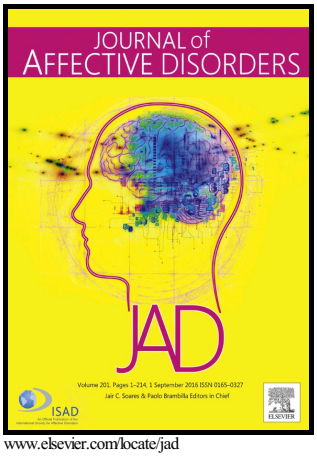

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Multimorbidity and Depression: A Systematic Review and Meta-analysis

Jennifer Read[a], Louise Sharpe[a*], Matthew Modini[a], Blake F. Dear[b]

[a]University of Sydney

[b]Macquarie University

[*]**Corresponding Author:** Louise Sharpe, University of Sydney, Room 450, Brennan McCallum, University of Sydney NSW 2006 Australia. Telephone: +61 2 9351 4558 Facsimile: +61 2 9351 7328. Email: louise.sharpe@sydney.edu.au

Abstract

Background

Multimorbidity, the presence of two or more chronic conditions, is increasingly common and complicates the assessment and management of depression. The aim was to investigate the relationship between multimorbidity and depression.

Method

A systematic literature search was conducted using the databases; PsychINFO, Medline, Embase, CINAHL and Cochrane Central. Results were meta-analyzed to determine risk for a depressive disorder or depressive symptoms in people with multimorbidity.

Results

Forty articles were identified as eligible (n=381527). The risk for depressive disorder was twice as great for people with multimorbidity compared to those without multimorbidity [RR: 2.13 (95% CI 1.62 to 2.80) $p<.001$] and three times greater for people with multimorbidity compared to those without any chronic physical condition [RR: 2.97 (95% CI 2.06 to 4.27) $p<.001$]. There was a 45% greater odds of having a depressive disorder with each additional chronic condition compared to the odds of having a depressive disorder with no chronic physical condition [OR: 1.45 (95% CI 1.28 to 1.64) $p<.001$]. A significant but weak association was found between the number of chronic conditions and depressive symptoms [$r = 0.26$ (95% CI 0.18 to 0.33) $p <.001$].

Limitations

Although valid measures of depression were used in these studies, the majority assessed the presence or absence of multimorbidity by self-report measures.

Conclusions

Depression is two to three times more likely in people with multimorbidity compared to people without multimorbidity or those who have no chronic physical condition. Greater knowledge of this risk supports identification and management of depression.

Keywords: depression; multimorbidity; chronic illness; meta-analysis

Introduction

Multimorbidity, a term which is now commonly used to describe the presence of two or more chronic physical conditions (van den Akker et al., 2001), is a growing presentation found in medical practice. The prevalence of multimorbidity is increasing, largely due to the global aging population trend (Lutz et al., 2008) with people living longer with clusters of illnesses. A study of the prevalence of multimorbidity conducted through general practice surgeries in Australia found that 75% of those aged 65–74 years had multimorbidity with the proportion rising to 80% of those aged 75 years or older (Britt et al., 2008). Multimorbidity, however, is not confined to older adults with a recent population based study in Ontario showing rates from 7% to 35% for adults aged 18 to 65 years (Koné Pefoyo et al., 2015). As multimorbidity becomes increasingly common, demanding further attention and new ways of managing healthcare, (Boyd and Martin Fortin, 2010) support in terms of building a greater understanding of the impact of multimorbidity on overall patient health is required. In addition to the increased complexity in the management of medical needs of people living with multimorbidity, compared to those with a single illness, there are a range of impacts on social and emotional function which require consideration (Roland and Paddison, 2013). An important one of these is the risk for depression.

Depression is one of the leading diseases contributing to global disease burden (Lopez et al., 2006). Lifetime prevalence of depression is estimated to be between 10% and 15% based on large epidemiological surveys (Lepine and Briley, 2011) with over 350 million people currently affected (Marcus et al., 2012). Prevalence rates for depression in various settings include 3-10% in the general population (Lazarou et al., 2010), 4.9% of people in community samples (Blazer et al., 1994), 10% of primary care patients (Craven and Bland, 2013) and 10-14% of hospital patients (Katon and Schulberg, 1992). A study conducted with older adults in Australia (Anstey et al., 2007) identified rates of depression at 14.4% for community dwellers and 32.0% for those in residential care. Although depression prevalence

is generally lower in population groups aged 60 years and over, compared to younger age groups, higher rates are found in sub-groups such as those with chronic physical conditions (ATHW, 2015). Particular risk factors for depression include stressful life events (Kendler et al., 1999), genetics (Sullivan et al., 2000), adverse childhood incidents (Cassano and Fava, 2002), disability, new illness, poor health status, prior depression, bereavement and sleep disturbance (Cole and Dendukuri, 2003).

Over past decades, interest in the relationship between chronic physical conditions and depression has grown. Higher prevalence of depression has been found for patients with a range of conditions including cardiovascular disease (17 – 27%) (Rudisch and Nemeroff, 2003), diabetes (11-31%) (Anderson et al., 2001a) and arthritis (10-24%) (Matcham et al., 2013b). The WHO World Health Survey found a greater prevalence of depression in people who had at least one chronic physical condition (9.3-23%) compared to those with none (3.2%).(Moussavi et al., 2007) Additionally, a meta-analysis by Chang-Quan et al., (2010) found that older adults with a chronic physical condition had a higher risk for depression.

There are numerous potential reasons why multimorbidity may be associated with depression, with the relationship between illness and depression suggested to be bidirectional (Katon, 2011). Multimorbidity may lead to depression through factors such as increasing symptom burden, disability, decreasing quality of life,(Katon, 2003) pain, (Bair et al., 2003) beliefs about disease and coping style (Ziarko et al., 2014). The presence of significant depressive symptoms, on the other hand, may increase the probability of engaging in health risk behaviours, which may contribute to the development of multimorbidity. In addition, poorer disease management may occur in people with depressive symptoms as they may be less likely to adhere to their medical regimens, (Alexopoulos et al., 2008) contributing to increasing risk for multimorbidity. An example of this bi-directional relationship is found

with cardiovascular disease and depression, in that depression increases the risk for onset of cardio-vascular disease by 80 to 90% (Nicholson et al., 2006) and depression is three times more likely after a heart attack (Williams, 2011).

