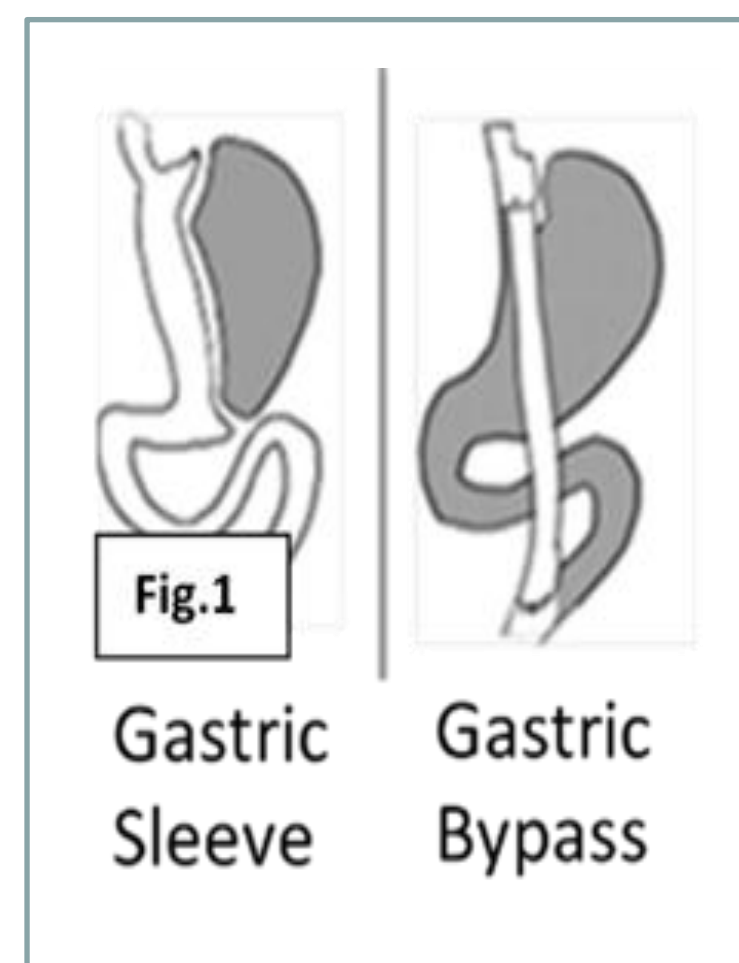


BACKGROUND

Patients with Alzheimer's disease usually present with concomitant diseases, including hypertension, obesity, diabetes mellitus type 2 (T2D), and dyslipidemias.¹ Many of these individuals also have central obesity, associated with visuospatial, executive ability, and language function and elevated Aβ40, Aβ42, and tau protein serum levels.²

