# Psychopathological characteristics in patients with arginine vasopressin deficiency (central diabetes insipidus) and primary polydipsia compared to healthy controls

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## Abstract

**Objective:** Distinguishing arginine vasopressin deficiency (AVP-D; central diabetes insipidus) from primary polydipsia (PP), commonly referred to as psychogenic polydipsia, is challenging. Psychopathologic findings, commonly used for PP diagnosis in clinical practice, are rarely evaluated in AVP-D patients, and no comparative data between the two conditions currently exist.

**Design:** Data from two studies involving 82 participants [39 AVP-D, 28 PP, and 15 healthy controls (HC)].

**Methods:** Psychological evaluations were conducted using standardized questionnaires measuring anxiety [State-Trait Anxiety Inventory (STAI)], alexithymia [Toronto Alexithymia Scale (TAS-20)], depressive symptoms (Beck's Depression Inventory-II (BDI-II)), and overall mental health [Short Form-36 Health Survey (SF-36)]. Higher STAI, TAS-20, and BDI-II scores suggest elevated anxiety, alexithymia, and depression, while higher SF-36 scores signify better overall mental health.

**Results:** Compared to HC, patients with AVP-D and PP showed higher levels of anxiety (HC 28 points [24–31] vs AVP-D 36 points [31–45]; vs PP 38 points [33–46], $P < .01$), alexithymia (HC 30 points [29–37] vs AVP-D 43 points [35–54]; vs PP 46 points [37–55], $P < .01$), and depression (HC 1 point [0–2] vs AVP-D 7 points [4–14]; vs PP 7 points [3–13], $P < .01$). Levels of anxiety, alexithymia, and depression showed no difference between both patient groups ($P = .58$, $P = .90$, $P = .50$, respectively). Compared to HC, patients with AVP-D and PP reported similarly reduced self-reported overall mental health scores (HC 84 [68–88] vs AVP-D 60 [52–80], $P = .05$; vs PP 60 [47–74], $P < .01$).

**Conclusion:** This study reveals heightened anxiety, alexithymia, depression, and diminished overall mental health in patients with AVP-D and PP. The results emphasize the need for careful interpretation of psychopathological characteristics to differentiate between AVP-D and PP.

**Keywords:** habitual polydipsia, psychogenic polydipsia, psychopathology, mental health, anxiety, alexithymia, depression, hypopituitarism, posterior pituitary, quality of life

### Significance

Differential diagnosis between arginine vasopressin deficiency (AVP-D; central diabetes insipidus) and primary polydipsia (PP) is challenging. In clinical routine, psychopathologic findings are often used as a hallmark for diagnosing PP. Yet, psychopathologic characteristics are rarely assessed in patients with AVP-D and no data exist comparing psychopathological findings between these two conditions. This analysis aimed to compare psychopathological characteristics in patients with AVP-D and PP using standardized questionnaires. The results demonstrate comparable increases in anxiety, alexithymia, depression, and reduced overall mental health in both groups. Based on these data, psychopathological characteristics should be used cautiously when differentiating AVP-D and PP. In addition, attention should be drawn to the high levels of undiagnosed and untreated psychological problems in patients with AVP-D.

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# Background

The correct discrimination between arginine vasopressin deficiency (AVP-D, formerly known as central diabetes insipidus) and primary polydipsia (PP) is crucial because treatment strategies differ, and incorrect treatment may lead to serious complications.[1-3]

Primary polydipsia is characterized by excessive osmolality-independent fluid intake with physiologically suppressed arginine vasopressin (AVP) levels.[3,4] Although the exact pathogenesis is obscure, psychological comorbidities are often used as a hallmark pointing toward PP in routine clinical practice. For this reason, PP is also commonly referred to as psychogenic polydipsia.[1,5] Accordingly, in previous diagnostic algorithms, a history of psychiatric disease in the evaluation of polyuria–polydipsia was recommended as suggestive for PP.[5] Besides a presumed psychogenic etiology, a high prevalence of health-conscious individuals tend to become habituated to drinking and develop polydipsia owing to the belief that water improves health, referred to as habitual polydipsia.[4]

Arginine vasopressin deficiency is caused by disruptions of the hypothalamic–pituitary axis, leading to uncontrolled diuresis and polyuria.[3] In contrast to PP, physicians do not typically associate AVP-D with psychological issues. Treatment primarily focuses on managing polyuria using desmopressin (AVP V2 receptor analog).[6] However, recent evidence suggests that psychological issues are present in these patients despite successful treatment and control of polyuria.[7-12] More precisely, available limited data indicate heightened anxiety levels and depressed mood, difficulties in emotion recognition, and lower empathy levels, leading to an overall lower quality of life.[7-12]

To date, no data exist comparing patients with AVP-D and PP regarding their psychopathological characteristics. Therefore, in this study, we aimed to investigate anxiety, alexithymia, depression, and mental health in patients with AVP-D and PP compared to healthy controls (HC). We hypothesized that patients with AVP-D would demonstrate similarly increased levels of anxiety, alexithymia, depression, and reduced overall mental health, compared to patients with PP.

