The negative impact of vitamin D on antipsychotic drug exposure may counteract its potential benefits in schizophrenia

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Aims: Patients with schizophrenia frequently show insufficient vitamin D levels, which are associated with somatic comorbidity and may contribute to psychopathology. For many reasons, vitamin D supplementation may be indicated for this patient cohort. However, there is growing evidence for a vitamin D-mediated increase of drug metabolism by induction of cytochrome P450 (CYP) 3A4. Hence, this study aimed to assess vitamin D’s impact on both antipsychotic drug concentrations and psychopathology in a non-interventional manner.

Methods: Totals of 107 serum concentrations of different antipsychotic drugs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine and risperidone), 80 serum concentrations of vitamin D and psychopathological assessments were obtained from 80 patients with schizophrenia. The impact of Vitamin D on antipsychotic drug concentrations and symptomatology was assessed using a generalized linear model, path and correlation analyses.

Results: We observed a negative relationship between vitamin D and dose-adjusted antipsychotic drug concentrations, which was particularly pronounced for drugs which are predominantly metabolized via CYP3A4 (i.e., aripiprazole and quetiapine). A path analysis suggested a relieving effect of vitamin D on symptomatology which, however, counteracted by its negative impact on antipsychotic drug levels. Finally, patients with vitamin D levels above the median exhibited a significantly higher proportion of therapeutically insufficient dose-normalized drug concentrations of aripiprazole and quetiapine.
Conclusion: Despite vitamin D’s potential benefits on physical and mental health, clinicians should be aware of its negative impact on blood concentrations of antipsychotics metabolized by CYP3A4 in patients with schizophrenia. Therefore, when considering its supplementation, therapeutic drug monitoring should be applied to guide dose adjustment.

1 | INTRODUCTION

Vitamin D deficiency is a frequent finding in patients suffering from severe mental illnesses such as schizophrenia. Beside its well-established role in bone metabolism and calcium homeostasis, growing evidence suggests that vitamin D is also an important factor in cardiovascular health. Indeed, vitamin D deficiency is associated with increased cardiovascular, cancer and all-cause mortality. Hence, it might be one of the factors contributing to reduced life expectancy in patients suffering from schizophrenia. Outside the purely somatic domain, vitamin D deficiency is also associated with increased burden of psychopathology, particularly negative and depressive symptomatology. Nevertheless, it remains unclear whether vitamin D deficiency is a consequence of (e.g., through reduced sunlight exposure due to negative symptomatology) or a driving factor for schizophrenia. Evidence supporting the latter comes from studies suggesting that vitamin D deprivation in prenatal or early life elevates the risk of later developing schizophrenia, which might be explained by vitamin D’s effects on brain development and dopaminergic neurotransmission. Facing these different sources of evidence, screening for vitamin D deficiency with subsequent treatment regimens appears to be a reasonable strategy for clinicians treating this vulnerable patient cohort. However, there is a growing body of evidence that vitamin D increases drug metabolism by induction of cytochrome P450 (CYP) 3A4. Since several antipsychotic drugs are at least partially metabolized via CYP3A4, vitamin D supplementation might lead to reduced antipsychotic drug concentrations in blood, thereby counteracting its potential beneficial effects on psychopathology.

The aim of this study was to assess the impact of vitamin D on antipsychotic drug concentrations and psychopathology in patients with schizophrenia using vitamin D serum levels, therapeutic drug monitoring and clinical data addressing psychopathology obtained from a large brain imaging study. We hypothesized a negative correlation between vitamin D levels and serum concentrations of antipsychotics depending on the involvement of CYP3A4 in their metabolism. The highest impact of vitamin D on antipsychotic drug concentrations was expected for drugs that are mainly metabolized via CYP3A4. Moreover, we assumed that this effect would counteract vitamin D’s relieving properties on general psychopathology that was addressed by a path analysis. Finally, we hypothesized that, when considering antipsychotics with a high involvement of CYP3A4 in drug metabolism, patients with above median vitamin D levels should more frequently exhibit therapeutically insufficient drug levels as compared to patients with lower vitamin D levels.

What is already known about this subject

- Patients with schizophrenia frequently exhibit insufficient vitamin D levels, which are associated with somatic comorbidity and may contribute to psychopathology.
- Vitamin D increases drug metabolism by inducing cytochrome P450 (CYP) 3A4.
- There has been no study comprehensively assessing the complex interplay between vitamin D, antipsychotic drug levels and psychopathology.