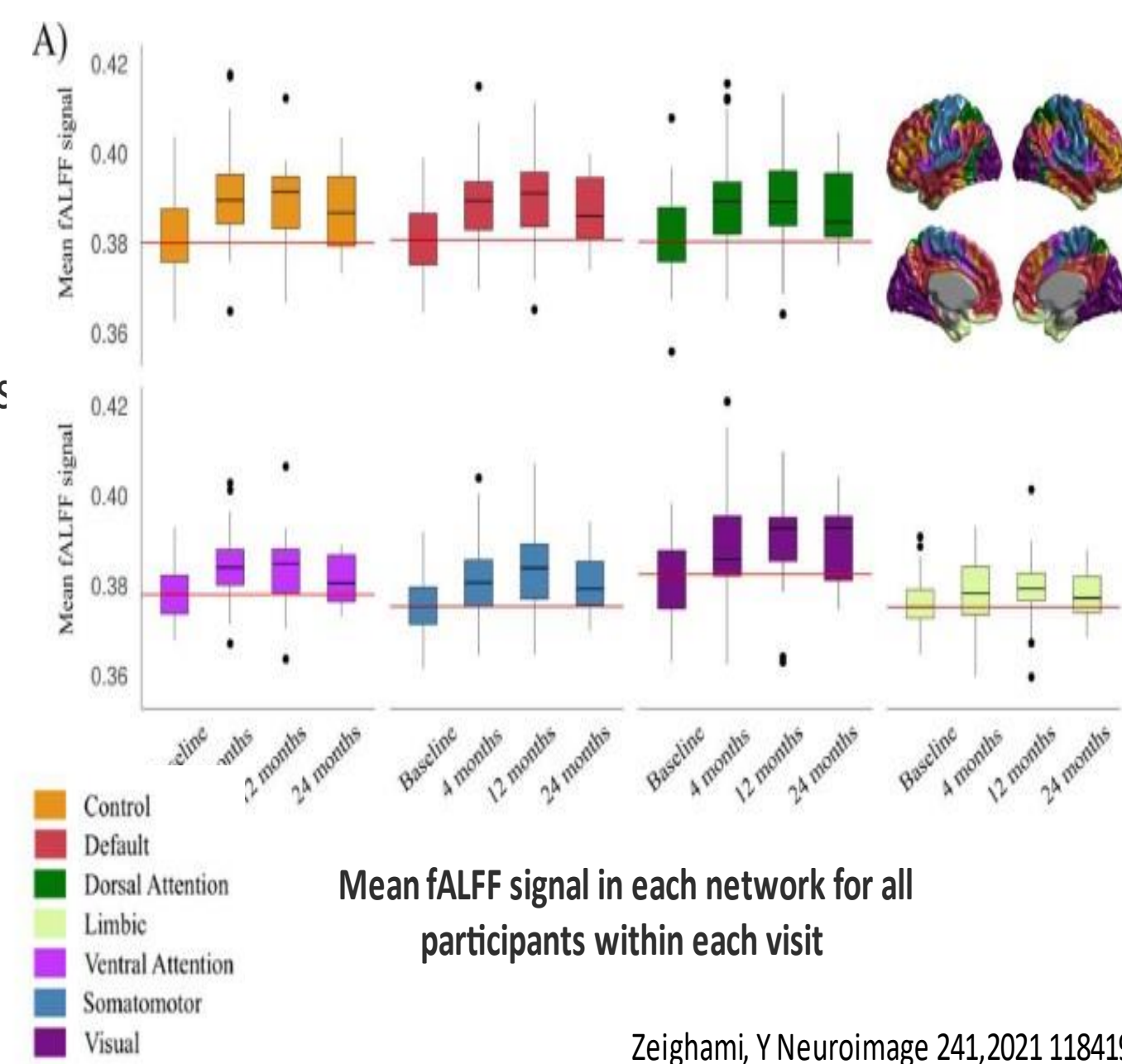
