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Review

The association between C-reactive protein, Interleukin-6 and depression among older adults in the community: A systematic review and meta-analysis

Kimberley J. Smith[a,*,1], Bonnie Au[b,c,1], Lucie Ollis[a], Norbert Schmitz[b,c,d,e]

[a] Department of Psychological Sciences, School of Psychology, Faculty of Health and Medicine, University of Surrey, Guildford, UK
[b] Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada
[c] Douglas Mental Health University Institute, Montreal, Quebec, Canada
[d] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[e] Montreal Diabetes Research Center, Montreal, Quebec, Canada

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ABSTRACT

Previous research indicates there may be an association between inflammation and depression in older adults but results are inconsistent. Therefore, the aim of this review was to determine the cross-sectional and longitudinal associations of two inflammatory markers C-reactive protein (CRP) and Interleukin-6 (IL-6) with depression in older adults. We searched five databases for cross-sectional and longitudinal studies reporting an association between CRP or IL-6 with depression among adults sampled from the community aged 50 or older. We found 32 studies (23 cross-sectional, 7 longitudinal, and 2 assessing both cross-sectional and longitudinal associations) that met eligibility criteria. These studies were entered into a random-effects meta-analysis to determine the cross-sectional association and longitudinal direction of association between both IL-6 and CRP with depression.

Results indicated a cross-sectional and longitudinal association between both CRP and IL-6 with depression in older adults, with inflammation leading to depression in longitudinal studies rather than depression to inflammation. However, there was notable heterogeneity between studies as results differed based on adjusting for confounders and on how inflammation and depression were measured. These sources of heterogeneity could explain differences in study results.

1. Introduction

Estimates suggest that 1% to 12% of community-dwelling older adults are affected by major depression (Copeland et al., 2004; Fiske et al., 2009; Hasin et al., 2005), while depressive symptoms are present in 10% to 39% of community-dwelling older adults (Blazer, 2003; Djernes, 2006; García-Peña et al., 2008). Depressive symptoms among older adults can adversely affect quality of life in terms of functioning and well-being (Penninx et al., 1998) and also increase the risks for morbidity and mortality (Lee et al., 2001; Fiske et al., 2009; Blazer and Hybels, 2005).

One biological theory that could explain depression in older adults is the inflammatory theory of depression. This theory posits that increased levels of inflammation can cause depression (Anisman, 2009; Dantzer et al., 2008b; Slavich and Irwin, 2014; Alexopoulos and Morimoto, 2011). It is possible that this biological theory of depression could be especially important for older adults as they tend to have higher circulating levels of inflammation than younger adults (Krabbe et al., 2004; Bruunsgaard et al., 2001; Chung et al., 2011; Chung et al., 2009), and they also have an increased risk of chronic illness (Wolff et al., 2002) which is associated with increased inflammation.

Two indicators of inflammation commonly examined in relation to depression are the acute-phase protein C-reactive protein (CRP) and the proinflammatory cytokine Interleukin-6 (IL-6). CRP is a non-specific marker of inflammation, infection, and tissue damage (De Berardis et al., 2009) shown to be linked with depression (Haapakoski et al., 2015; Howren et al., 2009; Valkanova et al., 2013). IL-6 is a broad acting inflammatory cytokine that has a role in stimulating an immune response to stressors such as fever (Hunter and Jones, 2015). IL-6 has been shown to be increased in the bloodstream of older adults (Ershler

* Corresponding author at: Psychological Sciences, University of Surrey, Stag Hill Campus, Guildford GU2 7XH, UK.
E-mail address: Kimberley.j.smith@surrey.ac.uk (K.J. Smith).
[1] Joint first authors.

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and Keller, 2000; Hager et al., 1994), and has also been linked with depression (Haapakoski et al., 2015; Howren et al., 2009).

There have been three previous meta-analyses that have investigated the association of depression with both CRP and IL-6. The first review conducted by Howren et al. (2009) found a positive association between both CRP and IL-6 with depression. However, the collection of studies were restricted to cross-sectional designs and the meta-analysis consisted of all age groups with no subgroup analysis based on age. A second meta-analysis published by Haapakoski et al. (2015) found a moderate association between both CRP and IL-6 with major depression as diagnosed by structured clinical interviews across twenty and thirty one studies, respectively. However, most studies were conducted in clinical populations meaning results might not be applicable to a community sample, and no subgroup analysis based on age was provided. A third meta-analysis used only longitudinal studies and found a small association between raised CRP levels with subsequent development of depressive symptoms and a trend towards significance for IL-6 (Valkanova et al., 2013). However, this study was based on eight studies and only three studies assessed the association between CRP and depression specifically among older adults, while only three studies examined IL-6 and depression in total for all age groups. Two additional meta-analyses investigated the association of IL-6 with depression, and both found a significant positive association (Dowlati et al., 2010; Hiles et al., 2012). However, neither conducted an age-specific subgroup analysis.

