Obesity and inflammation
A recipe for depression in women

It has been known for some time that obesity is linked to depression and that this relationship is bi-directional. Controlling and treating obesity is therefore key to reducing these co-morbidities. The Geelong Osteoporosis Study, a population-based study beginning in 1993, was originally designed to understand the epidemiology of osteoporosis, but it has also enabled insight into other physical and mental disorders over time. Now, Pasco and team delve into this wealth of data again, this time unmasking a link between metabolically unhealthy obesity and depression.

Obesity can be divided into different phenotypes based on metabolic health status. This has led to the somewhat controversial terms ‘metabolically healthy obesity’ and ‘metabolically unhealthy obesity’. There are different ways to classify ‘metabolically unhealthy’, with the conditions present in metabolic syndrome often used to define it. However, in a first-of-its-kind study, Pasco and colleagues put the spotlight on obesity-related inflammation as opposed to metabolic syndrome conditions to determine obesity’s role in depression risk.

METABOLIC HEALTH
Changes to normal metabolism, altering it from its native homeostatic state, affect physiological processes in our cells, organs, and body. Poor metabolic health presents as metabolic syndrome, a mixture of conditions including fat build-up in organs, high blood glucose, high blood pressure, and imbalanced blood lipids. The presence of even one of these conditions indicates metabolic abnormality. Such metabolic abnormalities are a risk factor for cardiovascular disease and are termed cardiometabolic disorders.

Individuals with such disorders have a greater chance of heart attack, stroke, and coronary heart disease (fat build-up in coronary arteries). Globally, the prevalence of cardiometabolic disorders is increasing, with two-thirds residing in low- and middle-income countries. One of the many contributing factors to this is obesity, defined as excessive fat accumulation that can be detrimental to health. This body fat, known as adipose tissue, can act as a reservoir of pro-inflammatory cytokines, thereby promoting inflammation.

Health & Medicine | Julie Pasco

A team led by Dr. Julie Pasco, Professor of Epidemiology at Deakin University and Barwon Health, Australia, analysed data from the longitudinal Geelong Osteoporosis Study over 16 years. The researchers discovered that metabolically unhealthy obesity, defined by low-grade inflammation in combination with obesity, puts women at higher risk of depression.

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Inflammation is an immune reaction and a broad term indicating a state where pro-inflammatory markers outweigh anti-inflammatory responses. It can occur acutely or chronically, and examples include fighting off a foreign pathogen, auto-immune disorders, and prolonged exposure to irritants or allergies. Conditions such as obesity can promote inflammation due to fat deposits being a potential source of pro-inflammatory cytokines.

Metabolic dysregulation combined with persistent low-grade inflammation is known as immunometabolic dysregulation and in obese individuals constitutes an obesity phenotype. Research is growing on the association between this phenotype and psychiatric disorders. Another type of obesity is sarcopenic obesity, a condition occurring in ageing obese individuals who are often insulin resistant and also have low skeletal muscle mass and strength.

Dr Pasco and team are unmasking a link between metabolically unhealthy obesity and depression.

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Obesity can be divided into different phenotypes based on metabolic health

A well-known marker of inflammation is C-Reactive Protein (CRP). Existing evidence implicates circulating CRP, indicative of systemic inflammation, in obesity-related depression. One study found that high CRP levels were linked to worsening depression scores over time in a fifth of obese individuals. More than that, lower CRP levels following gastric bypass surgery complemented weight loss and are associated with improved depression scores. Now, in a well-characterised cohort of women followed for several years, Pasco and researchers demonstrate clear and strong evidence for an association between low-grade inflammation and depression in obese individuals.

The Geelong Osteoporosis Study, a unique epidemiological cohort study, began in the 1990s and has followed women living in Southeast Australia for decades, providing a wealth of data to better understand osteoporosis and risk factors for fragility fractures. The study also collects metabolic and mental disorders data. The study by Pasco and team focuses on a sub-analysis of 808 women followed for an average of 16 years. According to the researchers, one of their study’s strengths rests in the methods used to classify obesity. Measures included the well-known body mass index (BMI), which represents overall body mass adjusted for height, and more specific measures of body fatness wherein fat mass is detected.
Behind the Research
Dr Julie Pasco

Research Objectives
Professor Julie Pasco examines the link between metabolically unhealthy obesity characterised by systemic inflammation and depression.

