Identification of Potential Protein Biomarkers in a Depressed Chinese Malaysian University Student using Liquid Chromatography-tandem Mass Spectrometry

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Depression in Malaysia

- Mental disorder is one of the biggest health issues affecting Malaysians.

	National Health and Morbidity Survey 1996	National Health and Morbidity Survey 2006	National Health and Morbidity Survey 2015
Prevalence of psychiatric morbidity **(5 to 15 years old)**	**13%**	**20.3%**	**12.1%**
16 and above	**10.6%**	**11.2%**	**29.2%**

Image source: Suicide on the rise among Malaysian youth: New Straits Times (online)

Mukhtar & Oei, 2011; Institute for Public Health (IPH), 1996; IPH, 2008; IPH, 2015

Depression in Malaysia

- National Health and Morbidity Survey 2019 reported that nearly **half a million** of Malaysian adults suffered from depression.
- A 2020 study reported that **42.3%** of Malaysian adults had depression.
- Another nationwide survey among general population has showed an alarming prevalent rate of depression (**59.2%**) during the COVID-19 pandemic.
  - The prevalence of depression was apparently increasing.

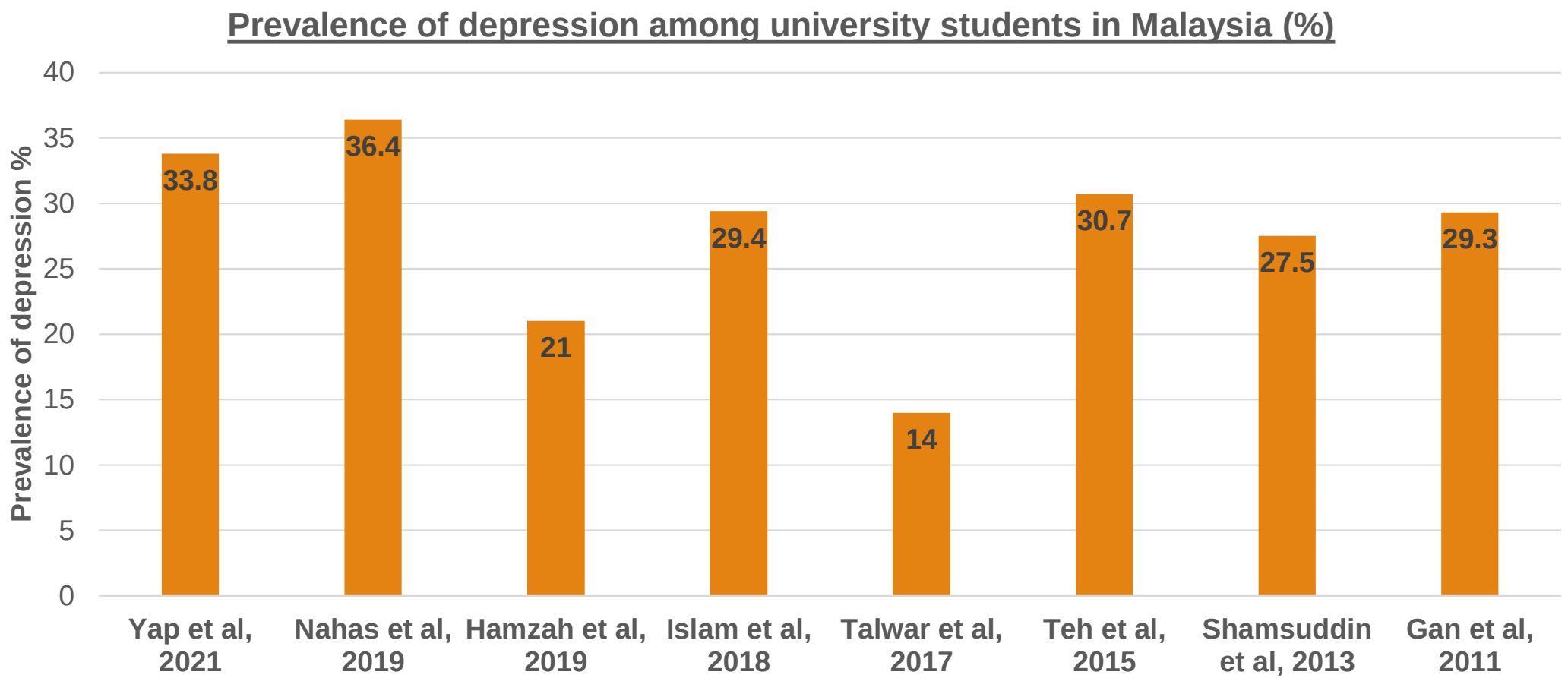
IPH, 2020; Chua, 2020; Perveen et al, 2020; Wong et al, 2021

