Analysis of Diabetes Mellitus and Obese BMI as Risk Factors for Alzheimer's Disease and Vascular Dementia

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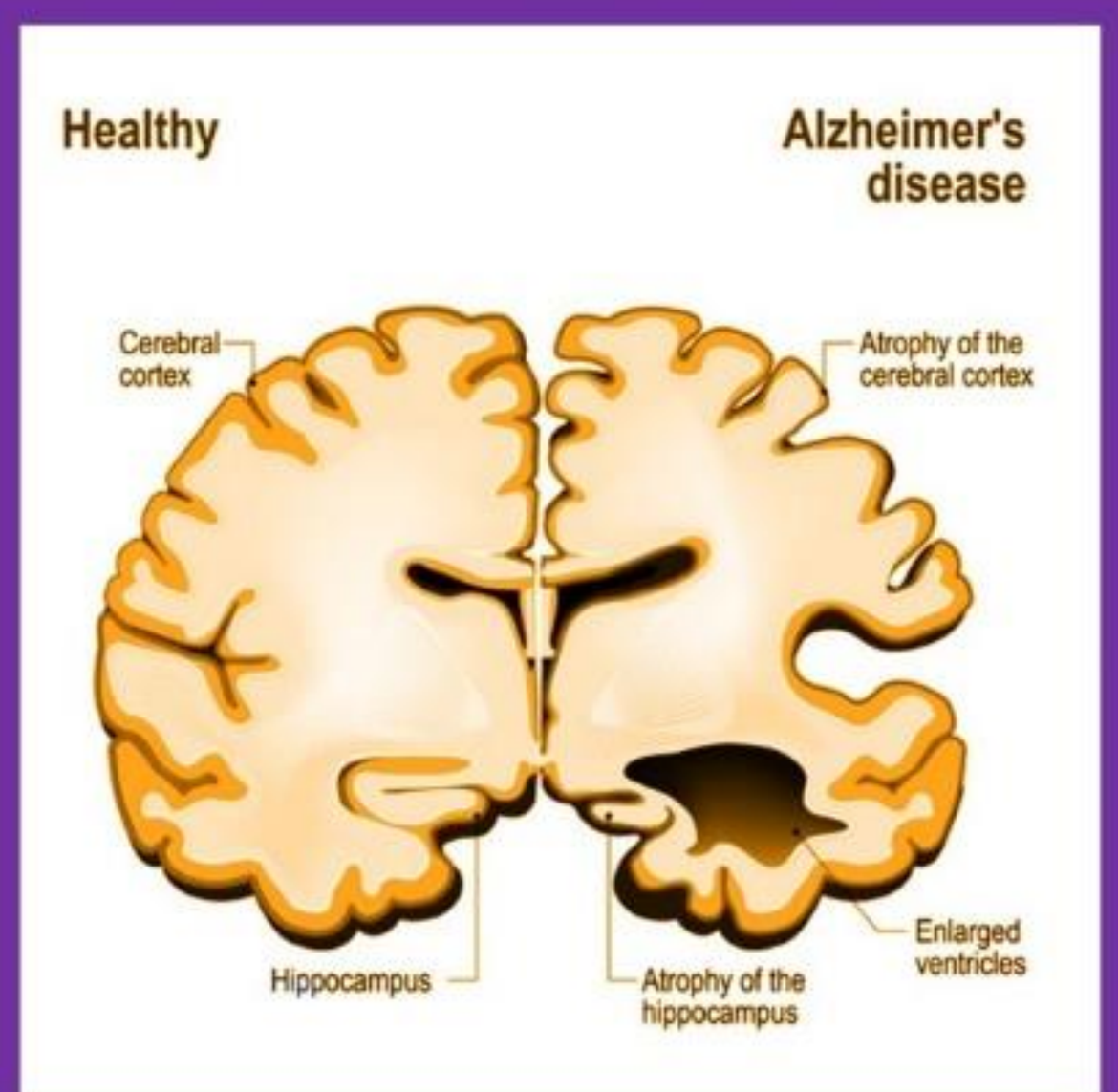
BACKGROUND



https://www.lifespan.io/news/distinct-amyloid-beta-prion-strains/

Dementia is a term used to describe a state of progressive cognitive decline and memory loss, for which there is currently no cure nor clear method of prevention. Dementia can be caused by a wide range of conditions including Alzheimer's disease, vascular dementia (sometimes termed vascular cognitive impairment), and Parkinson's Disease. Although these diseases all have differing physiopathology, they are united by their ability to bring ruin upon the afflicted and their families as the afflicted slowly loses most cognitive abilities and memory. On a personal level, I have had multiple family members pass away due to dementia caused by Alzheimer's disease and other conditions. As I began to study Alzheimer's disease and the different proposed risk factors, I grew particularly interested in some of the commonalities that Alzheimer's disease appeared to share with obesity symptoms and symptoms of Diabetes Mellitus, namely atherosclerosis. Interested to learn more about what united these conditions, as well as vascular dementia and all dementia, I began this study.