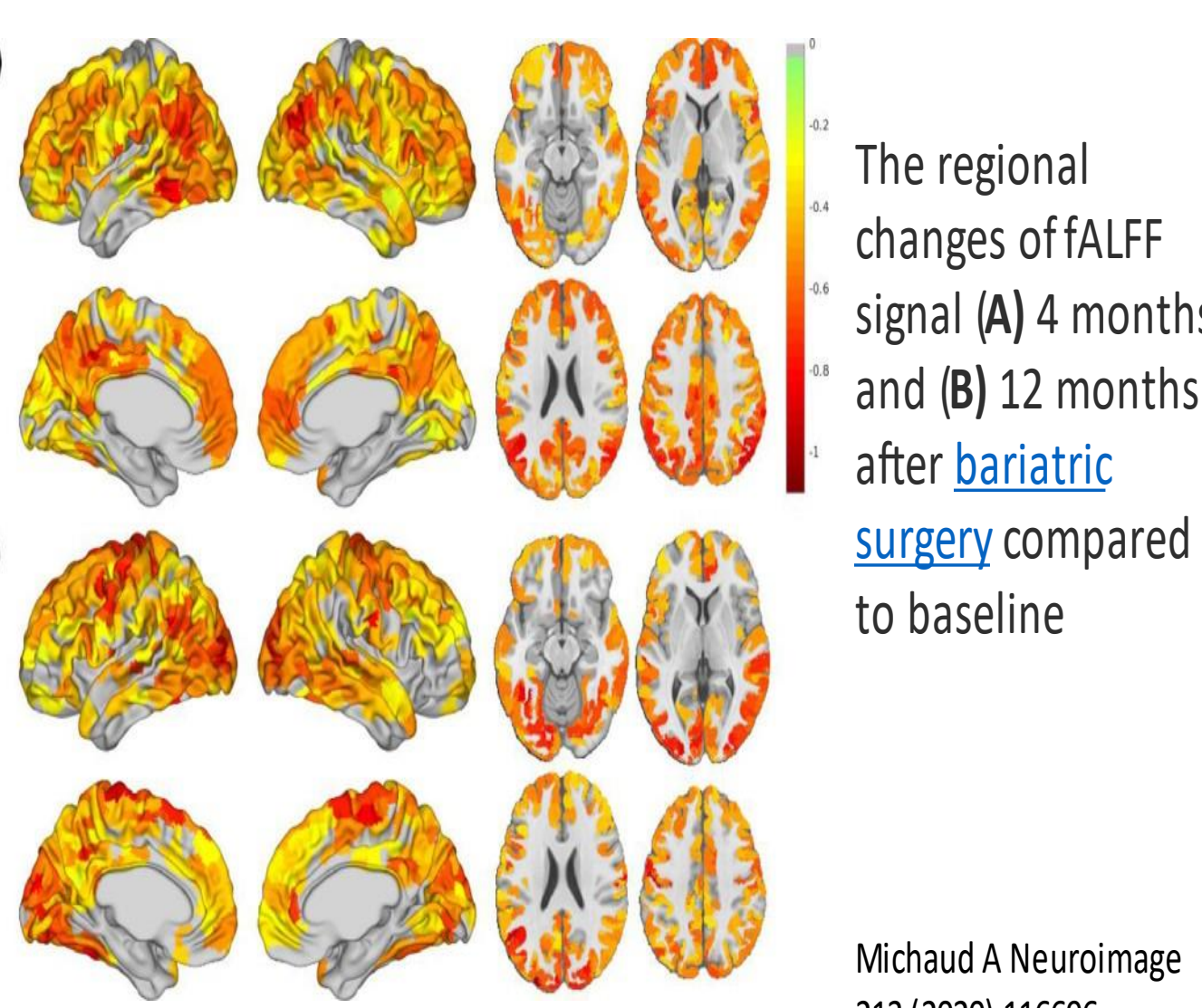