# Methods

## Study design

This study combined data from two prospective diagnostic studies conducted at the University Hospitals of Basel and Zürich, Switzerland, and the Hospital of Clinics of the Federal University of Minas Gerais, Brazil. In total, 39 patients with AVP-D, 28 patients with PP, and 15 HC underwent a psychological evaluation at study inclusion. The studies conformed to the Declaration of Helsinki and were approved by the local ethics committee (Ethics Committee Northwest Switzerland). Written informed consent was obtained from all study participants. The studies were registered on ClinicalTrials.gov, identifiers NCT04648137 and NCT03572166.

## Participants

The studies' rationale, design, procedures, and statistical analyses have been published elsewhere.[12,13] In brief, 24 patients with AVP-D and 28 patients with PP underwent diagnostic evaluation of polyuria–polydipsia syndrome (a subset of the original study), and 15 patients with AVP-D and 15 HC, matched by body mass index (BMI), sex, and age, underwent

diagnostic evaluation for oxytocin (OXT) deficiency, respectively.[12,13] Healthy controls were examined for somatic and psychological comorbidities and only included if no somatic and no psychological disorder were present. The main exclusion criteria in HC were regular consumption of alcoholic beverages, tobacco smoking, documented cardiovascular disease or uncontrolled arterial hypertension, current or previous major psychiatric disorder or psychotic disorder in first-degree relatives (assessed by the Semi-structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Axis I disorders), lifetime prevalence of illicit substance use >10 times (except for tetrahydrocannabinol) or any time within the previous 2 months and during the study period, and the use of medications that may interfere with the study medications (eg, any psychiatric medication).

## Study procedure

All participants underwent a detailed psychological baseline evaluation at study inclusion consisting of a physician interview and four self-reported questionnaires. The physician interview included an inquiry about predefined physical and psychological disorders—with previous and current duration and type of psychological treatment. The self-reported questionnaires included the assessment of anxiety using Spielberger's State-Trait Anxiety Inventory (STAI—Trait subscale),[14] alexithymia (ie, describing own and others emotions) using the Toronto Alexithymia Scale (TAS-20),[15] depression using Beck's Depression Inventory-II (BDI-II),[16] and overall mental health using the Short Form 36 Health Survey (SF-36).[17]

## Psychopathological assessment

The STAI is a validated and reliable instrument for assessing state and trait anxiety. Based on the responses to 40 items, with scores ranging from 1 ("almost never") to 4 ("almost always"), a total score is calculated. The STAI has two sub-scales, the State-Anxiety Scale (20 items) and the Trait-Anxiety Scale (20 items). The State-Anxiety Scale evaluates the current state of anxiety, asking how respondents feel "right now," using items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. The Trait-Anxiety Scale evaluates relatively stable aspects of "anxiety proneness," including general states of calmness, confidence, and security. We used the Trait-Scale to determine the general anxiety levels for this analysis. The total scores range from 20 to 80, with higher scores indicating more pronounced anxiety. A score above >39/80 indicates clinically significant anxiety symptoms.

The TAS-20 questionnaire evaluates the ability to express and identify one's emotions. Alexithymia is the difficulty of identifying and describing emotions experienced by oneself or others characterized by difficulty in consciously experiencing, identifying, and describing emotions and reduced introspection. Based on responses to 20 items ranging from 1 ("strongly disagree") to 5 ("strongly agree"), a global score is calculated. A score of ≥61 indicates alexithymia (difficulty understanding one's emotions), a score of 52–60 is possible alexithymia and a score of ≤51 nonalexithymia. Further, the TAS 20 has three sub-scales: difficulty identifying and describing feelings and externally oriented thinking.

The BDI-II is a validated and reliable self-reported questionnaire to assess the severity of depressive symptoms. The BDI-II

uses 21 items ranked from 0 ("symptom absent") to 3 ("severe symptoms") to measure the severity of depression. The total scores range from 0 to 63, with higher scores indicating greater severity of depressive symptoms (score ≤16, mild mood disturbance; 17–20, borderline clinical depression, 21–30, moderate depression, and score ≥31, severe depression). Further, the BDI-II has four sub-scales: cognitive-affective, somatic, cognitive, and somatic-affective.

The SF-36 is a self-reported measure of general health status with 36 items which assesses eight multi-item variables: physical functioning (10 items), social functioning (2 items), role limitations due to emotional issues (3 items), overall mental health (5 items) energy and vitality (4 items), pain (2 items), and general perception of health (5 items). The overall physical health dimension is calculated using the scores obtained from physical functioning, bodily pain, role limitations due to physical health issues, and general health perception scales. The overall mental health dimension is calculated using the scores obtained from role limitations due to personal or emotional issues, general mental health, social functioning, and energy/fatigue scales. For each overall dimension, the scores range from 0 to 100, with higher scores indicating a more favorable health state and less disability.