Previous work that has been undertaken in older adults examining the association between inflammation and depression has found inconsistent results with some studies indicating an association (Lu et al., 2013; Penninx et al., 2003b) and some indicating no association (Stewart et al., 2008; Valentine et al., 2011). These differences make interpretation of the literature difficult. Researchers have pointed to differences in study populations, gender, assessment of depression, inflammatory marker investigated and adjustment for important confounders such as chronic conditions or adiposity as being possible reasons for inconsistency in results (Almeida et al., 2007; Au et al., 2015; Das, 2016; Hiles et al., 2015). A previous meta-analysis by Hiles et al. (2012) undertook a comprehensive assessment of sources of heterogeneity in studies that examined depression and IL-6 in all age groups. They found that results varied by depression assessment, population setting (i.e., inpatient, outpatient or community) and presence of chronic conditions (Hiles et al., 2012). Thus, considering sources of heterogeneity across studies may be important for uncovering why inconsistencies in results may exist. However, we lack work that has systematically investigated potential sources of heterogeneity in older adults.

Given the paucity of synthesis that has explicitly examined the link between CRP and IL-6 with depression in older adults, the main aim of this review was to examine the relationship between both CRP and IL-6 with depression in community-based samples of adults aged 50 or older. Further, due to the inconsistency in findings from previous work we undertook a comprehensive qualitative and quantitative assessment of potential sources of heterogeneity that could explain differences in findings.

2. Methods

2.1. Search strategy

A systematic literature search for studies describing the relationship between CRP or IL-6 with depression was undertaken between January 2017 and May 2017 (with an update undertaken in September 2017). No language restriction was implemented, but only English papers were reviewed. Furthermore, no restriction was placed on date of publication, type of analysis employed or length of follow-up for longitudinal studies.

Three search themes, “C-reactive protein”, “Interleukin-6” and “depression” were combined using the Boolean operator “and.” (see Appendix A) in five major databases: MEDLINE via PUBMED (United States National Library of Medicine, Bethesda, MD, USA), EMBASE (Elsevier, Amsterdam, Netherlands), PsycINFO (American Psychological Association, Washington, DC, USA), ISI Web of Knowledge (Thomson Reuters, New York, NY, USA), and ProQuest (ProQuest, Ann Arbor, MI, USA). In addition, we manually searched the reference lists of all identified relevant published primary studies and review articles.

2.2. Study selection

Individual studies were considered for inclusion in the systematic review if they assessed the relationship between either CRP and depression in a community sample of adults 50 or older or they assessed the relationship between IL-6 and depression in a community sample of adults 50 or older. Furthermore, the following inclusion criteria were specified: 1) the authors reported data from an original, observational peer-reviewed journal article (i.e., not review articles, reports, letters, theses, posters, published abstracts or comments); 2) the authors provided cross-sectional or longitudinal associations (or both) between CRP and depression or IL-6 and depression; 3) depression was measured with a validated scale or determined using a diagnostic framework or clinical interview (e.g., ICD or DSM) 4) the study population was a cohort of non-institutionalized older adults (age ≥ 50 years at baseline); 5) for prospective studies, the study accounted for/controlled for baseline levels of their outcome. Only studies where participants were sampled from the community were included because the epidemiological inferences are more easily applicable to the general population. Within this definition, we included any study where participants were community-dwelling older adults who have been sampled from primary care. Chronic disease populations (i.e., cancer, diabetes, cardiovascular disease, uremia, renal disease, or respiratory disease) were excluded as were intervention studies. For publications using the same study cohort, the higher quality publication was included for final analysis. When both publications had the same quality rating, the paper that analyzed the larger number of participants was included.

Two authors (L.O. and K.J.S.) firstly screened the titles and abstracts of identified studies (see Fig. 1). Full-text articles were then screened by two authors (B.A and K.J.S). Discrepancies were resolved by consensus, or, when necessary, by a third author (N.S.). Those studies that were eligible for inclusion following full-text analysis were put forward for data extraction and quality assessment.

2.3. Data extraction and quality assessment

Data extraction and quality assessment of eligible studies were performed independently by two reviewers (B.A. and K.J.S.). The following information was extracted: study characteristics, participants' characteristics at baseline, method of assessment for depression, method of assessment for CRP and IL-6, analysis strategy, and brief results (least adjusted and most adjusted effect measure was reported if available). For the purpose of this review, the term ‘depression’ is used as a general descriptor that incorporates any assessment of depression (i.e., depressive symptoms or clinical depression). Clinical depression refers to studies where clinical diagnostic criteria were used to determine depression, while depressive symptoms refer to studies that examined depression using a symptom scale.

The quality of both cross-sectional and longitudinal studies was assessed using the modified Newcastle-Ottawa Scale (NOS) for observational studies. The NOS is a comprehensive instrument that has established content validity and inter-rater reliability (Wells et al., 2014; Gariepy et al., 2010). The interpretation of the scale is based on a “star” system wherein a study is assessed on three broad categories: the selection of study groups; the comparability of the study groups; and the measurement of exposure/outcome. Only those studies determined