King's Research Portal

DOI:

[10.1017/S0033291719002381](https://doi.org/10.1017/S0033291719002381)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Edwards, C. J., Garety, P., & Hardy, A. (2019). The relationship between depressive symptoms and negative symptoms in people with non-affective psychosis: a meta-analysis. *Psychological Medicine*, 49(15), 2486-2498. <https://doi.org/10.1017/S0033291719002381>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

The relationship between depressive symptoms and negative symptoms in people with non-affective psychosis: a meta-analysis

Clementine Jane Edwards^{*1,2}, Philippa Garety^{1,2}, Amy Hardy^{1,2}

¹ King's College London, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, De Crespigny Park, SE5 8AF.

² South London & Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Monks Orchard Road, Beckenham, Kent, BR3 3BX.

*Corresponding Author:

Dr. Clementine Edwards,

Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, De Crespigny Park, SE5 8AF.

Tel: 02078480980

Email: clementine.edwards@kcl.ac.uk

Abstract Word Count: 250

Total Word Count: 4,947

Abstract

The negative symptoms of psychosis and depressive symptomatology share several features e.g. low motivation, apathy and reduced activity. Understanding the associations between these two sets of symptoms will support improved assessment and the development of interventions targeting these difficulties in people with psychosis. This is the first large systematic review and meta-analysis to quantify the relationship between these two categories of symptoms, as measured in studies to date. PsycInfo, Embase and Medline were systematically searched to identify eligible studies. Inclusion criteria ensured the studies measured both depression and negative symptoms using validated measures in a sample of over 8000 participants with non-affective psychosis diagnoses. The search led to 2020 records being screened and 56 included in the meta-analysis and review. Both meta-analyses and meta-regressions were conducted to explore the main effect and potential moderating variables. A clear pattern emerges showing that higher ratings of negative symptoms are associated with higher levels of depressive symptoms, with a small effect (Standardised Effect Size = 0.19, $p < .05$). This did not vary greatly with the measures used (SES = .19 to .26) and was not moderated by demographic variables or quality ratings. Interestingly, higher depressive symptoms predict a significant relationship with co-occurring negative symptoms. However, higher negative symptoms predict that it is less likely there will be a relationship with co-occurring depressive symptoms. Heterogeneity was high across these analyses. The findings support the adoption of a symptom-specific approach to understanding the interplay between negative and depressive symptoms in psychosis, to improve assessment and intervention.

Introduction

The negative symptoms of psychosis include low motivation, anhedonia, alogia, social withdrawal and blunted affect ¹. Research has shown that these symptoms have a significant impact on functioning ²⁻⁴, with some studies suggesting these difficulties are a bigger barrier to recovery than other symptom domains ^{5, 6}. Negative symptoms were initially conceptualised as primary, a core feature of schizophrenia-spectrum diagnoses, or secondary – present due to other factors such as substance misuse, medication side-effects, depression or as a response to the positive symptoms ⁷. This conceptualisation allows for the co-occurrence of depressive and negative symptoms in non-affective psychosis. Recent research has focused on a further distinction within negative symptoms – experiential vs. expressive ⁸ which enables more reliable measurement. Experiential symptoms include low motivation, anhedonia and withdrawal whereas expressive symptoms are identified as blunted affect and alogia. Depression also includes a range of symptoms with similarities to experiential negative symptoms, with loss of pleasure (anhedonia), low motivation and low mood highlighted as key in the diagnostic criteria ⁹. A narrative review concluded that depressive symptoms are very common in people with a schizophrenia diagnosis and worsen their prognosis; it has been reported that up to 50% would also meet criteria for depression ^{10, 11}.

The diagnostic conceptualisation of negative and depressive symptoms is that they relate to distinct disorders which are driven by different organic processes and commonly occur ¹². It is important to consider that depression is defined by self-report criteria (experiential), whereas psychosis is defined by clinician-rated (expressive) criteria. Some attempt has also been made to identify people for whom low mood is a significant problem alongside psychosis and this has resulted in diagnoses such as “schizoaffective disorder”, “depression with psychotic features” and applies of course to bipolar

disorder. The usefulness of these diagnostic labels in clinical practice, particularly schizoaffective disorder, is still debated in the field ¹¹. The DSM-V ⁹ recommends the assessment of eight domains in schizophrenia-spectrum disorders, including depression, which represents a move towards dimensional as well as categorical assessment. Kirschner, Aleman, Kaiser ¹³ concluded in their narrative review that the presence of depressive symptoms in someone with psychosis may be missed because of the lack of clarity regarding how to assess them reliably and this may negatively impact on their treatment options. A more recent review of the field highlights the continuing lack of clarity regarding how to validly distinguish whether reported phenomenology are reflective of psychotic or depressive disorder ¹⁴.