What this study adds

- There is a negative association between blood concentrations of vitamin D and antipsychotics predominantly metabolized by CYP3A4.
- Concentrations of these drugs tend to be therapeutically insufficient for higher vitamin D levels.
- Vitamin D’s negative impact on antipsychotic drug exposure seems to counteract its beneficial effects on psychopathology.

2 | METHODS

2.1 | Participants

Laboratory and clinical data were obtained from 121 in- and outpatients suffering from schizophrenia. Patients were recruited within the framework of a larger consortium of brain imaging trials conducted at the Department of Psychiatry, Psychotherapy and Psychosomatics of RWTH Aachen University Hospital and four academically associated regional psychiatric hospitals (Alexianer Krankenhaus, Aachen; ViaNobis Gangelt; LVR Klinik Langenfeld; and LVR Klinikum Düsseldorf).
The study protocol was approved by the ethics committee of the North Rhine medical association (AEKNO) and by the local regulatory authority of RWTH Aachen University Hospital (EK 156/16). Written informed consent was obtained from all participants, following a complete description of the study. Diagnosis of schizophrenia was confirmed according to DSM 5 criteria by trained clinical psychiatrists using the structured clinical interview for DSM disorders (SCID). Furthermore, symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS).

2.2 Quantification of antipsychotic drug concentrations and vitamin D levels

Within this study, blood samples were taken each year between August 2015 and March 2020. According to the study protocol, blood samples for the analysis of vitamin D and antipsychotic drug levels were withdrawn together if patients were already under antipsychotic treatment. If drug treatment was yet to start, therapeutic drug monitoring was conducted in the course of treatment. For clinical reasons, the exact time-point of blood sampling varied between patients. For therapeutic drug monitoring, blood samples should be ideally withdrawn just before drug administration (trough levels) and at steady-state conditions (>4 elimination half-lives under the same drug dose). If these conditions were not met, we reviewed the hospital charts in order to identify accurate drug levels obtained during the clinical routine within a maximum temporal window of 2 months before or after the determination of vitamin D levels. Drug levels that still did not meet steady-state conditions (17/171), for which the dose or time of intake were unknown (29/171) or which were obtained during the drug absorption phase (14/171) were excluded from the study. If blood samples were not immediately withdrawn before the next drug intake (e.g., blood samples were obtained in the morning, but the drug was administered as a single dose in the evening), expected trough levels \(C_{\text{min}}\) were calculated using the drug's half-life \((t_{1/2})\) and the following exponential function:

\[
C_{\text{min}} = C(t) \times e^{-k_e \cdot (t_{\text{min}} - t)}
\]

with \(C(t)\) as the drug concentration measured at time \(t\), \(t_{\text{min}}\) as the time at \(C_{\text{min}}\) and \(k_e\) as the elimination rate constant \((k_e = \ln 2 / t_{1/2})\).

The remaining 111 drug serum concentrations comprised the following antipsychotic drugs (all taken orally): amisulpride \((n = 15)\), aripiprazole \((n = 12)\), clozapine \((n = 12)\), flupentixol \((n = 2)\), haloperidol \((n = 1)\), olanzapine \((n = 28)\), perazine \((n = 1)\), quetiapine \((n = 11)\) and risperidone \((n = 29)\). Serum concentrations of flupentixol, haloperidol and perazine were excluded due to their insufficiently low number to permit appropriate statistical comparisons. For aripiprazole, clozapine, olanzapine, quetiapine and risperidone, serum concentrations of their respective main metabolites were also determined: dehydroaripiprazole \((n = 12)\), norclozapine \((n = 12)\), desmethylolanzapine \((n = 28)\), norquetiapine \((n = 11)\) and 9-OH-risperidone \((n = 29)\). Hence, 107 serum concentrations of antipsychotic drugs and 80 serum concentrations of vitamin D obtained from 80 in- and outpatients with schizophrenia were eligible for analysis. One patient was under vitamin D supplementation for 6 weeks when participating in this study. Treating physicians were informed when insufficient or deficient vitamin D concentrations were detected, which led to subsequent initiation of vitamin D supplementation in some of the patients. In those cases, all drug concentrations that we used for the analysis had been determined before the beginning of vitamin D supplementation.

All drug and metabolite concentrations were determined in the same laboratory by liquid chromatography with tandem mass spectrometry (LC-MS/MS). Vitamin D levels (25-OH vitamin D) were determined using chemiluminescent immunoassays (CLIA).

2.3 Statistical analysis

Statistical analysis was carried out using MATLAB 2020a (The MathWorks, Inc., Natick, MA, USA), IBM SPSS Statistics 26 and IBM SPSS Amos 26 (IBM, Armonk, NY, USA). Histograms provided evidence of a non-normal, right-skewed distribution of antipsychotic drug concentrations and vitamin D levels, which was also confirmed by significant Kolmogorov–Smirnov tests. Therefore, we adhered to non-parametric statistical tests.