As stated previously, dementia in itself is not a disease, but rather a condition of continuous cognitive decline and loss of neurons usually marked by lesions in brain tissue or build up in cerebrovascular vessels caused by different diseases. The two diseases that will be studied here are vascular dementia and Alzheimer's disease, the two most common causational diseases of dementia. Vascular dementia is a condition where the blood vessels of the brain become blocked or otherwise damaged, leading to eventual tissue damage and cognitive decline as parts of the brain become damaged by these injuries in the blood vessels. The condition frequently arises after an episode like a stroke, where blood clots in the brain asphyxiate neurons and cause damage; dementia has also been associated with conditions like small vessel disease, cerebrovascular lesions, and cerebro-amyloid angiopathy. This differs from Alzheimer's disease, which causes a similar state of cognitive decline, but has different physiological markers. Alzheimer's disease is marked by an aggregation of plaques in the brain tissue and blood vessels made up of the beta amyloid protein (Aβ plaques). Beta amyloid is produced by the Alzheimer's Precursor Protein (APP) and has properties of neurotoxicity that lead to eventual brain damage and cognitive decline. It is also characterized by inclusions which cause microscopic lesions known as neuro-fibullary tangles made up of phosphorylated tau protein. A higher concentration of apolipoprotein E (APOE Ɛ4) has also been associated with the condition, and like the amyloid plaques, it is neurotoxic and leads to cognitive decline. Some of the main enzymes regulating the formations of these structures are the insulin degradation enzyme and others that normally break down Aβ protein, but they fail to work in dementia cases. For this meta-analysis, these conditions will be diagnosed by the original makers of the studies used, based largely on symptoms and the aforementioned bio-markers.

RATIONALE

The two risk factors being studied in this case are Diabetes Mellitus (types 1 and 2) and obese and overweight BMI. Diabetes Mellitus is a condition marked by hyperglycemia and a lack of or malfunctioning insulin protein. In this study, obesity is being defined as a BMI over 30, Overweight BMI will be categorized as any BMI between 20 and 25. As a reference point, any BMI under 20 will be considered normal. Diabetes is being classified on a yes/no diagnosis basis. These two conditions were chosen for this study because despite their interconnected nature, they have separate pathologies and understanding which has the stronger risk associated with each type of dementia may enlighten which specific mechanisms of these conditions are correlated with the types of dementia studied, or if shared mechanisms are more closely related.

Although some studies have established a connection between Diabetes Mellitus and obese/overweight BMI and a higher risk for Alzheimer's disease or vascular dementia, especially in the case of obesity, it is still contested; the exact links between these conditions are unclear. By analyzing a large number of studies on this topic through meta-analysis of odds and hazard ratios, this study seeks to understand the true correlation between these two conditions and Alzheimer's disease and vascular dementia. The conditions (Diabetes Mellitus and obese/overweight BMI) were chosen because they are the two most prevalent causes of dementia worldwide. The independent variables were chosen because of their previously established (but contested) connections to vascular dementia and Alzheimer's disease and their pathological links to the cerebrovascular system. For the sake of this meta-analysis, odds and hazard ratios will be equated because they both look at the risk that exposure to the variables (Diabetes or obesity) creates in becoming a case or control (demented or non-demented) over the period of the study with a defined end point for both.

INDEPENDENT/DEPENDENT VARIABLE

IV: Diabetes Mellitus and Categorical BMI

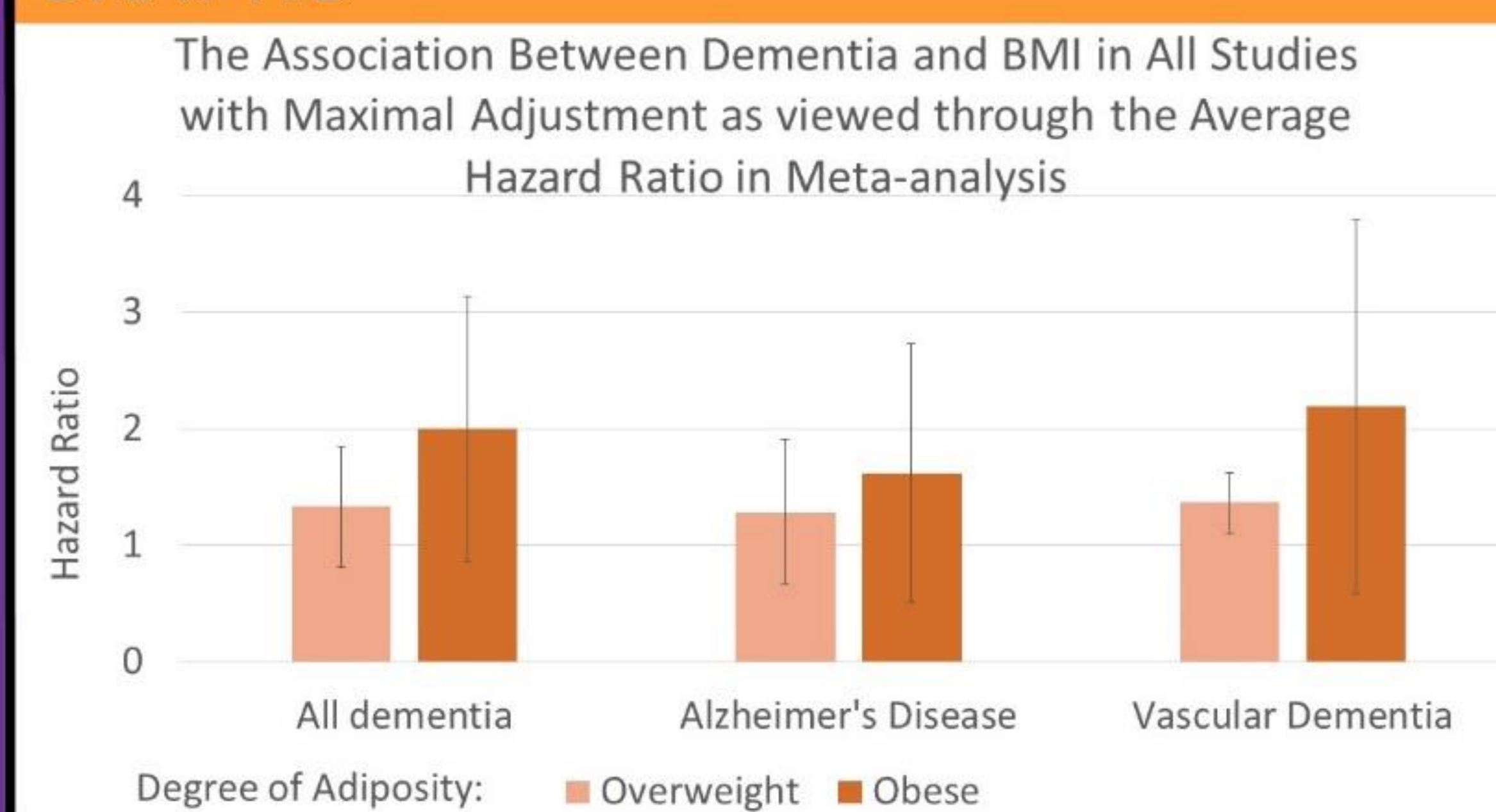
Diabetes Mellitus	Overweight BMI	Obese BMI
Based on yes/no diagnosis	25 ‹ x ‹ 30	x › 30

