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DOI:

[10.5281/zenodo.23121801](https://doi.org/10.5281/zenodo.23121801)

2026

Document Version:

Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for published version (APA):

D'Imperio, A., Damiani, S., Stefanelli, R., Patron, S., Santilli, F., & Fusar-Poli, P. (2026). *Pseudospecificity of Negative Symptom Improvement in the Schizophrenia Spectrum: A Meta-Analytic Investigation of Associations with Depression, Quality of Life and Extrapyramidal Symptoms*. Poster session presented at 2026 Annual Congress of the Schizophrenia International Research Society (SIRS), Florence, Italy.
<https://doi.org/10.5281/zenodo.23121801>

Total number of authors:

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Pseudospecificity of Negative Symptom Improvement in the Schizophrenia Spectrum:

A Meta-Analytic Investigation of Associations with Depression, Quality of Life and Extrapyramidal Symptoms

Improvement in negative symptoms tracks improvement in depression and quality of life, but not extrapyramidal symptoms, supporting the presence of pseudospecificity in schizophrenia-spectrum trials

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Background:

Negative symptoms are among the most disabling dimensions of schizophrenia-spectrum disorders and are strongly associated with poorer long-term functioning. However, their interpretation in treatment trials remains challenging because apparent improvement in negative symptoms may partly reflect change in other domains, including depressive symptoms, quality of life, or secondary phenomena such as medication-related motor side effects. This issue is commonly discussed in terms of primary versus secondary negative symptoms and of pseudospecificity, namely the risk of attributing non-specific cross-domain change to a selective effect on core negative symptoms (Kirkpatrick et al., 2006; Kirschner et al., 2017; Hopkins et al., 2018). Newer instruments such as the Brief Negative Symptom Scale (BNSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS) were specifically developed to better isolate the negative symptom construct (Kring et al., 2013; Weigel et al., 2023)

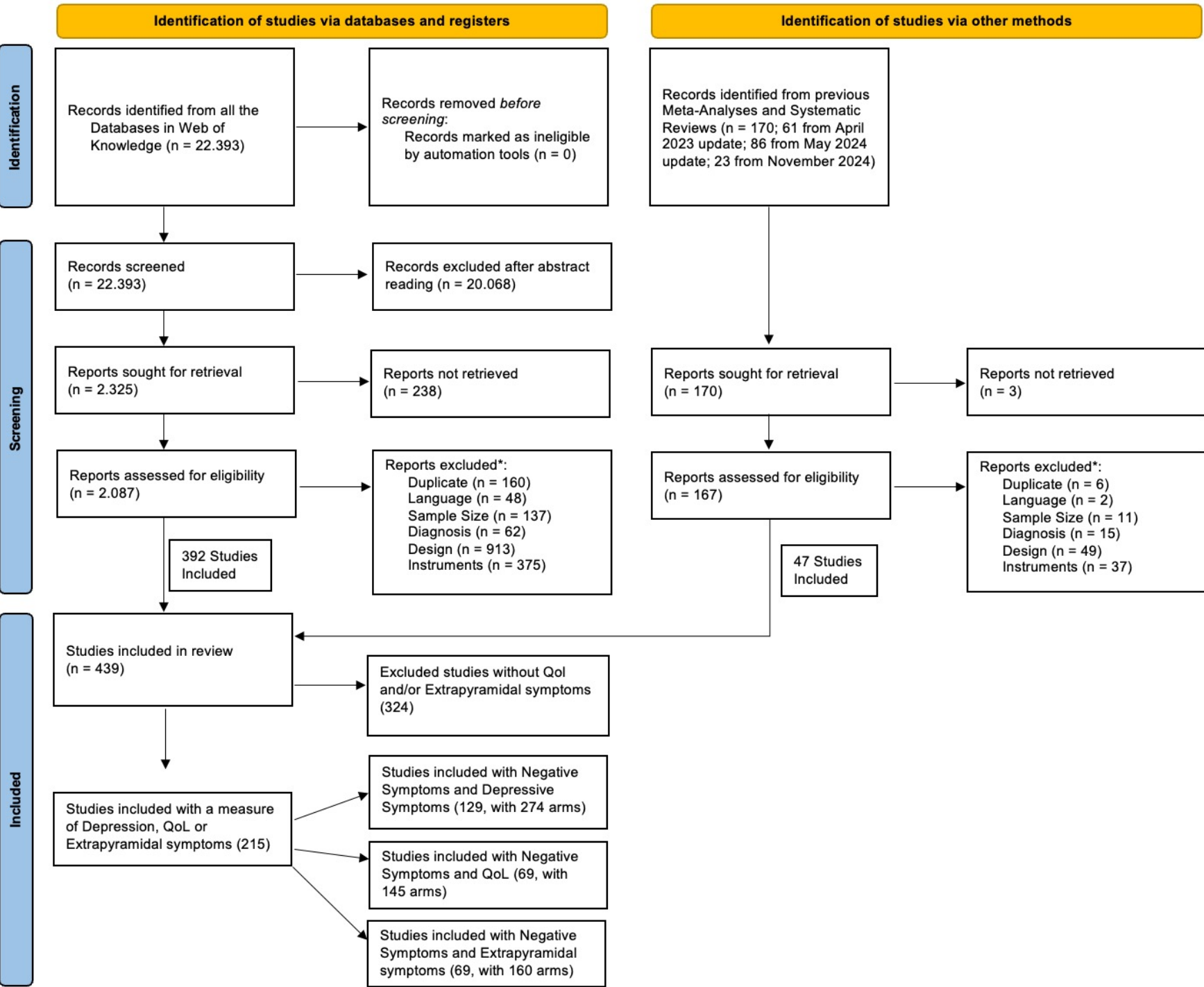
Aim:

