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The prevalence of negative symptoms across the stages of the psychosis continuum

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CONFLICT OF INTEREST

None.

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The prevalence of negative symptoms across the stages of the psychosis continuum

ABSTRACT

Background: Patients in every stage of the psychosis continuum can present negative symptoms. While no treatment has yet been developed to address these symptoms, a more refined characterization of their course over the lifetime could help in elaborating interventions. Previous reports have separately investigated the prevalence of negative symptoms within each stage of the psychosis continuum. Hence, we aimed to review the scientific literature to compare these prevalence rates across stages so as to unfold the course of negative symptoms. Methods: We searched several databases for studies reporting prevalence rates of negative symptoms in each one of our predetermined stages of the psychosis continuum – namely clinical or ultra high-risk (UHR), first-episode of psychosis (FEP), younger (y) and older (o) patients who have experienced multiple episodes of psychosis (MEP). We combined results using the definitions of negative symptoms detailed in the Brief Negative Symptom Scale (BNSS), a recently developed tool. For each negative symptom, we averaged and weighted by the combined sample size prevalence rates of each negative symptom in each stage. Results: We selected 47 studies totaling 1872 UHR, 2947 FEP, 5039 yMEP and 669 oMEP patiens. For each negative symptom, the prevalence rates showed a comparable course. First, it decreased between the UHR and FEP stages to subsequently increase during the yMEP stage (Anhedonia: FEP-26%, yMEP-57%; Avolition: UHR-50%, FEP-28%, yMEP-73%; Asociality: UHR-49%, FEP-34%, yMEP-48%; Blunted affect: UHR-21%, FEP-9%, yMEP-41%, oMEP-23%; Alogia: UHR-15%, FEP-7%, yMEP-33%). Conclusions: Certain psychological-, environmental- and treatment-related factors may influence the cumulative impact of negative symptoms.

Keywords: Schizophrenia; Anhedonia; Avolition; Asociality; Blunted affect

1. INTRODUCTION

Negative symptoms represent an important component of schizophrenia and have consistently been associated with poor outcome.[1-6] Yet, they remain an unmet therapeutic need as current treatments have shown only modest benefits.[7-9] Considering that such symptoms emerge early on (in prodromal phase and in clinical high risk populations) and persist over time, it is fundamental to examine their course across the different stages of the illness. Such an endeavor can provide fresh new insights into more targeted and potentially more efficient treatments.

The National Institute of Mental Health (NIMH) consensus statement proposed that, for the present, the domains of negative symptoms include anhedonia, avolition, asociality, blunted affect and alogia.[10,11] Following this consensus meeting, experts in the field have developed the Brief Negative Symptom Scale (BNSS)[12] and the Clinical Assessment Interview for Negative Symptoms (CAINS)[13,14], which offer a clear description of each symptom in addition to providing novel scales for their assessment. Both are semi-structured interviews, which measure the current severity level (the past week) of negative symptoms in schizophrenia and schizoaffective disorders. Thus, according to the BNSS and the CAINS, *anhedonia* refers to the reduced ability to experience pleasure during an activity and/or anticipate pleasure from a future activity. Both the intensity and the frequency of all sources of pleasure (i.e., social activities, work/school, recreational activities and physical sensations) can be affected. *Avolition* reflects a reduction in the persistence, desire and motivation to initiate and participate in activities that are related to work/school, hobbies, self-care and social activity. *Asociality* represents a decreased desire for affiliation or in forming close social relationships. Both the quantity and quality of engagement in social interactions with others can be diminished. *Blunted affect* refers to

decreased outward emotional expression reflected by facial and vocal manifestations as well as expressive gestures. Finally, *alogia* is a reduction in the quantity of speech and spontaneous elaboration. The intensity and frequency of the aforementioned symptoms can vary from mild to extremely severe and patients may experience several of them concurrently.[12]

There are different stages to the psychosis continuum and ratings of negative symptoms have been reported in each of them.[15-18] In the first stage, adolescents or young adults seeking help for sub-threshold symptoms or a combination of genetic risk plus functional deterioration are considered to be at *clinical* or *ultra-high risk of psychosis* (UHR)[19-21]; this may manifest in being more socially withdrawn and disorganized, behaving in an unusual manner and/or having vague perceptual abnormalities. While the term 'negative symptom' implies a history of full-blown psychotic illness, this has by definition not occurred in UHR patients; nonetheless, we refer here to the constitutive symptoms in UHR as 'negative symptoms' in the context of our interest in the psychosis continuum. The *first episode of psychosis* (FEP) typically occurs between 19 and 26 years old[22] and is characterized by full-blown (supra-threshold) combinations of positive and negative symptoms.[23,24] Later on, a significant proportion of FEP patients will continue to experience recurrent *multiple episodes* of positive and negative symptoms (MEP), which can persist even during later life.[25,26] This cumulative effect of the presence of negative symptoms can have a considerable impact on patients' functioning and quality of life.[27-29]

Studies have separately reported the prevalence of negative symptoms in each of the aforementioned stages[30-33], but there is currently a need for knowing how the prevalence of each of the five negative symptoms changes between stages. This need stems from observations indicating that negative symptoms might follow different patterns across the psychosis continuum. For instance, blunted affect rarely occurs in UHR and FEP populations while being

highly prevalent in MEP patients.[30,34,35] Furthermore, results from large longitudinal studies with relatively long follow-up periods suggest that the severity of negative symptoms follow a fluctuating course. More precisely, Piskulic, Addington [30] have reported, in their study in which 138 UHR individuals were followed during 12 months, that the severity of anhedonia, avolition, asociality and blunted affect, decreased over time. In a study by Herbener and Harrow [36], the severity of negative symptoms (only global measures of negative symptoms were reported) in 150 FEP patients remained stable over the course of 10 years. A recent meta-analysis of longitudinal findings reported in randomized controlled trials with MEP patients also suggested that the severity of all negative symptoms decreased (although with varying degrees) over time, regardless of the type of intervention (e.g., antipsychotics or non-pharmacological interventions).[37]

The objective of the current study was thus to examine the prevalence of the five negative symptoms domains across the stages of the psychosis continuum. To do so, statistical comparisons were applied on the prevalence data of these negative symptoms domains between stages as reported using any measuring method. This endeavor will help in identifying potential factors related to the psychosis continuum that could influence the prevalence of these symptoms. Furthermore, comparing the prevalence of negative symptoms ratings across the stages of the psychosis continuum will allow the investigation of their evolution over time, which is consistent with both contemporary staging models of mental illness[38] and the NIMH's Research Domain Criteria initiative.[39]

To achieve our goal, we used the NIMH's definition of point prevalence[40], which refers to the proportion of a population presenting a specific characteristic at a particular point in time. This prevalence measure is particularly well suited for (and commonly involves) cross-sectional

studies. We searched several databases for studies reporting the prevalence of negative symptoms in the psychosis continuum and then categorized them according to the previously described stages (i.e., UHR, FEP, MEP). The last category was further divided in two to distinguish between younger (y) and older (o) MEP patients since the cumulative effect of multiple episodes may be different for these two populations.

Based on findings from longitudinal studies reporting on the course of negative symptoms severity, we hypothesized that the prevalence of all negative symptoms would decrease following the UHR stage[30]; then remain stable between the FEP and yMEP stages[36]; and finally would decrease again during the oMEP stage.[37]

2. MATERIAL AND METHODS

2.1 LITERATURE SEARCH AND STUDY SELECTION

Pubmed, PsycInfo and Web of Science databases were searched on November 30th 2015 with no restriction regarding the year of publication. A first search was conducted using the following keywords: 'schiz*' OR 'psychosis' AND 'negative symptom* prevalence' OR 'prevalen*' AND 'anhedonia' OR 'alogia' OR 'flat affect' OR 'avolition' OR 'asociality' OR 'attentional impairment'. A second and complementary search was conducted by adding the keywords 'prodrom*' OR 'high* risk*' OR 'geriatric*' to help identify studies with such populations.

