

**THE INFLAMMATION HYPOTHESIS OF DEPRESSION:
CROSS SECTIONAL ASSOCIATIONS, TEMPORAL
RELATIONSHIPS AND THE CONFOUNDS OF COMORBIDITY**

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In order of appearance

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4. Hiles, S. A., Baker, A. L., de Malmanche, T., McEvoy, M., Boyle, M., & Attia, J. (under review). Inflammatory pathways to depression: Unhealthy behaviours as confounders or causes.
5. Hiles, S. A., Baker, A. L., de Malmanche, T., McEvoy, M., Boyle, M., & Attia, J. (under review). Inflammatory markers as mediators of the association between depression and cardiovascular events.

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List of conference presentations relevant to this thesis

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Hiles, S. A., Baker, A. L., de Malmanche, T. & Attia, J. Do unhealthy behaviours explain the relationship between depression and inflammatory markers. *Australasian Society for Behavioural Health and Medicine Annual Scientific Conference*, Newcastle, NSW, Australia, 6-8 February, 2013.

Hiles, S. A., Baker, A. L., de Malmanche, T. & Attia, J. The importance of depression in overall wellbeing: Depressive symptoms and inflammatory markers in predicting cardiovascular events. *Australasian Society for Psychiatric Research Annual Conference*, Fremantle, WA, Australia, 5-7 December, 2012.

Hiles, S. A., Baker, A. L. de Malmanche, T. & Attia, J. Modifiable lifestyle factors, depression & inflammation in the Hunter Community Study. *International Society for Affective Disorders Biennial Conference*, London, UK, 18-20 April, 2012.

Hiles, S. A., Attia, J, Baker, A. K. Systematic review and meta-analysis of inflammatory marker change following treatment in people with depression.

Australasian Society for Psychiatric Research Annual Conference, Sydney, NSW, Australia, 5-8 December, 2010.

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Hiles, S. A., Attia, J, Baker, A. L. Changes in interleukin-6, C-reactive protein and interleukin-10 in people with depression following antidepressant treatment: A meta-analysis. *Annual Meeting of the Psychoneuroimmunology Research Society*, Dublin, Ireland, 2-5 June, 2010.

Poster Presentations

Hiles, S. A., Baker, A. L., de Malmanche, T. & Attia, J. The inflammatory hypothesis of depression in the context of physical health: Depression and inflammatory markers in cardiovascular hospitalisations. *Annual Meeting of the Psychoneuroimmunology Research Society Psychoneuroimmunology Research Society*, Stockholm, Sweden, 5-7 June, 2013.

Hiles, S. A., Baker, A. L., Handley, T., de Malmanche, T. & Attia, J. Statins, depression and the inflammatory hypothesis of depression: A meta-analysis of randomized controlled trials. *Annual Meeting of the Psychoneuroimmunology Research Society Psychoneuroimmunology Research Society*, Stockholm, Sweden, 5-7 June, 2013.

Hiles, S. A., Baker, A. L. de Malmanche, T. & Attia, J. Cause or consequence? A series of meta-analyses regarding depression and inflammatory markers. *International Society for Affective Disorders Biennial Conference*, London, UK, 18-20 April, 2012.

Hiles, S. A., Baker, A. L. de Malmanche, T. & Attia, J. Changes in depressive symptoms following treatment with anti-inflammatory medications: A meta-analysis. *Australasian Society for Psychiatric Research Annual Conference*, Dunedin, New Zealand, 6-8 December, 2011.

Hiles, S. A., Attia, J, & Baker, A. L. Interleukin-6 in people with and without depression: Exploring moderators using meta-analytic techniques. *Annual Meeting of the Psychoneuroimmunology Research Society*, Dublin, Ireland, 2-5 June, 2010.

Hiles, S. A., Attia, J, Baker, A. L., & Clark, V. L. A meta-analysis comparing interleukin-6 levels in people with depression and non-depressed controls. *Australasian Society for Psychiatric Research Annual Conference*, Canberra, ACT, Australia, 2-4 December, 2009.