The symptom-specific conceptualisation views depressive symptoms as part of the maintenance cycle of negative symptoms, driven by psychological processes such as low self-efficacy beliefs and reduced anticipatory pleasure (see Sarkar, Hillner, Velligan ¹⁵). Indeed, psychological models of psychosis (e.g. Garety, Kuipers, Fowler, Freeman, Bebbington ¹⁶) have proposed a direct route from emotional changes to psychotic symptoms. The phenomenological overlap between negative and depressive symptomatology is more apparent with *experiential* negative symptoms which include low motivation and anhedonia, commonly seen in depression ⁹. Older measures of negative symptoms are in an interview format and conceptualise negative symptoms as a single construct including multiple symptoms, they do not make the distinction between experiential and expressive negative symptoms. Newer measures of negative symptoms include specific subscales of experiential symptoms and there is some evidence that they show good divergent validity from depressive measures ^{17, 18}. This has been achieved by focusing on low motivation across several areas of functioning (social, employment, hobbies) rather than using terms such as “low energy” or “low mood” which can measure affective and somatic depressive symptoms. Experiential subscales do not assess cognitive symptoms, specifically beliefs about self, world and the future, and there is some indication in the literature that this may be

where distinctions can also be drawn from depressive symptoms although findings are mixed ¹⁹.

Cognitions which seem to be more specific to depression are those related to guilt, hopelessness and suicidality. Some cognitions such as defeatist beliefs appear to play a role in negative symptoms and have been incorporated into the cognitive model of negative symptoms developed by Grant & Beck ²⁰. There is a clear need to investigate relationships between cognitive, somatic-affective and behavioural phenomena associated with depressive and negative symptoms to improve targeted treatments.

The evidence regarding the overlap between these symptoms has been mixed with some studies finding an association between depressive symptoms and negative symptoms and others reporting none ²¹⁻²⁴. Studies focusing on the primary and secondary conceptualisation of negative symptoms consistently report low levels of co-occurring depressive symptoms in people with psychosis identified as having primary negative symptoms ¹⁹. The variation in findings may also be due to the range of measures used to assess both depression and negative symptoms in people with psychosis. It has been shown that in depression, measures have very little overlap with one another, reflecting the heterogeneity of these symptoms ²⁵. Measures aim to have high divergent validity between depressive and negative symptoms, adopting the diagnostic rather than symptom-specific approach. However, a recent review ¹⁴ showed that the domains of anhedonia, avolition and anergia may be common to both and used this to suggest an overlapping, dimensional model of negative, positive and depressive symptoms. The findings of this narrative review concluded that the symptom domains of pessimism, low mood and suicidal ideation may be specific to depression, while alogia and blunted affect are specific to negative symptoms. Hopelessness is an important factor in terms of the relationship with suicidal intent and attempts, this has been shown to be present in both depression and psychosis, although hopelessness is more commonly seen in depression ^{26, 27}. The time is therefore ripe for a systematic

meta-analysis of this field which aims to establish whether there is a quantitative relationship between negative and depressive symptoms in psychosis.

This method improves on previous systematic reviews by applying rigorous meta-analytic techniques and will include studies which have assessed both negative and depressive symptoms. Finally, this meta-analysis will be the first to look at the relationships between depression measures and specific sub-domains of negative symptoms as assessed by newer measures, which may help to improve our understanding of how they interact.

The following research questions will be addressed in this review and meta-analysis:

1. Is there a significant relationship between negative symptoms and depression in people with a diagnosis of non-affective psychosis?
2. Does the relationship between negative and depressive symptoms vary according to the measures or subscales used?
3. Is this relationship moderated by depressive or negative symptom severity?
4. Is this relationship moderated by the diagnosis of the sample, quality of the study or demographic factors?

Method

Literature search

PROSPERO was examined for reviews with an overlapping research question, none were identified. This review was then registered on the PROSPERO database (ID: CRD42017083440). Relevant studies were identified through the systematic search of the databases Medline, Embase and PsycINFO in February 2017 with no time period specified. These databases were selected to fully capture the

range of journals in this field. The following search terms were used as heading or keyword searches: (SCHIZOPHREN* OR SCHIZOAFFECT OR PSYCHOSIS OR PSYCHOTIC) AND (NEGATIVE SYMPTOMS) AND (DEPRESS*). The use of search terms targeting specific depressive or negative symptoms (e.g. anergia, alergia, motivation) were considered but not included as the focus of this review is on the whole range of depressive and negative symptomatology and including individual symptoms may have biased the sample of papers identified. A recent narrative review¹⁴ which did include individual symptoms returned a similar number of papers as the current review suggesting this strategy captured all relevant papers.

The current review followed the flow of information as suggested by the PRISMA statement ²⁸. Following the initial search, duplicate records were removed, and the inclusion and exclusion criteria were applied. The search was conducted by CE and any studies where inclusion was unclear were discussed with AH and PAG.