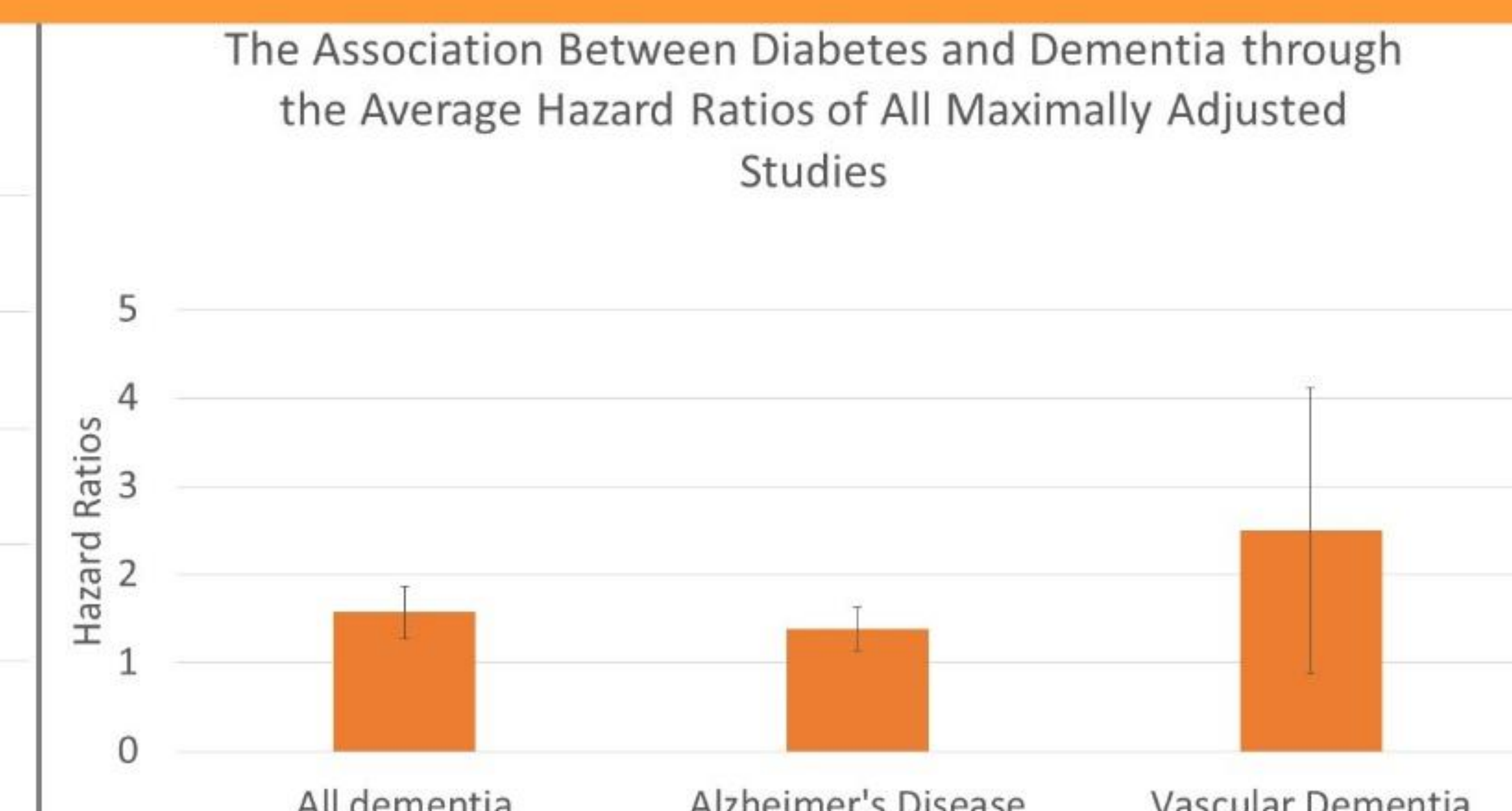
DV: The development of Alzheimer's Disease or Vascular Dementia