We tested our main hypothesis that vitamin D primarily affects drugs metabolized by CYP3A4 within the framework of a generalized linear model. Due to non-normality of the data, a gamma-distribution and logarithmic link function were applied. The model considered dose-adjusted drug concentrations \((C/D)\) (in \([\text{ng/ml}] / [\text{mg/day}]\)) as the dependent variable and vitamin D concentration as a covariate of interest. Antipsychotic drug (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine and risperidone) and CYP3A4 involvement in metabolism (negligible, modest and high) were included as categorical factors with the former variable being nested into latter variable. Within this categorization, amisulpride and olanzapine were considered as being negligibly, clozapine and risperidone as being modestly and aripiprazole and quetiapine as being highly metabolized via CYP3A4. Finally, the model also included the interaction term of vitamin D levels and CYP3A4 involvement to address our primary hypothesis. In addition, we assessed the relationship between vitamin D levels and dose-adjusted serum concentrations of each individual drug by calculating Kendall's tau rank correlation coefficients. For data visualization, linear regression plots were created.

In order to assess the impact of both vitamin D levels and antipsychotic drug concentrations on symptomatology within a single model, we also conducted a path analysis using structural equation modelling (SEM). Since the deviation from univariate and multivariate normality still was acceptable according to the general recommendations for SEM, we did not apply any transformation of the data for this analysis. We hypothesized that higher vitamin D levels would exert a relieving effect on positive and negative symptoms of patients with schizophrenia through a direct influence on symptomatology. Albeit, vitamin D levels were also assumed to exert a direct negative impact on antipsychotic drug concentrations which in turn were supposed to have a relieving effect on symptomatology (see Figure 3 for the full
Correlation between vitamin D and dose-adjusted drug concentrations. Due to the high variability in dosing, we first normalized drug and metabolite concentrations to typical antipsychotic doses, i.e. 15 mg for aripiprazole and 600 mg for quetiapine. For aripiprazole, the active moiety (AM; parent compound + active metabolite) was considered instead of the pure parent compound. Dose-normalized concentrations of quetiapine and the AM of aripiprazole were classified as being either below or above the lower limit of the respective therapeutic reference range (150 ng/mL for aripiprazole; 100 ng/mL for quetiapine). Finally, a χ²-test was applied to the pooled data of both drugs to assess for differences in the proportions of drug concentrations below or above the lower limit of the therapeutic reference range between patients with vitamin D levels below or above the sample median.

As vitamin D levels exhibited the greatest negative impact on aripiprazole and quetiapine serum concentrations, we tested whether patients on these drugs who had vitamin D levels above the median of the sample exhibited a higher proportion of therapeutically insufficient drug concentrations. Due to the high variability in dosing, we first normalized drug and metabolite concentrations to typical antipsychotic doses, i.e. 15 mg for aripiprazole and 600 mg for quetiapine. For aripiprazole, the active moiety (AM; parent compound + active metabolite) was considered instead of the pure parent compound. Dose-normalized concentrations of quetiapine and the AM of aripiprazole were classified as being either below or above the lower limit of the respective therapeutic reference range (150 ng/mL for aripiprazole; 100 ng/mL for quetiapine). Finally, a χ²-test was applied to the pooled data of both drugs to assess for differences in the proportions of drug concentrations below or above the lower limit of the therapeutic reference range between patients with vitamin D levels below or above the sample median.

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**2.4 | Nomenclature of targets and ligands**

Key protein targets and ligands in this article are hyperlinked to corresponding entries in [http://www.guidetopharmacology.org](http://www.guidetopharmacology.org), and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.15

**3 | RESULTS**

The overall sample exhibited a median 25-OH vitamin D level of 12.6 ng/mL (Q1 = 6.6 ng/mL; Q3 = 19.5 ng/mL) which is generally considered as insufficient (≤ 10 ng/mL: deficient; 11–20 ng/mL: insufficient; > 20 ng/mL sufficient19). Clinical and sociodemographic characteristics of the sample are provided in Table 1.