A total of 1,661 articles were located; duplicates and articles written in languages other than English or French were removed (**Figure 1**). The first author performed an initial selection based on the articles' titles and abstracts to select papers that potentially reported symptom prevalence data in patients along the psychosis continuum. Articles were included in the current

analysis because they 1) had a sample of patients with a disorder of the psychosis spectrum (e.g., schizophrenia, schizoaffective), 2) reported prevalence data of negative symptoms, and 3) provided sufficient information about the sample to be classified into one of our four predetermined stage categories. Articles were excluded mainly because they did not report prevalence data of negative symptoms, or had a mixed sample (i.e., patients from various stages were combined in one sample). We rapidly noticed that prevalence data were reported in studies across different topics, methodologies and populations. For example, we found that prevalence of negative symptoms was detailed in articles addressing topics such as genetics[41], predictors of remission[42], as well as in different types of investigations like clinical trials[2], cross-sectional[33] and psychometric validation papers.[43] We decided to proceed with a guided keyword-based search of several databases in addition to searching through the bibliography of included articles. We acknowledge that this approach has a potential risk of bias.

Selected articles were classified into one of our 4 predetermined categories: UHR (n=8), FEP (n=18), yMEP (n=17), oMEP (n=4), depending on the description of the samples provided by the authors, which can be found in the Supplemental Digital Content (see Table S1, Supplemental Digital Content). As for the distinction between the yMEP and oMEP categories, we included in the latter only the studies in which authors explicitly indicated that participants were either geriatric or elderly. Also, some articles examined negative symptoms in individuals with a late-onset psychosis (after 45 years old). Such articles were not included in the current study because these patients would not have been struggling with the illness for multiple years and this would thus not be in line with our objective.

2.2 DATA CHARTING AND STATISTICAL ANALYSIS

In the final sample, 16 different scales were used to measure negative symptoms. We first charted the prevalence data exactly as reported. To circumvent the problem of heterogeneous items/scales and in order to synthesize the charted data, each prevalence value was classified into one of the BNSS categories.[12] The BNSS scale was selected to synthesize the data because it was created following the NIMH consensus statement[10] and thus covered the most updated definitions of negative symptoms. This step was possible given that the majority of the scales used similar items to the ones found in the BNSS, but simply had different wording. For example, the SANS' item labeled as 'Unchanging facial expression' found under the 'Affective flattening or blunting' subscale has a similar definition to the BNSS' item labeled 'Facial expression' found under the 'Blunted affect' subscale. The items' descriptions provided in the articles were analyzed to find the most appropriate corresponding BNSS item (if the descriptions were insufficient, the original scales were retrieved). The prevalence value was categorized under 'other negative symptom' when: no BNSS item was appropriate, the scales did not provide enough detail of the symptoms' definition, or the item covered more than one BNSS category (Supplementary Digital Content Table S2).

The prevalence for each BNSS dimension was calculated using weighted averages. The reported prevalence values were averaged and weighted by their sample size, a method previously used in similar studies.[44,45] When several relevant patient groups (e.g., schizoaffective disorder) were reported in the same article for one negative symptom, the prevalence value of each group was first averaged and weighted by their sample size. It is then this value that was used in the aforementioned calculations of the prevalence for each BNSS dimension. A Kruskall-Wallis test was performed for each BNSS category in order to compare the weighted prevalence values across stages; the critical p-value was set at .05. This test is the non-parametric equivalent

of the one-way independent ANOVA and can be used when data are not normally distributed. When the Kruskall-Wallis analysis was significant, Pearsons' chi-square tests were subsequently performed to compare pairs of stages. When the expected count in more than one cell was inferior to 5, the Fisher's exact test was used instead.[46] The p-values were adjusted using the Bonferroni correction for multiple comparisons and all analyses were two-tailed.

3. RESULTS

3.1 DESCRIPTION OF INCLUDED STUDIES

Forty-seven studies were included in the present review and were categorized into one of our four stage categories (**Table 1**). None directly compared two (or more) different stages.

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Table 1. Studies description and classification in the BNSS' categories

Study	Sample size (patients)	Sex ratio[1] (%male)	Mean Age[1]	Scale	BNSS categories				
					Anhedonia	**Asociality**	**Avolition**	**Blunted affect**	**Alogia**
Individuals at ultra-high risk of developing psychosis (UHR)									
Jackson et al. (1995)[47]	313	63	25.5	RPMIP	Lack of initiative, interests, energy (scz = 24%, sczf = 29%, sczaf = 65%, del = 23%, nos = 31%)	Social isolation and withdrawal (scz=76%, sczf=42%, sczaf=61%, del=25%, nos=33%)	Impairment in role functioning (scz = 63%, sczf = 36%, sczaf = 47%, del = 19%, nos = 33%); Impairment in personal hygiene (scz = 22%, sczf = 10%, sczaf = 14%, del = 6%, nos = 10%)	Blunted, flat or inappropriate affect (scz = 33%, sczf = 18%, sczaf = 33%, del = 0%, nos = 14%)	
Lencz et al. (2004)[48]	82	68	16.3	SOPS		Social withdrawal, isolation (62%)	Decline in school functioning (38%)		
Lam et al. (2006) [49]	62	58	16.2	CAARMS			Avolition (21%)		
Iyer et al. (2008)[50]	128	68	22.6	CORS		Social withdrawal (56%)	Impaired role in functioning (57%); Poor hygiene, grooming (16%);	Blunted/Flat affect (23%)	
Piskulic et al. (2012)[30]	138	64	18.6	SOPS		Social isolation and withdrawal (50%)	Avolition (55%)	Decreased expression of emotion (27%)	
Binbay et al. (2012)[41]	932	42	37.4	CIDI	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Morcillo et al. (2015)[51]	60	51	19.9	PANSS, CAARMS			Passivity experiences (25%)		
Azar et al. (2016)[52]	123	55	19.4	SANS			Avolition (46.3%)	Flat affect (15.4%)	Alogia (14.8%)
Patients experiencing a first-episode of psychosis (FEP)									
Husted et al. (1992)[53]	66	75	21.9	Unpublished scale	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Mayerhoff et al. (1994)[54]	47	56	24.3	n/a	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Gerbaldo et al. (1997)[55]	89	n/a	n/a	SDS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Hafner et al. (1999)[56]	232	49	n/a	SANS		Social withdrawal-distrust (10%); Social withdrawal-	Poor work performance (11%)		

						communication (10%)			
Malla et al. (2002)[57]	110	79	24.9	SANS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Malla et al. (2004)[58]	71	82	24.3	SANS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Hafner et al. (2005)[59]	94	51	n/a	SANS		Social withdrawal (80%)	Reduced spare-time activities (64%); Reduced interests, citizen role (34%)		
Knapp et al. (2008)[60]	404	57	41.8	BPRS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Faerden et al. (2009)[61]	103	58	27.3	AES			Apathy (53%)		
Peralta and Cuesta (2011)[62]	100	53	36.0	SDS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Chang et al. (2011)[63]	93	45	31.2	HEN	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Lyne et al. (2012)[33]	387	53	33.7	SANS	Recreation interests and activities (scz=35%, del=21%, brp=0%, oth=23%)	Relationships with friends and peers (scz=49%, del=33%, brp=13%, oth=15%); Ability to feel intimacy and closeness (scz=23%, del=21%, brp=0%, oth=8%)	Global Avolition-Apathy (scz= 47%, del=12%, brp=13%, oth=14%)	Global affective flattening (scz=20%, del=6%, brp=0%, oth=7%)	Poverty of speech (scz=14%, del=0%, brp=0%, oth=5%); Blocking (scz=8%, del=0%, brp=0%, oth=6.3%); Increased latency of response (scz=13%, del=3%, brp=0%, oth=4%)
Hovington et al. (2012)[64]	158	71	22.5	SANS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Galderisi et al. (2013)[2]	345	58	26.3	PANSS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Lyne et al. (2014)[34]	155	62	29.7	SANS, Beiser scale (I)[2]		Social withdrawal (26%)	Marked reduction or loss of interest initiative and drive (29%); Deterioration in performance of usual activities, tasks (29%); Deterioration in hygiene, dressing (10%)	Blunted affect (6%)	
Gaebel et al. (2014)[42]	166	60	31.8	PANSS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Lyne et al. (2015)[65]	230	70	22.7	SANS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Lyne et al. (2015)[66]	97	59	31.2	SANS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Younger patients who have experienced multiple episodes of psychosis (yMEP)									