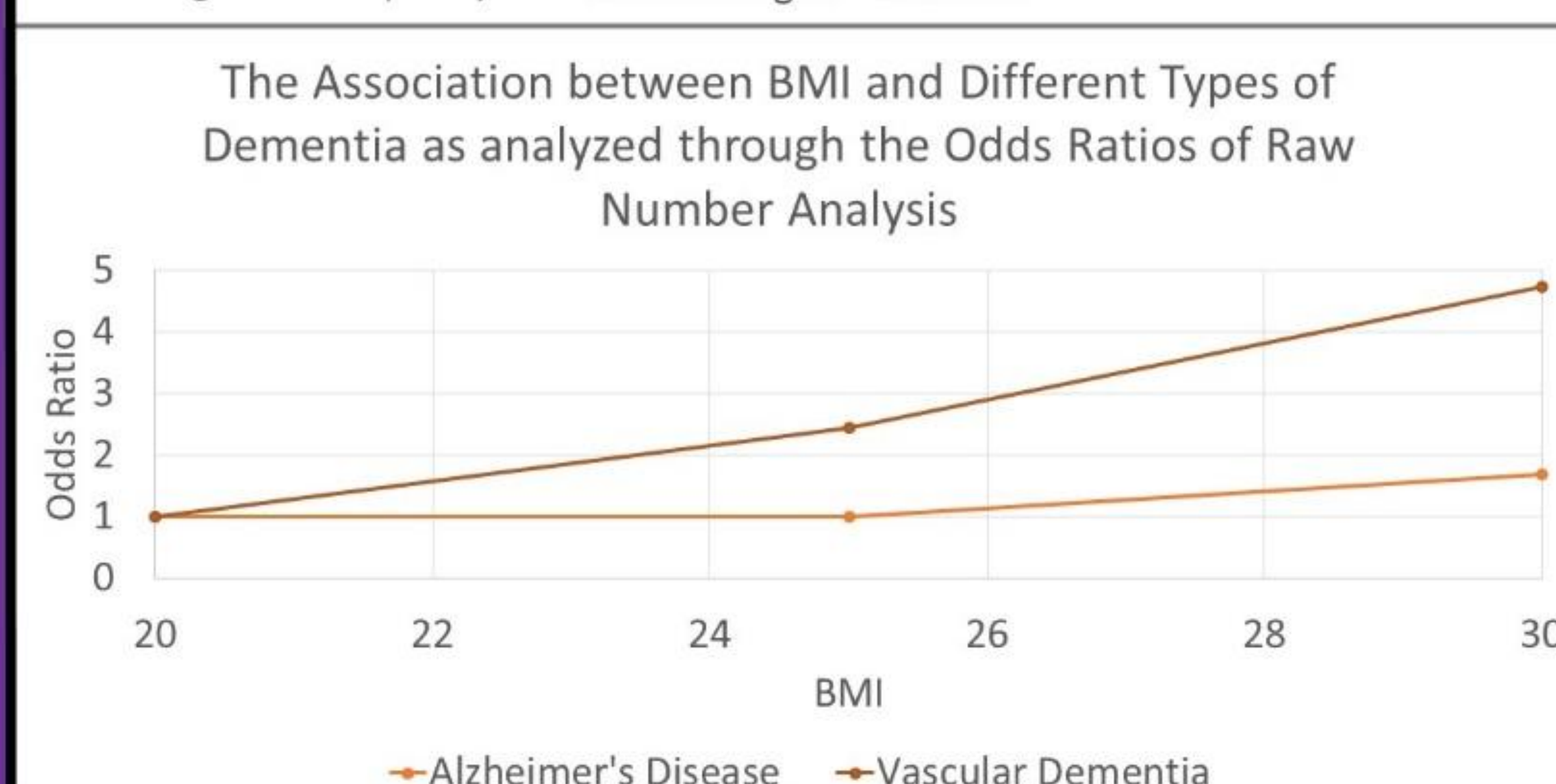
ABSTRACT

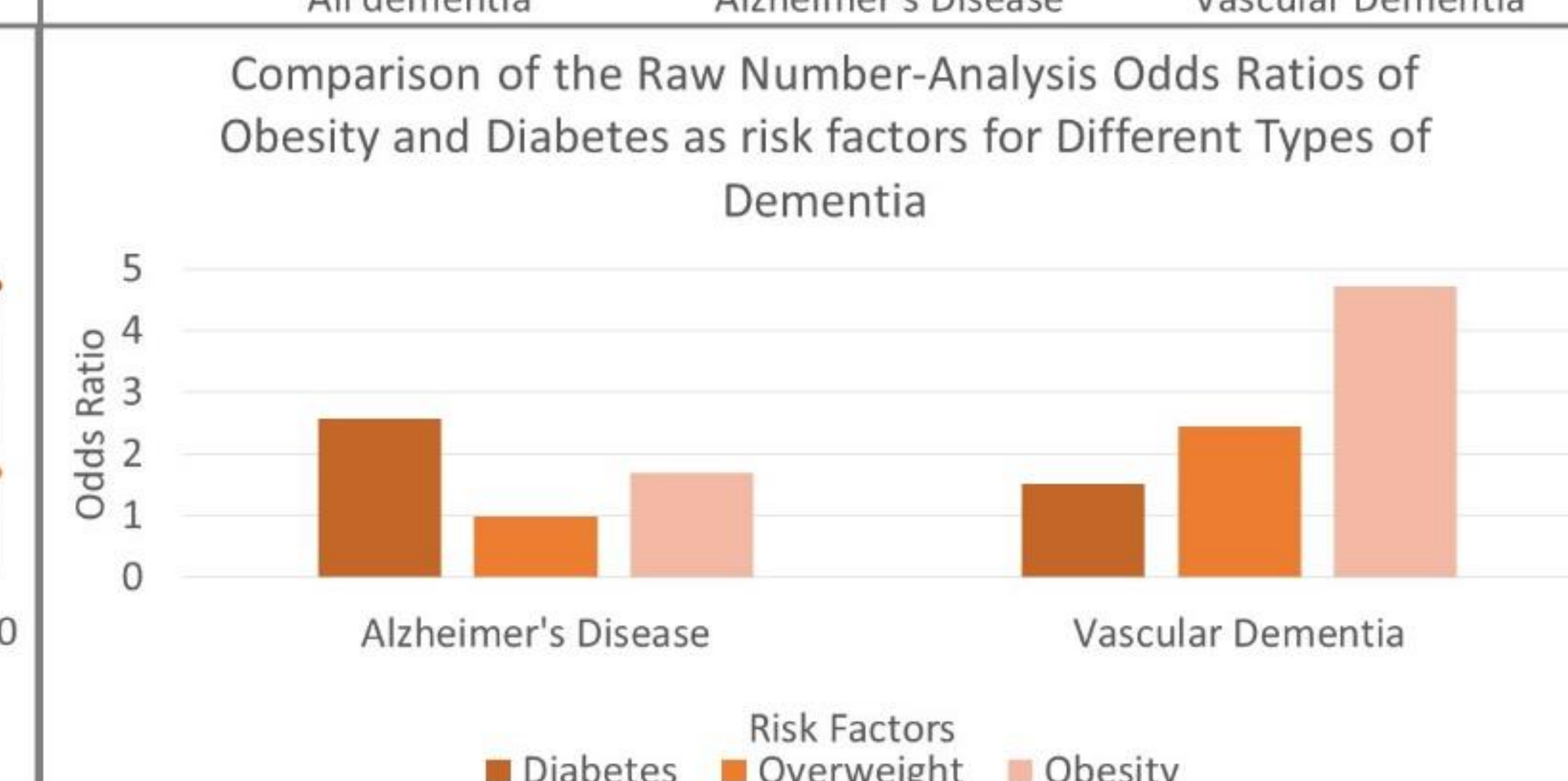
This study seeks to answer the question of the significance of Diabetes Mellitus and categorical obese BMI as risk factors for the development of dementia, particularly Alzheimer's disease and vascular dementia, and which risk factors were more significant for each type of dementia using a meta-analysis of previously published literature on the topic. Considering that dementia currently affects approximately 50 million people worldwide, with Alzheimer's disease and vascular dementia being the most common causes, understanding the answer to this question may highlight some overlooked elements of the pathologies of this dementia and enlighten new treatment routes. The meta-analysis came in two parts: first, where the average hazard ratio of different study subsets was compared across risk factors and the types of dementia, and second, an odds ratio analysis using the raw numbers provided by the studies. In all maximally adjusted studies, diabetes had an average hazard ratio of 1.39 and 2.50 when compared with Alzheimer's disease and vascular dementia respectively, and obesity had average hazard ratios of 1.996 and 2.19 when compared with Alzheimer's disease and vascular dementia respectively. In general, it was found that obesity and diabetes both had similarly strong correlations with all dementia, Alzheimer's disease, and vascular dementia. Obesity had a slightly stronger correlation for Alzheimer's disease and vice versa.