## Objectives, outcomes, and statistical analysis

The main objectives were to determine the differences in the total scores of STAI, TAS-20, BDI-II, and the SF-36 overall mental health subscale between patients with AVP-D and PP and to investigate differences between both patient groups and HC. Secondary objectives were the assessment of differences in sub-scores of the TAS-20 (ie, "Difficulty Describing Feelings subscale," "Difficulty Identifying Feeling," "Externally Oriented Thinking"), BDI-II (ie, "Cognitive-Affective," "Somatic," "Cognitive," "Somatic-Affective"), and SF-36 (ie, "Physical functioning," "Role limitations due to physical health," "Role limitations due to emotional problems," "Energy/fatigue," "Mental Health," "Social functioning," "Pain," "General health"), and the differences in pre-existing psychological comorbidities among the groups.

Furthermore, we performed sub-group analyses in the following groups: In patients with AVP-D, those with isolated posterior pituitary dysfunction vs combined anterior and posterior pituitary dysfunction. In patients with PP, those with a known psychological diagnosis (referred to as "psychogenic polydipsia") vs those without present or history of psychological diagnosis (referred to as "habitual polydipsia"). Analyses of these sub-scales and sub-groups were performed only descriptively.

Baseline characteristics are summarized using descriptive statistics. Discrete variables are expressed as frequencies (percentage [%] and number of patients [n]). Continuous variables are presented as median and interquartile range (IQR, 25th to 75th percentiles). Differences between the total scores were assessed using the Kruskal–Wallis test with a *post hoc* pairwise comparison using the Wilcoxon rank-sum test. All data were presented visually by boxplots. Hypothesis testing was two-sided, and *P*-values <0.05 were considered statistically significant. We adjusted the *P*-values for multiple testing using the conservative Bonferroni correction. All analyses were performed in R version 4.2.2 (2022-10-31). R Core Team, 2022. R: a language and environment for statistical computing. http://www.r-project.org/index.html.

## Results

### Baseline characteristics

The median age in HC was 35 years ([IQR 26–48], 53% ($n = 8$) females), in AVP-D 41 years ([28–50], 59% ($n = 23$) females), and in PP 34 years ([25–42], 68% ($n = 19$) females), respectively.

Sixty-four percent ($n = 25$) of patients with AVP-D, and 4% ($n = 1$) of patients with PP, had an additional anterior pituitary dysfunction. A diagnosed psychological condition was present at study inclusion in 13% ($n = 5$) of patients with AVP-D and 39% ($n = 11$) of patients with PP. Four percent ($n = 5$) of patients with AVP-D and 32% ($n = 9$) of patients with PP were treated with antidepressants. Baseline characteristics are summarized in Table 1.

### Psychopathological assessment

The total scores and sub-scales of the questionnaires for each group are visualized and demonstrated in Figure 1, Table 2. Between patients with AVP-D and PP, no differences were observed in terms of anxiety ($P = .58$), alexithymia ($P = .50$), depression ($P = .90$), and overall mental health scores ($P = .50$).

Compared to HC, patients with AVP-D and PP showed increased levels of anxiety (HC: 28 points [24–31] vs AVP-D: 36 points [31–45], $P < .01$; vs PP: 38 points [33–46], $P < .01$), increased levels of alexithymia (HC: 30 points [29–37] vs AVP-D: 43 points [35–54], $P < .01$; vs PP: 46 points [37–55], $P < .01$), and increased levels of depression symptoms (HC: one point [0–2] vs AVP-D: 7 points [4–14], $P < .01$; vs PP: 7 points [3–13], $P < .01$). Compared to HC, patients with AVP-D and PP reported comparable reduced self-reported overall mental health scores in the SF-36 (HC: 84 [68–88] vs AVP-D: 60 [52–80], $P = .05$; vs PP: 60 [47–74], $P < .01$).

The total scores and sub-scales of the questionnaires for each sub-group are visualized and demonstrated in Figure 2, Table 3. Regarding anxiety, alexithymia, and depression levels, no major differences were observed between patients with isolated AVP-D and those with combined anterior and posterior pituitary dysfunction. Similarly, regarding anxiety, alexithymia, and depression levels, no major differences were observed in patients with habitual PP and those with psychogenic PP. Comparable reduced overall mental health scores were observed in patients with isolated AVP-D, patients with habitual PP, and those with psychogenic PP, while patients with combined pituitary dysfunction seemed to have slightly better scores but were still lower than HC.

The total scores in anxiety, alexithymia, depression, and overall mental health in those with partial vs complete AVP-D; in those with or without desmopressin treatment; and in those with or without antidepressant treatment are visualized and demonstrated in Figures S1–S3 (Supplementary). Regarding anxiety, alexithymia, and depression levels, no major differences were observed between these sub-groups.

