Casual Friday Series

# Fatty Liver, Foggy Brain

A Biogenetix Clinical Presentation

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# Disclaimer

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- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Lifestyle + Genetics = NAFLD

National Institute of Diabetes and Digestive and Kidney Diseases

Nonalcoholic fatty liver disease (NAFLD) is a condition in which excess fat is stored in your liver. This buildup of fat is not caused by heavy alcohol use. When heavy alcohol use causes fat to build up in the liver, this condition is called alcohol-associated liver disease.

Two types of NAFLD are nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). People typically develop one type of NAFLD or the other, although sometimes people with one form are later diagnosed with the other form of NAFLD.

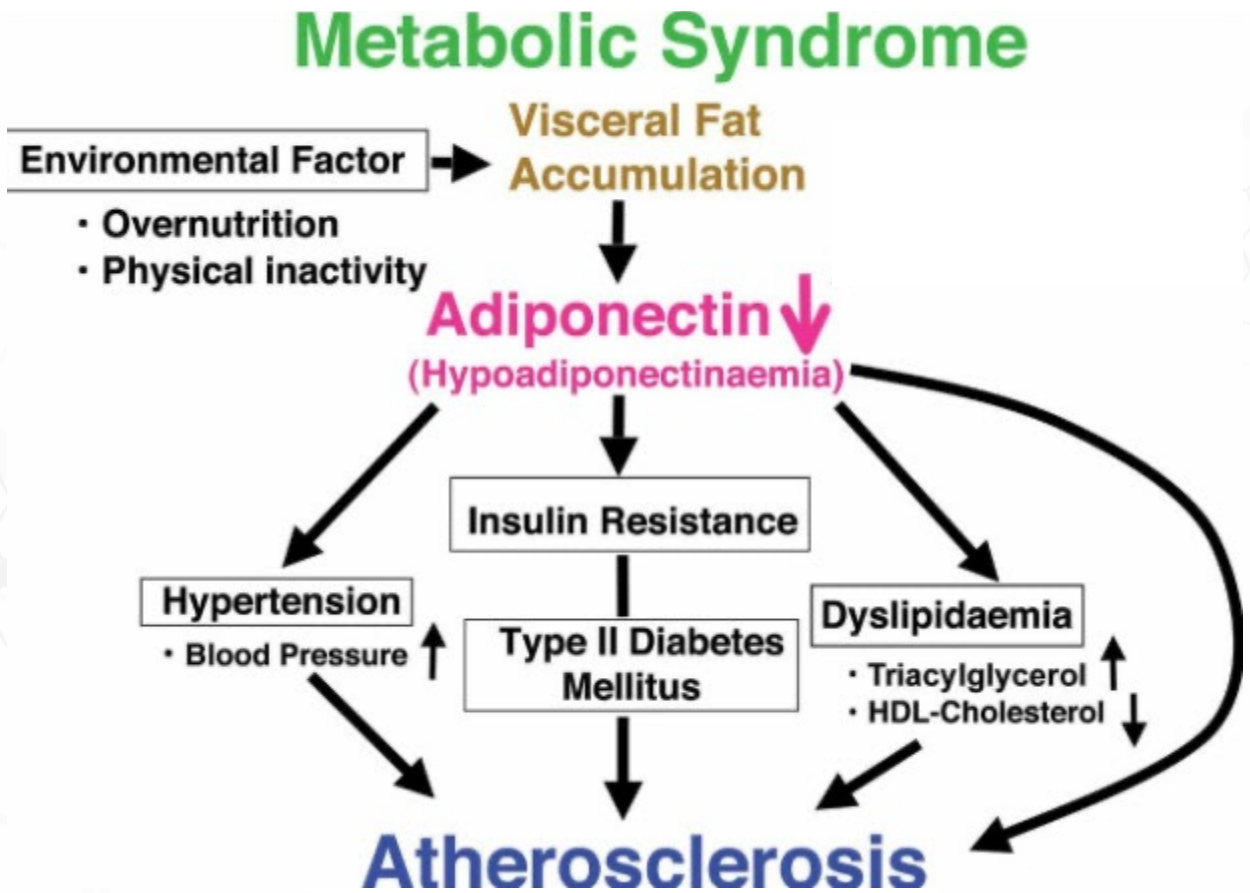
## NAFL

NAFL is a form of NAFLD in which you have fat in your liver but little or no inflammation or liver damage. NAFL typically does not progress to cause liver damage or complications. However, NAFL can cause pain from enlargement of the liver.