Inclusion criteria

Studies were included if they (i) include a sample with at least one of the non-affective psychosis diagnoses (ii) include a validated measure of negative symptoms in psychosis (iii) include a validated measure of depression in psychosis (iv) have been published in a peer-reviewed publication (v) have been written in English. Studies were included if the results reported a test of a direct association between the negative symptom measure and depression measure regardless of whether this was the primary outcome of the study. Validated measures of depressive and negative symptoms were identified organically through the literature search – if a validation paper was cited for the measure then it was considered eligible for inclusion.

Exclusion criteria

Studies were excluded if they were (i) conference abstracts (ii) book chapters (iii) theoretical or review articles (iv) qualitative data only was presented or (v) they were single case studies or dissertations. Studies were also excluded if: the sample included people with a diagnosis of bipolar affective disorder or depression with psychotic features as low mood is primary in these diagnoses; they removed people who met criteria for depression from their sample as we wished to analyse the relationship at all levels of depressive symptoms; they only used a single item to assess depressive symptoms as this was not considered sufficiently robust. Studies were also excluded if insufficient statistical information was provided for the paper to be included in the analyses e.g. only associations for change scores presented or authors did not respond to request for additional data within the time frame of the study (k=3)^{17, 29, 30}.

Quality assessment

Studies were assessed using an adapted version of the Quality Assessment Tool for Quantitative Studies³¹; see Supplementary Material for rating scale and instructions. This was included for the purpose of characterising the studies included, and to analyse quality as a potential moderator of our findings. The measure was adapted by removing sections C, D and G which were relevant for randomised controlled trials only. One additional item was added which assessed whether the analyses of negative and depressive symptoms was outlined in the design of the study or whether it was the result of secondary analyses. This was identified as an important quality criterion in this group of studies. All studies were rated by CE and a sample of 10% (k = 6) were rated by an independent assessor. One of these six papers had a discrepancy greater than 2 between raters which specific to the selection bias item. This was discussed, and a consensus reached. The ratings were shown to have excellent reliability (Intraclass Correlation = .94, 95% CIs = .76 - .99).

Data extraction and analytic procedure

Based on the inclusion criteria, 56 studies were considered eligible for inclusion in the final meta-analyses. The following data were extracted from each study by CE: sample size, age, gender, ethnicity, diagnosis (% schizoaffective disorder), mean scores on depression and negative symptoms measures, r statistic and p value for the correlation. To ensure each study was weighted appropriately where multiple Pearson's r values were presented for different subscales these were averaged to combine them for the main analysis, allowing all data points to be included without introducing bias ³². Individual subscales were reported in sub-group analyses. All scores were converted to Fisher's z scores to represent the continuous nature of the data and to minimise the risk of bias associated with Pearson's r ³². All analyses were conducted in *Stata* ³³ using the *metan* package for meta-analyses and *metareg* for meta-regressions. We hypothesised that the true effect sizes would vary with sample characteristics acting as moderating variables. Therefore, random effect models were chosen for the meta-analyses of main effects as well as meta-regressions and subgroup analyses ³⁴. The main analysis was conducted to assess the relationship between depressive and negative symptoms and included all the studies. Sub-group analyses were conducted to examine this relationship when different measures were used. Meta-regression analyses were carried out to examine whether the severity of depressive or negative symptoms, age, gender, ethnicity, diagnosis or quality score moderated the findings.

For all analyses, heterogeneity statistics (I^2 and τ^2) are reported to examine the amount of variance across studies. The I^2 statistic was included as it has greater power to detect true heterogeneity when analyses only include a small number of studies. The convention is to consider an I^2 statistic higher than 25%, 50% or 75% as representing low, moderate or high heterogeneity respectively. The τ^2 statistic measures the between-study variance in the meta-analyses and a value >1 is suggestive of very high heterogeneity ³⁵. For the reporting of the main effect, rather than the 95% confidence interval, the more

rigorous 95% prediction interval, which takes into account the heterogeneity and describes the range of values in which 95% of effect sizes in future studies can be expected to fall ³².

Publication bias was assessed with the *metabias* package in Stata which includes Egger's test for asymmetry ³⁶ and Begg's test ³⁷. A funnel plot will also be produced to aid our assessment of bias.

Egger's test is limited in its ability to detect bias in random effects models as it was designed for fixed effects analyses. The analysis of quality ratings as a potential moderator is also a method of bias analysis.

Results

-----Figure 1 approximately here-----

Characteristics of studies

Fifty-six papers were included in the analyses, see PRISMA flow diagram in Figure 1. The included studies are summarised in Table 1 below. Based on the data available, there were 8,177 unique participants in these studies and 66.79% were male. The mean age reported for the samples ranged from 22.3 – 59.35 with a composite mean age of 37.16 (SD = 9.58). Two studies selected people aged over 40 years old for inclusion in their sample ^{38, 39}. A further two studies did not report mean age or gender for their samples ^{40, 41} and one did not report mean age ⁴². Only ten studies reported the ethnicity of the sample, with an average of 49.25% of participants identifying as belonging to a Black and Minority Ethnic (BAME) group. This composite ethnicity categorisation was compared to a composite category of 'white' for the purposes of the meta-analysis to maximise power. Thirty-four of the studies included in the analyses only included people with a diagnosis of schizophrenia. Of the 23 studies that did include people with schizoaffective disorder, only 10 reported the percentage of their sample that had this diagnosis, with a mean of 16.12%. The majority of studies (k = 48) reported findings from community samples, two studies included mixed inpatient and outpatient participants and three studies included people solely

from an inpatient setting. Three studies reported findings from participants experiencing their first or second episode of psychosis.

