

Full-length Article

A Delphi-method-based consensus for clinical domains and assessment of the inflammatory subtype of major depressive disorder from the ASPIRE study

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<https://doi.org/10.1016/j.bbi.2026.106957>

Received 27 March 2026; Received in revised form 6 July 2026; Accepted 13 August 2026

Available online 16 August 2026

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ARTICLE INFO

Keywords:

Major depressive disorder
Inflammatory subtype
Immunopsychiatry
Delphi study
Symptom domains
Depression assessment
Lived experience
Precision psychiatry

ABSTRACT

Background: Elevated inflammatory biomarkers have been consistently associated with a subset of depressive symptoms, particularly atypical and energy-related features, as well as antidepressant treatment resistance. This evidence has supported the definition of an inflammatory subtype of major depressive disorder (ISMDD), characterized by immune-inflammatory dysregulation and reduced response to first- and second-line antidepressants. However, a lack of consensus on its definition and assessment tools limits research and treatment development.

Methods: Using a Delphi approach, international experts from the ASPIRE consortium (Advanced Stratification of People with Depression based on Inflammation, $n = 25$) identified ISMDD symptom domains, which were then evaluated by the European College of Neuropsychopharmacology Immuno-Neuropsychiatry Network (INPN-ECNP, $n = 12$). Using the same consensus structure, the coverage of these domains by depression rating scales was then assessed. People with lived experience (PWLE, $n = 11$) provided perspectives on the clinical relevance and impact of the emerged symptoms.

Results: ASPIRE consensus identified ten ISMDD symptom domains: fatigue/low energy, hypersomnia, increased weight/appetite, cognitive difficulties, lack of motivation, anhedonia, diminished interest, leaden paralysis, psychomotor retardation, and insomnia, with the first five being also confirmed by INPN-ECNP consensus. Except for increased weight/appetite, PWLE identified these domains as negatively affecting quality of life; most of them were also reported as not extensively assessed in clinical care. Among rating scales, the Inventory of Depressive Symptomatology tools, including their Quick versions, were the only instruments covering all or almost all the ISMDD domains.

Conclusion: These findings support a framework for ISMDD and highlight the importance of symptom assessment to improve clinical evaluation, research, and personalized immunopsychiatric treatment.

1. Introduction

Growing evidence is prompting the recognition of an ‘inflammatory subtype of major depressive disorder’ (ISMDD) (Miller, 2025), potentially ripe for adoption in the DSM-6, to describe depressive presentations characterized by a distinct clinical phenotype, dysregulation of immune–inflammatory pathways, and a reduced therapeutic response to first- and second-line antidepressant treatments (Jha et al., 2025; Milaneschi et al., 2020; Penninx et al., 2025; Réus et al., 2023; Worrell et al., 2026).

A substantial body of clinical and experimental lines of evidence strongly supports this conclusion. Central and peripheral aberrations in acute phase proteins (e.g., C-reactive protein, CRP), cytokine levels (e.g., interleukin-6, IL-6; tumor necrosis factor, TNF- α), as well as other related inflammatory markers like kynurenine pathway, oxidative stress metabolites, immune cell numbers and antibody titers have been demonstrated in MDD patients (Enache et al., 2019; Foley et al., 2023;

Goldsmith et al., 2016; Osimo et al., 2020; Pearlman & Najjar, 2014; Pitharoulis et al., 2021; Sørensen et al., 2023; Wang & Miller, 2018). Several findings suggest a causal relation between immune dysregulation and the onset of MDD. Chronic inflammatory diseases, including autoimmune illnesses, are associated with a 2–3 fold increased risk for co-morbid depression (Berk et al., 2023; Graff et al., 2009; Marrie et al., 2017), while immunomodulatory drugs can reduce or increase symptoms of depression (Capuron et al., 2000, 2004; Langley et al., 2010; MRC ImmunoPsychiatry Consortium et al., 2020; Udina et al., 2012; Zalachoras et al., 2016). In terms of mechanisms, inflammation may contribute to depression by activating microglia and astrocytes, disrupting synaptic plasticity, neurotransmitter signalling, brain connectivity, and glucocorticoid-mediated negative feedback, thereby promoting sustained proinflammatory signalling and sensitization of the hypothalamic–pituitary–adrenal axis (Dantzer et al., 2008; Haroon et al., 2017; Miller et al., 2013; Miller and Raison, 2016; Osimo et al., 2019; Stetler and Miller, 2011; Poletti et al., 2024a; De Picker et al., 2023; Treadway et al., 2025).

Consistent findings indicate that around 25–30 % of MDD patients are particularly vulnerable to dysregulation of immuno-inflammatory pathways. A meta-analysis, including > 11,000 depressed individuals

¹ Members of the ASPIRE Study Consortium are listed in the Acknowledgement section.

and > 155,000 matched controls, estimated that 27 % of MDD displayed low-grade inflammation (CRP > 3 mg/L), with higher odds for low-grade inflammation compared with matched healthy controls (OR = 1.46, 95 % CI 1.22–1.75) (Osimo et al., 2019). Coherently, in the Netherlands Study of Depression and Anxiety (NESDA; n = 1098) cohort, 28.3 % of depressed patients had a CRP of 3 mg/L or higher (Milaneschi et al., 2021). From a symptomatic perspective, this biological signature can contribute in shaping a distinctive phenotype of MDD. In both human and animal studies, systemic immune activation has been shown to induce sickness behaviour, a coordinated set of behavioral and motivational changes that overlaps with depressive symptomatology. Rather than reflecting isolated symptoms, sickness behaviour is conceptualized as an adaptive response to inflammation, encompassing reduced activity, fatigue, social withdrawal, altered sleep and appetite, diminished motivation, and cognitive changes (Dantzer & Kelley, 2007). This framework is particularly relevant to ISMDD, as it provides a mechanistic link between immune activation and the neurovegetative, energy-related, motivational, and cognitive dimensions that may distinguish this subtype from other depressive presentations (Dantzer & Kelley, 2007; Penninx et al., 2025). CRP levels, and other inflammatory markers such as interleukin-6, have been associated with the severity of these symptom domains, especially for increases in appetite, weight and sleep, anhedonia, and fatigue (Foley et al., 2021; Frank et al., 2021; Jokela et al., 2016; Köhler-Forsberg et al., 2017; Milaneschi et al., 2021; Moriarty et al., 2021). Furthermore, higher inflammation (e.g., CRP, and pro-inflammatory cytokines) at baseline can predict worse treatment response to first- and second-line antidepressants, with predominantly serotonergic action, including serotonin selective and serotonin-noradrenaline reuptake inhibitors, and tricyclic antidepressants (Arteaga-Henríquez et al., 2019; Chamberlain et al., 2019; Haroon et al., 2018; Strawbridge et al., 2015, 2019; Vreijling et al., 2024). In this sense, ISMDD patients may benefit from targeted immunomodulatory interventions, that can exert antidepressant effects through neuroprotective, anti-oxidative, and anti-inflammatory mechanisms (Köhler-Forsberg et al., 2019; MRC ImmunoPsychiatry Consortium et al., 2020; Worrell et al., 2026; Yin et al., 2024). However, findings from clinical trials of such interventions are highly heterogeneous, and some key issues remain unresolved, such as identifying which patients will most benefit from these adjunctive anti-inflammatory treatments and using appropriate rating scales to capture their effects (Arteaga-Henríquez et al., 2019; Baune et al., 2021; Kavakbasi et al., 2024; Miller et al., 2025; Otte et al., 2025).