## NASH

NASH is the form of NAFLD in which you have inflammation of the liver and liver damage, in addition to fat in your liver. The inflammation and liver damage of NASH can cause fibrosis, or scarring, of the liver. NASH may lead to cirrhosis, in which the liver is scarred and permanently damaged. Cirrhosis can lead to liver cancer NIH.

Experts are not sure why some people with NAFLD have NASH while others have NAFL.

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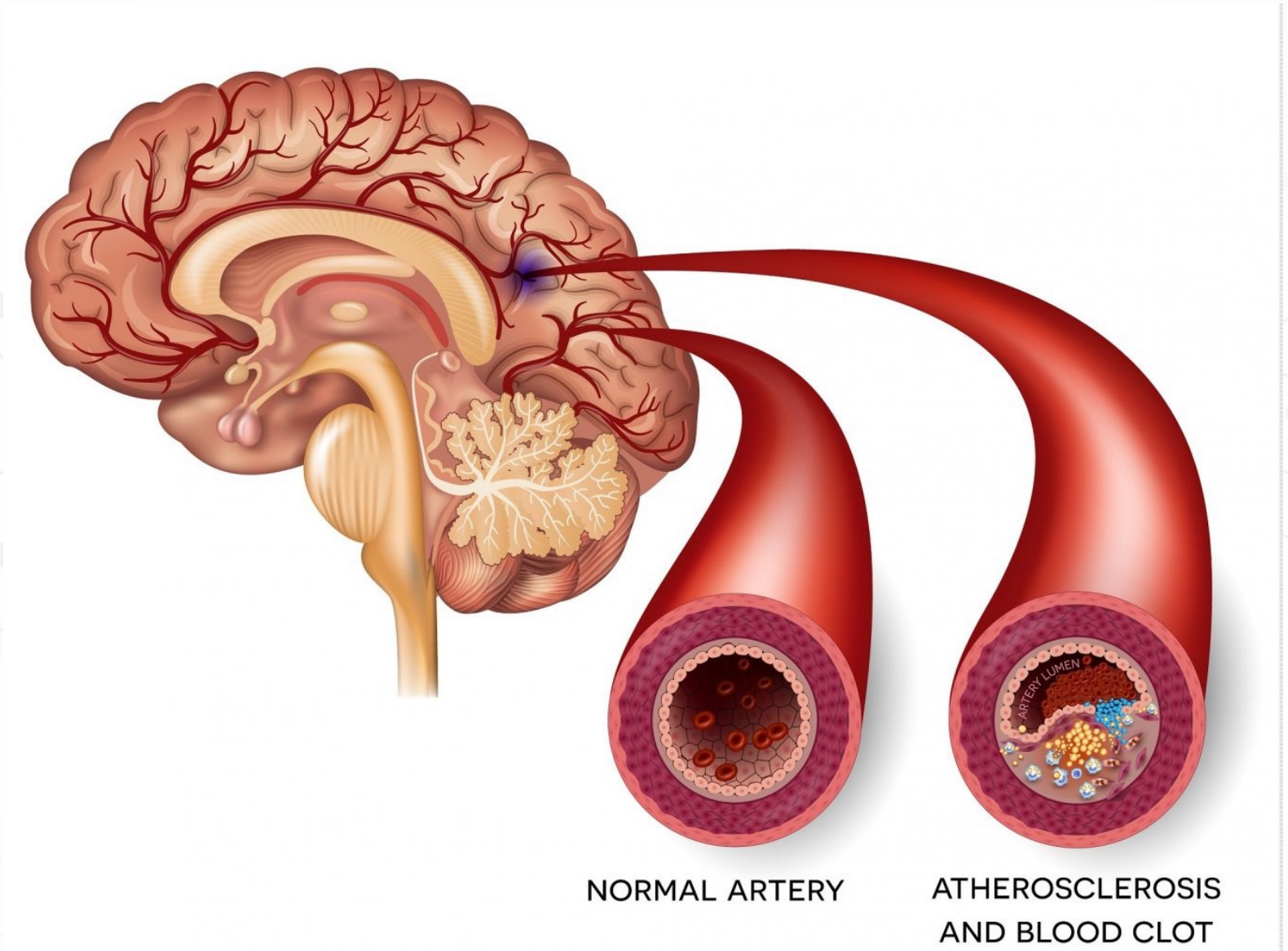