-----Table 1 approximately here-----

Quality Ratings of Studies

The quality scores are listed in Table 1. Studies generally scored moderate – high for selection of the sample with the majority recruiting from a wide pool of participants. Studies scored lower in this area when they sampled from clinic, service or ward only or their recruitment procedure was not described clearly. Studies did not consistently report subscales for the negative symptom measures used and this prevented them from achieving the full score in this section. The lower scores in the analysis section were given to studies which did not account for multiple correlational analyses in their analysis or significance levels.

Measures of negative symptoms

Four measures of negative symptoms were used in the studies included in the analysis; these are detailed in Table 1. The most commonly used assessment was the negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS) ⁴³ with 34 studies using this measure. The second most common was also an older measure of negative symptoms – the Scale for the Assessment of Negative Symptoms (SANS) ⁴⁴ with 17 studies using this measure. These measures are the most widely used which reflect the historical conceptualisation of primary and secondary negative symptoms. The newer measures – the Clinical Assessment Interview for Negative Symptoms (CAINS) ¹⁷(k = 5) and the Brief Negative Symptom Scale (BNSS) ⁴⁵(k=2) were used far less often in these studies. The most important differences in the newer measures is that they draw a distinction between expressive and experiential symptoms. Where these data were reported, expressive and experiential subscales from the CAINS, BNSS and SANS were analysed separately in the sub-group meta-analyses. Three is the minimum number of studies needed to conduct a robust sub-group analysis ³⁴ and therefore the studies which solely used the BNSS were not analysed separately.

Measures of depression

Four measures of depression were used in the sample of studies included in the analyses; these are also detailed in Table 1. The most commonly used measure was the Calgary Depression Scale for Schizophrenia (CDSS, $k = 34$)⁴⁶. This measure was designed specifically for use in this population and the scale was developed not to include items which overlap with negative symptoms and has been shown to reliably distinguish these two symptom clusters⁴⁷. The second most common measure was the Hamilton Depression Rating Scale (HDRS, $k = 16$)⁴⁸ which is a more general measure used in many different populations and includes many of the physical symptoms of depression. The other two measures used, the Beck Depression Inventory (BDI, $k = 9$)⁴⁹ and the Montgomery-Asberg Depression Rating Scale (MADRS, $k = 5$)⁵⁰, were developed initially for the assessment of people with mood disorders and include the full range of depressive symptoms, including cognitive features such as hopelessness and low self-esteem.

Meta-Analysis Findings

1. Is there a relationship between negative symptoms and depression in people with psychosis?

The meta-analysis testing the relationship between negative symptoms and depression showed a small but significant association between increased levels of reported negative symptoms and depressive symptoms in people with non-affective psychosis ($k = 56$, pooled standardised effect size (SES) = 0.194, 95% confidence interval (CI)=0.141, 0.247, $z = 7.20$, $p < .001$) (See Figure 2).

2. Does this relationship vary according to depression or negative symptom measures or subscales used?

The relationship was consistently present across the sub-group analyses looking at each depression and negative symptoms measure. When the most common combination– PANSS Neg and CDSS– was examined the effect size was also small but significant ($k = 23$, pooled $ES=0.135$, 95% $CI= 0.055, 0.216$, $z = 3.29$, $p=.001$). The expressive ($k =6$, pooled $ES= 0.189$, 95% $CI=0.090, 0.288$, $z= 3.75$, $p<.001$) and experiential ($k=12$, pooled $ES=0.263$, 95% $CI= 0.185, 0.341$, $z=6.58$, $p<.001$) subscales also had small but significant relationships with measures of depression which was numerically larger for experiential subscales. However, the CI s for the pooled ES s slightly overlap, and so it is not possible to conclude whether there is a stronger relationship between depressive and experiential symptoms than anhedonia and blunted affect.

Heterogeneity analyses

The full sample included in the main effect analyses showed high levels of heterogeneity ($p<.001$, $I^2=79.5\%$, $\tau^2=0.0283$) as expected given the wide range of different measures used. The 95% prediction interval ($-0.15, .54$) is displayed around the main effect size in the Forest Plot (See Figure 2).