Depression among university students

- Depression often develops at a young age and is often recurring.
- 18-29 year olds are **three times more likely** to be depressed than people of 60 year olds and above.
- University students are experiencing a stressful period:
  - Academic stress
  - Financial problems
  - Concern for their future
- Makes them more vulnerable to depression.

American Psychiatric Association, 2013; Yeoh et al, 2017

Depression among university students in Malaysia



Diagnosis and treatment of depression

- To date, the etiology of depression is not fully understood yet.
- There is no clinical laboratory tests available for the diagnosis of depression due to its complex nature.
- Currently, the diagnosis and treatment of depression is superior to symptom-based.

Diagnosis and treatment of depression

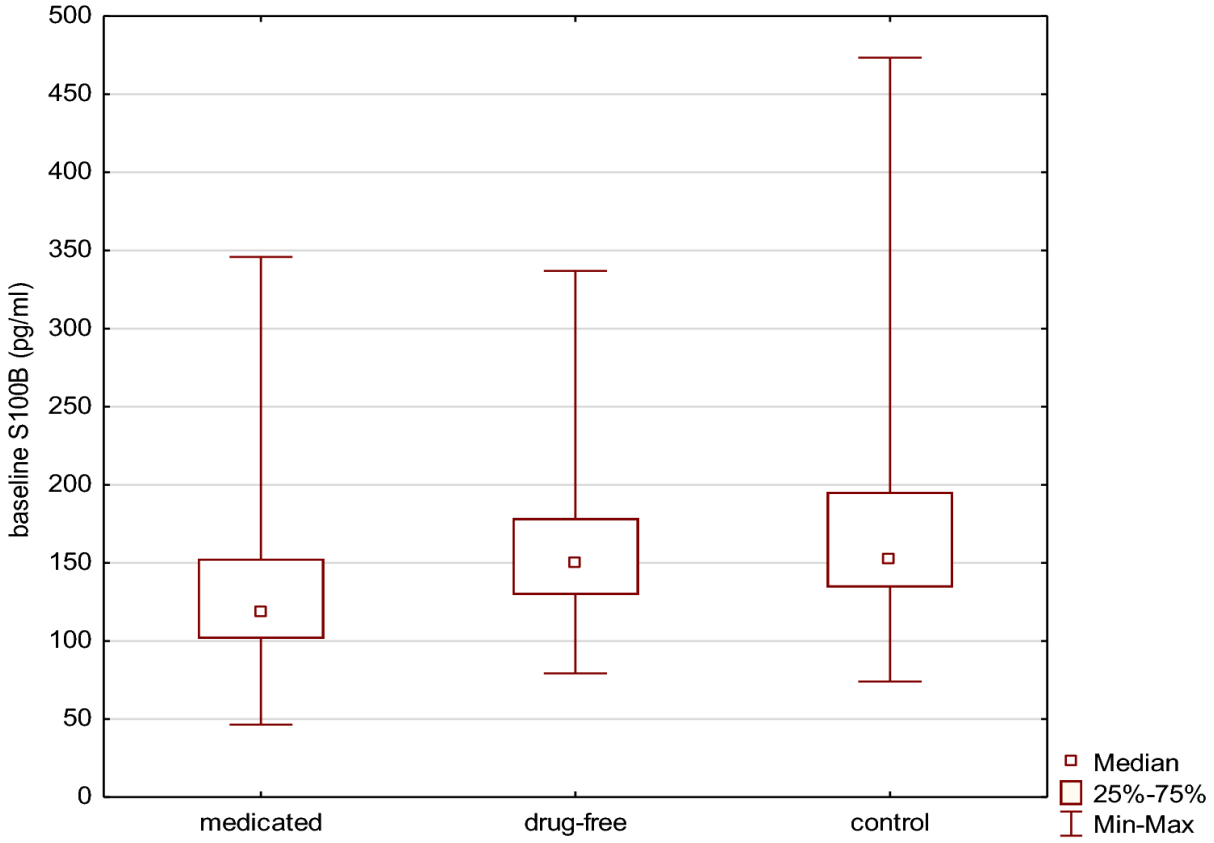
- Screening:
  - Questionnaires
- Diagnosis:
  - Patients' descriptions of symptoms
  - Clinical behavior observations
  - Diagnostic criteria (DSM-5 & ICD-11)
- Patients' management:
  - Refer to psychiatric services
  - Admit to the psychiatric ward
- There is a need for a convenient and effective way to detect depression:
  - Biomarker