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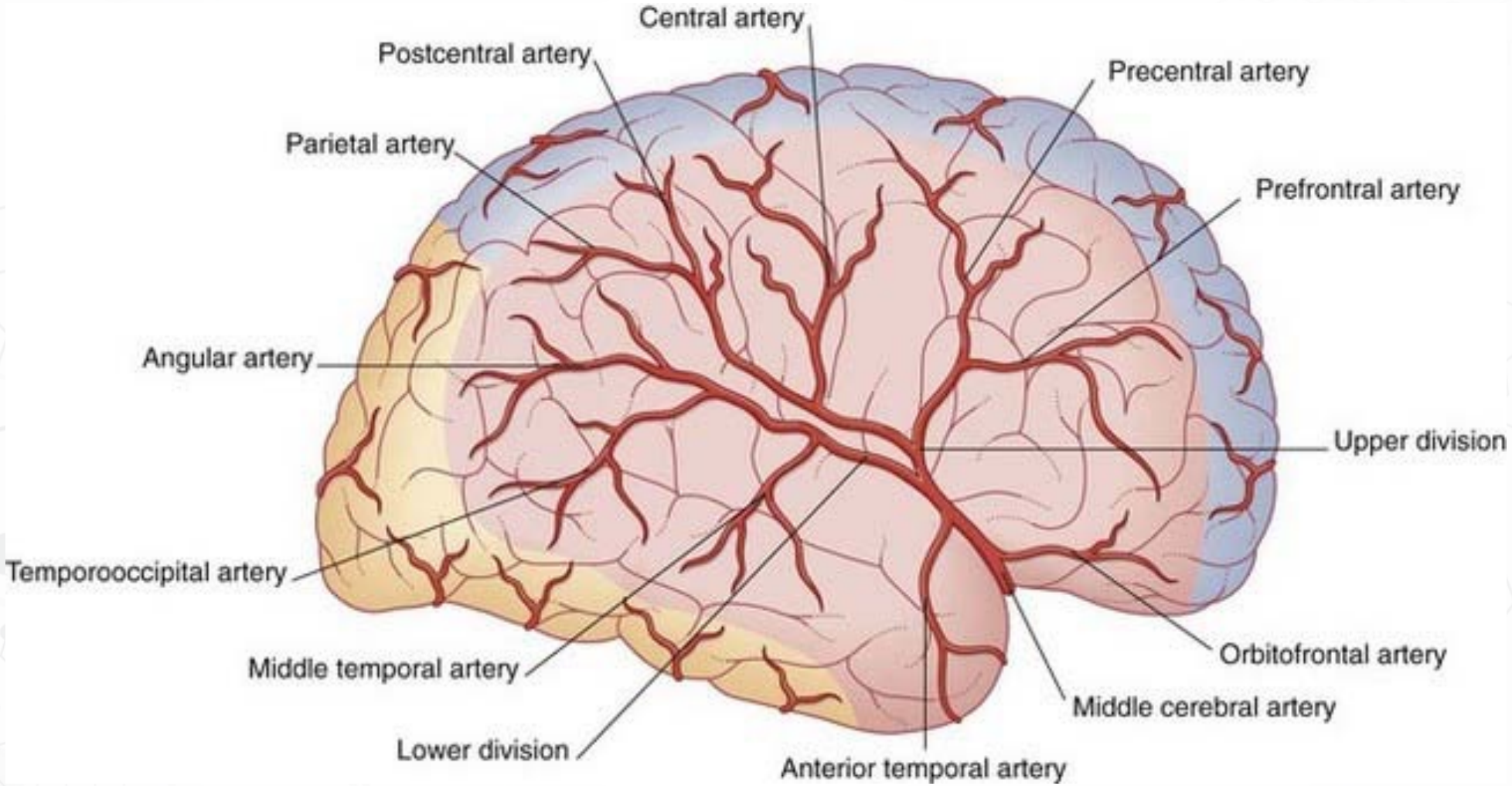