To examine whether improvement in negative symptoms across randomized controlled trials in schizophrenia-spectrum disorders is associated with parallel change in depressive symptoms, quality of life, and extrapyramidal symptoms, thereby testing the extent of pseudospecificity.

Methods:

We performed a meta-synthesis of randomized controlled trials identified in Web of Science and PsycINFO from inception to December 2024. Eligible studies compared an active intervention with a non-active control, included patients with chronic schizophrenia-spectrum disorders, and used validated scales to assess negative symptoms together with depression, quality of life, or extrapyramidal symptoms. For each eligible trial arm, baseline and endpoint values were extracted and percentage change from baseline was calculated. Associations between change in negative symptoms and change in the companion domains were analysed at arm level using Spearman correlations, overall and separately for active and control arms. Study selection is summarized in Figure 1.

Fig. 1: PRISMA Flow-Chart



Key Conclusions:

1. Improvement in negative symptoms is significantly associated with improvement in depressive symptoms and quality of life.
2. Improvement in negative symptoms is not meaningfully associated with change in extrapyramidal symptoms.
3. The overall pattern supports pseudospecificity in schizophrenia-spectrum trials and highlights the importance of better distinguishing primary from secondary negative symptoms.

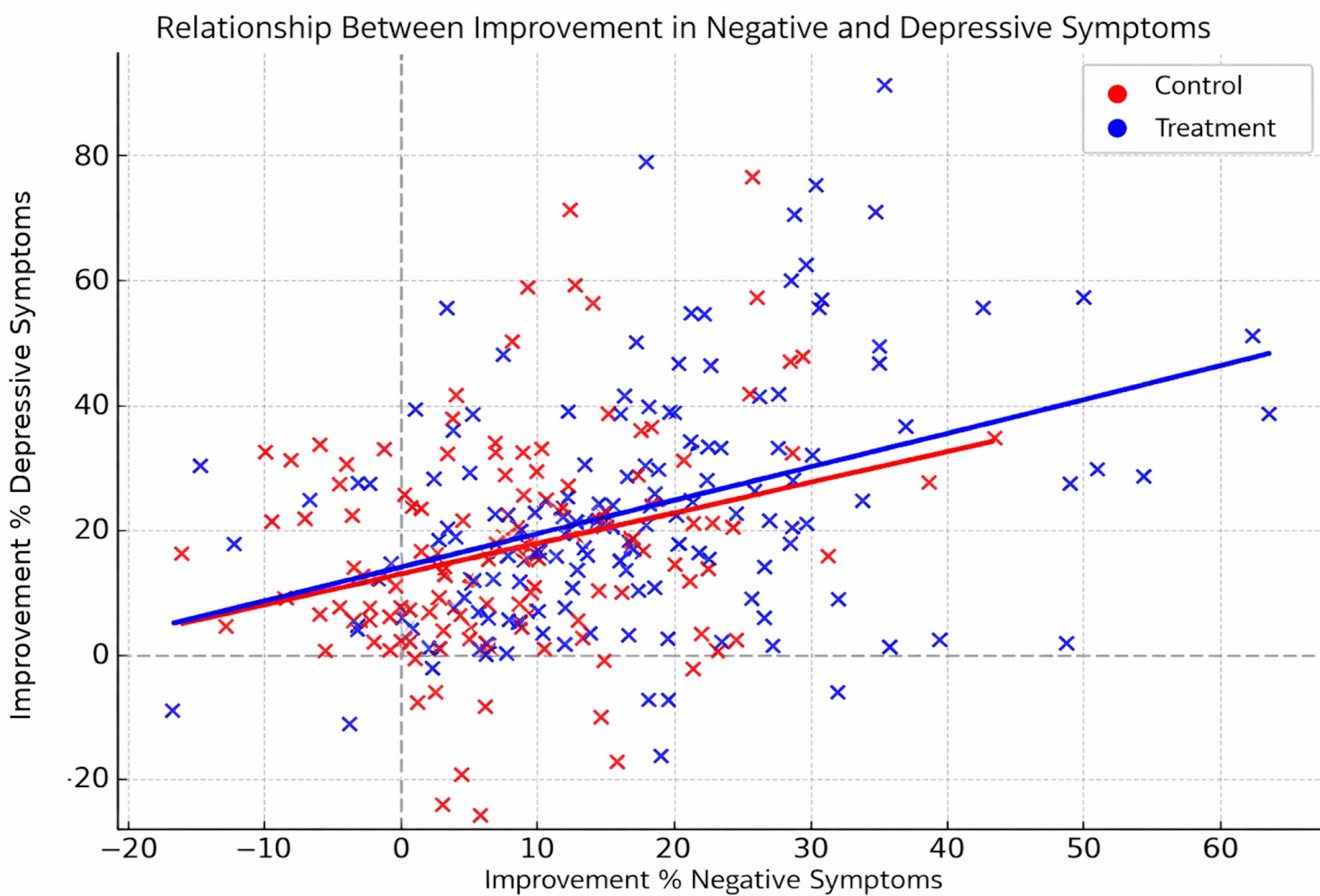
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Results - Depressive Symptoms:

Across 129 trials (274 arms), percentage improvement in negative symptoms showed a moderate positive association with improvement in depressive symptoms. The association was significant when all arms were pooled ($p = 0.359$, $p < 0.001$) and remained significant in both control arms ($p = 0.266$, $p = 0.002$) and active treatment arms ($p = 0.374$, $p < 0.001$). In practical terms, trials in which depressive symptoms improved more were also the trials in which negative symptoms improved more, regardless of treatment allocation.