Biomarker

- Biomarker is any measurable indicator of the state of a body.
- A biomarker can be a gene or a group of genes, proteins or other biomolecules.
- Bodily fluids like blood, urine, and cerebral spinal fluid are one of the easily accessible sources of psychiatric biomarkers.

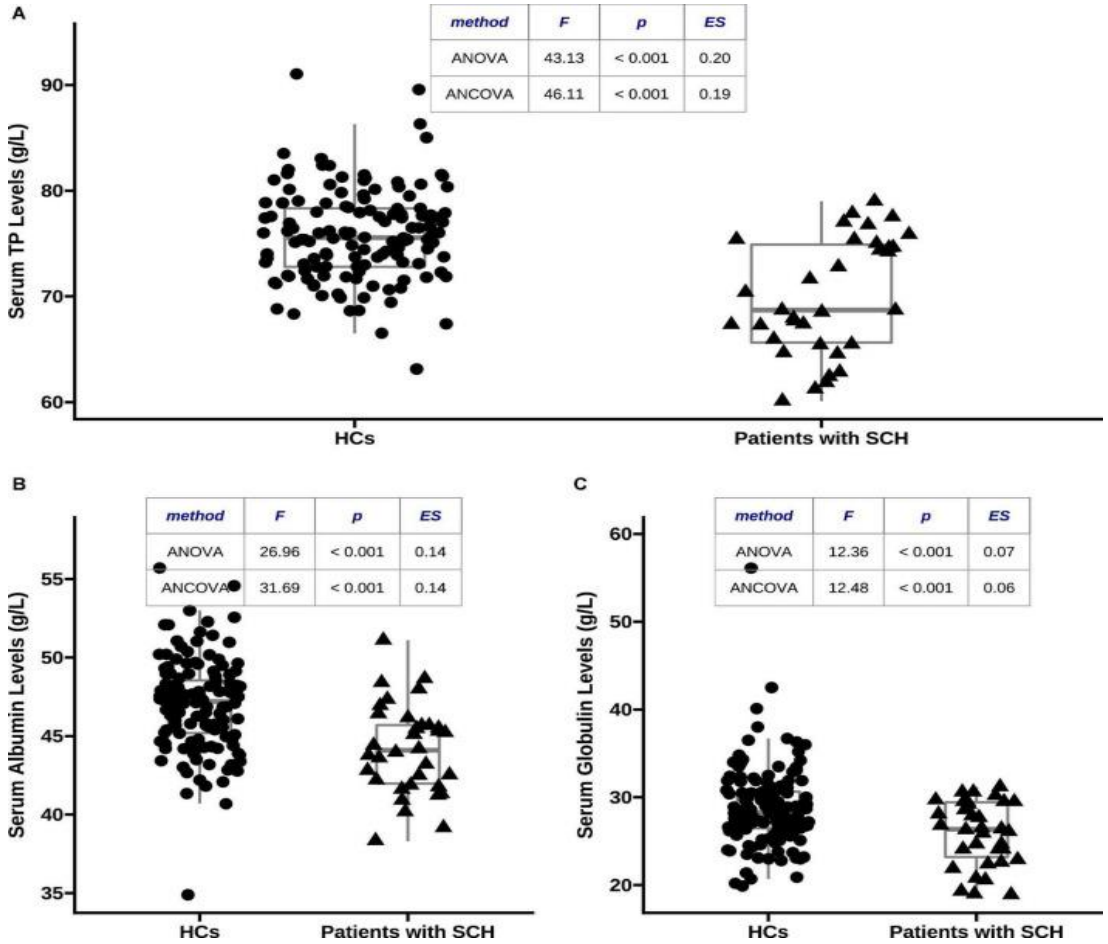
Biomarker Definitions Working Group, 2001; García-Gutiérrez et al, 2020