Theoretical explanations for the relationship between multimorbidity and depression can be found in Beck's Developmental Model of Depression (Beck, 2008b) which sees depressive symptoms manifesting from an individual's negative interpretation of their experience, which in this case is their experience of multimorbidity. These negative interpretations are rooted in dysfunctional attitudes and beliefs held about self, others and the world which have developed from early life experiences and may be activated during times of stress, such as when dealing with a number of chronic conditions. The Activity Restriction Model of Depressed Affect (Williamson and Shaffer, 2000) also provides a theoretical understanding of the relationship between multimorbidity and depression. This model attributes a substantial proportion of the depressive symptoms seen in patients with chronic illness to the psychological impact of having to give up valued activities in response to illness. The Psychological and Biological Pathways Model (Schulberg et al., 2000) also provides a representation of the relationship between illness and depression, proposing that physical illness can result in a decreased ability to implement strategies which help to maintain control of important aspect of life and that this, in conjunction with neurochemical and neuroanatomical changes associated with illness, may result in depressive symptoms.

There is growing evidence that neurobiological changes associated with some medical conditions, or related to the stress of having a medical illness, can contribute to the incidence of depression. Vascular lesions in the brain, commonly seen in patients with degenerative neurological diseases such as Alzheimer's disease and Parkinson's disease, appear to be associated with depressed mood (Camus et al., 2004). Additionally, vascular depression is

frequently present in patients with a history of stroke or chronic ischemic injury (Alexopoulos, 2005) and those with higher rates of cerebrovascular risk factors (Mast et al., 2004). Increased stress related to having a number of chronic conditions and subsequent prolonged activation of the hypothalamic-pituitary-adrenal axis is also likely to increase the chances of depressive disorder (Pariante and Lightman, 2008); particularly in individuals with a genetic predisposition or early life factors which contribute to hyperactivity of this axis. Additionally, both metabolic and immune-inflammatory dysregulation, which are common in many chronic conditions, are also associated with depression (Penninx, 2017).

Regardless of the causes of depression, the presence of co-occurring depression and multimorbidity is concerning because of the overall negative impact of having both. There is evidence that patients with both depression and chronic physical conditions have considerably poorer quality of life than those with a chronic physical condition who are not depressed (Moussavi et al., 2007). There is also evidence that people with depression die between five and ten years earlier due to chronic physical conditions (Chang et al., 2010). An additional concern is health care costs, which are approximately 50% greater for patients with depression and a chronic physical condition than for those with a chronic physical condition alone (Luber et al., 2000). Given there is evidence that depression management can reduce mortality related to the combined impacts of having multimorbidity and depression (Gallo et al., 2016), greater understanding of the risk for depression in people with multimorbidity is warranted.

There are a large number of studies that have observed the relationship between particular chronic physical conditions and depression (Anderson et al., 2001b; Matcham et al., 2013a; Rudisch and Nemeroff, 2003). There is also evidence that illness severity is associated with depression (Ostergaard and Foldager, 2011). There is less research, however,

that has investigated the relationship between multimorbidity and depression, and most of the studies have reported the relationship as a secondary focus. To our knowledge, there has been no meta-analysis of the literature specifically looking at multimorbidity and depression, nor examining the relationship between multiple physical illnesses and depression. As multimorbidity is a growing presentation found in medical settings, it is timely that this review be conducted to contribute to a greater understanding of the care needs of this patient group.

The aim of this meta-analysis is to assess the relationship between multimorbidity and depression in adults. It aims to do this by answering the following questions: 1) Is there a significant increased risk for depressive disorders in people with multimorbidity compared to those without multimorbidity, and compared to those with no chronic physical condition?; 2) Is there a significant increased risk of having a depressive disorder with increasing number of chronic physical conditions?; 3) Is there a significant positive relationship between the number of chronic physical conditions and level of depressive symptoms?; 4) If these risks and relationships are present, how strong are those relationships?; and 5) Do any of these risks or relationships differ significantly across age groups, settings or according to the way depression is measured?

Method

Defining Terms

Three groups were used for making comparisons in these meta-analyses; people with multimorbidity, people without multimorbidity and people with no chronic condition. People with multimorbidity are those identified in studies as having two or more chronic physical conditions. People without multimorbidity are those identified as having either no chronic physical condition or only one condition, therefore not falling into the category of people

with multimorbidity. People with no chronic condition are those without any chronic physical condition. Although the category of *people without multimorbidity* is not commonly seen in the literature, results for this group of patients are commonly reported. Naming and defining this category in the meta-analysis supports understanding of the term multimorbidity.

Data sources

A comprehensive literature search, using OVID and EBSCO search software, of five electronic databases, PsychINFO, Medline, Embase, CINAHL and Cochrane Central, was conducted in October 2015. The terms used in the search included multimorbidity, comorbidity, chronic illness, chronic disease, medical condition, health condition and depression. The search was limited to peer-reviewed journal articles available in English language. No limits were placed on the years searched for articles. In addition, the reference lists of all included articles were hand searched.

Study selection

Any studies which looked at the current depression in an adult population were considered for inclusion. This meant there needed to be measurement of the number of chronic physical conditions and depressive disorders or depressive symptoms. Studies were excluded if they counted symptoms, infectious diseases or psychological disorders rather than chronic physical conditions. Also excluded were studies which used a severity index to measure chronic diseases rather than a count. Studies that excluded participants with depression at baseline or in the sample were excluded from the review. This was to ensure that any reported relationships were not underestimated.

One reviewer (JR) conducted the initial search, screening of titles and identification of relevant abstracts. This reviewer then read the texts of articles identified through the screening process to identify studies for inclusion. For the purpose of a reliability check, a second reviewer (MM) screened, independently, 10% of the titles and abstracts (n = 2458). This 10% included all titles considered by the primary reviewer to be relevant, plus a random selection. This reviewer also read a random 10% of full texts of articles identified through the screening of titles and abstracts. Any discrepancies found during this process were resolved through discussion.

Data Extraction

The following data was extracted for each study: country of participants, number of participants, gender, age range, setting, measure of chronic physical conditions and measure of depression. Age range was further classified as either all adult, middle age or older adult. Study setting was classified as community, primary care or nursing home. Details on the number of chronic conditions considered in the study were extracted. Information of interest regarding the type of depression measure included the name of the measure, classification as a diagnostic tool or self-report questionnaire, and whether it measured a case of a depressive disorder or gave an indication of depressive symptoms.

Statistical data regarding the relationship between depression and number of chronic conditions was extracted i.e. prevalence rates of depression, risk or odds ratios, correlations between depression and illness, significance values. Articles which reported the required data or from which the required statistics could be calculated for at least one of the proposed meta-analyses, were included. The authors of articles where relevant data was not reported, but it was likely to be known, were contacted by email to request the information required for inclusion e.g. sub-group sample sizes or prevalence statistics.