Indeed, the capacity of clinical studies to evaluate associations and changes in clinical depression severity of patients with ISMDD can be heavily constrained by the measurement instruments employed (Miller et al., 2025). Most standardised rating scales used to evaluate depression severity are heterogeneous in the symptom domains they cover, with limited overlap across scales and several symptom domains assessed by only one or two instruments (Fried, 2020). Furthermore, instruments may differ in granularity, differentiating for example between “hypersomnia” and “insomnia” (e.g., Inventory of Depressive Symptomatology, IDS-SR) (Rush et al., 1996), or collapsing them into a more general item such as “sleep disturbance” (e.g., BDI-II). This heterogeneity can also leave certain “atypical” symptom domains under-assessed or neglected (e.g., weight gain, irritability), as many widely used tools prioritize the assessment of melancholic or more “typical” profiles (Veal et al., 2024). These variations can significantly impact the interpretation and comparability of findings across the studies investigating inflammation-related depressive symptoms and treatment response. Furthermore, neglecting specific symptom domains may also have detrimental and stigmatizing consequences for patients, reinforcing perceptions of care as inattentive or misaligned with their needs, particularly when these symptom domains negatively impact the quality of life.

To sum up, despite growing evidence, the field still lacks a shared definition of the symptom domains that best characterize ISMDD and

standardized depression symptom tools for assessing its clinical severity, monitoring symptom change, and evaluating treatment outcomes in depression trials. These gaps, limiting the comparability across studies, may obscure treatment effects, and hamper the identification of clinically meaningful inflammatory depressive phenotypes that can be examined in relation to biological and behavioral signatures and treatment outcomes. Addressing these gaps may enable more precise patient selection in clinical trials, improve the interpretation of treatment effects (Miller et al., 2025), and guide the development of targeted interventions, ultimately improving patient care and quality of life.

In this paper, as part of the ASPIRE study (Advanced Stratification of People with Depression based on Inflammation) (Worrell et al., 2026), we define ISMDD from a phenomenological perspective and evaluate the precision of the most used standardized depression rating scales in capturing the severity of the ISMDD symptom profile by applying a Delphi-method-based consensus approach. Consensus was sought through international consortia bringing together experts and stakeholders with complementary clinical, research, and lived-experience expertise in immunopsychiatry and depression. First, the ASPIRE consortium provided consensus on ISMDD symptoms and rating scales, including the perspectives of people with lived experience (PWLE) on the impact of ISMDD symptoms on quality of life and mental healthcare. An external independent evaluation was then obtained from the Immuno-Neuropsychiatry Network at the European College of Neuropsychopharmacology (INPN-ECNP). Finally, building on the insights gained from this consensus process, we provide recommendations and outline future research directions to further validate the proposed ISMDD framework within a precision psychiatry perspective (Fernandes et al., 2017).

2. Methods

To develop a consensus-based framework for the identification of core symptom domains of ISMDD, we employed a structured Delphi methodology involving expert members of the ASPIRE consortium. Furthermore, an external independent evaluation from INPN-ECNP was obtained. The Delphi methodology allows to gather and refine expert opinions through multiple rounds of structured feedback, continuing until consensus is reached (Dalkey & Helmer, 1963; Fink et al., 1984). It is the gold-standard to define guidelines in the field of healthcare research, particularly suited for topics where empirical evidence is evolving or fragmented (Moher et al., 2010). Our Delphi process included the following key components: 1) Expert Panel: all invited participants were trained psychiatrists, psychologists, researchers or PWLE of the ASPIRE consortium (n = 43 consortium members, 15 collaborators from 9 countries) and INPN-ECNP network (n = 38, from 16 countries), selected for their expertise in the field; 2) Anonymity: all questionnaire responses were anonymised to limit social biases; 3) Multiple Delphi rounds: multiple structured questionnaires with Likert-like response scales were administered iteratively, to collect and refine expert opinions; 4) Predefined Consensus Criteria: for each questionnaire delivered, consensus was defined a-priori basing on responses distribution.

Following this Delphi framework, the study was structured in three phases, each implemented through the circulation of structured questionnaires to the full pool of invited experts at every round: i) Phase 1, identification of symptom domains related to ISMDD; ii) Phase 2, selection and evaluation of the precision of rating-scale items in assessing ISMDD symptom domains; and iii) Phase 3, assessment of the impact of ISMDD-related symptom domains on patients' quality of life and access to mental health care. Given the voluntary nature of participation, response rates were monitored across Delphi phases and rounds, and the full participant flow is reported in [Supplementary Table S1](#).

This study was conducted in accordance with the ethical principles stated in Declaration of Helsinki and was approved by the ethical committee at King's College London (LRM-25/26-48772). After a

complete description of the study, participants' informed consent was obtained.