## Discussion

This analysis has the following main finding: levels of anxiety, alexithymia, and depression were comparably increased between patients with AVP-D and patients with PP but significantly higher than in HC. Based on these data, psychopathological findings should be used cautiously when differentiating AVP-D and PP.

In line with available data from patients with PP indicating a high prevalence of psychological comorbidities (41%), our

**Table 1.** Baseline characteristics.

| | Healthy controls | AVP deficiency (central diabetes insipidus) | Primary polydipsia |
|---|---|---|---|
| Number, *n* | 15 | 39 | 28 |
| Age | 35 [26–48] | 41 [28–50] | 34 [25–42] |
| Sex, female | 8 (53) | 23 (59) | 19 (68) |
| Weight (cm) | 68 [61–76] | 77 [65–88] | 72 [62–77] |
| Height (kg) | 173 [167–180] | 170 [165–176] | 170 [163–178] |
| BMI (kg/m$^2$) | 22 [23–25] | 26 [23–28] | 23 [21–27] |
| **Comorbidities** | | | |
| Chronic kidney disease | 0 (0) | 0 (0) | 1 (4) |
| Cerebrovascular disorder | 0 (0) | 3 (8) | 1 (4) |
| Cardiovascular disorder | 0 (0) | 4 (10) | 1 (4) |
| Metabolic and gastrointestinal disorder | 0 (0) | 7 (18) | 7 (25) |
| Pulmonal disorder | 0 (0) | 1 (3) | 1 (4) |
| **Psychological disorder** | 0 (0) | 5 (13) | 11 (39) |
| Depression | 0 (0) | 5 (13) | 4 (14) |
| Attention deficit hyperactivity disorder | 0 (0) | 0 (0) | 4 (14) |
| Anxiety disorder | 0 (0) | 2 (5) | 4 (14) |
| Other (autism spectrum disorder, personality disorder, obsessive-compulsive disorder) | 0 (0) | 0 (0) | 3 (11) |
| History of psychological disorder | 0 (0) | 10 (26) | 12 (43) |
| Treatment with antidepressants | 0 (0) | 4 (10) | 9 (32) |
| **Endocrine characteristics** | | | |
| Desmopressin treatment | 0 (0) | 30 (80) | 1 (4) |
| Anterior pituitary deficiency | 0 (0) | 25 (64) | 1 (4) |
| Adrenocorticotropin (ACTH) | 0 (0) | 20 (51) | 1 (4) |
| Thyrotropin (TSH) | 0 (0) | 22 (56) | 1 (4) |
| Growth hormone | 0 (0) | 6 (17) | 1 (4) |
| Gonadotropins | 0 (0) | 17 (44) | 1 (4) |

Data presented as median (interquartile range [IQR]) or frequency (%).
Abbreviations: AVP, arginine vasopressin; BMI, body mass index; BP, blood pressure; HR, heart rate.

results confirm these numbers, showing a prevalence of 39%.[4,18] The evaluation particularly demonstrates high levels of anxiety, alexithymia, and depression, as well as reduced overall mental health scores in patients with PP. Interestingly, sub-group analyses revealed elevated psychopathologic characteristics not only in those with psychogenic but also in patients with habitual polydipsia, although in a milder form. However, this finding also points out that there are currently no clear diagnostic criteria to distinguish between these two forms of PP.[1,19] Generally, little research has been devoted to the pathophysiological mechanisms of increased fluid intake, and the cause of the insatiable thirst in PP remains uncertain. Several assumptions have been provided in the literature:[1,20,21] Apart from PP most likely being multifactorial, theories involve dysregulation of the hippocampal region and hypothalamic thirst center, leading to increased sensation of thirst.[4] A second explanation could be that drinking water serves as a coping strategy to relieve psychological stress.[22] Thirdly, compulsive water drinking in PP shares features with addictive behavior that may be associated with other psychiatric disorders such as depression, anxiety, or alcoholism.[23-25] Regarding alexithymia, while there is no consensus on its classification as a personality trait, symptom, or psychological condition, alexithymia frequently co-occurs with other disorders such as autism, depression, and anxiety, but also compulsive behaviors.[26-29] However, the exact pathophysiological mechanisms are still elusive and further studies are needed.