Quality Assessment

The quality of research represented in the articles was assessed using three items from the Wong et al., quality assessment checklist (Wong et al., 2008b). This tool was developed for assessing observational studies looking at prevalence rates of HIV. The first two items assessed sampling method and response rate. The third item was modified to assess objective measurement of chronic physical conditions rather than HIV.

Statistical analysis

Four meta-analyses were conducted using the software Comprehensive Meta-Analysis Version 3. The first analysis calculated the overall risk ratio from the pooled results of studies which provided data to compare the risk for a depressive disorder in people with multimorbidity to those without multimorbidity. Similarly, the second analysis calculated the overall risk ratio to compare the risk for a depressive disorder in people with multimorbidity to those with no chronic conditions. The third analysis calculated the odds ratio for having a depressive disorder with increasing number of chronic physical conditions. The final analysis calculated the correlation between depressive symptoms and number of chronic physical conditions. Studies were included in all meta-analyses for which their data was relevant.

Tests of heterogeneity were conducted to determine whether a fixed or random effects model would be more appropriate for the analysis as well as identifying the magnitude of heterogeneity. Risk of publication bias was assessed for each meta-analysis using Egger's linear regression method and Rosenthal's fail-safe *N*.

Sub-group analysis

Sub-group analyses included comparing groups by age group, setting and depression measure. There were two categories used for the age group moderator. The adult category included studies with a general adult focus with participants in age groups ranging upwards from 18 years old. The older adult category included studies with an older age focus with participants in age groups ranging upwards from 50 years old. As there was only one study with a middle age group it was not used as a moderator category. Three categories were used for the setting moderator; community, primary care and nursing home. Two categories were used for the depression measure moderator; diagnosis of depressive disorder and probable depressive disorder based on a questionnaire cut-off score. Groups required at least four studies for comparisons to be considered justified.

Results

The search produced 39645 articles. After duplicates were removed, 24582 articles remained. Titles and relevant abstracts were screened and those not pertinent were excluded. After reading the full texts of the remaining 221 articles, another 174 articles were excluded. Of the remaining 47 relevant articles, the authors of 18 were contacted to request further information. After author responses, 40 articles were eligible for inclusion in the analyses, with seven articles excluded at this point because information, required for inclusion, was unavailable. The search of reference lists of these articles produced a further 20 possibly relevant articles but no further studies were identified for inclusion.

There was excellent agreement for the screening process of titles and abstracts (kappa = 0.80) as well as the screening of full texts (kappa = 0.77). The full texts of any additional articles identified as potentially relevant by the second reviewer were read by the first reviewer, but none were eligible for inclusion.

Figure 1 indicates the number of articles determined at each point of the procedure and the reasons for exclusion. Table 1 shows details for each study included. All studies were cross-sectional in nature.

Quality assessment

The overall quality of sampling methods was good with 76% of the studies using some form of probability sampling. The quality of response rate was satisfactory with 50% of studies reporting a rate over 60%. The quality of objective measurement of chronic physical conditions was poor with only two studies using this type of measurement.

Description of measures

A variety of depression measures were used in the studies. Thirty percent of the studies used a diagnostic interview for depression with the remainder using self-report questionnaires. For diagnostic interviews, the 12 months prevalence rate was used. Some studies (k=15) used a cut-off score for the questionnaires to classify participants as likely to be depressed and there was variation in cut-off scores used for some of the measures; in particular the GDS 30 item and the CES-D 20 item. Other studies used scores to indicate a level of depressive symptoms (*k*=11) rather than classifying patients as depressed. Details of the measure used and cut-off scores, for each study, are shown in Table 1.

Measurement of chronic physical conditions also varied considerably with the number of specific chronic physical conditions measured ranging from four to thirty, with an average number of twelve. Most measurements asked about specific chronic conditions such as heart disease, lung disease, diabetes, arthritis and stroke. There was no indication that relationship

with depression was influenced systematically by the number of chronic conditions asked about in the measures; nor the relationship between depression and multi-morbidity. Self-report measures were used in all but two of the studies. In one of the exceptions, self-reported conditions were verified against patients' clinical histories and, in the other, chronic physical conditions were measured by examining patients' medical records. Details regarding measurement of chronic conditions, including number of conditions measured in each study are shown in Table 1.

Prevalence of depression

The weighted average prevalence of depression in people with no chronic physical conditions was 3.91%, for people without multimorbidity was 5.88% and for people with multimorbidity was 21.14%. The average prevalence of depression calculated just from studies which measured depression by a diagnosis rather than a cut-off score, for the same groups, was 3.44%, 4.79% and 17.19%.

Comparison of those with and without multimorbidity

The test for heterogeneity was significant so a random effects model was used, Q=2117.69 df = 20 p<.001 I^2=99.06. Results from twenty-one studies were analysed to provide an overall risk ratio of 2.13 (95% CI 1.62 to 2.80) p<.001 for having a depressive disorder in people with multimorbidity compared to those without multimorbidity. Figure 2 displays a forest plot of this analysis.

A significant difference in risk was found when comparing age groups (p = .03). Although both significant, the overall risk ratio was greater in adults samples (k = 10) [2.49 (95% CI 1.72 to 3.60) p <.001] than older adult samples (k = 10) [1.65 (95% CI 1.55 to 1.76) p <.001]. A significant difference in risk was also found when comparing groups by

measurement of depression (p = .02). Although both significant, the risk ratio was greater in studies which used a diagnosis of depression (k = 9) [2.50 (95% CI 1.81 to 3.44) p <.001] compared to those that used a questionnaire cut-off score (k= 12) [1.67 (95% CI 1.53 to 1.84) p <.001]. Results of subgroup analyses for each meta-analysis are displayed in Table 2.

There was no evidence of significant publication bias, Egger's intercept = 3.15 (95%CI =-0.98 to 7.29) p=0.12. Additionally, Rosenthal's fail-safe N was very large, N=5268.0, which is supportive that any publication bias would have minimal impact on the overall results.(Rosenberg, 2005)

Comparison of those with multimorbidity to those with no chronic physical conditions

The test for heterogeneity was significant so a random effects model was used, Q=1703.18 df = 17 p<.001 I^2=99.00. Results from eighteen studies were analysed to provide an overall risk ratio of 2.97 (95% CI 2.06 to 4.27) p<.001, for having a depressive disorder in people with multimorbidity compared to those with no chronic physical conditions. Figure 3 displays a forest plot of this analysis.