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Synopsis

Depression is prevalent and causes substantial personal and economic burden. Yet, the cause of depression is unclear and existing serotonergic pharmacological treatments have limited effectiveness in some individuals. The inflammatory hypothesis of depression posits that subacute inflammation may cause depression. Thus, inflammation may be a target for intervention through pharmacological and behavioural means, and inflammatory markers may be appropriate biomarkers of disorder onset and resolution. Support for this theory includes experimental evidence where administering inflammation-inducing agents leads to depressive-like signs and symptoms in animal models and humans with clinical illnesses. Epidemiological studies provide necessary concurrent evidence for experimental effects. This thesis explores the epidemiological evidence for the inflammatory hypothesis of depression. The chapters employ meta-analysis to re-interpret existing data and generate new summary information, and explore primary cohort data to uncover new knowledge.

The bulk of epidemiological evidence for the inflammatory hypothesis of depression is cross-sectional. Given that these studies have been undertaken with various participant and measurement characteristics, meta-analysis provides a unique opportunity to explore whether these characteristics moderate the strength of the relationship between inflammatory markers and depression. The meta-analysis described in Chapter 2 highlights that although the inflammatory marker

interleukin(IL)-6 is clearly elevated in people with depression, study-level factors such as not verifying a clinical depression diagnosis, community cohort sampling, cardiovascular disease comorbidity and not matching participants on key variables were associated with smaller effect sizes. This study provides the most extensive moderator analysis in the literature to date.

Chapters 3 and 4 examine temporal associations between inflammation and depression via meta-analysis of treatment effects: whether treating depression with antidepressants is associated with changes in inflammatory markers, and whether taking a medication with anti-inflammatory effects – statins – is associated with changes in depression. Despite a limited number of studies and evidence of heterogeneity, there was preliminary evidence that antidepressant treatment is associated with a reduction in IL-6 and marginally significant reductions in C-reactive protein (CRP) and IL-10. Use of statins in randomised controlled trials was also associated with lower depressive symptoms and fewer occurrences of depression, compared with placebo.

Chapter 5 explores whether elevations in inflammatory markers precede depressive symptoms in a cohort of older people, to add to the evidence evaluating whether inflammatory markers may be useful biomarkers. Chapter 5 investigates this question in a primary cohort of older persons. Analysis of primary data allows for more refined research questions, which in this case, concerns evaluating the contribution of aspects of unhealthy lifestyle that have inflammatory consequences. In this

study, aspects of unhealthy lifestyle were important confounders, where adjusting for them rendered the relationships between inflammatory markers and later depression non-significant. However, in examining the relationship between baseline lifestyle factors and later depression, IL-6 was observed as a significant mediator, in the first analysis of its kind. Consequently, aspects of unhealthy lifestyle may be a source of elevated inflammatory markers observed in depression.

The inflammatory hypothesis proposes that one of its benefits is that it can explain high comorbidity between depression and other illnesses. The study in Chapter 6 sought to verify this. It explores whether the elevated inflammatory markers observed in depression have consequences for another prevalent and burdensome condition: cardiovascular disease. In a cohort of older persons, IL-6 was a mediator of the relationship between depression and later hospitalisations for cardiovascular events. As such, reducing levels of inflammation may be a way to address both depression and cardiovascular disease.

The thesis concludes with reflections on the implications of the data presented for the inflammatory hypothesis of depression and management of depression (Chapter 7). The original contribution of knowledge that this thesis provides includes summarising key epidemiological cross sectional and treatment data to verify that inflammation is a plausible associate with depression, and demonstrating the mediation effects of inflammatory markers in relationships between lifestyle and depression, and between depression and cardiovascular disease. This thesis highlights the

importance of unhealthy lifestyle and physical comorbidity to interpreting the inflammation hypothesis of depression. Inflammation-reducing lifestyle management may present a novel strategy to prevent and manage depression.