In line with this, the heterogeneity was lower in the sub-groups analyses (See Supplementary Material for full results) and for expressive ($p=.216$, $I^2=29.3\%$, $\tau^2=0.0308$) and experiential ($p=.263$, $I^2=25.3\%$, $\tau^2=0.007$) subscales the heterogeneity was even lower and non-significant.

Publication bias

Visual inspection of the funnel plots showed publication bias to be unlikely. This was confirmed by the Egger's and Begg's tests conducted which found no evidence of publication bias in the

main effect analyses (Egger's $p=0.962$, Begg's $p=0.772$). This was consistent across the negative symptom (Egger's $p=0.138-0.932$, Begg's $p=0.621-1.0$) and depression measures used (Egger's $p=0.224-0.687$, Begg's $p=0.419-0.917$).

3. Is this relationship moderated by depressive or negative symptom severity?

Meta-regression analyses using the subset of the full sample that reported severity scores showed that the severity of depressive symptoms positively predicted a relationship with negative symptoms ($k=51$, $t=2.08$, $p=.044$). Negative symptom severity also predicted the association with depressive symptoms but in the opposite direction ($k=43$, $t= -2.45$, $p=0.019$). As these analyses included the whole sample the heterogeneity was high ($I^2_{res} = 78.13\%$, 73.84% , $\tau^2=.02579$, $.02569$) and thus the results should be considered with caution. This analysis was not repeated by specific measure sub-groups as the overall relationship was consistent across all measures when analysed separately.

4. Is this relationship moderated by the diagnosis of the sample, quality of the study or demographic factors?

To investigate whether variables which differed between samples accounted for heterogeneity in findings meta-regression analyses were conducted for demographic data and study characteristics including those studies which reported this data (see Table 1). No significant results were found for age, gender or ethnicity ($ts=0.10-0.85$, $ps=0.418-0.924$). The proportion of the sample with schizoaffective disorder also did not significantly moderate the findings ($t=0.22$, $p=0.829$). The quality ratings for each study were also examined to assess whether they moderated the presence of an association between the measures, this analysis was non-significant ($t=0.51$, $p=0.61$).

-----Figure 2 approximately here-----

Discussion

The findings confirm that there is a relationship between negative symptoms and depressive symptoms in people with non-affective psychosis. In the first large meta-analysis to examine this, with data from 56 studies and over 8,000 unique participants, and across a range of measures, a clear pattern emerges showing that overall there is a small, significant relationship between depressive and negative symptoms. The relationship was consistent across measures, so it does not appear to be the result of measurement artefacts. The effect size did vary with the measure used, but not greatly. There were no significant moderating effects of demographic or study quality variables suggesting it is robust and generalisable. A non-reciprocal relationship was highlighted in the findings – higher depression severity was linked to higher negative symptom severity but there was an inverse relationship in the other direction whereby higher negative symptom severity was linked to lower depression severity. All these findings support the hypothesis that this relationship is consistent with a symptom-specific approach and highlights the phenomenological overlap in the dimensions of depression and negative symptoms.

These findings support the model proposed in the recent review by Krynicki, Upthegrove, Deakin, Barnes ¹⁴ which suggests that an overlapping, symptom-specific approach to these symptom categories may best represent their relationships. This approach allows the co-occurrence of specific symptoms in the dimensions, as suggested by the evidence. Depression may act as a driver of negative symptoms as proposed in cognitive models, which highlight the role of emotion in psychosis (e.g. Garety, Kuipers, Fowler, Freeman, Bebbington ¹⁶). This is also consistent with the secondary negative symptoms conceptualisation, where depression drives the presentation of negative symptoms¹⁹. Indeed,

the inverse reciprocal relationship found in this study supports the existence of primary negative symptoms which do not predict co-occurring depressive symptoms as highlighted in the work of Kirkpatrick and Carpenter^{51, 52}. A recent factor analysis concluded that a five-factor not two-factor solution is more appropriate within the category of negative symptoms, providing further evidence supporting a symptom-specific approach⁵³.

The sub-group analyses of negative symptom sub-domains and depression suggested that, as expected, the experiential negative symptoms have phenomenological overlap with depression, with expressive symptoms appearing more distinct from depression. These symptoms of low motivation, apathy and anhedonia are present in the majority of *both* the negative and depressive symptom measures used in the studies in this meta-analysis. However, an important difference in anhedonia in depression and psychosis is not commonly assessed in these measures. A recent review highlights that people with psychosis do not experience a reduction in their capacity to experience pleasure⁵⁴ whereas this is commonly seen in people with depression and described as anhedonia. Unfortunately, the subscales reported in the depression measures included are not detailed enough to analyse this difference in our findings, but it should be considered in future research. Measures such as the CDSS have attempted to reduce phenomenological overlap by excluding experiential symptoms in their assessment of depression, but this may result in false negatives and could therefore lack validity. It seems from recent reviews of the area that suicidal ideation, pessimism and guilt are more common characteristic of depression¹⁴. Expressive symptoms, with poorer verbal and emotional expression, are more uniquely found in people experiencing negative symptoms^{14,19}.

