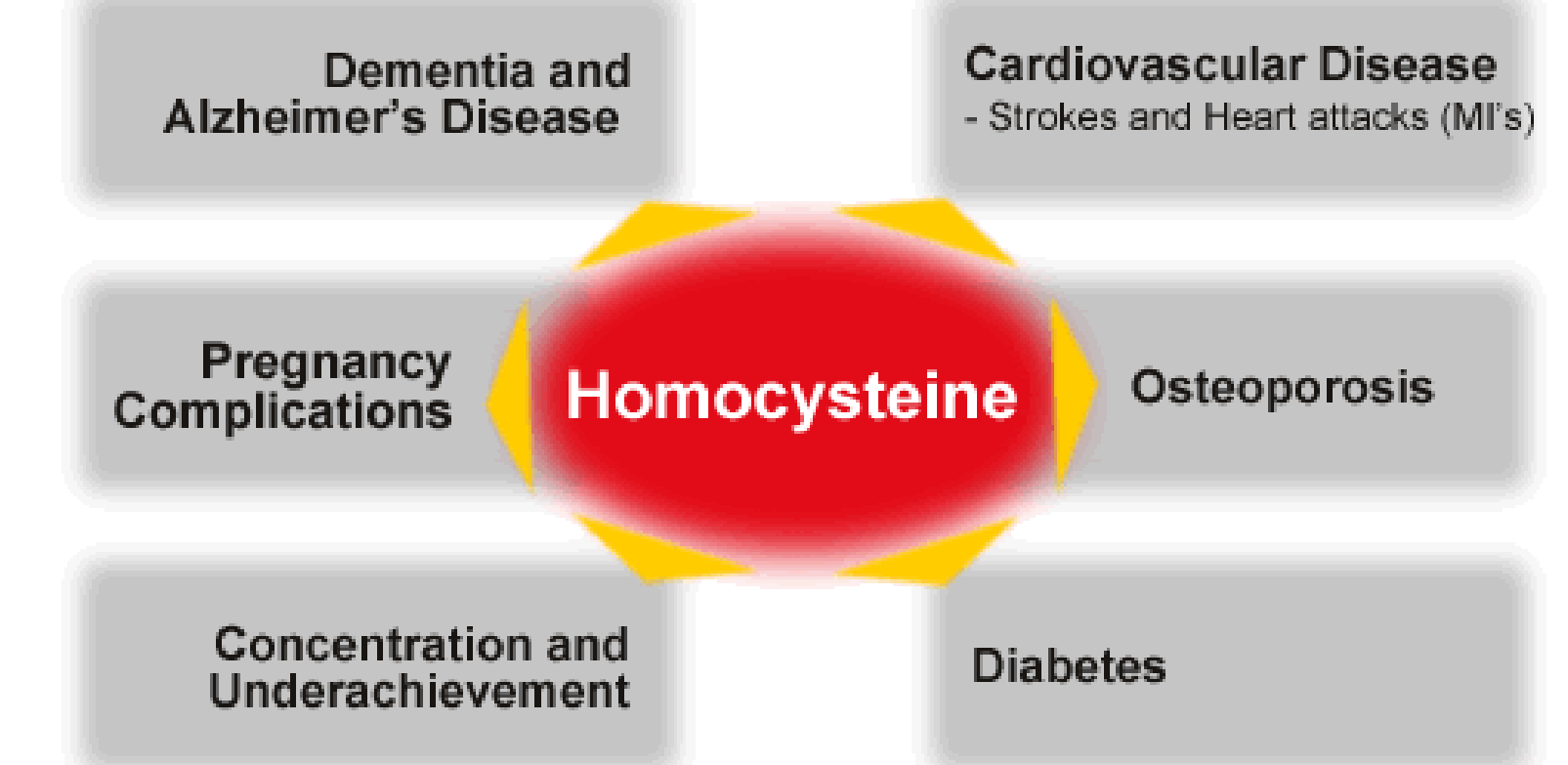
Figure 3. Line graph depicting a comparison in the change in Mini Mental Status Exam (MMSE) score from baseline to follow-up in those with elevated and normal homocysteine serum levels at baseline from Christine, et al.



DISCUSSION

- Many diseases see hyperhomocysteinemia as it progresses, as seen in figure 4.

Figure 4. Homocysteine is believed to contribute to a battery of metabolic, cardiovascular, and skeletal disorders⁶.