As a first step, we aimed to determine symptom domains associated with ISMDD (*Phase 1*). A structured questionnaire was sent to the pool of experts of the ASPIRE consortium, which served as the primary Delphi panel for domain identification. In this questionnaire, participants were asked to assess the extent to which each proposed symptom domain is associated with ISMDD through a 5-point Likert like scale: 1 = "a little", 5 = "very much". The symptom domains that were initially proposed were based on the literature on ISMDD, and included atypical, energy-related and cognitive domains (i.e., anhedonia/lack of pleasure, fatigue/low energy, leaden paralysis, psychomotor retardation, hypersomnia, increased weight or appetite, cognitive problems/concentration difficulties) (Morrens et al., 2022; Penninx et al., 2025). Moreover, at the end of the questionnaire, participants were asked to report any additional symptom domain they considered relevant to ISMDD. A second questionnaire was then created and distributed to evaluate the proposed additional symptom domains, using the same procedure as for the initial set. The symptom domains were considered related to ISMDD if rated by half or more ($\geq 50\%$) of the respondents as "much or very much related". Across all Delphi phases, consensus thresholds were defined a priori and applied uniformly, as follows: strong consensus $\geq 95\%$, moderate consensus 61–94%, weak consensus 50–60% (Sforzini et al., 2022). The symptom domains, identified from both the two rounds of questionnaires as related to ISMDD, were retained for the next steps of the study and are hereafter referred to as "ASPIRE-derived candidate ISMDD symptom domains". The domains, in the ASPIRE consensus, were then circulated to the INPN-ECNP network for external independent evaluation. Domains reaching consensus in both consortia are referred to as "cross-panel supported domains".

After defining ISMDD symptom domains, in *Phase 2*, we aimed to evaluate how precisely each of them can be assessed by the most commonly used self- and clinician-administered depression rating scales. We identified the tools through an independent systematic review of literature including clinical trials assessing the antidepressant effect of anti-inflammatory interventions in MDD patients. The search identified 149 eligible clinical trials (see registered research protocols PROSPERO ID: CRD42024559522) (Wessa et al., 2026; Wessa et al., manuscript under review). Among identified studies, i) 59 studies administered the Hamilton Depression Rating Scale – 17 item version (HDRS-17) (Hamilton, 1960); ii) 22 studies the Beck's Depression Inventory – 21 item version (BDI-21) (Beck et al., 1996); iii) 16 studies the Montgomery–Åsberg Depression Rating Scale (MADRS-10) (Montgomery & Åsberg, 1979), iv) 13 studies Hamilton Depression Rating Scale – 21 item version (HDRS-21) (Hamilton, 1960), v) 8 studies the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983); vi) 4 studies used Inventory for Depressive Symptomatology – Self Report (IDS-SR) (Rush et al., 1996); vii) 4 studies the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al., 2003), viii) 2 studies the clinician administered version of IDS (IDS-C) (Rush et al., 2000), and ix) 1 study the QIDS-Clinician version (QIDS-C). For these scales, we evaluated how accurately their individual items captured each of the ISMDD symptom domains. Two trained psychologists (CM, TC) independently identified all items potentially measuring the constructs of interest. Items were allowed to be assigned to more than one symptom domain when conceptually justified, acknowledging overlap across depressive symptom constructs. This screening step was intended to generate an inclusive pool of candidate items for subsequent expert evaluation. Therefore, all items rated as related to a domain from at least one trained psychologist were moved to the expert evaluation through Delphi consensus process for item precision. So, structured questionnaires were developed to evaluate how well each item captured its corresponding symptom domain. ASPIRE members were asked to assess each item's precision in evaluating the identified ISMDD symptom domains through a 4-item Likert scale: from 1 = low precision to 4 = very high precision. If the same item was used in

one or more tools (e.g., item n. 7 in QIDS and item n. 12 in IDS), it was repeated only once through the questionnaire. In this step, the items were considered representative of the relative symptom domain if rated by half or more ($\geq 50\%$) of the respondents as "high precision" or "very high precision". As previously described, Phase 2 was conducted in two main rounds assessing item precision for all the ASPIRE-derived candidate ISMDD symptom domains: the first comprised items related to symptom domains that achieved consensus in the first round of Phase 1 (i.e., anhedonia, fatigue, psychomotor retardation, leaden paralysis, hypersomnia, increased weight/appetite, cognitive problems), and the second round comprised items later emerged (i.e., lack of motivation, loss of interest, insomnia). For IDS tools, the items related to self-report or clinicians' versions were divided into separate questionnaires. As previously defined, the degree of consensus was extracted. An external independent following evaluation by the INPN-ECNP network was subsequently explored for items that achieved at least weak consensus.

In *Phase 3*, a structured questionnaire, co-designed with two representatives of PWLE (FLM, EVdE), was administered to PWLE in the ASPIRE Patient Advisory Board (PAB) ($n = 11$), with participants purposively chosen to ensure a maximally diverse and globally representative range of patient experiences. For each ISMDD symptom domain, we asked 9 questions assessing how the identified symptom domain affect patients' quality of life in different dimensions (interpersonal relationships, engagement in leisure or recreational activities, occupational or educational performance, autonomy), perceived stigma, self-judgment, access to mental health care, or evaluation and prioritization in clinical intervention (See [Supplementary Section S1](#)). For each question, participants rated on a 5-point Likert scale ranging from 1 = "not at all" to 5 = "extremely". A symptom domain was considered to have a relevant impact on a given quality-of-life domain when the majority of respondents ($\geq 50\%$) scored 4 ("very") or 5 ("extremely") on the corresponding item (Sforzini et al., 2022).

For all Phases, descriptive data regarding consensus rates were obtained with Excel software. The complete workflow of the Delphi process is reported in [Fig. 1](#).

3. Results

3.1. Phase 1: Identification of symptom domains related to ISMDD

All the symptom domains of the first questionnaire were rated as related to ISMDD (ASPIRE responders $n = 25/58$ invited participants). Moreover, the respondents suggested the addition of the following symptom domains: i) lack of motivation/drive, ii) weight loss, iii) loss of interest, iv) suicidal thoughts, v) anxiety, vi) insomnia, vii) irritability. Among these symptom domains, the second round of expert evaluation, which showed a reduced number of responses compared with the first round (ASPIRE $n = 16/58$ invited participants) confirmed the relevance of the following for ISMDD: i) lack of motivation/drive, ii) loss of interest, vi) insomnia. Considering the results of the two ASPIRE questionnaires, ten symptom domains met the predefined consensus threshold and were therefore classified as ASPIRE-derived candidate ISMDD symptom domains ([Supplementary Table S2](#)):

- with a strong consensus, fatigue/low energy,
- with moderate consensus, anhedonia/lack of pleasure, lack of motivation, hypersomnia, psychomotor retardation,
- with a weak consensus, loss of interest, increased weight/appetite, insomnia, leaden paralysis and cognitive problems.