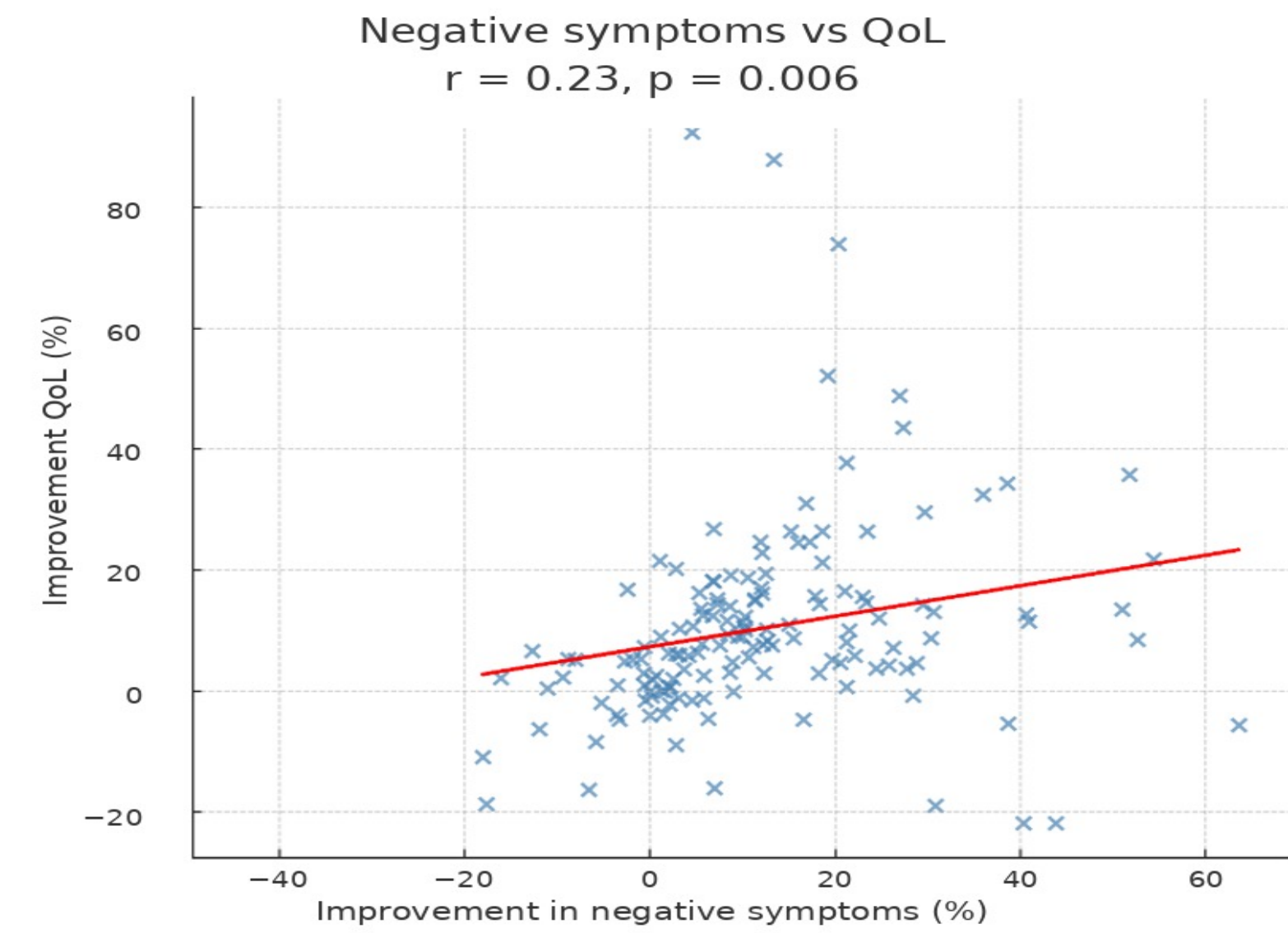
Fig. 2: Correlation between percentage change in negative symptoms and depressive symptoms across trial arms.



Results - Quality of Life:

Across 69 trials (145 arms), percentage improvement in negative symptoms was also significantly associated with improvement in quality of life. The overall association was significant ($p = 0.230$, $p = 0.006$) and remained significant in active intervention arms ($p = 0.290$, $p = 0.010$) and control arms ($p = 0.380$, $p = 0.001$). As illustrated in Figure 3, better negative symptom outcomes tended to occur in studies showing broader gains in subjective well-being and functioning.