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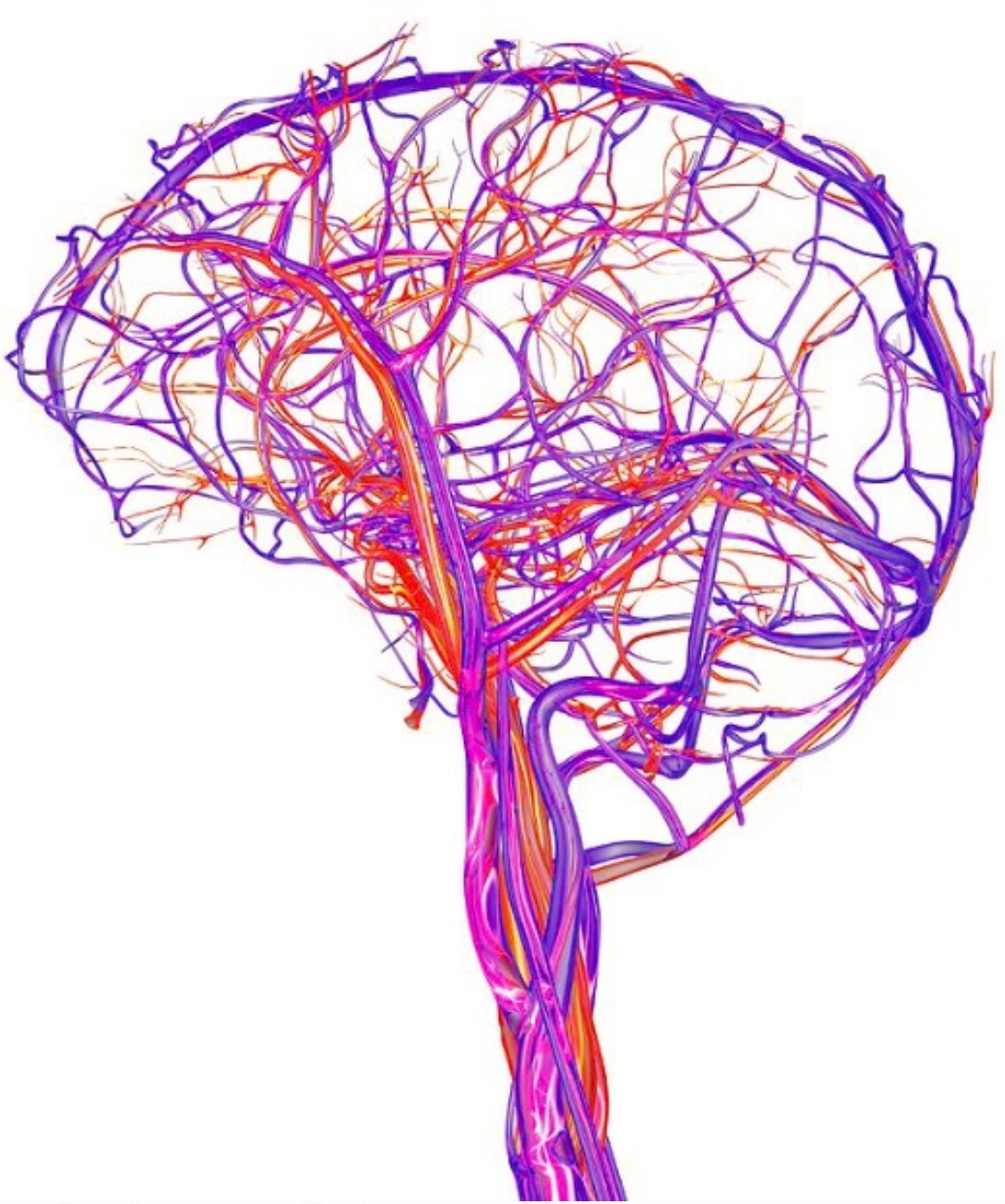

Neurology. 2016 Mar 22; 86(12): 1136–1142.
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# Nonalcoholic fatty liver disease is associated with cognitive function in adults

Sang Won Seo, MD, PhD,[✉] Rebecca F. Gottesman, MD, PhD, Jeanne M. Clark, MD, MPH, Ruben Hernaez, MD, MPH, PhD, Yoosoo Chang, MD, PhD, Changsoo Kim, MD, PhD, Kyoung Hwa Ha, PhD, Eliseo Guallar, MD, MPH, and Mariana Lazo, MD, PhD, ScM

In the United States and globally, nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease.[1,2] By definition, NAFLD occurs in the absence of excessive alcohol consumption,[3] and is associated with cardiovascular disease (CVD) and its risk factors including type 2 diabetes, obesity, hyperlipidemia, and hypertension.[4,5] Such risk factors are known to contribute to cognitive impairment with or without the mediation of CVD.[6,7] Furthermore, considering findings from previous studies suggesting that NAFLD could be an independent CVD risk factor,[8] it appears reasonable to hypothesize that NAFLD is independently associated with cognitive impairment. To our knowledge, the relationship between NAFLD and cognitive impairment has not been investigated previously.

In the current study, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III), covering a representative sample of the general US population. Our aim was to investigate the relationships between NAFLD determined by ultrasonography and cognitive impairment as assessed by 3 computerized tests. As a secondary objective, we investigated the relationships between liver enzyme activity, another common surrogate marker of inflammatory NAFLD, and cognitive impairment.