Jaeger et al. (1990)[43]	46	54	32.3	SDSS	Loss of ability to feel pleasure (28%)		Impoverished motivation, willpower, initiative (52%)		
Kuck et al. (1992)[67]	60	68	29.6	SANS			Avolition-Apathy (77%)	Bunted affect (83%)	Alogia (70%)
Kirkpatrick et al. (1993)[68]	99	79	34.7	SDS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Fenton and McGlashan (1994)[69]	187	n/a	28	SANS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Gerbaldo et al. (1995)[70]	26	n/a	n/a	SANS, SDS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Bottlender et al. (1999)[71]	245	28	33.6	AMDP-Deficit syndrome	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Wykes et al. (2000)[72]	17	71	38	PSE	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Selten et al. (2000)[32]	86	70	44.4	SANS	Anhedonia (73%)	Asociality (91%)	Poor grooming and hygiene (63%); Impersistence (93%); Physical anergia (88%); Decreased recreational interests (78%); Decreased recreational activity (78%); Lack of motivation (92%);	Unchanging facial expression (54%); Decreased spontaneous movement (40%); Paucity of expressive gestures (58%); Poor eye contact (38%); Lack of vocal inflections (50%)	Poverty of speech (45%)
Ross et al. (2000)[73]	466	64	24.1	SDS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Henderson et al. (2006)[74]	10	80	38.7	SANS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Thara et al. (2009)[75]	499	58	38.1	DIGS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Helldin et al. (2009)[35]	191	n/a	n/a	PANSS		Passive, apathetic and social withdrawal (73%)		Blunted affect (85%)	Lack of spontaneity and flow of conversation (87%)
Moller et al. (2010)[76]	323	28	35	AMDP, SANS, PANSS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Makinen et al. (2010)[77]	46	61	33.7	PANSS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*				
Bobes et al. (2010)[78]	1452	61	40.7	PANSS		Passive apathetic social withdrawal		Blunted affect (33%)	Verbal Fluency (32%)

					(46%)		
Sicras-Mainar et al. (2014)[17]	1120	58	47.3	PANSS	Passive apathetic social withdrawal (61%); Active social avoidance (26%)	Blunted affect (40%)	Low spontaneity and flow of conversation (22%)
Fervaha et al. (2015)[79]	166	83	25.5	QLS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*		
Older patients who have experienced multiple episodes of psychosis (oMEP)							
Pearlson et al. (1989)[80]	Late-onset (54); Early-onset (22)	Late-onset (13); Early-onset (23)	n/a	n/a		Affective blunting (late-onset= 7%, early-onset= 23%)	
Harris et al. (1991)[81]	46	71	62.2	SDS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*		
Soni and Mallik (1993)[82]	71	66	73.1	Manchester scale	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*		
Putnam et al. (1994)[83]	149	n/a	n/a	PANSS	*Data on 'other negative symptom' available in Supplemental Digital Content Table S2*		

[1]For patients groups (does not comprise control groups); [2] We chose to use data from the Beiser scale in our analyses because the SANS's global scores overlapped with the BNSS categories. SANS data can be found in Supplemental Digital Content Table S2. n/a=not available; *Scales abbreviations* (AES: Apathy evaluation scale; **AMDP**: Arbeitsgemeinschaft für methodik und dokumentation; **BPRS**: Brief psychiatric rating scale; **CAARMS**: Comprehensive assessment of at-risk mental states; **CIDI**: Composite international diagnostic interview; **CORS**: Circumstances of onset and relapse schedule; **DIGS**: Diagnotstic interview for genetic studies; **HEN**: High Royds evaluation of negativity scale; **PANSS**: Positive and negative syndrome scale; **PSE**: Present state examination; **QLS:** Heinrichs-Carpenter Quality of life scale; **RPMIP**: Royal Park multidiagnostic instrument for psychosis; **SANS**: Scale for the assessment of negative symptoms; **SDS**: Schedule for the deficit syndrome; **SOPS**: Scale of prodromal symptoms); *Samples abbreviations* (aff=affective disorders, brp=brief psychotic disorder, del= delusional disorder, nos= psychotic disorder not otherwise specified, oth= all other psychotic diagnoses, scz= schizophrenia, sczaf=schizoaffective, sczf=schizophreniform.

The combined sample sizes for each stage totalled 1838 UHR, 2945 FEP, 4939 yMEP, and 299 oMEP patients. UHR patients were on average 22.0 years old (SD = 7.0), while the FEP, yMEP, and oMEP patients were on average 29.5 (6.6), 35.7 (6.1), and 67.7 (7.7) years old, respectively. The proportion of males was not statistically different across the stages (UHR = 58.7%, FEP = 62.8%, yMEP = 61.5%, oMEP = 53.06%).

UHR studies did not mention the diagnosis of their participants because such diagnoses are not yet established at this early stage. For the other three stage categories, most studies reported the number of participants per diagnosis. **Table 2** presents the distribution of diagnoses per stage. Only two studies[33,47] reported prevalence data per diagnosis category preventing us from controlling for this variable in our analyses.

3.2 PREVALENCE OF NEGATIVE SYMPTOMS ACROSS THE DIFFERENT STAGES OF THE PSYCHOSIS CONTINUUM

Figure 2 presents the averaged prevalence of each negative symptom according to the different stages of the psychosis continuum. Two main patterns were observed, namely a drop of prevalence between the UHR and FEP stages and an increase of prevalence from the FEP to the yMEP stages. The drop could not be tested for anhedonia given that this symptom has not been examined in studies with UHR. There was an increase of prevalence as 26% of FEP individuals were rated anhedonic (based on one study) in contrast to 57% (range: 28-73%) in yMEP patients. The drops and increases were found in all other symptoms. For avolition, 50% of UHR individuals (range: 25-68%), 28% of FEP patients (range: 11-49%) and 73% of yMEP patients

(range: 52-82%) met the criteria. Asociality was rated as present in 49% of UHR (range: 43-62%), 34% of FEP (range: 10-80%), and 48% of yMEP patients (range: 43-91%). The affect of 21% of UHR individuals (range: 15-27%) were rated as blunt, while this was the case in 9% of FEP (range: 6-11%), 41% of yMEP (range: 33-85%), and 23% of oMEP patients (based on one study). The three other studies included in the oMEP category only reported prevalence data of the deficit syndrome or negative symptoms global/total scores. Finally, 15% of UHR participants (based on one study) met the criteria for alogia, as well as 8% of FEP (based on one study) and 33% of yMEP patients (range: 22-87%).

The omnibus Kruskall-Wallis tests were significant for the prevalence change of every symptom between 1) UHR and FEP and 2) FEP and yMEP (see **Table 3** for statistical results).

Instead of reporting the prevalence of individual negative symptoms, ten studies provided the number of participants who met criteria for persistent negative symptoms (classified as "other negative symptoms" in Supplementary Digital Content Table S1). Although there were differences within the operational definition and terminology of persistent negative symptoms (e.g., deficit syndrome, enduring/primary negative symptoms), a core element was always present, namely that such types of symptoms were not secondary to other external factors (e.g., medication, depression, environmental factors). The main differences between definitions regarded the duration of negative symptoms, the external factors to which the symptoms were secondary, and the number of negative symptoms that needs to be present. The prevalence of persistent negative symptoms in the FEP stage ranged from 7 to 34% (based on 4 studies) and varied between 8 and 25% (based on 4 studies) in yMEP patients, and between 37 and 64% (based on 2 studies) in oMEP patients.

4. DISCUSSION

In the current study, we reviewed the literature related to the prevalence of negative symptoms across the different stages of the psychosis continuum. Our results partially confirm our hypothesis and show two main trends: 1) the prevalence of negative symptoms ratings first decreased between the UHR and FEP stages, and then 2) increased from the FEP to yMEP stages. As expected, we observed a decrease in the prevalence rates of avolition, asociality, blunted affect and alogia. Yet, our results suggest that the prevalence of all negative symptoms ratings increased between the FEP and MEP stages, rather than stabilize as hypothesized.