GRAPHS







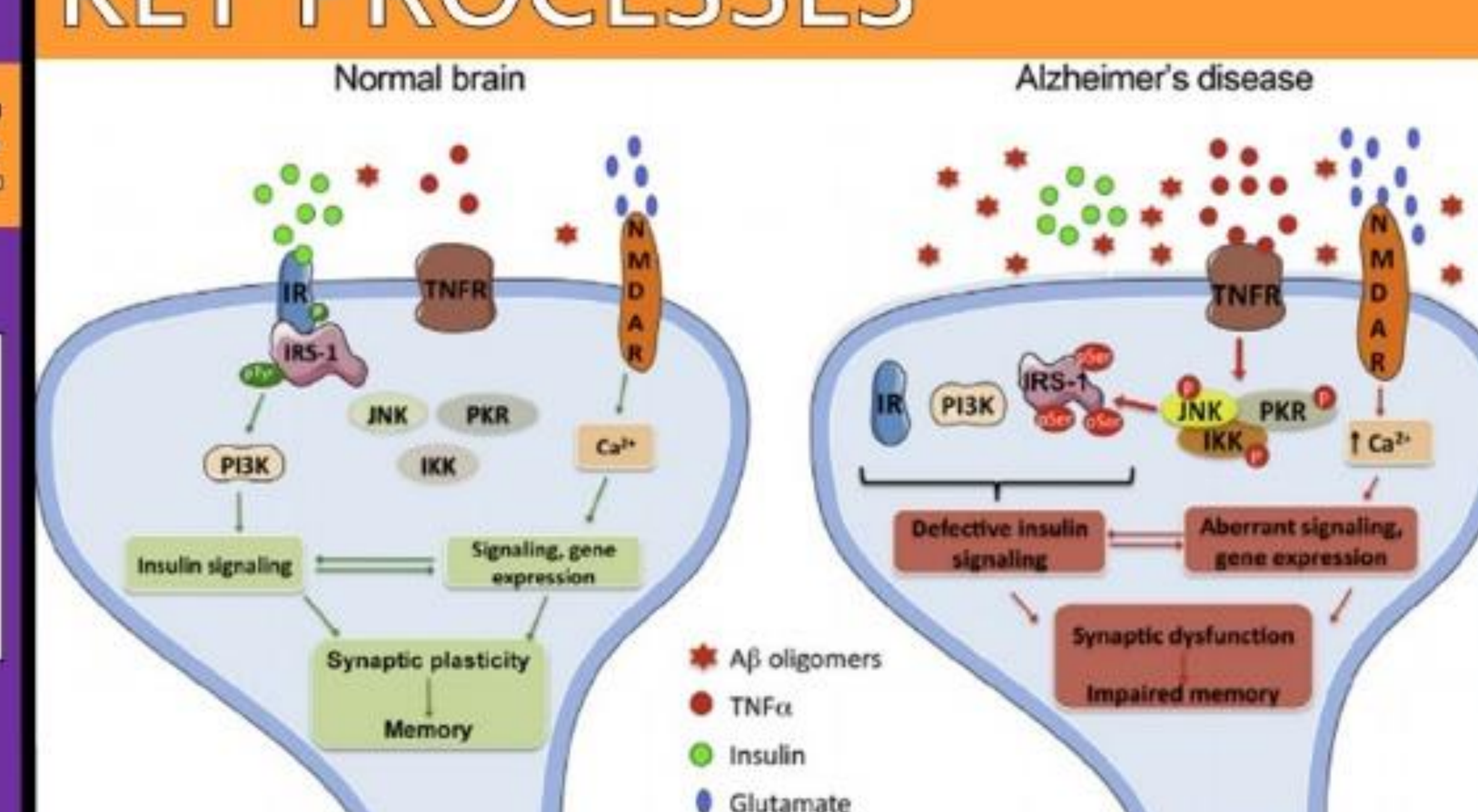


CONCLUSION

Alzheimer's disease had the highest correlation with obese BMI in the raw number analysis with an odds ratio of 2.58 compared to the correlation with obesity with an odds ratio of 1.69 and overweight BMI of .994. It should be noted, however, that in the meta-analysis portion, the average hazard ratios comparing Diabetes and Alzheimer's disease and the hazard ratios comparing obesity and Alzheimer's disease were much more similar. In the analysis of all studies with maximal adjustment, the Diabetes studies had an average hazard ratio of 1.39 compared to the average hazard ratio of obesity of 1.69. The average hazard ratio of the overweight BMIs was 1.28. Across all of the analyses, the hazard ratios and odds ratios displayed a pattern of being very close to or below 1, indicating a lack of significant correlation between overweight BMI and Alzheimer's disease. All risk factors had a decrease in their hazard ratio when adjusting for risk factors such as associated conditions (hypertension, heart disease, stroke). With the exception of the raw number analysis, obesity and Diabetes hazard ratios remained roughly similar with a difference of only .3 in the most extreme cases. This indicates that for Alzheimer's disease, both Diabetes and obesity are risk factors with no significant difference, with obesity having a slightly higher correlation. The association between Alzheimer's disease, Diabetes Mellitus, and obesity is supported by the pathologies of the conditions. For dementia and Diabetes Mellitus, there are links between insulin signaling and the build-up of amyloid plaques. Insulin is not only important to the metabolism of sugars in the blood, but also in basic neuron function. Insulin degradation protein is one of the important enzymes in breaking up amyloid plaque and aberrant insulin signaling leads to a greater accumulation of Aβ in the brain. Tau phosphorylation, another hallmark of Alzheimer's disease, is also connected to Diabetes pathology since the tau protein is modulated by insulin and insulin-like growth factors that regulate the phosphorylation of tau. Insulin deficiency increases abnormal activity of this kinase, leading to the creation of neuro-fibullary tangles. Although the connections between Diabetes and Alzheimer's disease were strong, the connections between obesity pathology and Alzheimer's disease were prevalent as well. An important protein in the production of Aβ, Bace1, reduces the signaling of leptin, an important protein in inhibiting hunger and maintaining energy balance in the body. The brains of obese individuals do not respond to leptin, contributing to overeating. The inhibition of Bace1 restores leptin signaling, in part explaining the connections between obesity and Alzheimer's disease.