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**Methods:** This was a cross-sectional study of 4,472 adults aged 20–59 years who participated in the Third National Health and Nutritional Examination Survey. The participants underwent assessment of liver enzyme activity and hepatic steatosis by ultrasound, and underwent cognitive evaluation using the following computer-administered tests: the Simple Reaction Time Test (SRTT), the Symbol-Digit Substitution Test (SDST), and the Serial Digit Learning Test (SDLT). We defined NAFLD as moderate/severe steatosis as determined by ultrasound in the absence of hepatitis B or C or excessive alcohol consumption. We used multiple linear regression models to examine the association between NAFLD and cognitive function while controlling for potential confounders.

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**Table 1** Characteristics of the study sample by NAFLD status

| | Total participants (n = 4,472) | Participants without NAFLD (n = 3,598) | Participants with NAFLD (n = 874) | *p* Value |
|---|---|---|---|---|
| Age, y | 37.3 (0.3) | 36.6 (0.3) | 40.9 (0.7) | 0.002 |
| Male sex | 47.5 (1.0) | 46.3 (1.1) | 53.7 (2.1) | 0.001 |
| Black race | 12.0 (0.9) | 12.2 (0.9) | 10.6 (1.5) | 0.307 |
| Education >12 y | 45.6 (1.5) | 47.8 (1.6) | 35.0 (2.8) | <0.001 |
| BMI category | | | | <0.001 |
| <18.5 | 2.4 (0.4) | 2.5 (0.4) | 1.9 (0.8) | |
| 18.5-24.9 | 43.4 (1.5) | 48.7 (1.5) | 17.0 (1.9) | |
| 25-29.9 | 31.4 (1.2) | 31.1 (1.3) | 32.9 (2.8) | |
| 30-34.9 | 14.0 (0.7) | 12.1 (0.7) | 23.5 (1.7) | |
| ≥35 | 8.8 (0.9) | 5.6 (0.8) | 24.7 (2.3) | |
| High waist circumference[a] | 33.7 (1.3) | 27.2 (1.3) | 66.1 (2.7) | <0.001 |
| Diabetes mellitus[b] | 6.6 (0.6) | 5.2 (0.6) | 13.6 (1.7) | <0.001 |
| Hypertension[c] | 20.7 (1.1) | 17.5 (1.0) | 36.3 (2.7) | <0.001 |
| Hypercholesterolemia[d] | 23.6 (1.0) | 22.2 (1.2) | 30.4 (2.7) | 0.004 |
| Acute MI | 1.5 (0.3) | 1.2 (0.2) | 3.3 (1.2) | 0.013 |
| Stroke | 0.6 (0.2) | 0.5 (0.2) | 1.5 (0.7) | 0.024 |
| ALT, U/L | 18.0 (0.4) | 16.5 (0.4) | 25.7 (0.9) | <0.001 |
| AST, U/L | 20.8 (0.2) | 20.0 (0.2) | 25.0 (0.8) | <0.001 |

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It remains possible that the association between NAFLD and cognitive impairment is an epiphenomenon, because cardiovascular risk factors and diseases are related to both NAFLD and cognition. However, in our study, the association with cognition still existed after controlling for these possible confounders. The pathobiology of the relationship between NAFLD and cognitive impairments remains unknown. Insulin resistance might explain the association between NAFLD and cognitive impairment, because insulin resistance plays critical roles in the pathogenesis of NAFLD and Alzheimer disease (AD).[4,24] A preclinical study has suggested that increased insulin resistance induced by exposure to nitrosamine leads to nonalcoholic steatohepatitis (NASH) and AD in rats.[25] Alternatively, NAFLD might affect cognitive impairment via inflammatory processes. Previous studies have shown that expanded and inflamed liver fat, especially in patients with NASH, releases inflammatory cytokines and adipokines, possibly accompanied by abnormal levels of lipoproteins, endothelial dysfunction, and oxidative stress, suggesting that NAFLD is a marker of inflammation.[26–28] Other previous studies have suggested that inflammation might be one of the most important causes of degenerative dementia.[29,30] In addition, carotid intimal thickness might provide a link, given that carotid intimal thickness is associated with both NAFLD and cognitive impairment.[31,32]