Global factors common to all symptoms as well as specific ones relating to individual symptoms could influence these two prevalence patterns. A common factor impacting the first trend might be that negative symptoms become more difficult to observe and rate when patients enter the FEP stage because of their full-blown positive symptoms.[84] Furthermore, FEP patients may receive additional attention and care (including education about their symptoms, new coping strategies, and antipsychotic medication) from health professionals, friends and family given the acute nature of their symptoms, which might play a role in temporarily lowering the ratings of negative symptoms during this stage.[85] It is important to mention that the majority of UHR patients (>60%)[86] will not develop a FEP, which brings one to ponder the conceptualization and terminology of negative symptoms in the context of UHR.[87] This issue is further discussed in the limitations section. To that extent, depressive symptoms, which are quite prevalent in UHR, are also probably partly confounding the assessment of negative symptoms (especially anhedonia).[52,88,89]

Other global factors might also have an effect on the second trend observed from our results. First, yMEP patients might receive fewer opportunities for social, vocational and recreational activities leading to more frequent ratings of negative symptoms compared to FEP individuals.[90] Second, cognitive deficits, which have been associated with global ratings of negative symptoms[91] and appear to be more important in yMEP patients[92,93], could also influence in part the increasing rates of negative symptoms in the yMEP stage.[94]

The different negative symptoms exhibit essentially similar patterns of prevalence changes across stages but these changes may be driven by very different causes. The specific factors that could potentially influence the main patterns observed will be discussed for each symptom separately. As reviewing every possible factor is outside the scope of this study, we will instead discuss those that could themselves vary across the stages and that could be addressed in a therapeutic context.

4.1 ANHEDONIA

Neural dysfunctions within the brain's reward system, more specifically the striatum, represent a specific factor that could play a role in the increasing rates of anhedonia observed between the FEP and yMEP stages. On the one hand, striatal *hypo*activation during reward-processing tasks correlating with the severity of anhedonia have been reported in yMEP patients in a recent meta-analysis.[95-97] On the other hand, some studies reported *hyper*activation of the striatum in FEP individuals, leading some authors to hypothesize that the reduced activity observed in yMEP samples could stem from the effects of long-term administration of certain antipsychotics given their possible effect on striatal dopamine levels.[98,99] Interestingly, striatal hypoactivation was observed in yMEP patients taking typical neuroleptics but not in those who were prescribed atypical ones.[100,101] In our sample, from the two studies reporting a prevalence

rate of anhedonia in the yMEP stage, only one reported the medication status of their patients (Supplementary Digital Content Table S1) and the majority of them were taking typical antipsychotics, which could further explain the increased prevalence of anhedonia ratings in this stage.[32,43]

4.2 AVOLITION

Anxiety elicited by psychotic symptoms could contribute to the decreased rates of avolition (and potentially asociality and blunted affect) observed between the UHR and FEP stages. New and unsettling subclinical symptoms may, by their very nature or by eliciting high levels of anxiety, make UHR individuals less motivated to pursue the activities during which these symptoms occur. A study by Schlosser, Fisher [102] reported that UHR individuals showed lower motivation compared to FEP participants, as well as a strong association between anxiety and behavioral inhibition avoidance.

On a different note, our results showed that avolition increases after multiple episodes of psychosis and different factors can be put forward for explaining this change. Patients in the yMEP stage may display higher rates of avolition as a way of protecting their self-esteem. Beck, Grant [103] proposed that patients experiencing longer durations of mental illness show defeatist beliefs that act as a protective mechanism to preserve their self-esteem following feelings of failure/disappointment. These feelings may stem from multiple sources such as stigma, lack of opportunities and impoverished environment.[90,104,105]

As well, the presence of avolition may precipitate the development of other negative symptoms. In other words, it is likely that individuals with a reduced anticipatory hedonic response (as opposed to consummatory hedonic responses which are not impaired in

psychosis[106,107]) for some activity will show less willingness and motivation to engage in such activity.[108-110]

Another factor may have to do with brain anomalies. In their review, Fervaha, Foussias [111] have suggested that yMEP patients tend to overestimate the effort necessary to obtain a reward resulting in avolitional tendencies, which could in part explain the increasing rates of this symptom in that stage. Such overestimation is believed to stem from dopaminergic dysfunction and disconnectivity within the nucleus accumbens and anterior cingulate cortex.[111] It is again possible that antipsychotics, which are more frequently prescribed to yMEP patients compared to the other stages, have an effect on these neuronal dysfunctions and contribute to the elevated rates of avolition found in the yMEP stage.[111,112]

4.3 ASOCIALITY

The global factor mentioned earlier (referring to the idea that FEP individuals often receive a greater intensity of care and services relative to subsequent stages) may be particularly relevant to explain the drop in prevalence of asociality between the UHR and FEP stages. As also mentioned above, higher levels of anxiety in UHR (caused by the lack of ability of patients to self-manage these relatively new positive symptoms or by their very nature) may apply here as well to explain the elevated rates of asociality in the UHR stage. Hence, it might not be the 'high clinical risk' per se that contributes to social disengagement of patients, but rather the fact that positive symptoms are relatively new, intimidating and even frightening.[113] It is also possible that persecutory ideas particularly drive the elevated rates of asociality in UHR populations.[114]

On the one hand, more yMEP patients may score high on asociality items partly because of the lesser number of social opportunities presented to them.[90] On the other hand, another

factor has to do with the effects of oxytocin. This molecule is a neuropeptide associated with prosocial behaviors that has been found to be at lower plasma levels in psychotic patients and which correlated with more severe negative symptoms.[115] This neurohormone interacts with other neurotransmitters like serotonine and dopamine in key regions of the brain (nucleus accumbens and amygdala) associated with asociality.[116] It has been suggested that such aberrant functioning could disrupt stimuli salience, ultimately leading to misguided social responses (e.g., withdrawal, isolation).[117] Despite our limited understanding of the oxytocin's role in psychosis, it is possible that inherent changes in the levels of this neuropeptide occur through the course of the illness therefore influencing the prevalence of asociality ratings.

4.4 BLUNTED AFFECT

The aforementioned idea of elevated anxiety levels in UHR in response to novel positive symptoms could also potentially cause a reaction of affective blunting. Another factor that could influence the prevalence drop in the ratings of blunted affect between the UHR and FEP stages has to do with the idea that UHR individuals may become less expressive to avoid attracting attention onto them. Such tendencies could be conceptualized as maladaptive social/coping strategies and/or 'safety behaviors'.[118-120] The latter refers to behavioral responses initiated by feelings of distress following the misinterpretation of different experiences aimed to maintain dysfunctional beliefs. Such behaviors might not be as present in FEP individuals given their higher probability of receiving pharmacological and psychosocial treatments acting on their feelings of distress and dysfunctional beliefs.

In a similar manner to avolition, defeatist beliefs (e.g., firmly expecting low chances of success/satisfaction) could have an effect on the increasing rates of blunted affect observed in the

yMEP stage.[121,122] Beliefs such as “showing my feelings will let others see my inadequacy” (p.252)[123] could lead to showing less emotions, which could in turn be interpreted as affective blunting.

Extrapyramidal symptoms (EPS), a common side-effect of antipsychotics portrayed by movement abnormalities, represent one factor that could partly explain the increasing prevalence of blunted affect in yMEP patients.[124] Individuals with EPS can find it effortful and more difficult to initiate motion, notably in face muscles and upper limbs, sometimes leading to less facial expression and/or expressive gestures, which can be perceived as blunted affect.[98,125] The increased rate of blunted affect observed between the FEP and yMEP stages could be associated with the elevated rates of EPS in the latter population given their higher likelihood of receiving antipsychotics.

The absence of a significant difference on the prevalence rates of blunted affect between the yMEP and oMEP stages could be in part due to the imprecise distinction between the two stages emanating from the potentially different operational definitions of ‘geriatric’ and ‘elderly’ patients across studies.

4.5 ALOGIA

A larger proportion of UHR compared to FEP individuals may meet the criteria for alogia in part because of a fear that disclosing their symptoms/thoughts/behaviors could lead to unwanted pharmacological treatment or hospitalization.[113] The reduced prevalence of alogia ratings in FEP individuals could stem partly from the fact that they may tend to confide more in their health care professional because frank psychotic symptoms have become even more frightening than the idea of receiving treatment or staying at the hospital.