Bariatric surgery leads to rapid, full and durable remissions of these associated illnesses, often grouped as the "metabolic syndrome".^{3, 4} For example, the gastric sleeve and gastric bypass (Fig. 1) produce remission of T2D within one week.

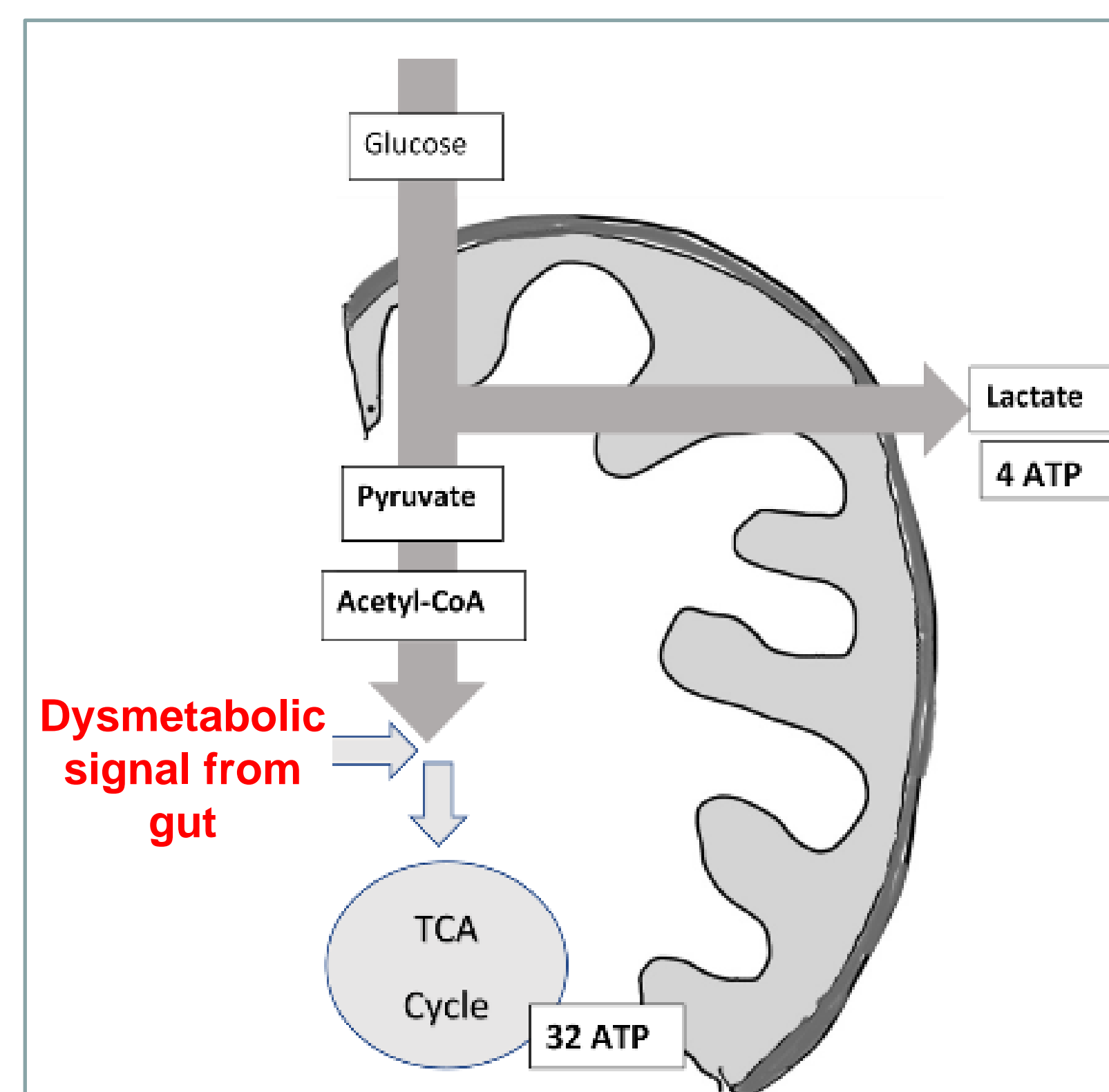
fMRI imaging comparing pre and postoperative brain status presents convincing evidence of improved brain function following bariatric surgery.