Importantly, the findings were not moderated by demographic variables such as age, ethnicity and diagnosis suggesting the depression and negative symptom relationship is present across the

population of people with schizophrenia-spectrum diagnoses. The quality ratings did not moderate the findings, although there was a limited range of scores because of the measure used and inclusion criteria applied to the studies. The lack of moderation by schizoaffective disorder is perhaps surprising as people with this diagnosis might be expected to report more symptoms related to mood. It therefore tentatively suggests that the overlap between depressive and negative symptoms is consistent across the diagnoses included.

The findings of the meta-regressions showed a non-reciprocal relationship between negative and depressive symptoms. As severity of depressive symptoms increases, the more likely they are to demonstrate a positive association with negative symptoms. However, if a person reports more severe negative symptoms, the less likely they are to be related to depressive symptoms. This is a cross-sectional finding and hypotheses regarding a directional relationship are therefore speculative at this stage. As negative symptom severity increases the person is more likely to experience expressive deficits and greater apathy or numbing of emotion. This may either limit their ability to report depressive symptoms or be protective against them. It is important to consider that depressive symptoms are more often self-reported whereas negative symptoms are always interviewer-rated. This may explain this non-reciprocal relationship in terms of how symptoms are expressed in an interview – which may be more challenging for someone with severe negative symptoms. Negative symptoms may also be a less potent bridge to co-occurring depressive symptoms⁵⁵. The role of depressive symptoms in driving psychosis has been discussed previously^{15, 16} and it may be that this is a more potent route to co-occurring negative symptoms. A true symptom-specific approach would explore the phenomena associated with the concepts of “depressive” and “negative” symptoms across a broad population. Such an approach will assist with determining the factors contributing to the presenting symptoms, and specifically whether apparent negative symptoms are primary or secondary to depressive symptoms.

The main analysis and some of the sub-group analyses had high heterogeneity in the included studies which is a limitation of including different measures in the analysis, although this did increase power. Only two studies were excluded due to missing data, however many studies did not report the sample demographics, with ethnicity data particularly lacking. Meta-analyses that consider symptoms are only as good as the measures of those symptoms used. Several studies did not report the measure total scores and so they could not be included in the meta-regressions, which limits these findings. More robust conclusions would have been possible with a greater number of studies in the sub-group analyses considering subscales of both negative (i.e. expressive and experiential) and depressive symptoms (e.g. behavioural, cognitive and somatic-affective symptoms). The role of positive and cognitive symptoms cannot be elucidated from the data available, future analyses may wish to include this data if possible to examine whether these difficulties play a moderating role in the relationship between depressive and negative symptoms. The narrow range of quality ratings provided by the scale used may have limited the power of the moderation analysis. Future meta-analyses addressing these questions may wish to include a wider range of bibliographical sources, although this may increase heterogeneity.

These important findings tell us that depressive and negative symptoms can both be present in people with non-affective psychosis. This means both should be assessed using the most current and robust measures, and care should be taken to ensure the measure selected captures the full range of symptoms the person is experiencing. It follows that treatment for both depressive and negative symptoms might be indicated, although further research is required to explore whether this requires targeting the same or different causal mechanisms.

The findings highlight the importance of mood across the psychosis spectrum as proposed in several cognitive models of psychosis ^{16, 56-58}. A symptom-specific approach to considering these difficulties in the context of fuzzy boundaries between diagnostic categories may have the greatest clinical utility ⁵⁹. Indeed, the findings of a recent factor-analysis suggest that negative symptoms are best conceptualised as five factors; blunted affect, alogia, anhedonia, avolition and asociality rather than the two expressive and experiential factors discussed previously ⁵³. Thus, it seems there is increasing evidence that each of these symptoms is best considered as a unique entity and subsequently each can be expected to have a different relationship with depressive symptoms. Although the findings of the review suggest that depressive and negative symptoms mirror each other we are aware that there is phenomenological complexity behind this and research focused on gaining a deeper understanding of these symptoms is required. This further work is needed to develop our theoretical understanding of the causes and maintenance factors underlying specific symptoms in order to improve therapeutic outcomes. Assessment of these individual symptoms is important, as the diagnostic and conceptual lines we have drawn so far appear to be more complex than we anticipated. The impact of these symptoms is at least as, if not more significant than any other group of symptoms and they are a priority for service users ⁶⁰.

Acknowledgements

PAG acknowledges support from the National Institute for Health Research (NIHR) Biomedical Research Centre of the South London and Maudsley NHS Foundation Trust and King's College London.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health.