The external independent evaluation of the INPN-ECNP (responders $n = 12/38$ invited participants) ([Supplementary Table S3](#)) confirmed fatigue/low energy, hypersomnia, increased weight/appetite, cognitive problems, and lack of motivation as cross-panel supported ISMDD symptom domains. In particular:

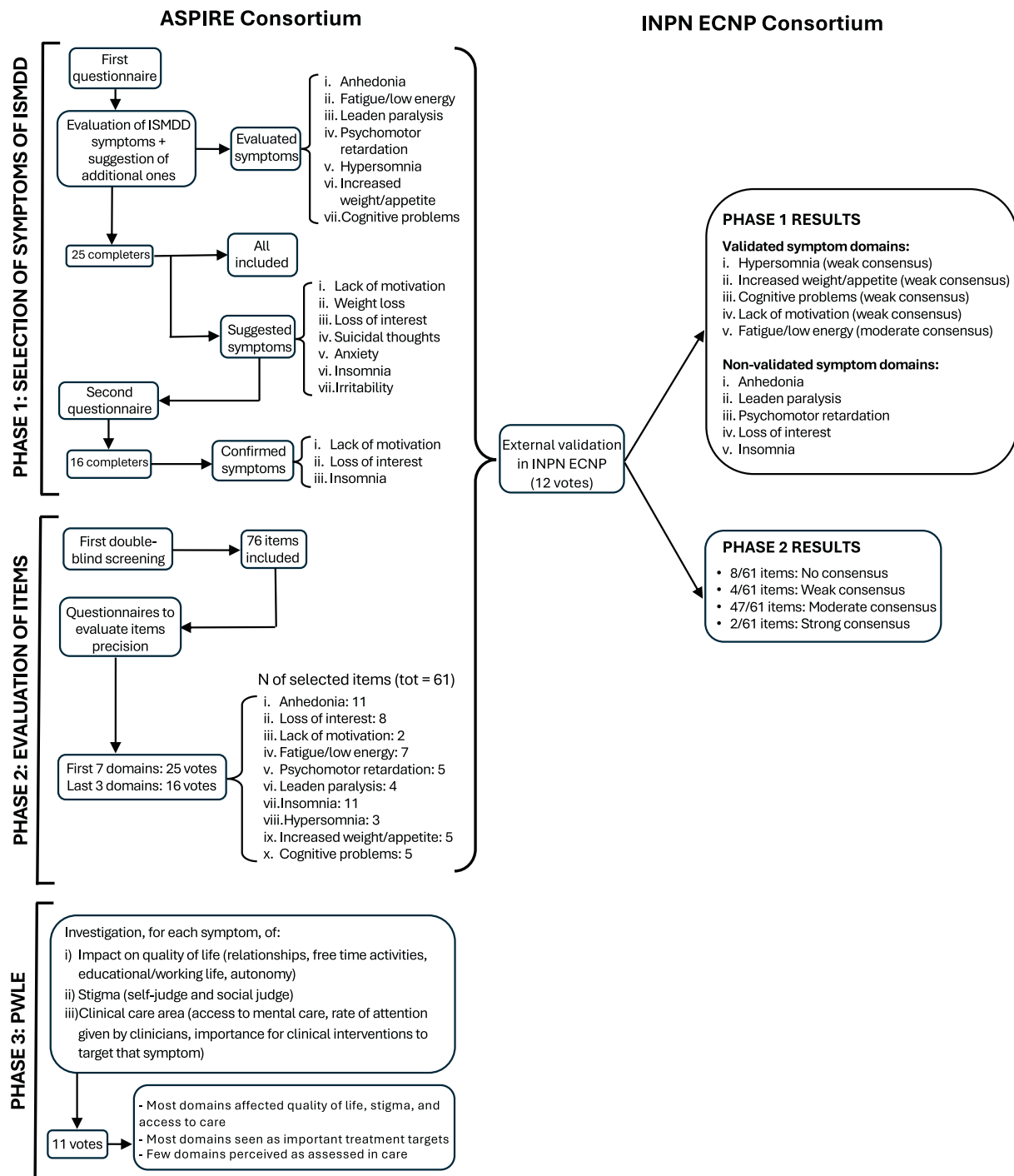


Fig. 1. Visual workflow of the procedures and results employed among phase 1 (selection of ISMDD symptom domains), 2 (Evaluation of ISMDD-related items) and 3 (PWLE evaluation of ISMDD impact).

- moderate INPN-ECNP consensus was reached for fatigue/low energy.
- weak INPN-ECNP consensus was reached for hypersomnia, increased weight/appetite, cognitive problems, and lack of motivation.

No consensus was found for anhedonia/lack of pleasure, leaden paralysis, psychomotor retardation, loss of interest, and insomnia. No domains obtained strong consensus.

3.2. Phase 2: Assessment of items rating ISMDD symptom domains

For the ten ASPIRE-derived candidate ISMDD symptom domains, 108 items were initially selected by the two trained psychologists (Supplementary Table S4). Because QIDS is derived from a subset of items included in the IDS, 32 items completely overlapped (18 from QIDS-C and 14 from QIDS-SR), resulting in a final list of 76 unique items for evaluation (6 with inter-rater disagreement). Among this list of non-repeated items, 15 items were selected for anhedonia/lack of pleasure, 9 for fatigue/low energy, 5 for leaden paralysis, 9 for psychomotor retardation, 3 for hypersomnia, 5 for increased weight or appetite, 5 for

cognitive problems/concentration difficulties, 4 for lack of motivation/drive, 10 for loss of interest, 11 for insomnia. Among this initial list, ASPIRE experts (responders $n = 21$ for the first round; $n = 16$ for the second round, 58 invited) identified 61 items reflecting immuno-inflammatory symptom domains with high or very high precision, 20 with a strong, 33 moderate, and 8 weak consensus. Among 6 items with no inter-rater agreement, 5 did not obtain consensus, and 1 weak.

When considering existing validated scales, it appears that coverage of immune-related symptom domains differed. The summary of the considered scales is reported below:

- BDI-21 did not provide items for lack of motivation/drive, psychomotor retardation, leaden paralysis (3/10 ISMDD domains not covered).
- HADS did not provide items for lack of motivation/drive, fatigue/low energy, leaden paralysis, hypersomnia, insomnia, increased weight/appetite, and cognitive problems (7/10 ISMDD domains not covered).
- HDRS did not provide items for lack of motivation/drive, fatigue/low energy, hypersomnia, increased weight/appetite, cognitive problems, and leaden paralysis (6/10 ISMDD domains not covered).
- MADRS-10 did not provide items for loss of interest, leaden paralysis, hypersomnia, increased weight/appetite (4/10 ISMDD domains not covered).
- IDS-SR and QIDS-SR covered all the ISMDD symptom domains.
- IDS-C and QIDS-C covered all ISMDD domains except for lack of motivation/drive (1/10 ISMDD domain not covered).