In contrast, over the years, only a few studies investigated psychological comorbidities in patients with AVP-D. The limited data from these studies, eg, in patients with craniopharyngioma, a condition carrying a high risk of AVP-D, revealed personality changes (31%) and increased psycho-social comorbidities (47%), including anxiety, depression, and social withdrawal.[8-10,30,31] Furthermore, patients with AVP-D were shown to exert heightened anxiety and alexithymia levels, reduced empathic abilities, higher levels of self-reported autistic traits, lower levels of joy when socializing, and lower scores in an emotion recognition task.[8-12] Consistent with these results from small studies, our previous data from the largest survey conducted in patients with AVP-D confirmed the high prevalence of self-reported psychological problems and changes (36%) and an overall reduced quality of life (64%).[7] The cause for these impairments may be multifactorial, and several causes can be speculated. Firstly, psychological comorbidities in patients with anterior pituitary dysfunctions are prevalent and, despite hormone replacement therapy, often persist. Therefore, the observed psychopathological findings might be explained by additional anterior pituitary dysfunctions. Interestingly, our previous data and the findings from this analysis show that the assessed psychological characteristics and the reduction in mental health are equally prevalent in isolated AVP-D and combined anterior/posterior pituitary dysfunction, challenging this assumption.[7] Secondly, in patients with AVP-D, polyuria and polydipsia itself might contribute to the lower quality of life and might impair several domains of mental health. However, 80% of the patients with AVP-D were already treated and well-controlled with desmopressin, and no major differences were observed between those treated with or not treated with desmopressin, again challenging this hypothesis. Third, due to the close anatomic proximity to the oxytocinergic system, disruptions leading to AVP-D could also disturb OXT pathways and lead to additional OXT deficiency. The central oxytocinergic system and related limbic networks affect complex neural circuits of socio-emotional behavior and promote pro-social effects.[32] In line with this, OXT acts as a stress-buffering hormone and
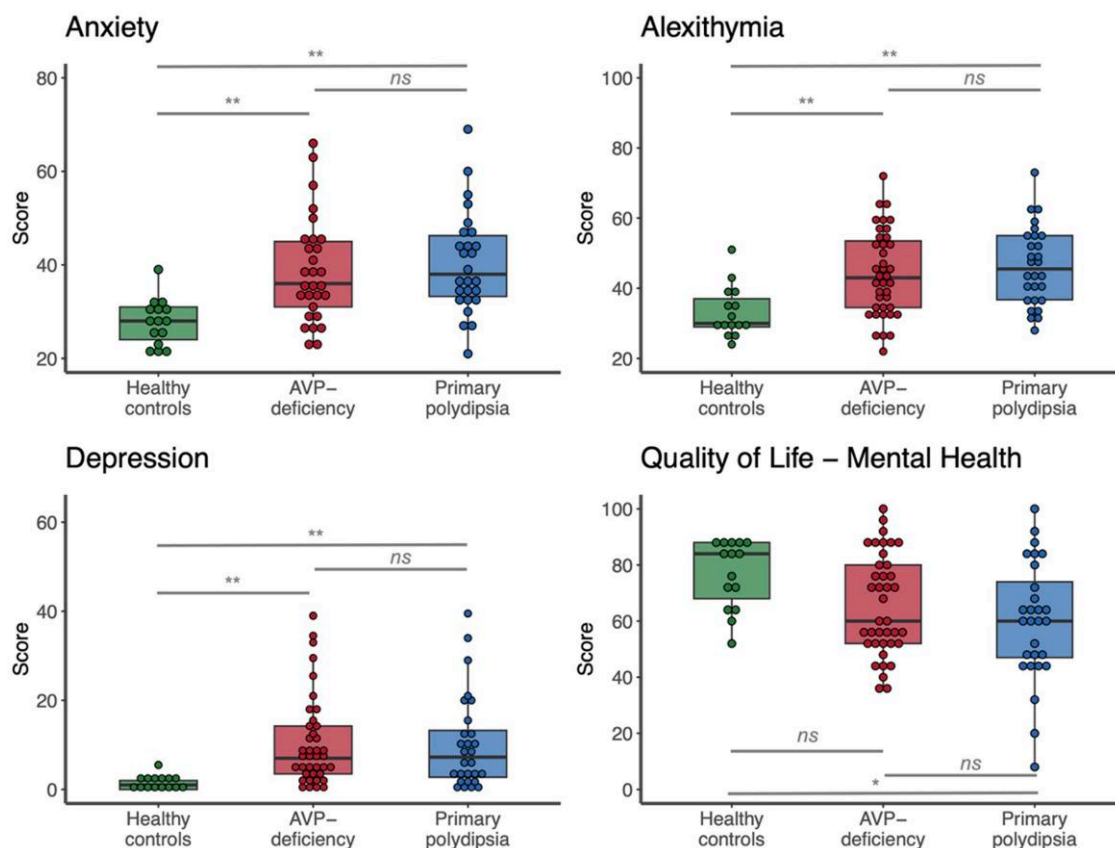
**Figure 1.** Psychological assessment. Symptoms of anxiety, alexithymia, and depression were greater in patients with arginine vasopressin deficiency (AVP-D, central diabetes insipidus) and primary polydipsia (PP) than in healthy controls (HC). Patients with AVP-D and PP reported comparable reduced self-reported overall mental health scores, compared to HC. Boxes span the interquartile range (IQR); the thick horizontal line is the median. Whiskers are the most extreme values lying within the box edge and 1.5 times the IQR. $*P < .05$; $**P < .01$; ns, not significant.