Protein markers of depression



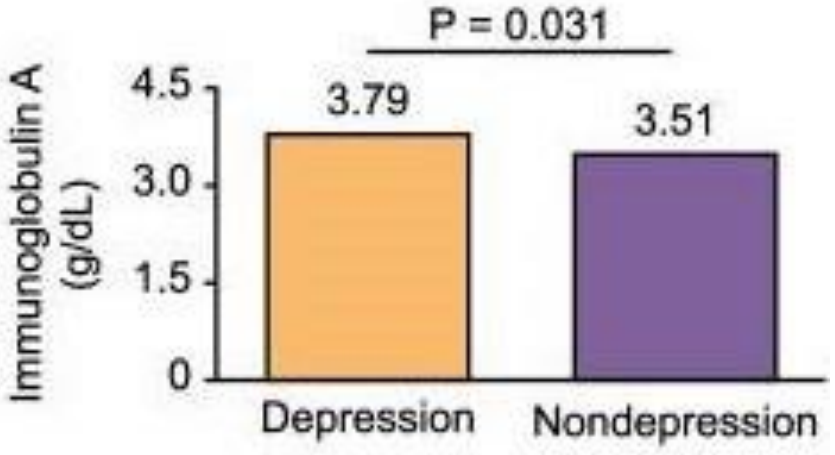
- **Serum S100B** were found to be lower in medicated youth patients, compared with those who were drug-free, and healthy controls.