As for blunted affect, defeatist beliefs and EPS represent factors that could also in part explain the increased prevalence of alogia in the yMEP stage. Defeatist beliefs such as 'I will not find the right words to express myself' (p.252)[123] could lead patients to speak less. Patients with EPS may also take more time to begin to speak and have more difficulty in maintaining speech.

In addition, disturbances in language-speech networks could also in part be related to the increased prevalence of alogia seen in yMEP patients given that connectivity alterations in the ventromedial prefrontal and parietal cortices have been associated with decreased verbal expression in patients struggling with psychosis.[116]

4.6 PRIMARY VERSUS SECONDARY NEGATIVE SYMPTOMS

Primary negative symptoms are believed to be representing an inherent and core aspect of the illness, while secondary negative symptoms originate from other factors such as positive symptoms, extrapyramidal side effects of antipsychotic medications, depression, etc.[126]

To this point, we have discussed how external factors could contribute to fluctuations in prevalence rates of negative symptoms, which implies that secondary negative symptoms were measured. Nonetheless, one cannot rule out the possibility that the prevalence of negative symptoms inherently and dynamically changes across stages as the illness evolves. In fact, the prevalence rates reported here probably reflect a mix of both primary and secondary negative symptoms since we did not specifically select studies according to such criterion and because our data from the 'other negative symptoms' category (Supplemental Digital Content Table S2) suggest that primary/persistent negative symptoms were numerically more prevalent in oMEP patients compared to FEP and yMEP individuals. Interestingly, the authors of a recent meta-analysis of longitudinal data on negative symptoms in yMEP patients interpreted their results

along the same lines.[37] Their results suggest that negative symptoms decrease over time in all types of interventions (pharmacological and psychosocial), including placebo and treatment as usual. Despite that several external factors were also proposed to explain these results[37,127,128], it remains that our understanding of the course of negative symptoms will highly benefit from studies distinguishing between primary and secondary negative symptoms. The development of operational definitions for primary and secondary negative symptoms will support such efforts (see Hovington, Bodnar [64,]Mucci, Merlotti [126]). In addition, a more thorough understanding of the factors influencing the emergence of negative-like symptoms reported in non-clinical populations could facilitate the distinction between primary and secondary negative symptoms in clinical populations.[129-131]

4.7 LONGITUDINAL COURSE OF NEGATIVE SYMPTOMS PREVALENCE

Longitudinal studies have identified negative symptoms as predictors of psychotic conversion and recurrent episodic relapse[76,132] highlighting the importance of interventions targeting such symptoms. Additionally, investigations examining the course of negative symptoms prevalence over long follow-up periods (10 years on average) have reported stable trajectories for UHR individuals and more decreasing ones for FEP patients.[132,133] Such findings could indicate that early interventions may show preventive value. As current pharmacological, psychosocial and psychological interventions have been found to be only modestly efficient in the reduction of negative symptoms[9,134], further development of such treatment options is encouraged.

5. LIMITATIONS

The current study presents limitations. Our review included a limited number of studies and this may stem from two sources. Given our aim of investigating the course of negative symptoms across the psychosis continuum, many studies were excluded because patients in different stages were grouped together. Also, the nature of our research question was constraining in the sense that prevalence rates could be reported in papers not necessarily focusing on negative symptoms and their prevalence. Since our keywords included names of negative symptoms and the word 'prevalence', it is almost certain, unfortunately, that some studies were missed. This limited number of studies also narrows the generalizability of our results given that sometimes the prevalence rate for a symptom in a stage was based on only one study. Future review and meta-analysis studies aiming to replicate or complement our findings are encouraged, as a larger number of studies on the subject will continue to be published.

We also wish to acknowledge that the term 'negative symptom' assumes the existence of a known psychotic illness. We use it here for the purpose of consistency (in the context of the psychosis continuum), but recognize that it may not be entirely appropriate in the context of early mental distress and risk of psychosis. More specifically, the behavioral phenomena characterizing anhedonia, avolition, asociality, blunted affect and alogia should only be referred to as 'negative symptoms' retrospectively after a FEP. If no psychotic illness develops (as is true in the majority of UHR subjects), such behaviors might be viewed differently (e.g., early signs of depression or anxiety disorders). This currently debated issue has important implications for early intervention and treatment (for further reading see Yung and McGorry [87,]Fusar-Poli, Yung [135,]Cross, Hermens [136,]Keshavan, DeLisi [137]).

Another limitation is that included studies used different scales to measure negative symptoms, which generated some heterogeneity in our findings. We attempted to circumvent this

limitation by synthesizing the extracted data using the BNSS, which was developed according to the NIMH consensus statement on negative symptoms.[12] Furthermore, Lyne, Kinsella [138] reported that the three most commonly used scales (i.e., SANS, PANSS, BPRS) are highly correlated suggesting that our results may not have been significantly impacted by the inclusion of diverse scales. Another important element that needs to be acknowledged relatively to the different scales is that the ones used in most of the included studies are first-generation scales that utilized different approaches to evaluate and measure negative symptoms compared to the newly developed scales (BNSS and CAINS). In particular, avolition and asociality were often rated based on behavioral information, which might have tapped more onto impairments in functioning (that could be caused by other external factors) rather than reflecting negative symptoms.[14] As described in the introduction, the rating of avolition and anhedonia in the newly developed scales now also takes into account the patients' perspectives on their experiences and internal states (e.g., motivation, interest, pleasure). Thus, it will be interesting to re-examine the prevalence course of negative symptoms across the stages of the psychosis continuum once new studies using the BNSS and CAINS will have been published. Also, another source of heterogeneity in our results could have been introduced by variables such as the dosage of medication intake or the variability of age within stages. Given that most of the included studies did not report detailed information on these variables (e.g., age range and doses of antipsychotics for groups of participants presenting each negative symptom), our analyses could not control for such confounds.

Also, our results are not specific to schizophrenia given that we included studies covering all schizophrenia-spectrum diagnoses (e.g., schizoaffective disorder). Including them all was more in line with our aim given that similar stages have been identified for these conditions as

well.[139,140] Furthermore, some of the studies included in our analyses also reported on participants with diagnoses such as delusional disorder and brief psychotic disorder for which there is scant research concerning their illness course. We nevertheless included them because there is currently no consensus as to whether these diagnoses should be considered within the ultra-high risk/prodromal framework and some authors have reported that these individuals can experience multiple relapses/episodes.[141-144] Another limitation in the between-stages comparison is the different proportion of patients with a diagnosis of schizophrenia. As can be seen in Table 2, the percentage of cases of schizophrenia increased from FEP to yMEP to oMEP. However, we note that each of those stages involved predominantly non-affective psychoses disorders hence, making these groups relatively homogeneous (a Kruskall-Wallis test showed no significant difference across stages).

It is also worth noting that there exists another at-risk population, namely individuals at familial or genetic risk. This group comprises individuals with a first-degree (sometimes second-degree) relative afflicted with a schizophrenia-spectrum disorder.[145] These individuals at familial/genetic risk are generally identified due to their relatives (index cases), and are not seeking help themselves.[146,147] In order to be considered at UHR of developing psychosis, individuals at familial/genetic risk must also present other features, such as subthreshold psychotic symptoms, cognitive impairments and/or functional decline.[137,148,149] We decided to exclude studies investigating the population at familial/genetic risk because there was only one article[150] that emerged from our search which included individual at genetic risk and the authors investigated negative symptoms in individuals with the 22q11.2 deletion syndrome. Some authors have suggested that this population may only share partial etiology with UHR individuals and show different clinical patterns and age at onset of symptoms.[150]

Also, we did not include synonyms or variant terms (e.g., we used “flat affect” and not “blunted affect”) in our search strategy, which could have narrowed the extent of our results. However, we believe that it did not influence our conclusions because: 1- different terms were used to refer to the negative symptoms domains in the studies included in our analyses, 2- the use of the search term “negative symptom” allowed to retrieve pertinent studies regardless of the terminology used, and 3- we found that the terms were sometimes used interchangeably in the literature related to negative symptoms in the context of the psychosis continuum.