The scoring distribution for all the items (ASPIRE), along with their degree of consensus, is reported in [Supplementary Table S4](#). The distribution of the 61 items across the 9 clinical scales is reported in [Fig. 2](#). [Supplementary Fig. S1](#) reports only items achieving strong consensus for precision, while [Supplementary Table S5](#) indicates whether each item

achieved consensus for one or more ISMDD symptom domain, together with the corresponding consensus level.

The external independent evaluation of the INPN-ECNP (responders $n = 12/38$ invited) ([Supplementary table S6](#)) confirmed consensus for 53 out of 61 items obtained in the ASPIRE consortium. Differences were found for the domains of: anhedonia (no agreement for item 7 in HDRS and item 19 in IDS-C), fatigue/low energy (no agreement for item 7 in MADRS), lack of motivation (no agreement for item 15 in IDS-SR), leaden paralysis (no agreement for item 23 items in IDS-SR and IDS-C), loss of interest (no agreement for item 22 in IDS-C), psychomotor retardation (no agreement for item 7 in MADRS). IDS items corresponded to item 13, 10 and 15 in QIDS tools.

Thus, 1 out of 5 items of HDRS was not validated, leading to 3 ISMDD domains covered by HDRS (i.e., insomnia, loss of interest, psychomotor retardation). Similarly, 2 domains of MADRS were not validated, ultimately covering 4/10 ISMDD domains (i.e., anhedonia, lack of motivation, cognitive problems, insomnia). All the items of BDI-21 and HADS were validated by the INPN-ECNP, thus covering 7 and 3 ISMDD domains, respectively.

Finally, although some IDS-C and IDS-SR items were not confirmed by the INPN-ECNP evaluation, IDS tools retained the highest coverage of ISMDD symptom with 9/10 domains, lacking only lack of motivation. Overall, the percentage of items referring to ISMDD ranged from 24 % of total items included in HDRS, to 62 % in QIDS.

3.3. Phase 3: Impact of ISMDD symptom domains on quality of life, stigma, and mental health care access.

Eleven PWLE representatives from the PAB completed the questionnaire (8 women, 44.4 ± 11.17 years old, from 8 countries – Belgium, Finland, Germany, Netherlands, Nigeria, Poland, UK, South Africa). All respondents reported lived experience of depression, and 8/11 (72.7 %) also reported experience of caregiving for a person with

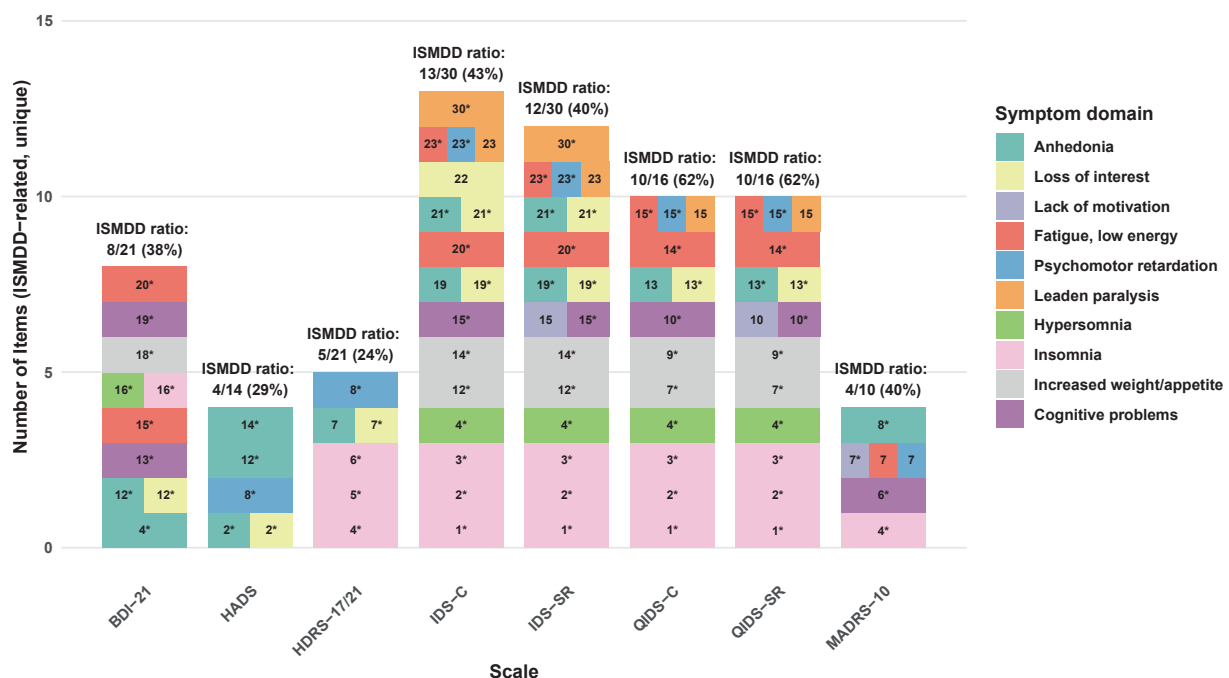


Fig. 2. Visual synopsis of items assessing ISMDD symptom domains across the depression rating scales considered. The numbers inside coloured boxes indicate the item number in each tool. ISMDD ratio indicates how many items (and related percentage) evaluated ISMDD symptom domains against the total number of items in each tool. Items marked with the asterisk reached the consensus also in the INPN ECNP consortium. Abbreviations: BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; HDRS-17–21, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; IDS-C: Inventory for Depressive Symptomatology - Clinician; IDS-SR: Inventory for Depressive Symptomatology – self rated; QIDS-C: Quick Inventory of Depressive Symptomatology - Clinician; QIDS-SR: Quick Inventory of Depressive Symptomatology - self rated. Note: Results regarding QIDS have been derived from the answers obtained on IDS, since all the items of QIDS are included in IDS.

depression. Regarding the ISMDD symptom domains, anhedonia, loss of interest, lack of motivation, fatigue/low energy, and cognitive problems were reported by 11/11 participants (100 %). Insomnia was reported by 9/11 (81.8 %), hypersomnia by 8/11 (72.7 %), increased weight/appetite by 7/11 (63.6 %), psychomotor retardation by 6/11 (54.5 %), and leaden paralysis by 4/11 (36.4 %).