Improved brain function following bariatric surgery reflected by functional MRI

Spontaneous neural activity changes after bariatric surgery

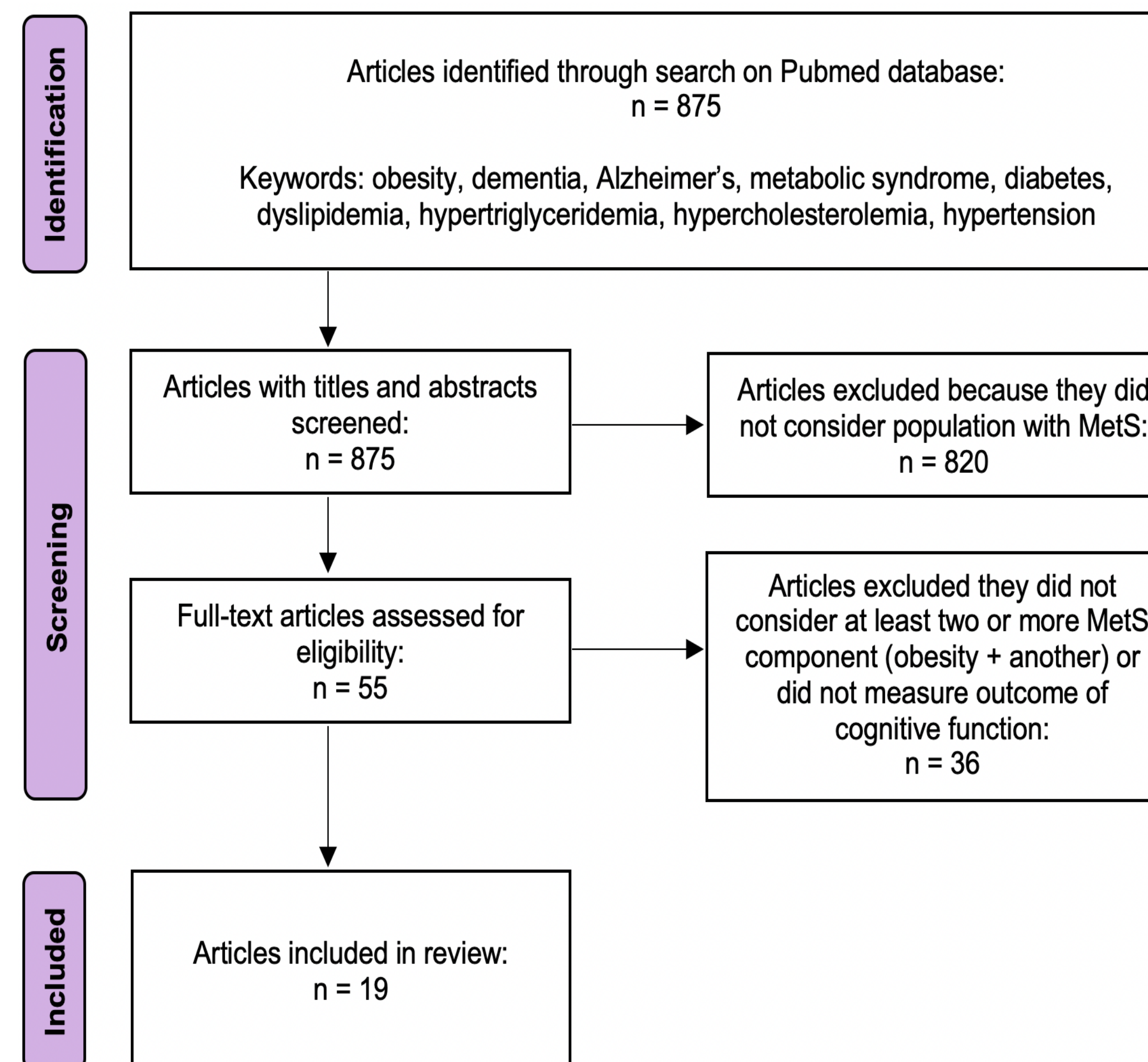


Because the only intervention is the surgery, these observations support the hypothesis that the metabolic syndrome is due to a dysmetabolic signal from the foregut that limits the pathway of glucose and fatty acids into the TCA cycle.



METHODS

PubMed was used to search for the following terms: dementia, Alzheimer's, metabolic syndrome, obesity, diabetes, dyslipidemia, hypertriglyceridemia, hypercholesterolemia, and hypertension. Included studies considered patients with obesity and at least one other MetS component at baseline with at least a 2 year follow-up screening for cognitive decline, as well as epidemiologic reviews.