A final limitation is that we only included one measure of prevalence (i.e., point prevalence). Investigating different types of prevalence would have led to different research questions and was outside the scope of this study. Complementary research on period or lifetime prevalence as well as incidence measures may unfold relevant information for the treatment of negative symptoms.

6. CLINICAL IMPLICATIONS

Given the findings of our study, we encourage the early monitoring and intervention on negative symptoms – especially the most prevalent ones, namely anhedonia, asociality and avolition – within clinical settings. To that effect, negative symptoms persistence and severity in UHR individuals reportedly predicts an increase of the incidence rate of subsequent psychotic experiences highlighting the potential benefits of early treatment.[49,132] Furthermore, as described in the discussion, we advocate that mental health professionals should attempt to minimize the impact of some external factors that can maintain or enhance the prevalence of negative symptoms, such as antipsychotics side effects. Furthermore, we believe that social/vocational/schooling opportunities should be maximized for patients from every stage as

these could foster healthy lifestyles, which could in turn reduce the functional limitations associated with negative symptoms. Such opportunities can be offered within psychosocial interventions like social skills training (e.g., communication or interpersonal skills)[151] or occupational therapy (e.g., supported employment programs, like the Individual Placement and Support program (IPS)[152], in which patients receive continuous clinical help in preparing, finding and maintaining employment), which are reportedly effective in improving negative symptoms.[134]

7. CONCLUSION

In sum, our review of the literature suggests that negative symptoms are already importantly prevalent in the early stages of the psychosis continuum and that they are most prevalent in yMEP patients. Early interventions have the potential to reduce the functional limitations associated with negative symptoms. Particular attention should be paid to anhedonia, asociality and avolition given their high prevalence rates. Despite the fact that our study did not distinguish between primary and secondary negative symptoms, our results suggest that there is a need to systematically monitor external factors (e.g., side effects of antipsychotics, social opportunities) that could act as potential contributors to negative symptoms ratings.

ONLINE SUPPLEMENTARY MATERIAL

Sauvé, Brodeur, Shah & Lepage, The prevalence of negative symptoms across the stages of the psychosis continuum, *Harvard Review of Psychiatry*

Table S1. Stage classification criteria and medication per study

Study	Classification criteria provided by authors	Medication
Individuals at ultra-high risk of developing psychosis (UHR)		
Jackson et al. (1995) [47]	The study conducted retrospective analyses on data from FEP patients. Included individuals were admitted to an inpatient unit part of an early psychosis prevention and intervention centre. Patients were between 14 to 46 years old. Prodromal symptoms were investigated with the Illness Duration Interview. Prodromal ratings were focused on the period between the first evidence of change from the premorbid status and the first evidence of frank psychotic features.	n/a
Lencz et al. (2004) [48]	Included individuals presented at a recognition and prevention of psychosis clinic and were classified in three groups: 1) attenuated negative symptoms (score of 3+ on any item of the negative subscale of the SOPS), 2) attenuated positive symptoms (at least one significant SOPS symptom rating between 3 and 5 (i.e., moderate to severe) on any positive items), 3) schizophrenia-like psychosis (one or more score of 6 (i.e., at psychotic level) on the positive SOPS items). Individuals with a diagnosis of any specified DSM-IV psychotic syndrome were excluded.	n/a
Lam et al. (2006) [49]	Individuals were between 9 and 25 years old and met one of the three operationalized criteria defined in the CAARMS 2002 version: 1) combination of trait risk factors, that is a family history of psychosis in a first degree relative and a significant deterioration in functioning as measured by a 30% drop in GAF score, 2) attenuated psychotic symptoms, that is symptoms that deviated from normal phenomena but are not yet frankly psychotic (i.e., sub-threshold intensity), 3) brief limited intermittent psychotic symptoms that are of psychotic intensity but very infrequent, or which have a total duration of less than 7 days before resolving spontaneously.	Individuals with previous or current treatment with antipsychotic or mood stabilizer drugs were excluded.
Iyer et al. (2008) [50]	The study conducted retrospective analyses on data from FEP patients. Early signs and symptoms were investigated and measured using the Circumstances of Onset and Relapse Schedule (CORS), which provides information regarding lifetime history of illness prior to the onset of the presenting psychotic episode. Included individuals presented at a first episode clinic and were between 14 and 30 years old.	Included individuals did not have previous antipsychotic therapy for more than 1 month.
Piskulic et al. (2012) [30]	All individuals met one of the three established criteria for a psychosis risk syndrome (clinical high risk): 1) attenuated psychotic symptoms state, 2) brief intermittent psychotic symptom state, 3) genetic risk with deterioration. All participants met the first criteria.	8 individuals were receiving antipsychotics compared to 60 who were not.
Binbay et al. (2012) [41]	The study included individuals (1) with a past or current DSM-IV diagnosis of any disorder with psychotic symptoms, or (2) who scored positive on the psychosis screening questions but did not have a psychotic disorder (according to the SCID).	n/a
Morcillo et al. (2015) [51]	Help-seeking individuals (16-35 years old). All individuals met the criteria for clinical high risk according to the CAARMS. All individuals fulfilled the criteria for attenuated psychotic symptoms and 7 individuals (11.7%) also had a family history of psychosis in a first-degree relative or schizotypal personality disorder plus a 30% drop in Global Assessment Functioning (GAF) score from premorbid level, sustained for a month, occurring within the previous 12 months or GAF score of 50% or less for the previous 12 months.	Individuals who had a prior total treatment with antipsychotics for more than 1 week were excluded.
Azar et al. (2016) [52]	Individuals presented at a prevention and early intervention clinic and were identified to be at ultra-high risk for developing psychosis and were between the ages of 14 and 35 years old. Admission criteria are based on Comprehensive Assessment of At-Risk Mental States (CAARMS).	Individuals who had been treated with antipsychotic medication for a period exceeding seven days over the course of their lifetime were excluded.
Patients experiencing a first-episode of psychosis (FEP)		
Husted et al. (1992) [53]	Included individuals were experiencing a first lifetime episode of psychosis. Participants were between 15 and 54 years old and had experienced psychotic symptoms within the past 12 months that could not be attributed to drugs, alcohol or other organic factors.	Participants did not receive prior treatment with neuroleptics, antidepressants or lithium.
Mayerhoff et al.	Title: The deficit state in a prospective study of first-episode schizophrenia.	n/a