A significant difference in risk was found when comparing groups by setting (p=.04). Although both significant, the risk ratio was greater for community samples (k = 12) [3.14 (95% CI 2.04 to 4.84) p <.001] than in primary care samples (k = 5) [1.97 (95% CI 1.69 to 2.28) p <.001].

There was no evidence of significant publication bias, Egger's intercept = -6.01 (95%CI =-12.17 to 0.14) p=0.055. Additionally, Rosenthal's fail-safe N was very large, N= 4921.0.

Risk for depressive disorder with number of chronic physical conditions

The test for heterogeneity was significant so a random effects model was used, Q=126.49 df = 11 p<.001 I^2=91.30. Ten studies, providing twelve sets of results, were analysed to provide an overall odds ratio of 1.45 (95% CI 1.28 to 1.64) p<.001, for having a depressive disorder with increasing number of chronic physical conditions. This means, that with each additional chronic physical condition, the odds of having a depressive disorder were 45% greater than the odds of having a depressive disorder for people with no chronic physical conditions. Figure 4 displays a forest plot of this analysis. There were not enough studies to compare by setting for this analysis and no significant differences were found between other sub-groups in this analysis.

There was no evidence of significant publication bias, Egger's intercept = 1.17 (95%CI =-2.55 to 4.89) p=0.50. Additionally, Rosenthal's fail-safe N was very large, N=1092.0.

Relationship between number of chronic physical conditions and depressive symptoms

The test for heterogeneity was significant so a random effects model was used, Q=206.33 df = 12 p<.001 I^2=94.18. Twelve studies, providing thirteen results, were analysed to give an overall correlation between number of chronic physical conditions and depressive symptoms of 0.26 (95% CI 0.18 to 0.33) p <.001. Figure 5 displays a forest plot of this analysis. The range of studies did not allow for any sub-group comparisons in this analysis.

There was no evidence of significant publication bias, Egger's intercept = 3.15 (95%CI =-0.98 to 7.29) p=0.12. Additionally, Rosenthal's fail-safe N was very large, N=2004.0.

Discussion

The findings of this meta-analysis demonstrate a substantial relationship between multimorbidity and depression showing people with multi-morbidity at twice the risk of depressive disorder compared to those without multimorbidity and almost three times the risk compared to those with no chronic physical condition. The robust nature of the relationship is demonstrated in that significant relationships between multimorbidity and depressive disorder were found across age groups, settings, cultures and regardless of whether depression was measured by a diagnosis or cut-off score. Considering the growing number of people, worldwide, affected by multimorbidity this relationship deserves considerable attention.

Although significant relationships were identified between the number of chronic physical conditions and risk for depressive disorder, as well as depressive symptoms, it should not be assumed that the relationship between the number of chronic physical conditions and depression is a simple linear one. Many of the studies reported on the relationships between illness and depression in different ways, such that the number of chronic conditions was collapsed into various categories (e.g. 0-1; 2-3; > 4 etc.). Owing to this, although the meta-analysis has identified the significant risk for increasing number of conditions, further analyses examining possible exponential change or alternately plateauing in depressive symptoms, or risk for depressive disorder, for patients with a large number of conditions, could not be conducted.

The correlation found between number of chronic physical conditions and depressive symptoms, although statistically significant, would be considered a weak positive association, whereas the relationship between multimorbidity and depressive disorder appears to be more substantial. Typically, one would expect a more robust relationship between two continuous variables, rather than two dichotomous variables. This finding highlights that although there is evidence for a relationship between the number of chronic physical conditions and depressive symptoms, the relationship is likely to be influenced by other factors, such as the nature and severity of the chronic physical conditions; with combinations of conditions resulting in greater overall medical burden expected to present a stronger association (Lyness et al., 2006). The result also supports the notion that the relationship between number of chronic conditions and depressive disorders and depressive symptoms, as noted earlier, may not be linear. Importantly, however, self-report measures used to measure depressive symptoms are considerably more likely to be affected by shared-method variance and symptom overlap than diagnostic interviews. Hence, the fact that the relationship between clinical depression and multi-morbidity appears stronger than the relationship between depressive symptoms and number of illnesses, only lends weight to the robust nature of the impact of multimorbidity on mood.

There were some one-off moderating effects found for greater risk for depression in people with multimorbidity in primary care compared to the community, all adults compared to older adults and when using a diagnosis of depression rather than a cut-off score. However, as these effects did not hold across the four meta-analyses they should be interpreted with caution.

The significantly higher risk for depression found, for people with multimorbidity compared to those with no chronic physical conditions, in the community compared to

primary care was unexpected given that prevalence rates for depression in community samples are generally lower than those of primary care. This result underscores that people with physical and mental illness do not always seek help; although it cannot be assumed that people in community samples are not connected to services. It may also be indicative that those connected to primary care services are receiving greater care to manage their physical and mental health. For example, patients groups known to be at risk for depression related to their chronic physical illness may be identified to receive integrated care including psychological therapy which has been shown to be effective (Arean et al., 2008; Coventry et al., 2015).

The significantly higher risk for depression in all adults with multimorbidity compared to older adults with multimorbidity is not surprising given that rates of depressive illness are usually higher in age groups less than 60 years of age than those above 60 years (ATHW, 2015). The relationship may be explained in this context by the considerable impact that having a number of chronic conditions can have on younger adults achieving developmentally significant goals, and consequently on their mental wellbeing (Ireys et al., 1994). In keeping with this, it should be noted that the only study in the meta-analysis that failed to find a relationship between number of conditions and depression was conducted with a small sample of very old people aged over 90 years. A possible reason for the lack of association in this group might be that multimorbidity is very much the norm by this age and life goals have been adjusted in keeping with expectations.

Obviously, the relationship between illness and depression is a complex matter with a number of theoretical explanations, supported by empirical evidence, used to explain the relationship (Beck, 2008a; Beck and Bredemeier, 2016; Schulberg et al., 2000). Despite the multifaceted and bi-directional relationship, the results of these meta-analyses provide

justification for the worth of considering multimorbidity as a reliable risk factor for depression. As there are generally poor rates of identifying depression in primary care (Kamphuis et al., 2012), raising awareness of multimorbidity as a significant risk factor for depression may help with detection. Equally, it is likely that many patients who present with depression may also have chronic physical health problems and multimorbidity. Assessment for depression needs to take physical health into account and therefore awareness of the complexities of multimorbidity in people with depression will become increasingly important, as rates of multimorbidity increase.