- Bakeberg et al, Christine, et al., and Licking, et al, found inversely proportional relationships between serum homocysteine levels and some aspects of cognition in specific populations in PD patients.
- Two variables, age and length of disease, amongst several other confounding variables, have an association with elevated serum homocysteine and cognitive decline in PD, as seen in Figure 5.

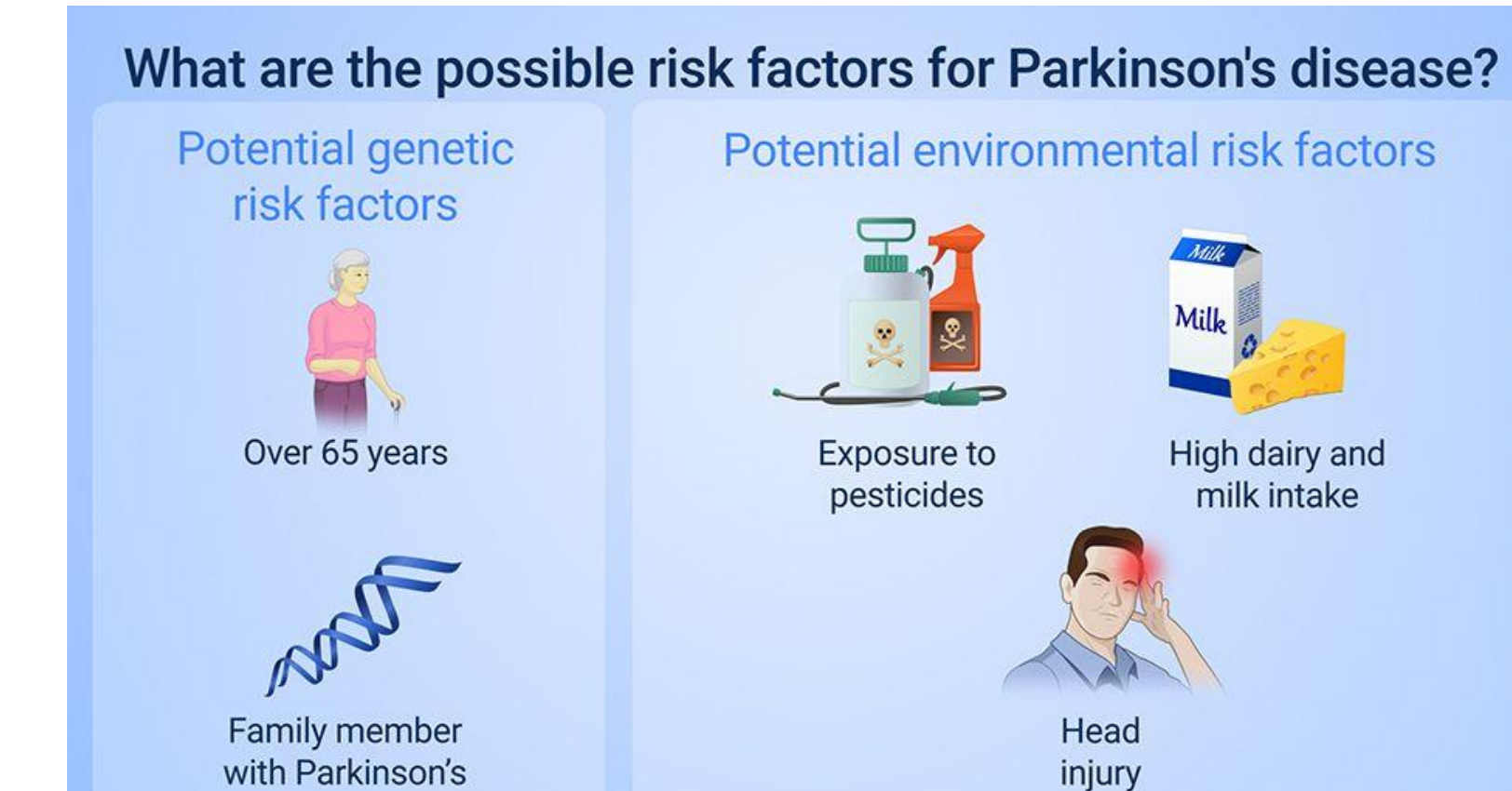


Figure 5. Though the pathophysiology of PD is not entirely understood, several factors are believed to contribute, making it difficult to isolate which ones can be attributed to its progression⁷.

- Due to confounding variables, it is difficult to isolate homocysteine in these studies as the cause of the cognitive decline.
- If future studies were able to better support the theory of the inverse relationship between homocysteine and cognitive decline in PD, treatment and monitoring of the disease could be changed and potentially improved.

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