(1994) [54]		
Gerbaldo et al. (1997) [55]	Included individuals were admitted to a psychiatric hospital for the first time and had a diagnosis of schizophrenia, schizophreniform or schizoaffective disorder. Participants were 18 and older.	n/a
Hafner et al. (1999) [56]	Included individuals were admitted for the first time with a first episode of schizophrenia (broadly defined, ICD 295, 297, 298.3/.4).	12% of FEP participants had received antipsychotics before first admission.
Malla et al. (2002) [57]	Included individuals presented at a FEP clinic and had a first episode of non-affective psychosis.	Participants were either drug naïve or had been on antipsychotic medication for less than 1 month prior to admission to the program.
Malla et al. (2004) [58]	Included individuals presented at a first episode clinic and had a preliminary diagnosis of a non-affective psychotic disorder (SCID-DSM-IV).	Participants had a previous history of antipsychotic treatment no greater than 1 month.
Hafner et al. (2005) [59]	Included individuals were admitted for the first time with a diagnosis of schizophrenia (ICD-9). Individuals who had experienced episodes of psychotic symptoms of at least 14 days duration before their first admission were excluded. Participants were between 12 and 59 years old.	n/a
Knapp et al. (2008) [60]	Participants had a diagnosis of schizophrenia (ICD-10) and had received mental health services within the preceding 3 months. Patients who were currently in forensic settings or who had been in inpatient care for more than 1 year were excluded. Included individuals were between 18 and 65 years old.	n/a
Faerden et al. (2009) [61]	Participants consisted of in- and outpatients experiencing a first episode of psychosis. Included individuals had a DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective disorder, psychosis not otherwise specified, delusional disorder, brief psychosis, or major depressive or bipolar I disorder with mood-incongruent psychotic symptoms. Participants were between 18 and 65 years old.	81 participants were taking antipsychotic medication.
Peralta and Cuesta (2011) [62]	Included individuals experienced a first episode of non-affective psychosis (DSM-IV). Participants were between 15 and 65 years old.	All participants were antipsychotic-naïve.
Chang et al. (2011) [63]	Included individuals were in- and outpatients diagnosed with a first-episode of schizophrenia, schizophreniform or schizoaffective disorder (DSM-IV). Participants were between 18 and 55 years old.	48 patients were medication-naïve and 45 were evaluated within 7 days of starting antipsychotic treatment.
Lyne et al. (2012) [33]	Participants consisted of in- and outpatients of an early intervention program. Included individuals were aged between 16 and 65 years.	Participants had less than 30 days of antipsychotic treatment.
Hovington et al. (2012) [64]	Included individuals presented at a first episode clinic and were suffering from either affective or non-affective psychosis. Participants were between 14 and 30 years old.	Participants had not taken antipsychotic medication for more than one month.
Galderisi et al. (2013) [2]	Participants met DSM-IV criteria for schizophrenia, schizoaffective or schizophreniform disorder, had a recent onset of psychosis with less than two years elapsed between the onset of positive symptoms and recruitment into the study. Participants were between 18 and 40 years old.	All participants had a previous use of antipsychotic drugs less than two weeks during the preceding year and less than six weeks lifetime.
Lyne et al. (2014) [34]	Participants consisted of in- and outpatients presenting a suspected FEP between 16 and 65 years old.	All participants had less than 30 days of previous antipsychotic treatment.
Gaebel et al. (2014) [42]	Included individuals presented a first episode of schizophrenia, which was defined as the first inpatient treatment of the respective symptoms, with no former treatment with antipsychotic medication. Participants were between 18 and 56 years old.	All participants had no former treatment with antipsychotic medication.
Lyne et al. (2015) [65]	Included individuals presented at a first episode clinic and were between 14 and 30 years old.	All participants had taken less than 1 month of antipsychotic medication.
Lyne et al. (2015) [66]	Included individuals had a SCID psychosis diagnosis and were between 16 and 65 years old.	All had received less than 30 days of antipsychotic medication.
Younger patients who have experienced multiple episodes of psychosis (yMEP)		
Jaeger et al. (1990) [43]	Included individuals had a schizophrenia or schizoaffective disorder (DSM-III) with a chronic course.	n/a
Kuck et al. (1992) [67]	Included individuals met DSM-III-R guidelines and Research Diagnostic Criteria (RDC) for chronic schizophrenia.	87% of the sample were receiving ongoing antipsychotic therapy (primarily haloperidol and fluphenazine).
Kirkpatrick et al. (1993) [68]	Included individuals were outpatients with chronic schizophrenia (DSM-III and DSM-III-R), which was defined as having multiple hospitalizations.	All participants were judged to be appropriate candidates for maintenance neuroleptic treatment.
Fenton and McGlashan (1994) [69]	Participants had a diagnosis of schizophrenia (DSM-III). The study analyzed medical records of patients with the deficit syndrome, which was defined as presenting two or more primary negative symptoms always present for the 12 months preceding each hospital admission.	n/a
Gerbaldo et al. (1995) [70]	Included individuals were outpatients with a schizophrenia diagnosis (DSM-III-R). The study presents results of follow-up analyses on data collected 5 years after admission from index hospitalization.	Participants were free of neuroleptics.

Bottlender et al. (1999) [71]	Participants were inpatients first admitted to a psychiatric hospital who were suffering from functional psychosis with a diagnosis of schizophrenia (broad definition, ICD-9). The study presents results of follow-up analyses conducted 15 years after first hospitalization.	n/a
Wykes et al. (2000) [72]	Participants had a diagnosis of schizophrenia or affective/depressive psychosis (DSM-IV). Title: The prevalence and stability of an executive processing deficit, response inhibition, in people with chronic schizophrenia.	n/a
Selten et al. (2000) [32]	Included individuals had a schizophrenia diagnosis (DSM-III-R) and were recruited from medium- and long-stay wards of a psychiatric hospital. Participants were between 20 and 65 years old. The length of illness was defined as the number of years since first admission. The length of admission ranged between 1 and 495 months.	5 patients were treated with clozapine and the remaining 81 patients were treated with classic neuroleptics.
Ross et al. (2000) [73]	Included participants met one of the following criteria: 1) having a diagnosis of schizophrenia (DSM-III-R), 2) having a schizoaffective disorder (DSM-III-R) with poor outcome, 3) simple schizophrenia.	n/a
Henderson et al. (2006) [74]	Participants had a schizophrenia or schizoaffective diagnosis (DSM-IV).	Subjects were treated with open-label aripiprazol 15 mg daily for 4 weeks. After 4 weeks, aripiprazol could be increased to 30 mg daily if the subject and research physician determined it was necessary based on clinical symptoms. Subjects on clozapine for at least 1 year and a stable dose for at least 1 month were included in the trial and the clozapine dose remained unchanged during the trial.
Thara et al. (2009) [75]	Participants had a schizophrenia diagnosis (DSM-IV) and were 18 years old or older.	n/a
Helldin et al. (2009) [35]	Included individuals were free from a relapse for at least the last six months and had a diagnosis of schizophrenia, schizoaffective or delusional disorder (DSM-IV). 93 patients met the criteria for cross-sectional remission, while 149 did not.	n/a
Moller et al. (2010) [76]	Participants had a diagnosis of schizophrenia or affective disorder (ICD-9). To be eligible, participants had to be 65 years or younger.	Patients' acute episode in the hospital was treated with first generation antipsychotics.
Makinen et al. (2010) [77]	Participants had a schizophrenia diagnosis (DSM-III-R) and had suffered from this illness for at least 2 years.	n/a
Bobes et al. (2010) [78]	Included individuals had a diagnosis of schizophrenia, schizophreniform, schizoaffective (DSM-IV). To be eligible, participants had to be between 18 and 74 years old.	Participants received at least 12 weeks with one of the following antipsychotic drugs: risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, haloperidol. Patients receiving 2 or more antipsychotics at the time of evaluation were excluded.
Sicras-Mainar et al. (2014) [17]	Participants were 18 years old or older and had a diagnosis of schizophrenia (DSM-IV-TR). Included individuals presented 2 or more healthcare records.	All participants were under antipsychotic treatment and were part of a long-term prescriptions program (with a record of daily dose, time interval and duration of each treatment administered).
Fervaha et al. (2015) [79]	Included individuals had a DSM-IV diagnosis of schizophrenia. Participants were between 18 and 35 years old. FEP patients (defined as patients who had experienced psychotic symptoms for less than 3 years or if they began antipsychotic treatment within the past year) were not included.	Participants had received antipsychotic medication for 5 years or less.
Older patients who have experienced multiple episodes of psychosis (oMEP)		
Pearlson et al. (1989) [80]	Participants were elderly patients with early-onset (before age 45) schizophrenia (DSM-III-R).	n/a
Harris et al. (1991) [81]	Included individuals were elderly schizophrenic patients of age 46 and older who met DSM-III-R criteria for chronic schizophrenia.	Most patients were treated with neuroleptic drugs.
Soni and Mallik (1993) [82]	Included individuals had a diagnosis of schizophrenia (RDC) and were elderly chronic schizophrenic inpatients.	n/a
Putnam et al. (1994) [83]	Participants were geriatric schizophrenic inpatients.	n/a

CAARMS: Comprehensive assessment of at-risk mental states; CORS: Circumstances of Onset and Relapse Schedule; FEP: First-Episode of Psychosis patients; GAF: Global Assessment of Functioning; ICD: International Statistical Classification of Diseases and Related Health Problems; oMEP: older Multiple Episode of Psychosis patients; RDC: Research Diagnostic Criteria; SCID: Structured Clinical Interview for DSM; SOPS: Scale of prodromal symptoms; UHR: Ultra-High Risk of psychosis patients; yMEP: younger Multiple Episode of Psychosis patients.

Information contained in the following table is complementary to the data reported in the manuscript's Table 1.