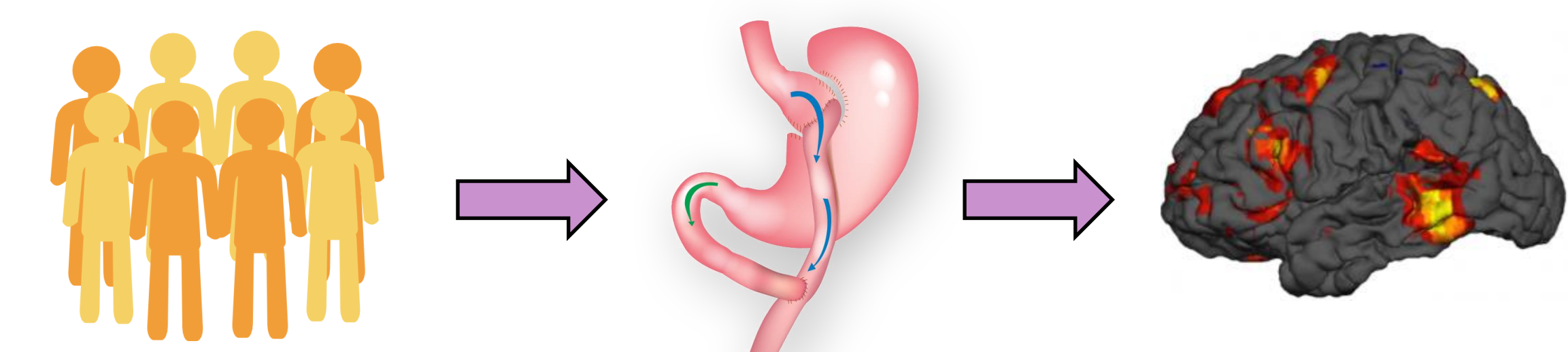
RESULTS

Our systematic review corroborated our hypothesis that Alzheimer's disease was related to the metabolic syndrome.

| Author, Year | Methods | Results / Conclusions |
|-----------------|---|---|
| Sanderlin, 2017 | 113 patients with MCI were grouped based on BMI and BMI related disorders. Cognitive data was collected over a 10 year period | Within mild cognitive impairment, body mass index and related disorders, type-2-diabetes mellitus and obstructive sleep apnea, showed a higher rate of psychopathologic changes |
| Clark, 2019 | 207 participants completed neuropsychological evaluations and a PET scan or lumbar puncture as well as risk factor assessments in 3-5 visits (6-10 years follow-up) | The presence of hypertension and obesity in midlife may exacerbate subtle cognitive decline associated with Aβ deposition. These results have potentially important implications for asymptomatic adults with elevated Aβ |
| Luchsinger 2008 | Review of the epidemiologic evidence linking the continuum of adiposity, hyperinsulinemia, and diabetes with Alzheimer's disease | These associations suggest a large proportion of the world population may be at increased risk of Alzheimer's disease given the trends for increasing prevalence of overweight, obesity, hyperinsulinemia, and diabetes |
| Tsai 2016 | 2252 individuals were enrolled in this study which surveyed the effects of characteristics of Mets on the individuals' cognitive performances as measured with the digit symbol substitution test (DSST) over 2 year period | Cognitive decline was correlated with each of the constituents of MetS. The characteristics of Mets that were most strongly associated with cognitive decline were high plasma glucose and elevated blood pressure |
| Marseglia 2021 | 1131 participants were examined during 2014-2016 for MetS and five domains of cognitive function | MetS was associated with poorer cognitive performance, particularly in the domains of attention/perceptual speed, executive function, and verbal fluency |
| Angoff 2022 | 2170 participants were divided into 4 groups based on obesity and metabolic health status (MH, MH obese, MU, MU obese) and brain structure and function were measured | In this cross-sectional cohort study of younger to middle-aged adults, poor metabolic health and obesity were associated with structural and functional evidence of brain aging |

CONCLUSION

We hypothesize that **dementia is an expression of the metabolic syndrome**. We are participating in an application to the NIH to conduct an exploratory prospective trial to evaluate the potential effect of bariatric surgery on improving cognitive function in obese patients with chronic brain disease. This is possibly the first effective treatment for Alzheimer's disease.



Patients with mild to moderate chronic brain disease, obesity, and T2D → Patients undergo bariatric surgery → Evaluation of cognitive function

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