The Authors have declared that there are no conflicts of interest in relation to the subject of this study

References

1. Kirkpatrick B, Fenton WS, Carpenter WT, Jr., Marder SR. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophrenia Bulletin* Apr 2006;32(2):214-219. Epub 2006 Feb 2015.
2. Rocca P, Montemagni C, Zappia S, Pitera R, Sigaud M, Bogetto F. Negative symptoms and everyday functioning in schizophrenia: a cross-sectional study in a real world-setting. 2014(1872-7123 (Electronic)).
3. Robertson BR, Prestia D, Twamley EW, Patterson TL, Bowie CR, Harvey PD. Social competence versus negative symptoms as predictors of real world social functioning in schizophrenia. 2014(1573-2509 (Electronic)).
4. Menendez-Miranda I, Garcia-Portilla MP, Garcia-Alvarez L, et al. Predictive factors of functional capacity and real-world functioning in patients with schizophrenia. 2015(1778-3585 (Electronic)).
5. Marchesi C, Affaticati A Fau - Monici A, Monici A Fau - De Panfilis C, De Panfilis C Fau - Ossola P, Ossola P Fau - Ottoni R, Ottoni R Fau - Tonna M, Tonna M. Decrease of functioning in remitted and non-remitted patients 16 years after a first-episode schizophrenia. 2015(1539-736X (Electronic)).
6. Berenbaum H, Kerns JG, Vernon LL, Gomez JJ. Cognitive Correlates of Schizophrenia Signs and Symptoms: III. Hallucinations and Delusions. *Psychiatry research* 04/18 2008;159(1-2):163-166.
7. Peralta V, Cuesta MJ, Martinez-Larrea A, Serrano JF. Differentiating Primary From Secondary Negative Symptoms in Schizophrenia: A Study of Neuroleptic-Naive Patients Before and After Treatment. *American Journal of Psychiatry* 2000/09/01 2000;157(9):1461-1466.
8. Messinger JW, Trémeau F, Antonius D, Mendelsohn E, Prudent V, Stanford AD, Malaspina D. Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. *Clinical Psychology Review* 2011/02/01/ 2011;31(1):161-168.
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*: Washington, DC; 2013.
10. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric Comorbidities and Schizophrenia. *Schizophrenia Bulletin* 2009;35(2):383-402.
11. Siris SB, C. . Depression and schizophrenia In: Hirsch S, Weinberger, D., ed. *Schizophrenia*. 2nd ed. Oxford, UK: Blackwell; 2003:142-167.
12. Malaspina D, Walsh-Messinger J, Gaebel W, Smith LM, Gorun A, Prudent V, Antonius D, Trémeau F. Negative symptoms, past and present: A historical perspective and moving to DSM-5. *European Neuropsychopharmacology* 2014/05/01/ 2014;24(5):710-724.
13. Kirschner M, Aleman A, Kaiser S. Secondary negative symptoms - A review of mechanisms, assessment and treatment. *Schizophr Res* May 23 2016.
14. Krynicki CR, Uptegrove R, Deakin JFW, Barnes TRE. The relationship between negative symptoms and depression in schizophrenia: a systematic review. *Acta Psychiatrica Scandinavica* 2018;0(0).
15. Sarkar S, Hillner K, Velligan DI. Conceptualization and treatment of negative symptoms in schizophrenia. *World Journal of Psychiatry* 2015;5(4):352-361.
16. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychol Med* Feb 2001;31(2):189-195.

17. Forbes C, Blanchard JJ, Bennett M, Horan WP, Kring A, Gur R. Initial development and preliminary validation of a new negative symptom measure: the Clinical Assessment Interview for Negative Symptoms (CAINS). *Schizophr Res* Dec 2010;124(1-3):36-42.
18. Llerena K, Park SG, McCarthy JM, Couture SM, Bennett ME, Blanchard JJ. The Motivation and Pleasure Scale-Self-Report (MAP-SR): reliability and validity of a self-report measure of negative symptoms. *Compr Psychiatry* Jul 2013;54(5):568-574.
19. Kirkpatrick B. Progress in the Study of Negative Symptoms. *Schizophrenia Bulletin* 02/20 2014;40(Suppl 2):S101-S106.
20. Grant PM, Beck AT. Defeatist Beliefs as a Mediator of Cognitive Impairment, Negative Symptoms, and Functioning in Schizophrenia. *Schizophrenia Bulletin* 02/27 2009;35(4):798-806.
21. Edwards CJ, Cella M, Tarrier N, Wykes T. Investigating the empirical support for therapeutic targets proposed by the temporal experience of pleasure model in schizophrenia: A systematic review. *Schizophr Res* 2015;168(1):120-144.
22. Amr M, Volpe FM. Relationship between anhedonia and impulsivity in schizophrenia, major depression and schizoaffective disorder. *Asian Journal of Psychiatry* 12// 2013;6(6):577-580.
23. Blanchard JJ, Horan WP, Brown SA. Diagnostic differences in social anhedonia: a longitudinal study of schizophrenia and major depressive disorder. *J Abnorm Psychol* Aug 2001;110(3):363-371.
24. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? *Ann Gen Psychiatry* Oct 8 2009;8:22.
25. Fried EI. The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *Journal of affective disorders* Jan 15 2017;208:191-197.
26. Warman DM, Forman EM, Henriques GR, Brown GK, Beck AT. Suicidality and psychosis: beyond depression and hopelessness. *Suicide & life-threatening behavior* Spring 2004;34(1):77-86.
27. Radomsky ED, Haas GL, Mann JJ, Sweeney JA. Suicidal behavior in patients with schizophrenia and other psychotic disorders. *Am J Psychiatry* Oct 1999;156(10):1590-1595.
28. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339.
29. Schennach R, Riedel M, Obermeier M, et al. What are depressive symptoms in acutely ill patients with schizophrenia spectrum disorder? *Eur Psychiatry* Jan 2015;30(1):43-50.
30. Dollfus S, Petit M. Negative symptoms in schizophrenia: their evolution during an acute phase. 1995(0920-9964 (Print)).
31. Thomas BH, Dobbins M, Fau M, Micucci S. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. 2004(1545-102X (Print)).
32. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Introduction to meta-analysis*. Chichester, UK: Wiley; 2009.
33. *Stata Statistical Software: Release 15* [computer program]. Version. College Station, TX: StataCorp LLC; 2017.
34. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. 2010(1759-2879 (Print)).
35. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. *Systematic Reviews in Health Care: Meta-Analysis in Context, Second Edition* 2008:285-312.
36. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-634.

37. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. 1994(0006-341X (Print)).
38. Zisook S, McAdams La Fau - Kuck J, Kuck J Fau - Harris MJ, Harris Mj Fau - Bailey A, Bailey A Fau - Patterson TL, Patterson TI Fau - Judd LL, Judd LI Fau - Jeste DV, Jeste DV. Depressive symptoms in schizophrenia. 1999(0002-953X (Print)).
39. Mausbach BT, Cardenas V, Goldman SR, Patterson TL. Symptoms of psychosis and depression in middle-aged and older adults with psychotic disorders: the role of activity satisfaction. *Aging Ment Health* May 2007;11(3):339-345.
40. Addington D, Addington J, Maticka-Tyndale E. Specificity of the Calgary Depression Scale for schizophrenics. *Schizophr Res* 1994;11:239-244.
41. Chemerinski E, Bowie C, Anderson H, Harvey PD. Depression in schizophrenia: methodological artifact or distinct feature of the illness? *J Neuropsychiatry Clin Neurosci* Fall 2008;20(4):431-440.
42. Norman RMG, Manchanda R, Harricharan R, Northcott S. The course of negative symptoms over the first five years of treatment: Data from an early intervention program for psychosis. *Schizophr Res* Dec 2015;169(1-3):412-417.
43. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.
44. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry Suppl* Nov 1989(7):49-58.
45. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, Marder SR. The Brief Negative Symptom Scale: Psychometric Properties. *Schizophrenia Bulletin* 06/17 2011;37(2):300-305.
46. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res* Jul-Aug 1990;3(4):247-251.
47. Lako IM, Bruggeman R, Knegtering H, Wiersma D, Schoevers RA, Slooff CJ, Taxis K. A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. *Journal of Affective Disorders* 9// 2012;140(1):38-47.
48. Hamilton M. A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry* 1960;23(1):56.
49. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review* 1988/01/01/ 1988;8(1):77-100.
50. Williams J, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). *Br J Psychiatry* Jan 2008;192(1):52-58.
51. Kirkpatrick B, Galderisi S. Deficit schizophrenia: an update. *World Psychiatry* 2008;7(3):143-147.
52. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICES Consensus Statement on Negative Symptoms. *Schizophrenia Bulletin* 02/15 2006;32(2):214-219.
53. Strauss GP, Nunez A, Ahmed AO, Barchard KA, Granholm E, Kirkpatrick B, Gold JM, Allen DN. The Latent Structure of Negative Symptoms in Schizophrenia. *JAMA psychiatry* Sep 12 2018.
54. Strauss GP, Cohen AS. The schizophrenia spectrum anhedonia paradox. *World Psychiatry* 2018/06/01 2018;17(2):221-222.
55. Borsboom D. A network theory of mental disorders. *World Psychiatry* 2017/02/01 2017;16(1):5-13.
56. Freeman D, Garety PA, Kuipers E, Fowler D, Bebbington PE. A cognitive model of persecutory delusions. *The British journal of clinical psychology* Nov 2002;41(Pt 4):331-347.
57. Chadwick PDJ, Birchwood MJ, Trower P. *Cognitive therapy for delusions, voices and paranoia*. . Chichester: Wiley 1996.

58. Birchwood M. Pathways to emotional dysfunction in first-episode psychosis. *British Journal of Psychiatry* 2003;182(5):373-375.
59. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* 06/05 2016;15(2):118-124.
60. Rose D. The mainstreaming of recovery. *Journal of Mental Health* 2014/10/01 2014;23(5):217-218.