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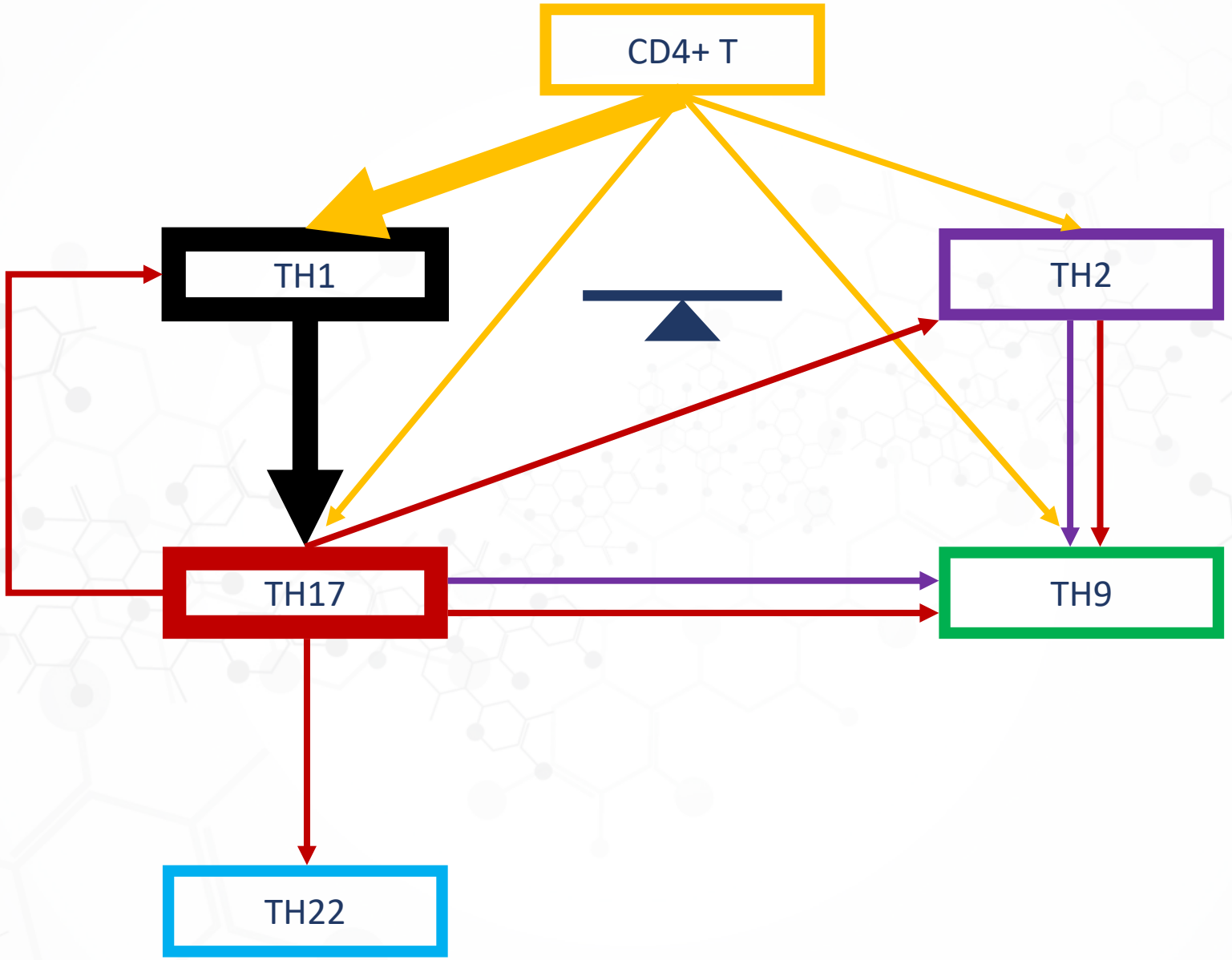
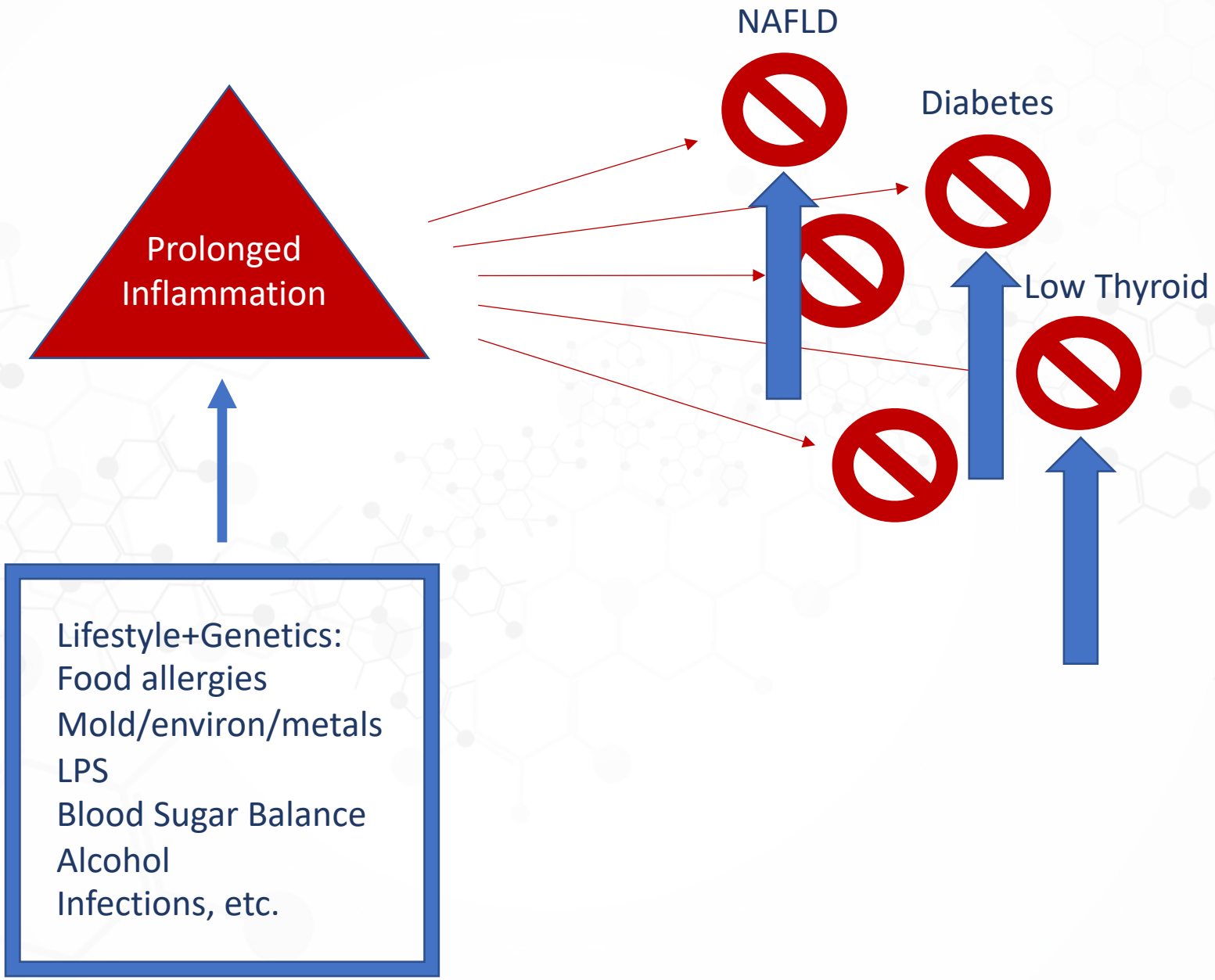
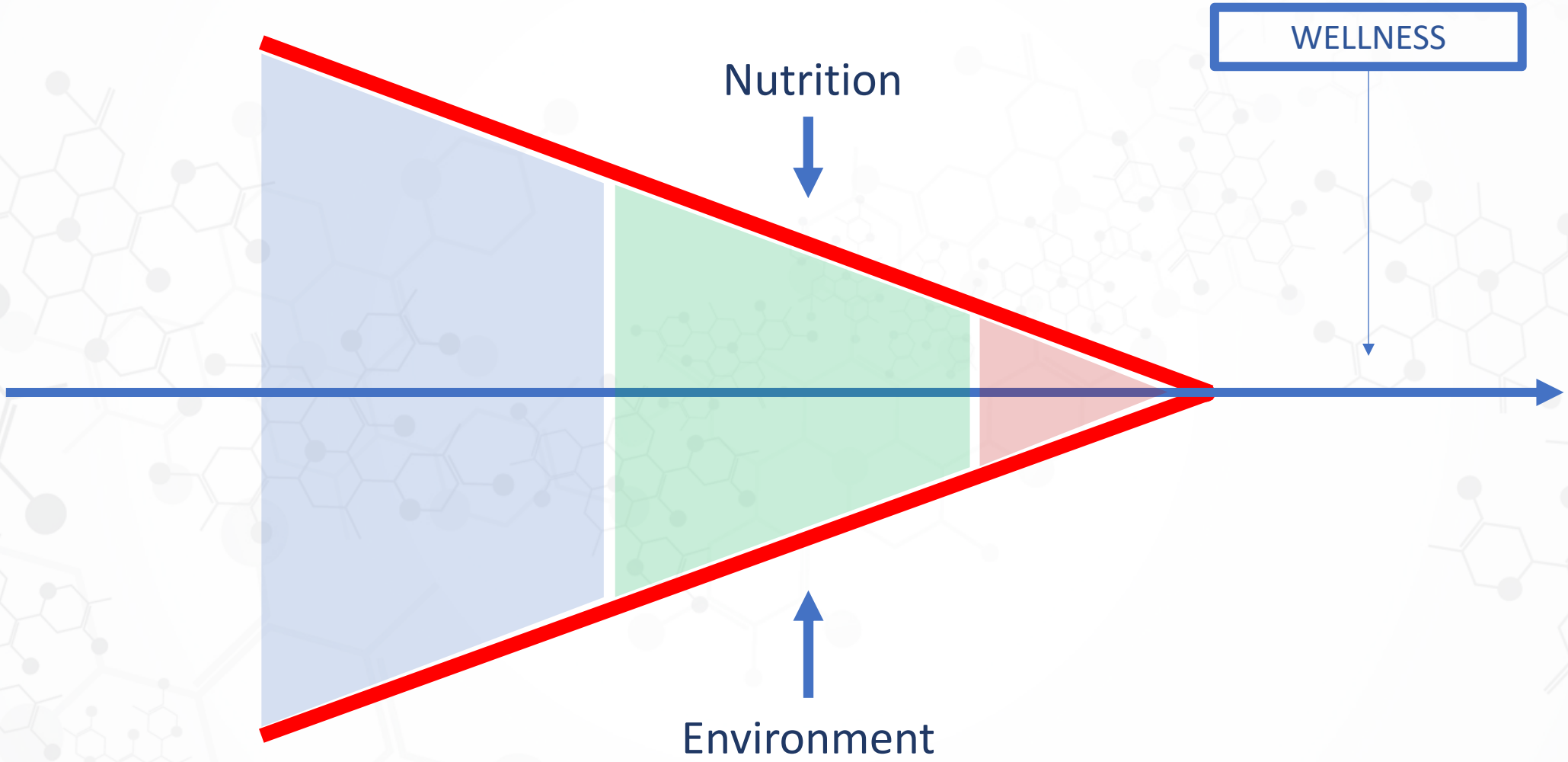
Interestingly, the association between NAFLD and cognitive impairment varied across the cognitive tests. That is, NAFLD was associated only with SDLT scores, independent of cardiovascular risk factors and diseases, while the association with SRTT and SDST scores disappeared after adjusting for metabolic components and cardiovascular diseases. SRTT, SDST, and SDLT are designed to assess psychomotor speed, visual attention, and learning, recall, and concentration function, respectively. Previous studies suggest that SDLT scores are generally influenced by the presence of medial temporal lesions in the hippocampus, although SDLT performance also requires some frontal related processes. Therefore, our findings suggest that NAFLD might affect brain function through region-specific processes rather than diffuse cortical dysfunction. Further studies are required to examine this hypothesis in detail.