Although there is evidence for increased risk for depression in people with multimorbidity, and the average prevalence rate was 21.1%, it is worth noting that this also demonstrates that the majority of people with multimorbidity do not have a depressive disorder. This highlights that although practitioners should keep the significant risk for depression in mind when treating patients with multimorbidity, it should not be assumed that having a depressive disorder is expected or considered normal, for people with multimorbidity.

Limitations

The overall quality of the included studies could be considered good in that many of the samples sizes were large, the majority used probability sampling, and most studies used well-validated measures of depression. There is a considerable limitation however in that measurement of chronic physical conditions in 95% of the studies relied on self-report, as there is mixed evidence regarding the reliability of self-reported chronic physical conditions (Heliövaara et al., 1993; Okura et al., 2004). It is notable however, that results from the two studies which confirmed chronic physical conditions from medical records showed considerably stronger relationships than the overall results. This is encouraging and suggests

that the predominant method of self-reported measurement of chronic physical conditions did not result in an overestimation of the relationship.

Another limitation of the meta-analysis was that the number of specific chronic physical conditions measured was not uniform across the studies. Given however that only three of the studies measured less than seven common chronic physical conditions, the measurement should be considered sufficiently thorough to draw conclusions from the results, especially given the consistency of the findings across studies. Future research could consider more standardised means of measuring multimorbidity.

An additional limitation to consider is that all the studies included in the meta-analysis were cross-sectional in nature. As a result, we cannot determine the direction of causality for these relationships. The relationship between illness and depression however, is generally thought to be bi-directional.

A further consideration, in regard to interpreting the results, is the variability within the analyses. Each analysis had high heterogeneity, some of which is likely to stem from the different depression measures used in the studies. Despite the variability however, the majority of studies used widely recognised, valid and reliable measures. Nonetheless, the results should therefore be interpreted with caution. The average prevalence of depression, found in the groups of interest, was slightly lower when depression was assessed by diagnostic interview rather than a cut-off score which indicates that cut-off scores may overestimate cases of depression. Another limiting factor is the variability in cut-off scores used across the studies. Nevertheless, it is interesting to note that in the group analysis which found a significant difference in risk between studies using a diagnosis rather than a cut-off score, there was a higher risk found in studies which used a diagnosis; further supporting the robust nature of the findings.

Conclusion

The aim of this meta-analysis was to examine the relationship between multimorbidity and depression. It has provided substantial support that the risk for depressive disorder is twice as great for people with multimorbidity compared to those without multimorbidity and three times as great compared to those with no chronic physical conditions. Patient assessment requires consideration of numerous factors and the quantification of risk for depression in people with multimorbidity, although having limitations, serves to provide useful knowledge to practitioners managing patients with multimorbidity. Raising awareness of the magnitude of this risk also supports early identification and treatment of depression in people with multimorbidity, which is a priority given the compounded decrements to overall health and mortality, (Chang et al., 2010) and additional health care costs (Bhattarai et al., 2013). Given the considerable risk for depression identified in this meta-analysis, future research on prevention and treatment of depression in people with multimorbidity is warranted.

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Conflict of Interest Disclosures

None

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Table 1 Studies included in the meta-analyses and their characteristics

Author,Year	Country	N	Setting/Group	Age	CPC measure	Dep measure	Analysis	Statistics
Aktas 2013	Turkey	512	Emergency Department	65+	Self-report	GDS (30 item) cut-off score ≥20 for severe dep	0vMM 0-1vMM	0: 3.4 % 0-1:14.0% 2+: 19.1%
Albrecht Junghans 1998	Mexico	193	Community	60+	No details	DSMIII-R Diagnosis	0-1vMM	0-1: 21.8 2+: 41.3
Aragones 2004	Spain	306	Primary Care	18-70	Self-report	SCID-1 (DSM IV)	0vMM 0-1vMM	0: 10.7% 0-1: 9.6& 2+: 23.5%
Arokiasamy 2015	6 LMIC	42236	Community	18+	Self-report 8 CPC	CIDI	0vMM 0-1vMM	0: 3.2 % 0-1:4.1% 2+: 13.2%
Assari 2014	U.S.A.	3570 1438 891	Community Afri American Caribbean Black White	18+	Self-report 14 CPC	CIDI	NCPC & Dep	O.R 1.34 O.R1.38 O.R. 1.42
Beekman 1995	Netherlands	224	Community	55-89	Self-report 6 CPC	CES-D (Dutch) 20 item	NCPC & Sym	*r*=0.21
Black 1998	U.S.A.	2823	Community	65+	Self-report 8 CPC	CES-D cut-off score	0-1vMM	0-1:18.3% 2+:32.6

						≥16		%
Blay 2007	Brazil	7040	Community	60+	Self-report 18 CPC aggregated to 3.	Short Psychiatric Evaluation Schedule cut-off of ≥2	0vMM 0-1vMM	0: 24.9% 0-1:33.0% 2+: 53.0%
Caplan 2015	U.S.A.	177	Primary Care	18+	No details	PHQ-9 cut-off score ≥10	0vMM 0-1vMM	0: 14.1 % 0-1:20.5% 2+: 38.2%
Chang 2011	Taiwan	152	Male Veterans Home	70-99	Self-report CPC	GDS - Taiwanese cut-off score ≥15	0-1vMM	O.R. 1.90 for 2+ (0-1 as ref.)
Chang-Quan 2008	China	400	Not stated	≥90	Self-report CPC over the past 3 years	GDS-Chinese (23 item)	NCPC & Sym	M *p* = .72 F *p* = .47

Table 1 Studies included in the meta-analyses and their characteristics

(continued)

Author and Year,	Country	N	Setting/Group	Age	CPC measure	Dep Measure	Analysis	Statistics
Chong 2010		104	Primary Care	18+	Self-report of	PHQ-9 cut-off	0vMM	0: 9.4 %