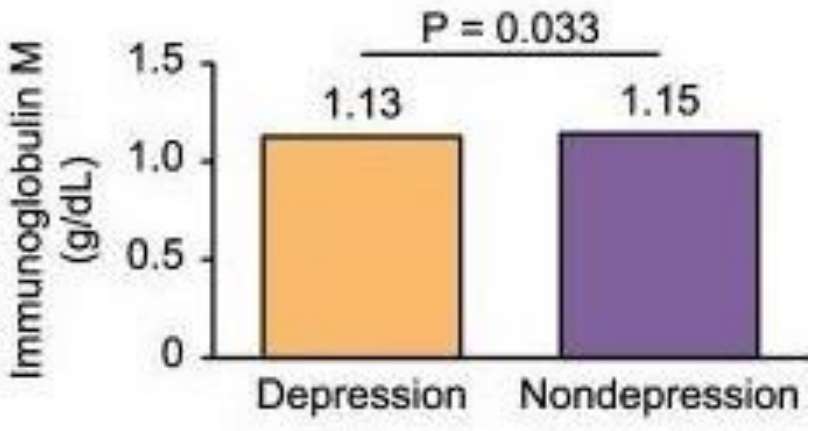
Protein markers of depression

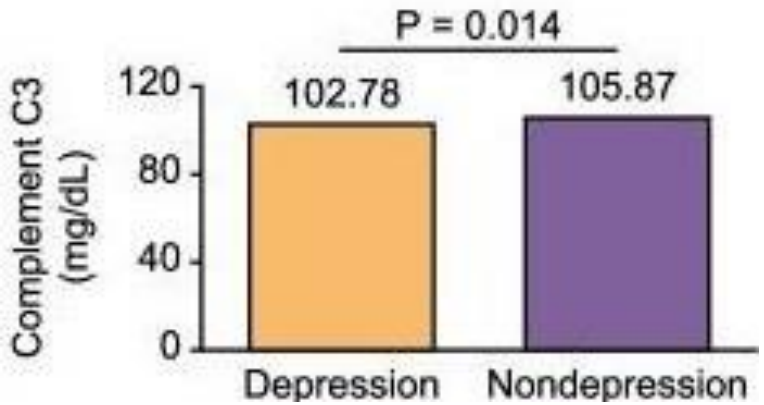


- Decreased serum **total proteins**, **albumin**, and **globulin** were found associated with depressive severity in schizophrenia.