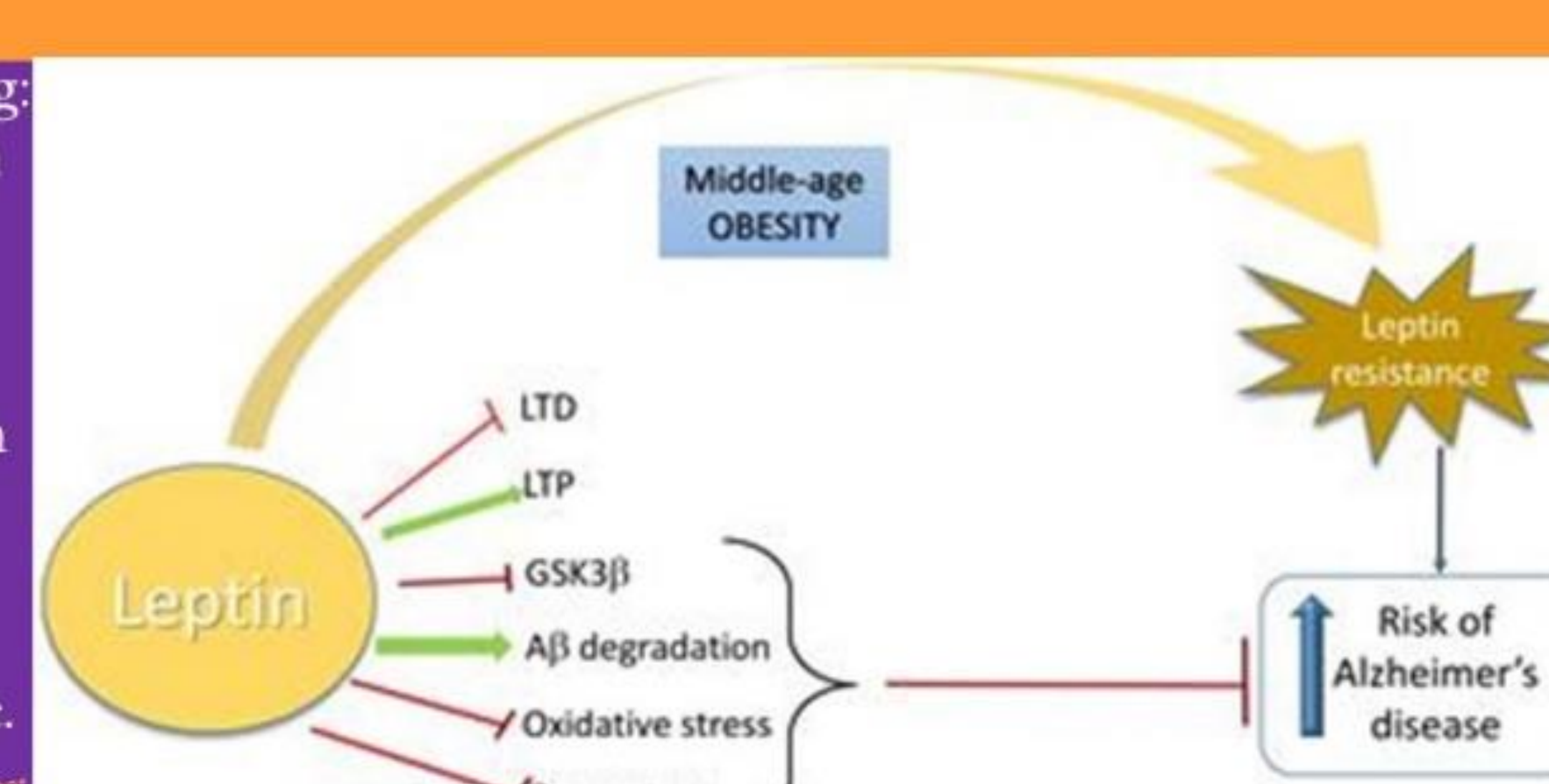
Vascular dementia, in comparison to the results for Alzheimer's disease, had a slightly clearer answer to which of the risk factors was the most significant in all studies by the raw number analysis. In all maximally adjusted studies, the average hazard ratio for obesity was 2.19 while the average hazard ratio for dementia was 2.50. The raw number analysis differed dramatically from the rest since its odds ratio for obesity was 4.73 compared to 1.52 for the Diabetes hazard ratio. The hazard ratios for overweight BMI, as in the studies for Alzheimer's disease, almost always remained near 1. These results indicate that among the meta-analyzed studies, Diabetes was the stronger risk factor (but not significantly different from obesity), and in the raw number analysis, obesity was by far the strongest risk factor, but its standard deviation was large and completely overlapped with the standard deviation for the diabetes studies, indicating that they are not statistically different. Unlike Alzheimer's disease, the exact definitions of vascular dementia are unclear. It is generally accepted to be any form of dementia or cognitive impairment caused by lesions or blockages in the brain's blood vessels. Some of the main causational conditions are believed to be Small and Large Vessel Disease and vascular lesions. One of the possible explanations for its relationship with obesity lies in obesity's prevalent role in vascular dysfunction and the development of atherosclerosis. This is especially significant since the atherosclerosis of the brain's blood vessels is one of the most common traits of vascular dementia. The connection with Diabetes is less clear. It has been suggested that hyperglycemia indicative of Diabetes may trigger oxidative stress that activates PKC, triggering APP to produce Aβ. This could lead to an expression of cognitive decline by previously discussed mechanisms. Although not completely definitive, there does appear to be a connection between the pathology of vascular dementia and Diabetes and obesity that is supported by this lab's meta-analysis.