**Table 2.** Psychological and quality of life questionnaires.

| | Healthy controls | AVP deficiency (central diabetes insipidus) | Primary polydipsia |
|---|---|---|---|
| Number, $n$ | 15 | 39 | 28 |
| **STAI Trait, total score** | 28 [24–31] | 36 [31–45] | 38 [33–46] |
| **TAS-20, total score** | 30 [29–37] | 43 [35–54] | 46 [37–55] |
| Difficulty describing feelings | 8 [7–9] | 12 [9–15] | 12 [10–15] |
| Difficulty identifying feelings | 9 [7–11] | 13 [9–19] | 14 [12–19] |
| Eexternally oriented thinking | 15 [13–18] | 17 [15–21] | 18 [13–22] |
| **BDI-II, total score** | 1 [0–2] | 7 [4–14] | 7 [3–13] |
| Cognitive-affective | 0 [0–1] | 4 [2–11] | 3 [1–8] |
| Somatic | 0 [0–2] | 4 [2–6] | 4 [1–6] |
| Cognitive | 0 [0–1] | 1 [0–5] | 1 [0–3] |
| Somatic-affective | 1 [0–2] | 6 [3–9] | 7 [2–10] |
| **SF-36** | | | |
| Physical health | 100 [100–100] | 95 [83–100] | 95 [75–100] |
| Role physical | 100 [100–100] | 100 [50–100] | 88 [44–100] |
| Role emotional | 100 [100–100] | 100 [33–100] | 100 [67–100] |
| Energy/fatigue | 65 [45–75] | 40 [28–55] | 30 [25–50] |
| Mental health | 84 [68–88] | 60 [52–80] | 60 [47–74] |
| Social functioning | 100 [100–100] | 85 [73–100] | 75 [44–100] |
| Pain | 100 [100–100] | 100 [53–100] | 65 [20–100] |
| General health | 90 [77–94] | 57 [36–82] | 53 [29–68] |

Data presented as median (interquartile range [IQR]).
Abbreviations: AVP, arginine vasopressin; BDI-II, Beck's depression inventory-II; SF-36, Short Form 36 Health Survey; STAI, State-Trait Anxiety Inventory; TAS-20, Toronto Alexithymia Scale.

influences the hypothalamic–pituitary–adrenal axis by reducing cortisol levels in response to psychological stress.[19] Using 3,4-methylenedioxymethamphetamine, which strongly activates the central oxytocinergic system, as a provocation test, we recently provided evidence for an additional OXT deficiency in patients with AVP-D.[12,33,34] Therefore, it is tempting to assume that some of these difficulties are attributable to undiagnosed and, thus, untreated OXT deficiencies.
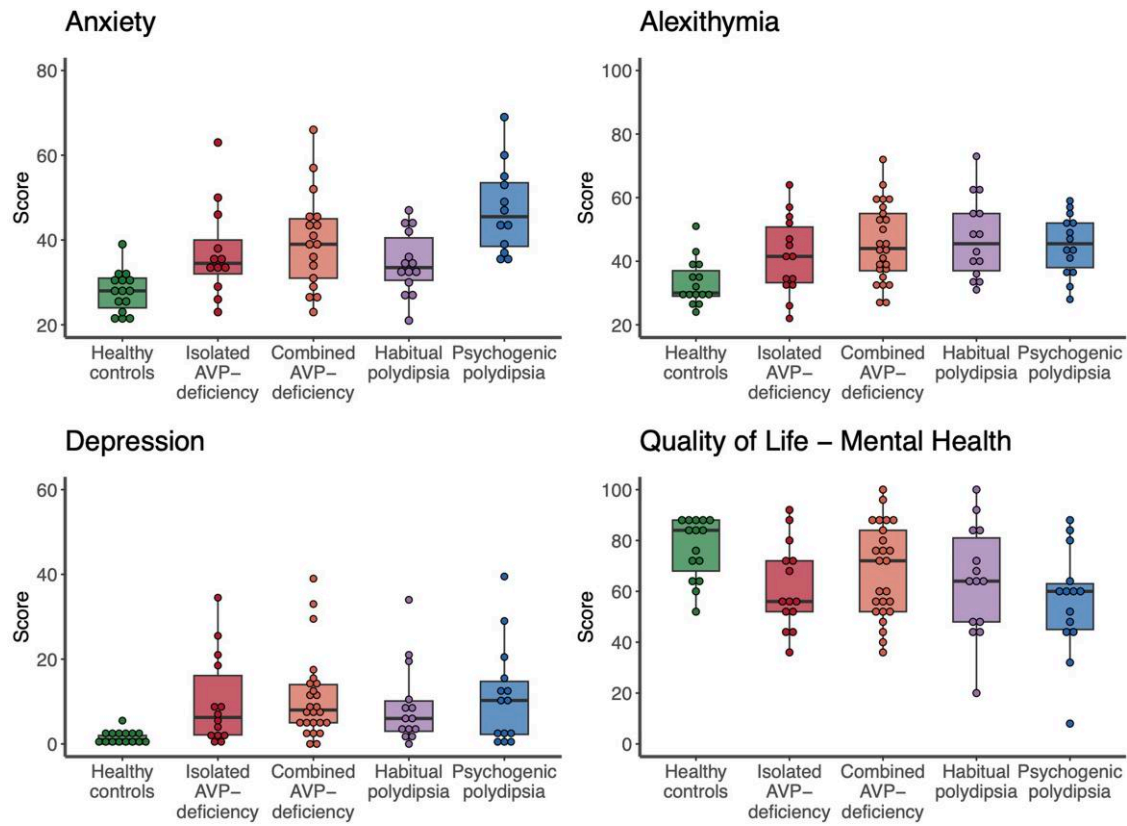
**Figure 2.** Psychological assessment in the sub-groups. Symptoms of anxiety, alexithymia, and depression were greater in patients with arginine vasopressin deficiency (AVP-D, central diabetes insipidus) (isolated posterior pituitary dysfunction and combined anterior/posterior pituitary dysfunction) and PP (habitual and psychogenic) than in HC. Comparable reduced overall mental health scores were observed in patients with isolated AVP-D, patients with habitual PP, and those with psychogenic PP, while patients with combined pituitary dysfunction showed slightly better scores but still lower than HC. Boxes span the IQR; the thick horizontal line is the median. Whiskers are the most extreme values lying within the box edge and 1.5 times the IQR. Analyses of these sub-scales were performed only descriptively.