					CPC	score ≥10	0-1vMM NCPC & Dep NCPC & Sym	0-1:9.9% 2+: 34.8% *p<.05* *r*=0.41
Egede 2007	U.S.A.	30,801	Community	18+	Self-report 7 CPC	CIDI-SF	0vMM 0-1vMM	0: 4.7% 0-1: 5.5% 2+: 10.5%
Fernandez 2006	Spain	244	Rural community	64+	Self-report verified by clinical history	GDS 15 item cut-off score >5	0vMM 0-1vMM	0: 0% 0-1: 13.8% 2+: 24.2%
Galibondo 2012	Spain	2121	Population survey	18+	Self-report 14 CPC	CIDI (3.0) 12-month MDE	0vMM 0-1vMM	0: 7.9% 0-1: 6.6% 2+: 8.9%
Gallegoos-Carrillo 2009	Mexico	1085	Community	60+	Self-report 10 categories of CPC	GDS-15 cut-off score ≥6	0vMM 0-1vMM	0: 6.3% 0-1: 21.0% 2+: 39.9%
Gunn 2012	Australia	6738	Primary Care	18-76	Self-report 12 CPC	CES-D cut-off score ≥16	0vMM 0-1vMM	0: 16.4% 0-1: 19.7% 2+: 29.7%
Hailemariam 2012	Ethiopia	4768	Population survey	18+	Self-report of CPC	CIDI	0vMM 0-1vMM NCPC &	0: 5.5% 0-1:

							Dep	7.7% 2+: 27.0% *d*= 0.47
Jang, 2005	U.S.A.	707	Community	60-84	Self-reports CPC	GDS-SF	NCPC & Sym	*r*=0.35
Jang 2011	U.S.A.	675	Community - Korean Americans	60+	Self-report 9 CPC	GDS-SF Korean	NCPC & Sym	*r* =0.23
Lai 2004	Canada	444	Community - immigrants from Mainland China	55+	Self-reported CPC	GDS-SF Chinese	NCPC & Sym	*r*=0.41

Table 1 Studies included in the meta-analyses and their characteristics (continued)

Author and Year,	Country	N	Setting/Group	Age	CPC measure	Dep Measure	Analysis	Statistics
Lee 2010	Hong Kong	5004	Community	18-65	Self-reports of 8 CPC	DSM IV MDE 12 months	0vMM 0-1vMM	0: 6.5% 0-1:7.8% 2+: 21.5%
Lee 2001	Korea	1935	Community	60+	Self-report 12 CPC	CES-D	NCPC & Sym	*r*=0.346
Li 2015	China	3824	Community	60+	Self-report 14 CPC	CES-D Cut-off score 12	0vMM 0-1vMM	0: 24.7% 0-1: 29.6% 2+:

								50.1%
Lin 2007	Taiwan	138	Nursing Home	65 +	16 CPC from records	CES-D	NCPC & Sym	*r* = 0.352
Maharaj 2005	Trinidad	734	Primary Care	18 +	Self-report CPC	Zung (modified) Interview administered	NCPC & Dep	*p=.006*
McDougall 2007	United Kingdom	2614	Primary Care	65 +	Self-report CPC	GMS-AGECAT diagnosis	0-1vMM	O.R. 2+: 2.40
Moussavi 2007	World	237101	Community	15 +	Self-report 4 CPC	CIDI 12 month	0vMM 0-1vMM	0: 3.2% 0-1: 4.62% 2+: 23%
Nan 2012	Hong Kong	6195	Community	15 +	Self-report 10 CPC	PHQ-9 (Chinese)	NCPC & Sym	*r*=0.11
Penninx 1996	Netherlands	3076	Community	55-85	Self-report CPC	CES-D (Dutch Version)	NCPC & Sym	*r*=0.169
Richardson 2012	U.S.A.	378	Community	60 +	Self-report CPC	CIDI	NCPC & Dep	O.R. 1.28
Ruiz 2003	U.S.A.	99	Community Grandmothers with custody of grandchild	38-88	Self-report 10 CPC	CES-D (Y/N answers) Cut-off score ≥9	NCPC & Dep	O.R. 1.68
Tsai 2013	Taiwan	4054	Community and	53 +	Self-report list of	CES-D (10 item)	NCPC & Dep	O.R. 1.34

			Institutions		14 CPC	Mandarin Cut-off score ≥10		
Verhaak 2014	Netherlands	510	Mental health care and primary care	60+	Self-report of CPC	CIDI 6 months	NCPC & Dep	O.R. 1.03
Vilhajalmsson 1998	Iceland	852	Community	20-70	Self-report 30 CPC	SCL90-R	NCPC & Sym	*r*=0.398

Table 1 Studies included in the meta-analyses and their characteristics (continued)

Author and Year,	Country	N	Setting/Group	Age	CPC measure	Dep Measure	Analysis	Statistics
Wong 2008	Hong Kong	3394	Community	65+	Self-report 14 CPC	GDS (Chinese) cut-off score 8	NCPC & Dep	O.R. 1.27
Wong 2014	Hong Kong	347	Community (Women)	45-64	Self-reported medical history	PHQ-9 (Chinese)	0vMM 0-1vMM NCPC & Dep	0: 5.2% 0-1: 6.2% 2+: 32.8%
Woodward 2013		1950	Community	50+	Self-report 18 CPC	CIDI	0-1vMM	0-1: 6.9% 2+: 12.15%
Yumming, 2012	China	1486	Community	60+	Self-report 7 CPC	GDS (30 item) cut-off score ≥11	0vMM 0-1vMM	0: % 0-1: 6.2% 2+: 32.8%

Zauszniewski 2004	U.S.A.	314	Aged care	64-98	Self-report of 26 CPC	CES-D	NCPC & Sym	*r*= .24

CPC = chronic physical condition; Dep = depressive disorder; Sym = depressive symptoms; 0 = no chronic physical conditions; 0-1= no or one chronic physical condition; 2+ = 2 or more chronic physical conditions; NCPC = Number of chronic physical conditions; LMIC = Low and Middle Income Countries

ref. = reference group

Table 2 Summary of results for mixed effects sub-group analyses

Patients with multimbodity compared to patients without multimorbidity						Heterogeneity (between groups)	
	k	Risk Ratio	95% CI	*z-value*	*p-value*	Q-value	*p-value*
Age group							
Adults	10	2.49	1.72 to 3.60	4.853	<0.001		
Older Adults	10	1.65	1.55 to 1.76	15.416	<0.001		
						4.69	0.03*
Setting							
Community	14	2.236	1.61 to 3.10	4.82	<0.001		
Primary Care	4	1.925	1.38 to 2.69	3.85	<0.001		
						0.394	0.53
Measure							

Diagnosis	9	2.50	1.81 to 3.44	5.59	<0.001		
Cut-off score	12	1.67	1.53 to 1.84	10.92	<0.001		
						5.51	0.02*
Patients with multimbodity compared to those with no chronic condition							
Age group							
Adults	10	2.949	1.85 to 4.71	4.53	<0.001		
Older Adults	7	2.25	1.83 to 2.77	7.67	<0.001		
						1.07	0.30
Setting							
Community	12	3.14	2.04 to 4.84	5.19	<0.001		
Primary Care	5	1.97	1.69 to 2.28	8.85	<0.001		
						4.05	0.04*
Measure							
Cut-off score	10	2.35	1.95 to 2.84	8.95	<0.001		
Diagnosis	8	3.01	1.89 to 4.78	4.78	<0.001		
						0.93	0.33
Number of chronic conditions and depressive disorders							
	k	Odds Ratio	95% CI	*z-value*	*p-value*	Q-value	*p-value*