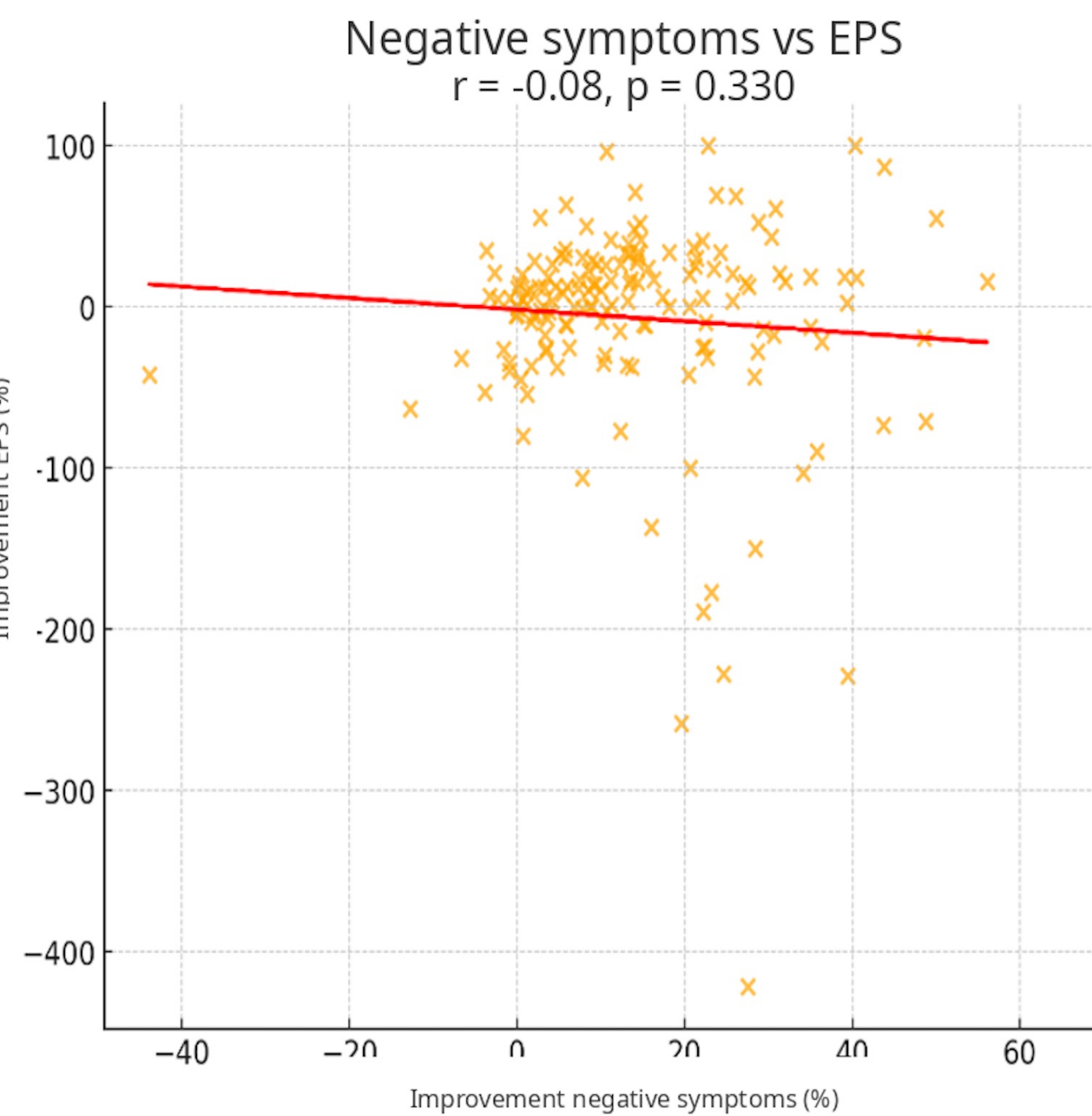
Fig. 3: Correlation between percentage change in negative symptoms and quality of life across trial arms.



Results - Extrapyramidal symptoms:

Across 69 trials (160 arms), improvement in negative symptoms showed a very weak negative and non-significant overall association with improvement in extrapyramidal symptoms ($p = -0.082$, $p = 0.330$). Stratified analyses were likewise non-significant in active arms ($p = 0.090$, $p = 0.420$) and control arms ($p = 0.140$, $p = 0.238$). As shown in Figure 4, the pattern observed for depression and quality of life was not reproduced for extrapyramidal symptoms.

Fig. 4: Correlation between percentage change in negative symptoms and extrapyramidal symptoms across trial arms.



Interpretation and Clinical Implications:

Overall, the pattern is consistent with pseudospecificity. Improvement in negative symptoms tended to occur together with improvement in depressive symptoms and quality of life, whereas no comparable relationship emerged for extrapyramidal symptoms. This suggests that part of what is often interpreted as “negative symptom improvement” may actually reflect broader change in mood, motivation, and well-being, rather than a fully selective effect on core negative symptoms (Kirkpatrick et al., 2006; Kirschner