**Table 3.** Psychological and quality of life questionnaires—sub-groups.

| | Healthy controls | Isolated AVP deficiency (central diabetes insipidus) | Combined pituitary deficiency | Habitual polydipsia | Psychogenic polydipsia |
|---|---|---|---|---|---|
| Number, *n* | 15 | 14 | 25 | 14 | 14 |
| **STAI Trait, total score** | 28 [24–31] | 35 [32–40] | 39 [31–45] | 34 [31–41] | 46 [39–54] |
| **TAS-20, total score** | 30 [29–37] | 42 [33–51] | 44 [37–55] | 46 [37–55] | 46 [38–52] |
|     Difficulty describing feelings | 8 [7–9] | 12 [7–14] | 12 [11–16] | 13 [10–15] | 12 [10–15] |
|     Difficulty identifying feelings | 9 [7–11] | 15 [8–19] | 11 [9–18] | 14 [12–17] | 15 [12–19] |
|     Externally oriented thinking | 15 [13–18] | 17 [15–18] | 19 [15–22] | 20 [16–25] | 16 [13–21] |
| **BDI-II, total score** | 1 [0–2] | 6 [2–16] | 8 [5–14] | 6 [3–10] | 10 [2–15] |
|     Cognitive-affective | 0 [0–1] | 2 [1–10] | 5 [2–11] | 3 [1–6] | 5 [0–8] |
|     Somatic | 0 [0–2] | 4 [1–6] | 4 [2–6] | 3 [2–4] | 5 [1.0–7] |
|     Cognitive | 0 [0–1] | 1 [0–3] | 2 [0–5] | 1 [0–3] | 1 [0–3] |
|     Somatic-affective | 1 [0–2] | 6 [2–11] | 7 [3–9] | 6 [2–8] | 8 [1–11] |
| **SF-36** | | | | | |
|     Physical health | 100 [100–100] | 95 [95–100] | 95 [70–100] | 98 [78–100] | 93 [76–100] |
|     Role physical | 100 [100–100] | 100 [100–100] | 75 [25–100] | 100 [50–100] | 75 [31–100] |
|     Role emotional | 100 [100–100] | 100 [75–100] | 67 [33–100] | 100 [100–100] | 83 [33–100] |
|     Energy/fatigue | 65 [45–75] | 40 [30–51] | 40 [25–55] | 35 [26–50] | 30 [21–49] |
|     Mental health | 84 [68–88] | 56 [52–72] | 72 [52–84] | 64 [48–81] | 60 [45–63] |
|     Social functioning | 100 [100–100] | 100 [85–100] | 75 [73–100] | 81 [64–100] | 74 [31–100] |
|     Pain | 100 [100–100] | 100 [90–100] | 90 [50–100] | 83 [23–100] | 53 [26–100] |
|     General health | 90 [78–94] | 81 [49–84] | 53 [34–67] | 54 [33–76] | 46 [28–66] |

Data presented as median (interquartile range [IQR]).
Abbreviations: AVP, arginine vasopressin; BDI-II, Beck's depression inventory-II; SF-36, Short Form 36 Health Survey; STAI, State-Trait Anxiety Inventory; TAS-20, Toronto Alexithymia Scale.