Age group							
Adults	6	1.59	1.23 to 2.06	3.56	<0.001		
Older Adults	5	1.28	1.19 to 1.37	7.18	<0.001		
						2.65	0.10
Measure							
Cut-off score	6	1.35	1.26 to 1.46	7.99	<0.001		
Diagnosis	6	1.43	1.12 to 1.81	2.90	0.004		
						0.17	0.68

*significant result; Cut-off score = cut-off score on questionnaire indicating likely depression; Diagnosis = Diagnosis of depressive disorder; *k= number of studies Q-value is Cochran's Q statistic which is a test of heterogeneity and is used to determine whether there is a significant difference between effects of the groups being compared.*

Figure 1. PRISMA flow diagram demonstrating the process for identifying articles for the meta-analysis.

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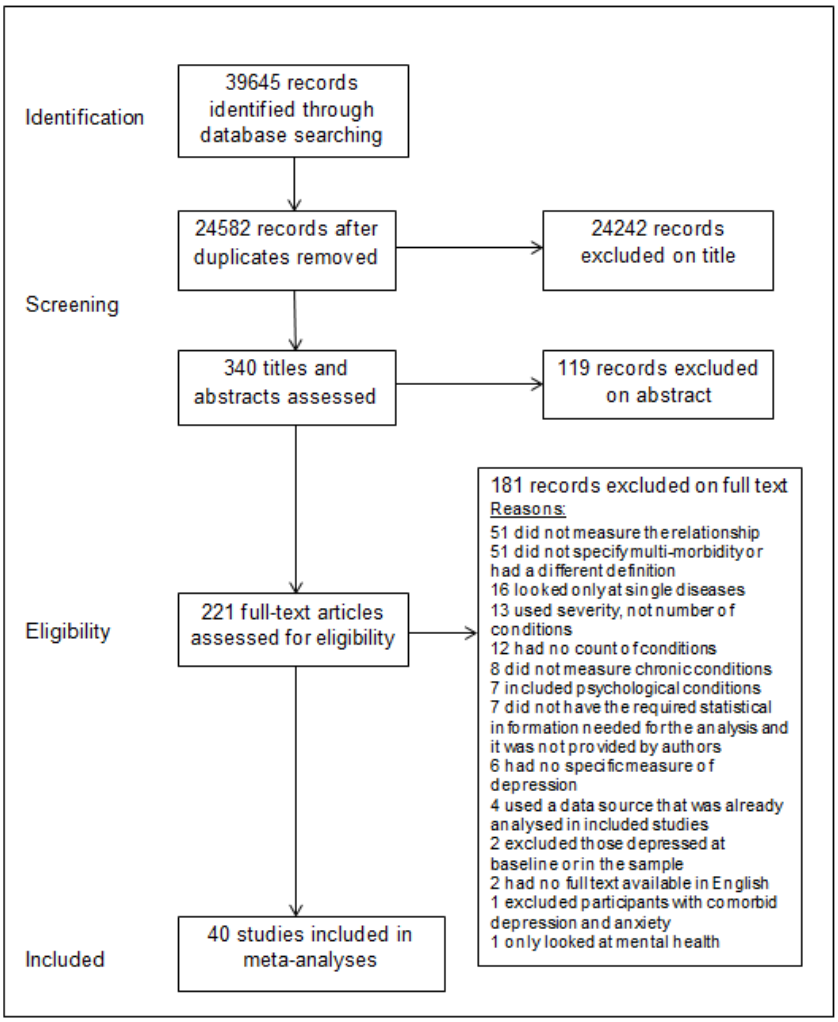
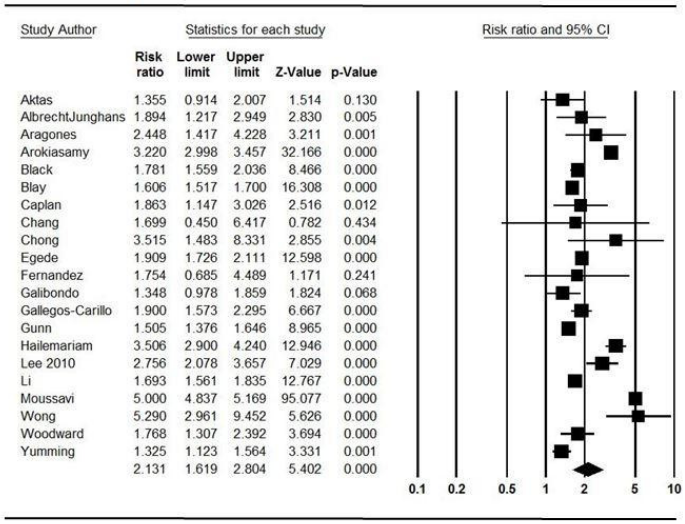


Figure 2. Forest plot of all studies showing the relative risk for depressive disorder in people with multimorbidity compared to those without multimorbidity. Values >1.0 indicate that multimorbidity is associated with an increased risk for depressive disorder. The magnitude of the square indicates the weight given to the study in the analysis. The horizontal line coming either side of the square indicates the 95% CI. The diamond indicates the overall result.

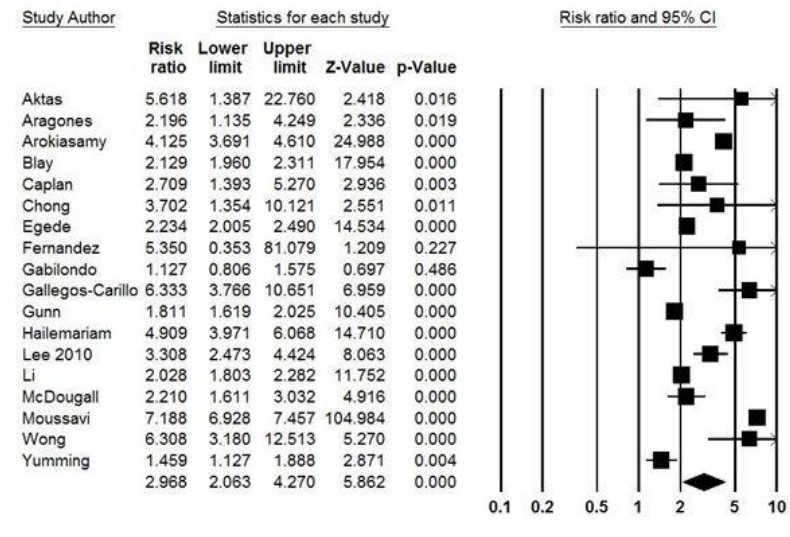
Figure 2. Forest plot of all studies showing the relative risk for depressive disorder in people with multimorbidity compared to those without multimorbidity.