CD4+ T
TH1
TH2
TH17
TH9
TH22
(Dermatologic)


NAFLD
Diabetes
Low Thyroid
Prolonged Inflammation
Lifestyle+Genetics:
Food allergies
Mold/environ/metals
LPS
Blood Sugar Balance
Alcohol
Infections, etc.

# Protocols




# Supplement Facts

Serving size: 1 Capsule
Servings per container: 120

| | Amount Per Serving | % Daily Value* |
|---|---|---|
| BCM-95® Turmeric Extract (*Curcuma longa*)(rhizome)(95% total curcuminoids complex, including curcumin, curcuminoids, and volatile oils)(86% curcuminoids) (65% curcumin) | 500 mg | † |

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.


# Supplement Facts

Serving size: 1 Capsule  Servings per container: 90

| | Amount per serving | % Daily Value |
|---|---|---|
| **Calories** | **0** | |
| Sodium | 5 mg | <1% |
| Total Carbohydrate | 0 g | 0% |
| Dietary Fiber | 0 g | 0% |
| Magnesium Threonate | 75 mg | ** |
| Citicoline | 125 mg | ** |
| Bacopa Monieri Extract | 250 mg | ** |
| Whole Coffee Fruit Extract | 50 mg | ** |

Daily Values are based on a 2,000 calorie diet.
** Daily Value Not Established


## Supplement Facts

| Serving size: 1 Capsule<br>Servings per container: 120 | Amount per serving | % Daily Value |
|---|---|---|
| Broccoli powder | 25mg | ** |
| Carnitine (as L-Carnitine L-Tartrate) | 125mg | ** |
| Choline (as choline citrate) | 100mg | ** |
| Folate (as levomefolate calcium) | 70mcg | 19% |
| Inositol | 25mg | ** |
| L-Methionine | 25mg | ** |
| Magnesium (as magnesium citrate) | 5mg | 1% |
| Milk thistle extract | 30mg | ** |
| N-Acetyl L-Cysteine | 25mg | ** |
| Taruine | 30mg | ** |
| Vitamin B6 (as pyridoxal 5'-phosphate) | 2.5mg | 125% |

** Daily Value Not Established

**Other ingredients:** Gelatin capsule (Gelatin, Purified water).

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