Protein markers of depression



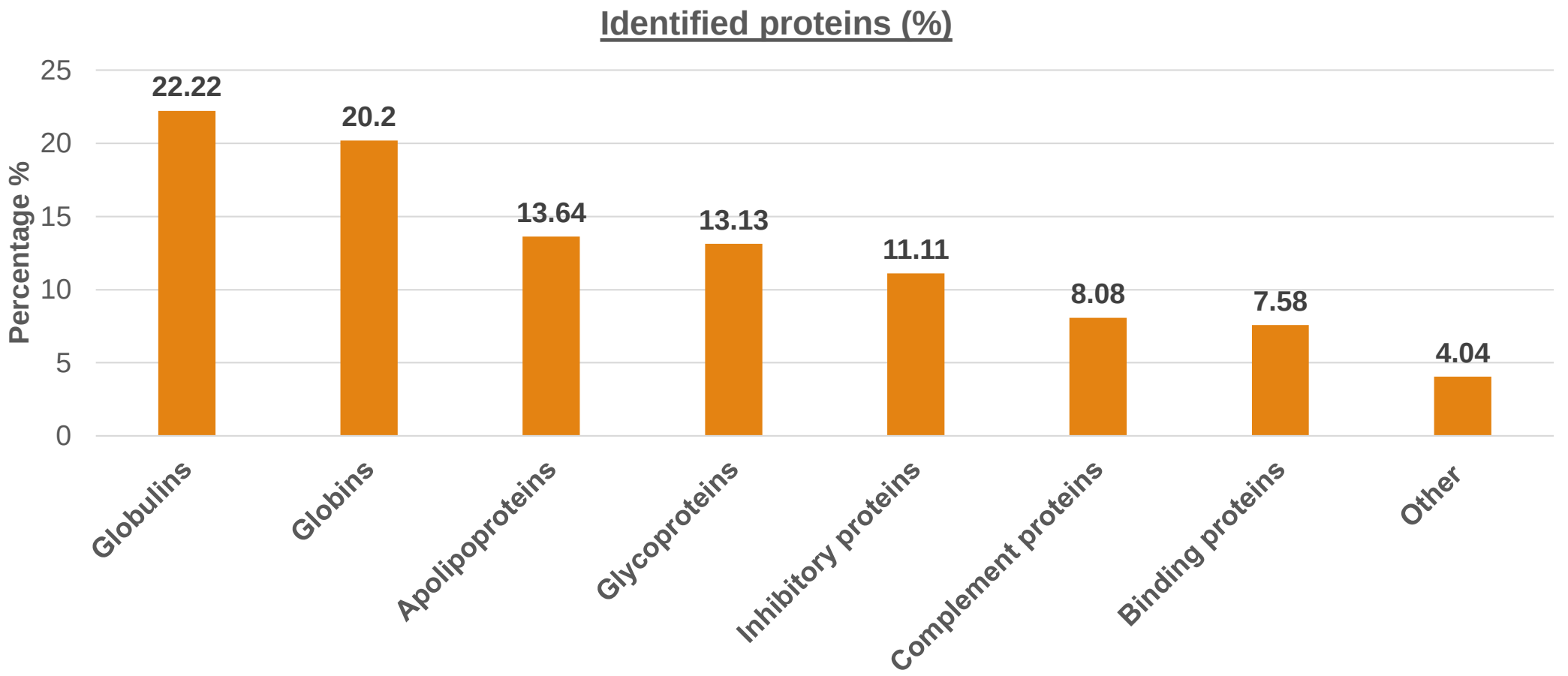




- Chinese older adults with depression had higher levels of **immunoglobulin A** and lower levels **immunoglobulin M** and **complement C3** than the group without depression.

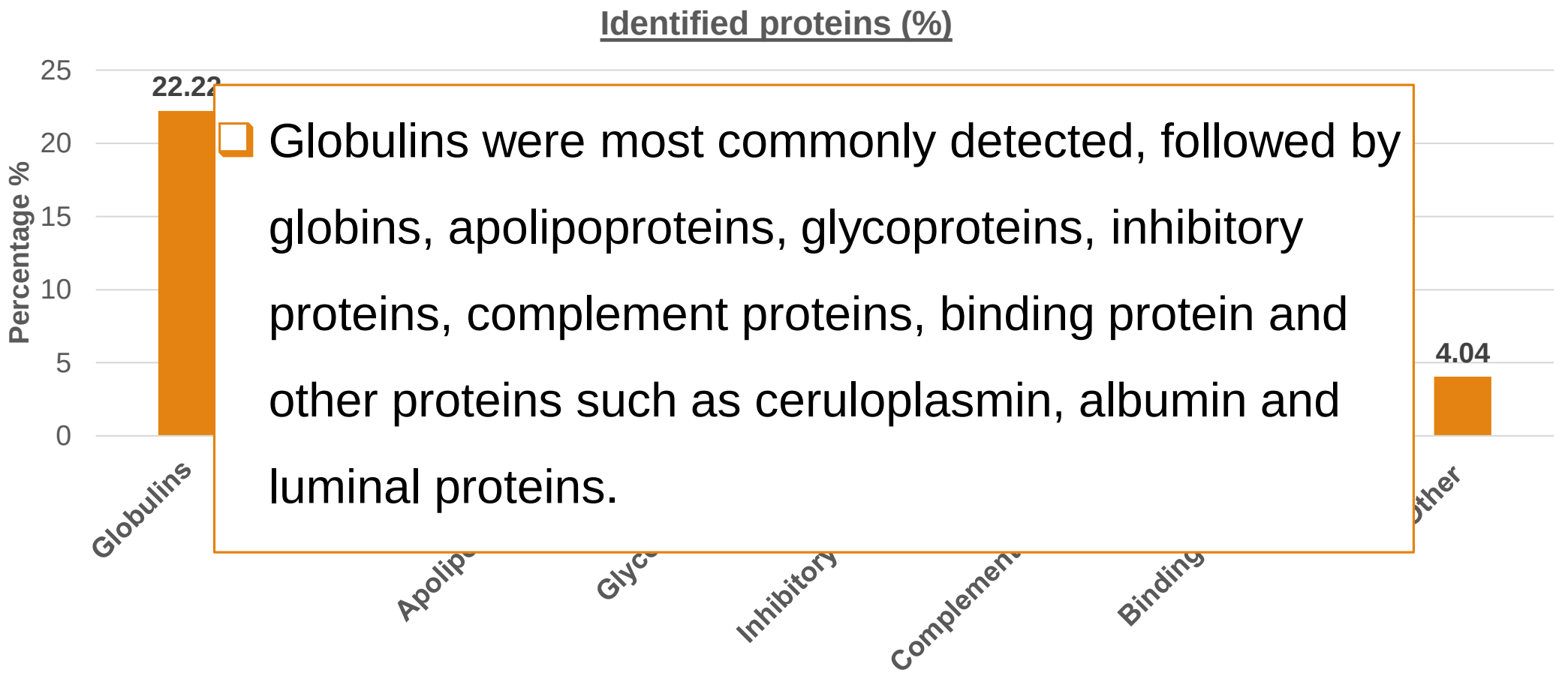
Sun et al, 2022

Our results



Note Other proteins: ceruloplasmin, albumin and luminal proteins

Our results



- Globulins were most commonly detected, followed by globins, apolipoproteins, glycoproteins, inhibitory proteins, complement proteins, binding protein and other proteins such as ceruloplasmin, albumin and luminal proteins.