KEY PROCESSES



Aberrant Insulin Signaling: Normal insulin signaling in neurons leads to the activation of P13K aiding downstream in memory plasticity, but when insulin signaling pathways are disrupted, amyloid beta blocks insulin signaling, leading to cognitive decline.

1. fig1_260215925 https://www.researchgate.net/figure/Impaired-neuronal-insulin-signaling-in-Alzheimers-disease-AD-Schematic-outline-of
2. https://www.frontiersin.org/articles/10.3389/fnins.2019.00508/full



Leptin Resistance: Leptin, via negative feedback pathways can decrease insulin release and lead to aberrant signaling. Leptin resistance can result from obesity as it is also linked to hunger resistance.

DIABETES ANALYSIS PROCEDURE

1. Locate the database from which studies will be drawn. For this meta-analysis, the AlzRisk database was the primary source.
2. To locate and gather diabetes studies, go to the database and search for studies that are defined as studying the relationship between Alzheimer's disease or vascular dementia and Diabetes, with diabetes categorized as a yes or no diagnosis.
3. Go through all available studies and rule out any that are inaccessible to the researcher or do not focus on the relationship between Vascular Dementia, Alzheimer's Disease, and Diabetes.
4. From all studies, organize the available hazard ratios into tables based upon their sourced study and what type of dementia they examine, noting the confidence intervals for each Hazard Ratio and if/how the Hazard Ratio has been adjusted.
5. If available, take the raw subject numbers of each study, add, and organize them into groups of Diabetes Present/not present (exposed/unexposed) Alzheimer's disease present/not present (cases/controls). Repeat for numbers pertaining to vascular dementia.
6. Take the data groups from step 5 and organize them into a table based on their exposed/unexposed and case/control statuses: this is the raw numbers data table.
7. For all hazard ratios that only adjust for gender and education, or nothing at all, label them as minimally adjusted and exclude them from this meta-analysis.
8. For all hazard ratios that adjust for upwards of 5 confounding factors (hypertension, Heart Disease APOE ε4 lipoprotein allele, etc), label them as maximally adjusted.
9. Organize these values into a data table differentiating hazard ratios that apply to VD and AD, noting which studies correlate with which numbers.
10. For each table, take the averages of the hazard ratios for Vascular Dementia, Alzheimer's Disease separately.
11. Taking the raw numbers from the raw numbers data table collected in steps 5-6. use the odds ratio equation for the numbers pertaining to each type of dementia.
12. Record and analyze data.

$$\text{Odds Ratio} = \frac{(exposed\ cases)/(non{-}exposed\ cases)}{(exposed\ controls)/(non{-}exposed\ controls)}$$

OBESITY ANALYSIS PROCEDURE

1. Repeat step 1 of the Diabetes analysis.
2. To locate and gather diabetes studies, go to the database and search for studies that are defined as studying the relationship between dementia and obesity, with obesity treated as a categorized variable based on BMI.
3. Go through all available studies and rule out any that are inaccessible to the researcher or do not focus on the relationship between vascular dementia, Alzheimer's disease, and obesity.
4. Rule out any studies where the normal/reference BMI for hazard ratio calculation does not closely line up with the normal BMI value of this meta-analysis (‹ 25).
5. Repeat step 4 of the Diabetes procedure.
6. Label hazard ratios as following: those that pertain to a BMI of under 25 as normal weight, between 25 and 30 as overweight, and over 30 as obese.
7. If available, take the raw subject numbers of each study, add, and organize them into groups of overweight/normal weight (exposed/unexposed) Alzheimer's Disease present/not present (cases/controls). Repeat for numbers pertaining to vascular dementia.
8. Repeat step 7, but define exposed/unexposed as obese/normal weight.
9. Take the data groups from step 9-10 and organize them into a table based on their exposed/unexposed and case/control statuses; this is the raw numbers data table.
10. Repeat steps 7-8 of the diabetes analysis.
12. Based on the definitions outlined in steps 5-8, organize hazard ratios categorized as overweight into a data table. In this table, note to which type of dementia the hazard ratios apply.
13. Repeat step 14 for hazard ratios categorized as obese.
14. For the overweight hazard ratio table and the obese hazard ratio table take the averages of the hazard ratios for vascular dementia and Alzheimer's disease separately.
15. Taking the raw numbers from the raw numbers data table collected in steps 5-6, use the odds ratio equation for the numbers pertaining to each type of dementia, still separated by the obese and overweight categorizations.
16. Record and analyze data.

VD, AD, AND NORMAL MRI

1. https://radiopaedia.org/articles/vascular-dementia?lang=us 2. https://radiopaedia.org/cases/normal-brain-mri-4?lang=us
3. https://radiopaedia.org/articles/alzheimer-disease-1

Shown here are brain scans of Vascular Dementia (Left), Alzheimer's Disease (Middle), and a normal brain (Right). These images present clearly the degree of cognitive decay that can result from these three conditions. The Vascular Dementia and Alzheimer's scans both show dark areas where brain tissue has been killed from neurotoxic substances (such as tau tangles) or asphyxiation, as well as white matter lesions. Both of these are not present in the normal brain. The grey tissue is healthy brain, white and black areas inside the brain are damaged or dead.