With the exception of increased weight/appetite, all symptom domains reached at least moderate consensus for a negative impact across all four quality-of-life areas assessed (relationships, free time, work/education, autonomy), with a unanimous strong agreement (100 %) for: anhedonia impacting free time; loss of interest impacting both relationships and free time; fatigue/low energy impacting relationships; and cognitive problems impacting work/education. In contrast, increased weight/appetite did not reach consensus for any quality-of-life domain (18.2–27.3 %) (Fig. 3a). Responders reached a weak/moderate consensus for almost all questions related to stigmatization, indicating that people affected by depression can be negatively judged by others or by themselves for most of the proposed symptom domains, except for leaden paralysis, insomnia and hypersomnia which reached a weak consensus only for self-judgement questions (all 54.5 %). Leaden paralysis and insomnia did not reach consensus for social stigma (36.4 and 18.2 %, respectively) (Fig. 3b). Most responders (moderate consensus, 63.6–72.7 %) indicated that 7/10 symptom domains, except for hypersomnia (45.5 %), insomnia (27.3 %), and increased weight/appetite (18.2 %), can identify a barrier to access to mental care (e.g., talking to a mental health professional, participating in support groups or therapy sessions, engaging with crisis services) (Fig. 3c). Responders also agreed that 8 out of 10 symptom domains (moderate consensus, 63.6–90.9 %) were important targets of treatment in people affected by depression, except for loss of interest which achieved weak consensus (54.5 %), and leaden paralysis not reaching consensus (45.5 %). Interestingly, only fatigue/low energy and insomnia reached consensus for their severity

being extensively assessed and discussed by mental health professionals during the care (both weak, 54.5 %), while all other symptom domains fell below the threshold of consensus (9.1–45.5 %) (Fig. 3c). The complete PWLE results are reported in [Supplementary Table S7](#).

4. Discussion

This study provides a structured international consensus on symptom domains related to ISMDD. The primary ASPIRE Delphi process identified ten candidate ISMDD symptom domains, including fatigue/low energy, hypersomnia, increased weight/appetite, cognitive difficulties, lack of motivation, anhedonia, diminished interest, leaden paralysis, psychomotor retardation, and insomnia. First five of which were further classified as cross-panel supported following external INPN-ECNP evaluation. Together, these findings delineate a clinically coherent profile centred on disturbances in energy balance, motivation, neurovegetative regulation. Across expert panels and patient perspectives, this phenotype emerged as only partially captured by commonly used depression rating scales but associated with substantial multidimensional functional impairment.

Our Delphi consensus, involving up to 25 experts in the ASPIRE consortium, identified ten candidate symptom domains of ISMDD. Among these, a strong consensus (≥ 95 % of responders) was reached for fatigue/low energy, and moderate consensus (between 61 and 94 %) for psychomotor retardation, hypersomnia, anhedonia, and lack of motivation, echoing existing evidence that inflammation preferentially impacts these symptom domains (Penninx et al., 2025). As previously hypothesized, a consensus for ISMDD was reached for symptom domains commonly associated with atypical depression and somatic energy imbalance, potentially representing a distinct clinical phenotype from melancholic depression, typically characterized by pervasive feelings of guilt or worthlessness, early morning insomnia and weight loss.

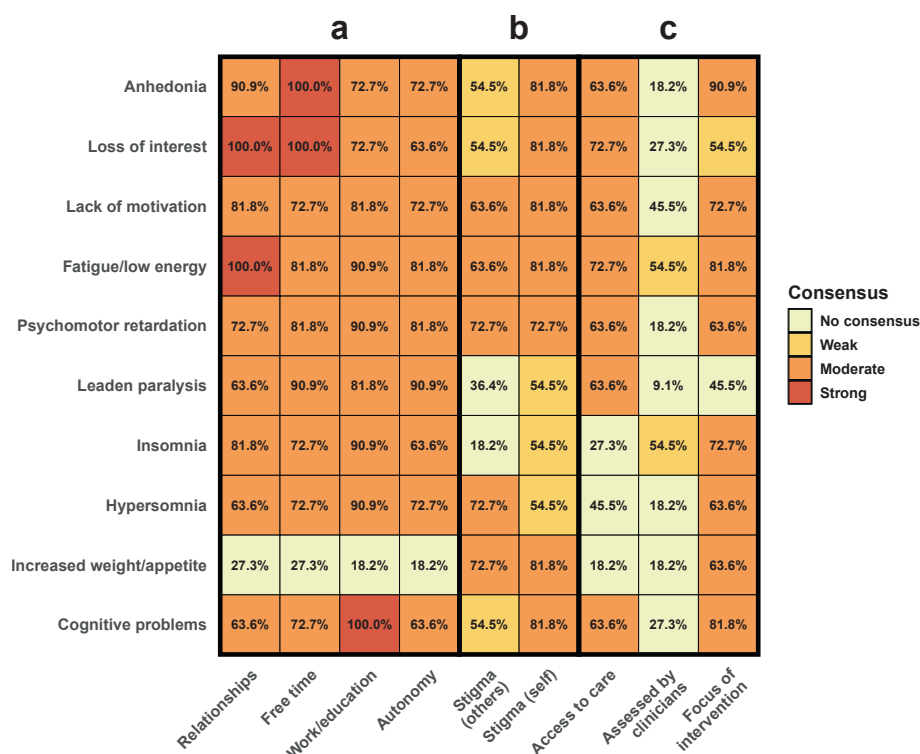


Fig. 3. Heatmap of PWLE ratings of the impact of ISMDD symptom domains on quality of life, stigma, and mental health care. Rows indicate symptom domains; columns indicate outcome domains grouped as a) quality of life (relationships, free time, work/education, autonomy), b) stigma/judgment (judgment by others; self-judgment), and c) mental health care (access to mental health care; symptom domain severity assessed by clinicians; importance of that symptom domain being a focus of intervention). Values represent the percentage of PWLE respondents ($n = 11$) endorsing each item with a score of 4 (“very”) or 5 (“extremely”) on a 5-point Likert scale. Cell colour denotes consensus level: Red, strong (≥ 95 %); Orange, moderate (61–94 %); Yellow, weak (50–60 %); Light Yellow, no consensus (< 50 %).