Both patient groups exhibit a relevant proportion of clinical anxiety and depression compared to HC. Although the healthy cohort is limited in size, we can draw parallels with data from larger population studies, like the *Leiden Routine Outcome Monitoring study*[35] of 1300 participants, showing comparable results for BDI-II scores in HC. Moreover, according to the 2022 *Swiss Mental Health* survey,[36] which assessed 5502 individuals, 12% reported moderate-to-severe depression symptoms, a figure notably surpassed by our analysis, with AVP-D patients reporting depressive symptoms of 20% and PP of 25% according to the BDI-II. In agreement with our data, data from the *Swiss Mental Health* survey report only a subset of 6% out of 11% exhibiting depressive symptoms received a formal diagnosis. For anxiety, 6% and 3% of Swiss participants reported moderate and severe symptoms, respectively. In contrast, according to the STAI-T in our study, about 36% of patients with AVP-D and 46% of those with PP met the diagnostic criteria for anxiety disorder. On a mental well-being scale ranging from 7 to 35, the Swiss population averaged 26 points, representing about 70% of the total score. Conversely, our data indicate a lower score, averaging 60% of the total possible score in both groups.

The growing evidence pointing to a high prevalence of psychological comorbidities in patients with AVP-D, also supported by our results, raises two main concerns: First, these findings are important to increase awareness for physicians to not prematurely diagnose PP in patients with polyuria–polydipsia with concomitant psychological symptoms contrary to the recommendation of previous diagnostic algorithms.[5] Second, our data highlight the discrepancies between diagnosed and treated psychological comorbidities and the observed high levels of psychological symptoms in patients with AVP-D. Treating physicians should also be sensitized to inquire about psychological disorders and, if necessary, refer patients for further diagnostic and therapeutic assessment.

Some limitations should be considered: First, although all questionnaires used for this study have been validated and used for clinical and research purposes over the past decades, the low specificity for the domain the questionnaires assess should be mentioned. Our results cannot answer whether these findings differentiate patients with a chronic condition from HC in general or whether these findings are directly attributed to the underlying disorder itself. Moreover, neither study was primarily designed to assess psychological endpoints. This emphasizes the importance of developing disease-specific questionnaires for patients with AVP-D in the future. Second, as a larger proportion of patients with PP were diagnosed and thus treated with antidepressants, it is likely that the assessed psychopathological deficits may have been worse without treatment; however, this fact also demonstrates the large population of untreated AVP-D patients in terms of psychological comorbidities. Third, the retrospective design and limited sample size did not allow for further detailed sub-group analysis and moreover lack of data on socioeconomic factors limited us for further correction on confounding factors.

To summarize, patients with AVP-D and PP both demonstrate comparable increased levels of anxiety, alexithymia, depression, and overall reduced overall mental health levels. These symptoms should, therefore, be used cautiously when differentiating AVP-D from PP. In addition, attention should be drawn to the high levels of untreated psychological issues in patients with AVP-D.

## Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

## Authors' contributions

Cihan Atila (Conceptualization [lead], Data curation [lead], Formal analysis [lead], Investigation [lead], Methodology [lead], Project administration [lead], Visualization [lead], Writing—original draft [lead]), Julia Beck (Formal analysis [lead], Investigation [lead], Visualization [lead], Writing—original draft [lead]), Julie Refardt (Conceptualization [equal], Funding acquisition [equal], Methodology [equal], Project administration [equal], Writing—review & editing [equal]), Zoran Erlic (Data curation [equal], Writing—review & editing [equal]), Juliana Drummond (Data curation [equal], Investigation [equal], Project administration [equal], Writing—review & editing [equal]), Clara Odilia Sailer (Conceptualization [equal], Data curation [equal], Investigation [equal], Writing—review & editing [equal]), Matthias E. Liechti (Conceptualization [equal], Methodology [equal], Project administration [equal], Writing—review & editing [equal]), Beatriz Rocha (Investigation [equal], Project administration [equal], Writing—review & editing [equal]), Felix Beuschlein (Investigation [equal], Project administration [equal], Writing—review & editing [equal]), Bettina Winzeler (Conceptualization [equal], Investigation [equal], Project administration [equal], Writing—review & editing [equal]), and Mirjam Christ-Crain (Conceptualization [lead], Funding acquisition [lead], Investigation [equal], Methodology [lead], Project administration [lead], Resources [lead], Supervision [lead], Writing—review & editing [lead])

## Data availability

We may share de-identified, individual participant-level data that underlie the results reported in this article and related documents, including the study protocol and the statistical analysis plan. Data will be available with the publication of

our main manuscript on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding author. The steering committee of this study will discuss all requests and decide, based on the scientific rigor of the proposal, whether data sharing is appropriate. All applicants are asked to sign a data access agreement.

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