Values >1.0 indicate that multimorbidity is associated with an increased risk for depressive disorder. The magnitude of the square indicates the weight given to the study in the analysis. The horizontal line coming either side of the square indicates the 95% CI. The diamond indicates the overall result.

Figure 3: Forest plot of all studies showing the relative risk for depressive disorder in people with multimorbidity compared to those with no chronic physical condition. Values >1.0 indicate that multimorbidity is associated with an increased risk for depressive disorder. The magnitude of the square indicates the weight given to the study in the analysis. The horizontal line coming either side of the square indicates the 95% CI. The diamond indicates the overall result.

Figure 3: Forest plot of all studies showing the relative risk for depressive disorder in people with multi-morbidity compared to those with no chronic physical condition.



Values >1.0 indicate that multi-morbidity is associated with an increased risk for depressive disorder. The magnitude of the square indicates the weight given to the study in the analysis. The horizontal line coming either side of the square indicates the 95% CI. The diamond indicates the overall result.

Figure 4. Forest plot of the odds ratio for depressive disorder with the number of chronic physical conditions. Values >1.0 indicate that multimorbidity is associated with an increased odds for depressive disorder compared to the odds for those with no chronic physical condition. The magnitude of the square indicates the weight given to the study in the analysis. The horizontal line coming either side of the square indicates the 95% CI. The diamond indicates the overall result. * results for African Americans, ^ results for Caribbean Blacks ~ results for Non-Hispanic Whites

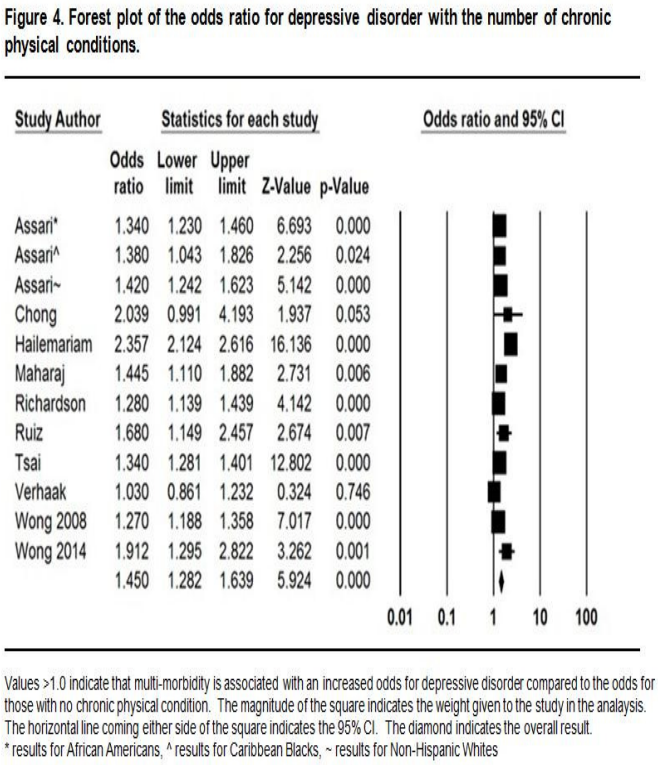
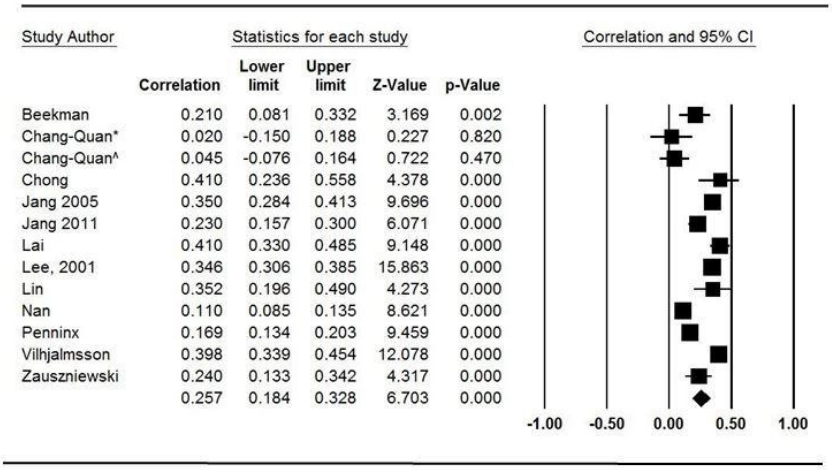


Figure 5. Forest plot of all studies showing the correlation between number of chronic physical conditions and depressive symptoms. The greater the value from 0.0 the greater the association between number of chronic physical conditions and increasing depressive symptoms. The magnitude of the square indicates the weight given to the study in the analysis. The horizontal line coming either side of the square indicates the 95% CI. The diamond indicates the overall result. * results for males, ^ results for females

Figure 5. Forest plot of all studies showing the correlation between number of chronic physical conditions and depressive symptoms.



The greater the value from 0.0 the greater the association between number of chronic physical conditions and increasing depressive symptoms. The magnitude of the square indicates the weight given to the study in the analysis. The horizontal line coming either side of the square indicates the 95% CI. The diamond indicates the overall result. * results for males, ^ results for females

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Highlights

- The first meta-analysis looking at multimorbidity and risk for depression.
- Risk is doubled with multimorbidity compared to those without multimorbidity.
- Risk is trebled with multimorbidity compared to those with no physical condition.
- Understanding of this risk may enhance access to appropriate depression treatments.

Contributors

Jennifer Read (JR)

Louise Sharpe (LS)

Matthew Modini (MM)

Blake F. Dear (BFD)

JR, LS and BFD conceived and designed the study. JR and MM collected data (in the form of selecting suitable manuscripts), under the supervision of LS. JR conducted the primary analyses and wrote the first draft of the manuscript. All authors contributed to interpretation of the statistical analysis, commented on drafts of the manuscript and approved the final version of the manuscript.