Accordingly, the external independent evaluation from INPN-ECNP, conducted by 12 immunopsychiatry experts, confirmed the ISMDD relevance for fatigue/low energy, hypersomnia, increased weight/appetite, cognitive difficulties, and lack of motivation. Existing symptom-level evidence supports the biological plausibility of the cross-panel supported ISMDD domains. Large cohort, pooled symptom-level, genetic, immune-metabolic, and mechanistic studies have linked inflammatory signalling, including CRP, IL-6, TNF- α , and composite inflammatory indices, to fatigue/low energy, hypersomnia or sleep disturbance, cognitive difficulties, increased appetite/weight, reduced motivation, anhedonia, and psychomotor slowing (Lamers et al., 2020; Frank et al., 2021; Kappelmann et al., 2021; Milaneschi et al., 2021; Miller, 2025; Felger et al., 2016; Mac Giollabhui et al., 2025). Overall, this evidence supports the view that inflammation preferentially maps onto energy-related, neurovegetative, and motivational dimensions of depression rather than uniformly across all depressive symptoms. Cross-panel consensus was not reached for melancholic symptom domains (e. g., anhedonia/lack of pleasure, loss of interest, and insomnia) or other features, such as leaden paralysis. It should be noted for loss of interest, increased weight or appetite, insomnia, leaden paralysis, and cognitive difficulties, that only a weak level of consensus was achieved in ASPIRE. The incomplete agreement across consortia as well as the weak consensus on these symptoms may reflect several non-mutually exclusive factors, including genuine uncertainty regarding the boundaries of ISMDD and melancholic or more typical depressive presentations, and differences in how expert panels weighted symptom specificity versus clinical relevance. Future studies should clarify whether the assessment of ISMDD should primarily focus on the most specific symptomatological domains, such as atypical and neurovegetative symptoms, or also retain less specific features that may nevertheless contribute significantly to patient burden, functional impairment, and treatment response. When looking at ASPIRE and INPN-ECNP consensus on the ability of commonly used depression rating scales to capture ISMDD symptom domains, substantial gaps emerged. Overall, the proportion of items specifically referring to ISMDD ranged from 24 % in HDRS to 62 % in QIDS, underscoring the limited representation of these domains in standard instruments. Among the tools examined, the self-report versions of the IDS and QIDS (IDS-SR and QIDS-SR) were the only instruments judged capable of capturing all ten ISMDD symptom domains in ASPIRE consortium, whereas the clinician-rated versions (IDS-C and QIDS-C) did not adequately capture lack of motivation. Overall, IDS-based tools appeared particularly suitable for clinical and research settings focused on inflammation-related depression, despite practical limitations such as length and respondent burden. Previous studies using these instruments confirmed associations between peripheral inflammation and depressive symptoms (Lamers et al., 2020; Van Eeden et al., 2020) and the efficacy of immunomodulators in reducing depressive symptomatology (Poletti et al., 2024b). In contrast, the two main clinician-administered instruments used in regulatory approval processes for antidepressants, captured only four (HDRS) or six (MADRS) out of the ten candidate ISMDD symptom domains (European Medicines Agency, 2025; Food and Drug Administration, 2018), the rate was even lower for the INPN-ECNP consensus, further decreasing to respectively three and four domains. The most neglected domains were hypersomnia, increased appetite and weight, lack of motivation, and leaden paralysis, confirming a systematic bias toward the evaluation of melancholic and typical depressive symptom domains, which can contribute to the under recognition of ISMDD in clinical practice (Miller et al., 2025). Neglect toward atypical symptom domains in common rating scales previously emerged as potential bias in the assessment of MDD with seasonal pattern, and it was remediated by developing targeted instruments by adding new items to the existing ones (Williams et al., 1992) and the recognition of seasonal affective disorder as a separate diagnostic category or seasonal pattern as a specifier in mood disorders (American Psychiatric Association, 1987; World Health Organization, 2022). Consensus here is that the IDS rating framework, encompassing both the

clinician-rated and self-rated versions, together with the shorter version of QIDS, can provide sufficient instruments to rate ISMDD symptom domains. Thus, they identify the most suitable outcome measures in clinical trials of interventions targeting ISMDD.

Nevertheless, the relevance of improving symptom assessment was further supported by PWLE responses, which highlighted gaps in the clinical evaluation of ISMDD symptom domains. Except for fatigue/low energy and insomnia, symptoms severity of other domains were reported as not extensively assessed or discussed by mental health professionals during care, even though they are considered important treatment targets in depression. This is paralleled by a clear picture in terms of multidomain detrimental impact of these symptom domains on quality of life. With the exception of increased weight/appetite, all symptom domains reached at least moderate consensus for being perceived as negatively impacting all four quality-of-life areas assessed (relationships, free time, work/education, autonomy), with a unanimous strong agreement (100 %) for a symptom domains such as anhedonia, loss of interest; fatigue/low energy and cognitive problems for specific dimensions related to relationships, free time and work education quality of life. The overall pattern is consistent with ISMDD extending beyond mood and encompassing broader functional and psychosocial impairment, suggesting that assessing ISMDD related symptomatology through a functional lens may be informative for capturing patient burden and monitoring clinical improvement. This is particularly relevant given that PWLE reached moderate consensus that most of these symptoms may constitute barriers to accessing mental health care resources and identified all of them as potential drivers of both self- and public stigma.

In general, we recommend that clinicians, researchers and regulators consider incorporating questionnaires that capture ISMDD symptom domains, such as the IDS or QIDS, when evaluating patients in whom an inflammatory contribution to depression is suspected or assessed, as well as in studies exploring the efficacy of treatments modulating directly or indirectly the immuno-inflammatory pathways. In this sense, these tools can support trial enrichment, clinical screening, and the selection of sensitive outcome measures by identifying profiles plausibly linked to immune-inflammatory mechanisms. However, future prospective studies in biomarker-enriched samples are needed to determine whether these scales and their individual items are associated with biological inflammatory dimensions, thereby supporting their formal recommendation as preferred outcome measures in immunopsychiatry trials. Their systematic use may help disentangle the heterogeneity observed in trials of anti-inflammatory treatments and enable more rigorous testing of whether immune-inflammatory processes define a vulnerable depressive subtype (Miller et al., 2025). From a broader clinical perspective, mental health professionals should thoroughly assess and discuss ISMDD related symptomatology with their patients, including its potential impact on quality-of-life domains.