Note Other proteins: ceruloplasmin, albumin and luminal proteins

Our results

- Majority of the identified proteins have functions related to:
  - Inflammation
  - Lipids transport

Inflammation

- When we are sick:
  - Our immune system creates an inflammatory response so that we can heal.
- When inflammatory cytokines in body reach a certain threshold, our brain will initiate its own inflammatory response:
  - The macrophages will pump out more cytokines that attack both invaders and healthy tissues.

Via neurotransmitter systems

- Cytokines can also alter the neurotransmitter systems involved in the development of depression.
  - Meta-analysis in 2019 demonstrated alterations of **cytokines levels** in patients with antidepressant outcomes.

Via neurotransmitter systems

- C-reactive protein (CRP) is an inflammation protein marker that increases during infection.
  - Meta-analysis consists of 30 studies with 11 813 participants showed that presence of **low-grade inflammation** and elevated **CRP levels** were found in depressed patients.
  - Higher **CRP levels** was associated with depressive symptoms from Netherlands Study of Depression and Anxiety (NESDA) and UK Biobank cohorts.

Osimo et al, 2019; Milaneschi et al, 2021

Neurotransmitter systems

- Monoamines neurotransmitters like dopamine, norepinephrine, and serotonin are primarily associated with the development of depression.
  - Increased **dopamine signalling** and lower levels of depressive symptoms among Asian, however, contradictory result was found among Caucasian samples.
  - Reduction of depression-like behavior was found in rat models with significantly increased **norepinephrine** levels.

Shao & Zhu, 2020; Avinun et al, 2020; Du et al, 2020

Neurotransmitter systems

- Neurotransmitters like glutamate and GABA are also related to depression:
  - Patients with first episode depression had significantly decreased **glutamate** and increased **GABA levels** compared to healthy controls.

- These neurotransmitters are also associated with inflammation:
  - Depressed adolescents found higher levels of **pro-inflammatory cytokines** associated with higher levels of **glutamate**.
  - Hybrid molecules targeted **GABA-A** and **serotonin 5-HT6** receptors showed **anti-inflammatory** and antidepressant activity in recent in vivo studies.

Draganov et al, 2020; Ho et al, 2021; Marcinkowska et al, 2023

Serum lipids and depression

- Serum lipids may be linked to depression via alteration of serotonin metabolism.
- Cholesterol has crucial role in brain development and in neuron-to-neuron signaling.
  - Patients with a major depressive episode show increased levels of **LDL cholesterol**.
  - **LDL cholesterol** can reduce availability of **serotonin** and increase depression risk by directly impair the function of the serotonin 1A receptor in the brain.

Serotonin and depression

- A recent study found rapid response to **selective serotonin reuptake inhibitors** (SSRIs) in post-COVID depressed patients:
  - Suggests that SSRIs could be an effective depression treatment option for the **neuroinflammation** triggered by SARS-CoV-2.
- However, there is a recent review opposes the idea that serotonin cause depression:
  - Found no consistent evidence showing association between serotonin and depression.

Mazza et al, 2022; Moncrieff et al, 2022

In short

- Most protein markers identified in this study were related to inflammation and lipid transport.
- Biomarkers can be used to distinguish between depressed and healthy groups.
  - Can also enhance our current diagnosis method and allowing individualized treatment.

In short

- Future studies:
  - With healthy controls are much needed to further confirm the role of these biomarkers in depression.
  - Could look into the relationship between these inflammation markers and dietary patterns, so that we can modify our food intake for early prevention of depression.

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