Table S2. List of symptoms from the "other negative symptoms" category

Study	Other negative symptoms
Individuals at ultra-high risk of developing psychosis (UHR)	
Lam et al. (2006) [49]	Irritability (29%)
Iyer et al. (2008) [50]	Decreased energy and initiative (59%); Mood elation (23%); Inappropriate affect (11%); Catatonia (6%); Passivity experiences (2%)
Piskulic et al. (2012) [30]	Decreased experience of emotion and self (30%); Deterioration in role functioning (62%); Decreased ideational richness (17%)
Binbay et al. (2012) [41]	Presence of negative symptoms in subclinical group (8%); low-impaired group (15%); high-impaired group (20%)
Azar et al. (2016) [52]	Anhedonia-Asociality (59%)
Patients experiencing a first-episode of psychosis (FEP)	
Husted et al. (1992) [53]	Negative symptoms syndrome (53%)
Mayerhoff et al. (1994) [54]	Definite Deficit syndrome (7%), Questionnable Deficit syndrome (19%)
Gerbaldo et al. (1997) [55]	Deficit syndrome (17%)
Hafner et al. (1999) [56]	Difficulties with thinking and concentration (16%); Lack of energy, slowness (12%)
Malla et al. (2002) [57]	Any negative symptoms (70%); Negative symptoms excluding depression (36%); Negative symptoms excluding depression and extrapyramidal syndrome (27%)
Malla et al. (2004) [58]	23% presented PNS after 1-year follow-up
Hafner et al. (2005) [59]	Loss of energy/slowness (82%)
Knapp et al. (2008) [60]	61% presented at least one negative symptom
Peralta and Cuesta (2011) [62]	Catatonia (19%); Deficit Syndrome (12%)
Chang et al. (2011) [63]	26% presented primary negative symptoms (i.e., total score of HEN ≥ 6, without depression or extrapyramidal symptoms)
Lyne et al. (2012) [33]	Any negative symptom (scz=87%, del=64%, brp=29%,oth=51%); Impersistence at work or school (scz=58%, del=24%, brp=13%, oth=21%); Unchanging facial expression (scz=28%, del=9%, brp=13%, oth=12%); Decreased spontaneous movements (scz=8%, del=0%, brp=0%, oth=12%); Paucity of expressive gestures (scz=11%, del=3%, brp=0%, oth=3%); Poor eye contact (scz=8%, del=3%, brp=0%, oth=4%); Affective nonresponsitivity (scz=13%, del=0%, brp=0%, oth=4%); Lack of vocal inflections (scz=17%, del=0%, brp=0%, oth=3%); Grooming and hygiene (scz=22%, del=3%, brp=0%, oth=6%); Physical anergia (scz=40%, del=21%, brp=17%,oth=22%); Recreation interests and activities (scz=35%, del=21%, brp=0%, oth=23%); Sexual activity (scz=20%, del=18%, brp=0%, oth=12%); Social inattentiveness (scz=12%, del=3%, brp=8%, oth=6%); Inattention during mental status testing (scz=7%, del=6%, brp=8%, oth=7%)
Hovington et al. (2012) [64]	PNS was present in 28% (PNS_1), 13% (PNS_2), 13% (PNS_H) depending on the PNS definitions. PNS definition: PNS_1= a score of 3 or more on at least 1 global item of the SANS; PNS_2 = a score of 3 or more on at least 2 global items of the SANS; PNS_H = a SANS score of 3 or more on either one or both of the following dimensions: 1) diminished expression (i.e., affective flattening + poverty of speech), 2) amotivation (i.e., avolition/apathy + anhedonia/asociality)
Galderisi et al. (2013) [2]	54% had a PANSS score greater than 3 on at least 1 negative symptom
Lyne et al. (2014) [34]	Beiser scale: Emotional withdrawal (19%); Any Beiser scale symptom (50%). SANS*: Global affective flattening/blunting (21%); Global Alogia (14%); Global Avolition-Apathy (48%); Global Anhedonia-Asociality (47%). **We chose to use data from the Beiser scale in our analyses because the SANS's global scores overlapped with the BNSS categories.*
Gaebel et al. (2014) [42]	After first-year follow-up: Blunted affect (46%); Passive/Apathetic and social withdrawal (54%); Lack of spontaneity and flow of conversation (36%)
Lyne et al. (2015) [65]	Persistent negative symptoms were present in 25% of short-DAP group and in 44% of long-DAP group (DAP: duration of active psychosis)
Lyne et al. (2015) [66]	Expressivity (which comprises SANS items "affective flattening" and "alogia", 23%); Motivation/Pleasure (which comprises SANS items "anhedonia-asociality" and "avolition-apathy",

	62%)
Younger patients who have experienced multiple episodes of psychosis (yMEP)	
Kuck et al. (1992) [67]	Anhedonia-Asociality (82%); Attentional impairment (60%)
Kirkpatrick et al. (1993) [68]	Deficit syndrome (23%)
Fenton et al. (1994) [69]	Deficit syndrome (25%) at index admission
Gerbaldo et al. (1995) [70]	At least two negative symptoms have been present for the preceding 12 months according to SDS (65%), according to SANS (88%)
Bottlender et al. (1999) [71]	Markedly expressed negative symptoms in terms of a deficit syndrome (26%); At least one negative symptom (with a score >2) (52%)
Wykes et al. (2000) [72]	Negative symptoms (76%)
Selten et al. (2000) [32]	Ability to feel intimacy and closeness (85%); Relationships with friends and peers (92%); Affective nonresponsivity (63%); Increased latency of response (19%); Sexual activity (71%)
Ross et al. (2000) [73]	Deficit syndrome (14%)
Henderson et al. (2006) [74]	At least one negative symptom (100%)
Thara et al. (2009) [75]	Negative symptoms (94%)
Moller et al. (2010) [76]	At least one negative symptom assessed with AMDP (scz=72%, sczaf=68%, aff=44%); with SANS (scz=78%, sczaf=74%, aff=47%); with PANSS (scz=59%, sczaf=53%, aff=34%)
Makinen et al. (2010) [77]	Negative symptoms present (39%)
Bobes et al. (2010) [78]	Emotional withdrawal (39%); Poor rapport (36%); Presence of at least one negative symptom (58%); Presence of all negative symptoms (18%)
Sicras-Mainar et al. (2014) [17]	Emotional withdrawal (50%); Poor rapport (42%); Motor retardation (30%)
Fervaha et al. (2015) [79]	Severe deficits in motivation (15%); Some degree of motivational impairment (77%)
Older patients who have experienced multiple episodes of psychosis (oMEP)	
Harris et al. (1991) [81]	Deficit syndrome (37%)
Soni and Mallik (1993) [82]	Presence of a negative score (99%)
Putnam et al. (1994) [83]	Stable negative subtype – at 2 assessments (64%), at one assessment only (21%)

DAP: Duration of Active Psychosis; PNS: Persistent Negative Symptoms; <u>*Scales abbreviations*</u> (AES: Apathy evaluation scale; **AMDP**: Arbeitsgemeinschaft für methodik und dokumentation; **BPRS**: Brief psychiatric rating scale; **CAARMS**: Comprehensive assessment of at-risk mental states; **CIDI**: Composite international diagnostic interview; **CORS**: Circumstances of onset and relapse schedule; **DIGS**: Diagnotstic interview for genetic studies; **HEN**: High Royds evaluation of negativity scale; **PANSS**: Positive and negative syndrome scale; **PSE**: Present state examination; **QLS:** Heinrichs-Carpenter Quality of life scale; **RPMIP**: Royal Park multidiagnostic instrument for psychosis; **SANS**: Scale for the assessment of negative symptoms; **SDS**: Schedule for the deficit syndrome; **SOPS**: Scale of prodromal symptoms); <u>*Samples abbreviations*</u> (aff=affective disorders, brp=brief psychotic disorder, del= delusional disorder, nos= psychotic disorder not otherwise specified, oth= all other psychotic diagnoses, scz= schizophrenia, sczaf=schizoaffective, sczf=schizophreniform.

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FIGURE LEGENDS

Figure 1. Studies selection flowchart.

Figure 2. Averaged prevalence rates of negative symptoms across the psychosis continuum stages categorized according to the Brief Negative Symptom Scale items.