These findings should be interpreted in light of several limitations. Although our expert consensus is supported by empirical evidence showing association between ISMDD symptom domains and increased inflammation in depressed individuals (Lamers et al., 2020), additional studies are needed to validate and refine our first insights, especially for domains where a weak consensus or no inter-consortium agreement was achieved (anhedonia/lack of pleasure, leaden paralysis, increased weight or appetite, loss of interest, insomnia and cognitive difficulties). Moreover, the relatively low participation rate across Delphi rounds (25–16/58 and 12/38 experts) may have also introduced selection bias, as respondents may not fully represent the broader psychiatric community, especially within the ASPIRE consortium, where we observed attrition in response rates across rounds. Results could also be affected by a confirmation bias considering prior interest of participants in immunopsychiatry or inflammation-related models of depression as expected in members in both ASPIRE and INPN-ECNP. In addition, the consensus panel comprised a heterogeneous group of contributors, including researchers and individuals with lived experience. Although

this diversity represents an important strength of the consensus approach, it may have influenced the relative weighting and interpretation of certain clinically nuanced presentations. Moreover, despite providing a clinical framework for ISMDD, our study did not focus on biomarker panels or algorithms to identify it at the individual level, underscoring the need for prospective validation (Miller et al., 2025). Future work should assess if distinct inflammatory subtypes (e.g., autoimmune, allergic/atopic) exhibit unique associations with specific clinical phenotypes. Concerning the perspective of PWLE on individual ISMDD symptom domains, the small sample size did not allow us to stratify responses according to direct experience of people of each symptom. Therefore, some ratings may partly reflect hypothetical judgments rather than direct lived experience for specific domains.

A further methodological consideration is that some single rating-scale items were identified as covering more than one symptom domain (e.g., anhedonia and loss of interest; fatigue/low energy and psychomotor retardation), which may have inflated the apparent coverage of ISMDD domains across instruments. In addition, the rating scales considered in this study were selected based on their use in anti-inflammatory intervention trials identified through our systematic review. Therefore, future studies should evaluate the suitability of other depression outcome measures, including those supported for new exploratory use from international guidelines (e.g. the Symptoms of Major Depressive Disorder Scale) (Bushnell et al., 2019; FDA 2018), for assessing ISMDD. Future research may also consider the development and validation of novel assessment strategies, including refined symptom-specific scales, behavioral tasks (e.g., effort-based decision-making paradigms) (Treadway et al., 2012), or digital and smart technologies, to more precisely capture the dynamic and context-dependent features of ISMDD-related symptomatology (Miller et al., 2025).

5. Conclusion

The identified ISMDD symptom domains provide a pragmatic framework to study links with inflammatory biomarkers, refine symptom measurement, and improve outcome assessment in trials targeting inflammatory pathways in depression. Enhancing the precision and validity of symptom assessment in immunopsychiatry is a critical step toward advancing personalized treatment strategies and better aligning interventions with patients' needs.

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Funding

This work was supported by the Wellcome Trust - Advanced Stratification of People with Depression based on Inflammation (ASPIRE) Study (30312/Z/23/Z).

Declaration of competing interest

Carmine M. Pariante reports financial support was provided by Wellcome Trust. Andrew H. Miller reports a relationship with Cerevel Therapeutics, Freedom Biosciences, Sirtsei Pharmaceuticals that includes: consulting or advisory and speaking and lecture fees. Bernhard T. Baune reports a relationship with AstraZeneca, Lundbeck, Pfizer, Takeda, Neurotorium, Servier, Bristol Myers Squibb, Otsuka, LivaNova, Biogen, Angelini, Medscape, Boehringer Ingelheim, Viatrix, Janssen-Cilag that includes: consulting or advisory and speaking and lecture fees. Brenda W.J.H. Penninx reports a relationship with Neurotorium, Boehringer Ingelheim that includes: consulting or advisory and speaking and lecture fees. Carmine M. Pariante reports a relationship with Värde Partners, Compass Pathways, UCB that includes: consulting or advisory. Christian Otte reports a relationship with Boehringer-Ingelheim, Eli Lilly, Janssen, Limes Klinikgruppe, Peak Profiling that includes: consulting or advisory and speaking and lecture fees. Dan Stein reports a relationship with Discovery Vitality, Johnson and Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda, Vistagen that includes: consulting or advisory and speaking and lecture fees. Femke Lamers reports a relationship with Noema Pharma, Novo Nordisk, Johnson & Johnson that includes: consulting or advisory and speaking and lecture fees. Igor Branchi reports a relationship with Angelini that includes: speaking and lecture fees. Janet L. Cunningham reports a relationship with Otsuka Pharma Scandinavia, Janssen-Cilag AB, Alfa-sigma Sweden AB, H. Lundbeck AB that includes: speaking and lecture fees. Jennifer C. Felger reports a relationship with Ventus Therapeutics that includes: consulting or advisory and speaking and lecture fees. Livia De Picker reports a relationship with Boehringer Ingelheim Belgium, Johnson and Johnson that includes: speaking and lecture fees. Michael Berk reports a relationship with Orygen that includes: speaking and lecture fees. Stefan M. Gold reports a relationship with Boehringer Ingelheim, Hexal, KISO Health, Tegus, Angelini, Streamed Up that includes: consulting or advisory and speaking and lecture fees. Thomas A. Pollak reports a relationship with Arialys Therapeutics that includes: consulting or advisory. C.M.P. is Editor-in-Chief of the journal. J.F.C., N. A.H., and V.M. are associate editors, and L.D.P. and F.L. are Editors of Special Issue. Given their role they had no involvement in the peer-

review of this article and had no access to information regarding its peer review. Full-responsibility for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The European College of Neuropsychopharmacology (ECNP) Immuno-NeuroPsychiatry Network has supported this paper, and its members contributed to the consensus development; AB, AC, AL, BCMH, BTB, BV, BWJHP, CO, CP, EFO, FB, FL, IB, JLC, JRC, LC, LDP, MB, ML, NES, PF, TAP VM are members of the Network. We also thank people with lived experience and their carers for their insights and contributions, which helped shape the perspectives and priorities reflected in this work.

During the course of this work, Professor Dan Stein sadly passed away. Professor Stein was a much-loved member of our ASPIRE team and is greatly missed. He was an inspiring psychiatrist and researcher and had a profound impact on advancements in the fields of mood disorders, public mental health, and medical ethics.

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The original draft of the manuscript was written by B.V., L.D.P. and T.C., and all authors contributed to reviewing and editing the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2026.106957>.

[org/10.1016/j.bbi.2026.106957](https://doi.org/10.1016/j.bbi.2026.106957).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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