References
- Pasco, JA, et al. (2023) Obesity and sarcopenic depression in women. Front Nutr, 10, 122919.
- Pasco, JA, et al. (2021) Operational definitions of sarcopenia should consider depressive symptoms. JCM Clin Rep, 6(2), 62-68.

Bio
Julie Pasco is Professor of Epidemiology at Deakin University and Barwon Health, Director at the Epi-Centre for Healthy Ageing, and Population Health Theme Leader at the Institute for Mental and Physical Health and Clinical Translation (IMPACT). Her population-based research evaluates the progression of chronic cardiometabolic and musculoskeletal disorders and the nexus between physical and mental health.

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Competing interest statement
While there are no specific conflicts of interest to declare, Pasco currently receives grant/research support from the National Health and Medical Research Council (NHMRC), the Medical Research Future Fund (MRFF), the Norman Beischer Medical Research Foundation, and Deakin University for projects which focus on musculoskeletal, cardiometabolic, and mental health.

Detail
- Pasco’s study highlights the pro-inflammatory state of obesity as a potential target to decrease depression risk.
- Highest depression rates at follow-up, regardless of whether obesity was defined by BMI, body fat mass index, or body fat percentage. Importantly, this consistent finding was independent of age or any prior history of depression, and it could not be explained by socio-economic status or sedentary lifestyles.
- Findings were noted for women with a high ratio of body fat-to-muscle, typically seen in sarcopenic obesity, adding a mixed body of evidence for muscle quality. The researchers suggest that to improve our understanding of the conflicted literature for sarcopenic obesity, both a consensus on the definition is needed as well as better data on muscle quality in the condition. The researchers also note that women with depressive symptoms commonly have poor muscle strength which is a key characteristic of sarcopenia.
- Other large cohort studies implicated metabolically unhealthy obesity as a risk factor for depression. The study by Pasco and colleagues supports these findings, stacking up the evidence for a strong link between metabolically unhealthy obesity and depression. The difference is this novel study focused on the harmful obesity type that is accompanied by heightened systemic inflammation which, in tandem, increase the risk of developing subsequent depression. This research provides valuable insight into the complex interplay of factors associated with MDD.
- Pasco’s study untangles the complex web of inflammation, obesity, and depression in women.
- New treatments for depression that target inflammation in metabolic disorders are needed. Pasco’s study highlights the pro-inflammatory state of obesity as a potential target to decrease depression risk. The team speculate that diet and insulin sensitisers may improve metabolic abnormality, but more therapies should be considered, including behavioural changes with capacity to interrupt the cascade of metabolic downstream consequences including cardiovascular disease, diabetes, stroke, and musculoskeletal disorders.
- Depressive disorders are highly comorbid with medical disorders especially those with metabolic disturbances such as obesity, fatty liver and fatty muscle, and downstream consequences including cardiovascular disease, diabetes, stroke, and musculoskeletal disorders. The purpose of our research is to unravel mechanistic pathways underlying this association. We anticipate that targeting the pro-inflammatory state of obesity may thwart the onset and progression of major depression in some vulnerable people.

Personal Response
What inspired you to conduct this research?
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You mention in the publication that an extension to your study has the possibility of identifying novel treatments or behavioural modifications targeting metabolic disorders. Can you please elaborate further on this extension with an emphasis on the translational aspect of your work?
In addition to affecting weight reduction, some new anti-obesity medications known as GLP-1 receptor agonists show great promise for suppressing inflammation. Moreover, lifestyle changes such as increasing aerobic physical activity and modifying dietary intake to favour foods with a lower dietary inflammatory index reduce circulating levels of inflammatory markers, including CRP, and dampen chronic inflammation. These are examples of novel treatments and behavioural changes with capacity to interrupt the cascade of metabolic processes that link physical illness and depression.