et al., 2017; Hopkins et al., 2018). The findings also have clinical relevance: negative and depressive symptoms may overlap in domains such as avolition, anhedonia, and reduced engagement, which increases the risk of misclassifying secondary negative symptoms as primary ones. By contrast, the lack of a meaningful association with extrapyramidal symptoms suggests that not all potential confounders contribute equally. Future trials should examine pseudospecificity more directly and, where possible, use second-generation instruments such as BNSS and CAINS, which were developed to better separate primary from secondary negative symptoms (Kring et al., 2013; Strauss et al., 2012; Weigel et al., 2023).

Table 1: The main quantitative findings are summarized in Table 1.

Domain	Trials	Arms	Overall correlation	Active arms	Control arms	Interpretation
Depressive symptoms	129	274	$p = 0.359$, $p < 0.001$	$p = 0.374$, $p < 0.001$	$p = 0.266$, $p = 0.002$	Moderate, consistent association
Quality of life	69	145	$p = 0.230$, $p = 0.006$	$p = 0.290$, $p = 0.010$	$p = 0.380$, $p = 0.001$	Significant cross-domain association
Extrapyramidal symptom	69	160	$p = -0.082$, $p = 0.330$	$p = 0.090$, $p = 0.420$	$p = 0.140$, $p = 0.238$	No meaningful association

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