The generalized linear model exhibited a significant model fit as indicated by the omnibus test (likelihood ratio χ² [8] = 174.6; P < .001). The model revealed a significant impact of the factors vitamin D level (Wald χ² [1] = 15.16; P < .001), CYP3A4 involvement (Wald χ² [2] = 7.34; P = .026) and medication (CYP3A4 involvement) (Wald χ² [3] = 265.06; P < .001) on dose-adjusted drug concentrations (C/D). Moreover, we observed a significant interaction of CYP3A4 involvement and vitamin D levels (Wald χ² [2] = 6.60; P = .037), thus confirming our main hypothesis. For each drug, dose-adjusted serum concentrations were negatively correlated with vitamin D levels. The magnitude of this anti-correlation was clearly driven by the involvement of CYP3A4 in the drug metabolism with amisulpride and olanzapine exhibiting the lowest, clozapine and risperidone exhibiting intermediate, and aripiprazole and quetiapine exhibiting the highest anti-correlation (see Table 2 and Figure 1).

For aripiprazole and quetiapine, we also assessed the relationship between vitamin D levels and the metabolite to parent compound ratio (MPR), a direct measure of metabolizing enzyme(s) activity. As expected, MPRs of both antipsychotics showed a positive correlation

| TABLE 1 | Sociodemographic and clinical characteristics of the sample |
|----------------|-------------------|-----|-----|
| Characteristic | Median | Q1 | Q3 |
| **Biometrics** | | | |
| Age (years) | 30 | 24 | 41 |
| Weight (kg) | 77.4 | 66.3 | 90.5 |
| **C(25-OH-vitamin D3) (ng/ml)** | | | |
| Risperidone 29/C0 | 12.6 | 6.6 | 19.5 |
| **Positive and negative syndrome scale (PANSS)** | | | |
| Positive symptoms | 15 | 11 | 21 |
| Negative symptoms | 19 | 15 | 24 |
| **Gender** | | | |
| Female | 19 | | 23.7 |
| Male | 61 | | 76.3 |
| **Antipsychotic medication** | | | |
| Amisulpride | 15 | | 18.8 |
| Aripiprazole | 12 | | 15.0 |
| Clozapine | 12 | | 15.0 |
| Olanzapine | 28 | | 35.0 |
| Quetiapine | 11 | | 13.8 |
| Risperidone | 29 | | 36.3 |

| TABLE 2 | Correlation between vitamin D and dose-adjusted drug levels |
|----------------|-------------------|-----|
| Medication | n | Kendall's tau | P-value |
| Amisulpride | 15 | -0.21 | 0.298 |
| Aripiprazole | 12 | -0.48 | 0.031 |
| Clozapine | 12 | -0.14 | 0.580 |
| Olanzapine | 28 | -0.16 | 0.228 |
| Quetiapine | 11 | -0.64 | 0.006 |
| Risperidone | 29 | -0.13 | 0.345 |
with vitamin D levels (aripiprazole: Kendall's tau = 0.152; \( P = .493 \); quetiapine: Kendall's tau = 0.491; \( P = .036 \); see Figure 2).

Our path model postulated that both vitamin D and antipsychotic drug levels directly influence the symptomatology of schizophrenia and vitamin D also influences (reduces) antipsychotic drug levels. We indeed observed a good model fit: \( \chi^2 [3] = 1.69, \ P = .640 \); RMSEA < 0.001; PCLOSE = 0.728) with the signs of the path coefficients matching our hypotheses (see Figure 3). Our exploratory multi-group path analysis revealed that constraining the path coefficient representing the impact of vitamin D on drug concentration to be equal across groups resulted in a significantly reduced model fit, thus providing further evidence that this influence differs between

![Figure 1](image1.png): Linear regression plots illustrating the relationship between dose-adjusted drug concentrations (C/D) and 25-OH-vitamin D levels

![Figure 2](image2.png): Linear regression plots illustrating the relationship between the metabolite to parent compound ratios (MPRs) of the highly-affine CYP3A4 substrates aripiprazole and quetiapine, and 25-OH-vitamin D levels, respectively

![Figure 3](image3.png): Overview of the structural equation model (SEM). Red arrows label inhibitory influence as reflected by negative path coefficients. Adjacent to the arrows, the respective standardized path coefficients are presented. C (Antipsychotic) represents the serum concentrations of antipsychotic drugs.
drugs (for detailed statistics, see the supplementary results as well as Figure S1 and Table S2 in the Supporting Information).

To assess the therapeutic relevance of our findings, we conducted a χ²-test comparing the proportions of antipsychotic serum concentrations situated below or above the lower limit of the therapeutic reference range between patients with vitamin D levels below or above the median. Among the 23 serum concentrations of quetiapine and the active moiety of aripiprazole, 11 concentrations belonged to patients with vitamin D levels below and 12 to those above the median. Within the vitamin D group below median, 10 drug concentrations (91.0%) were found above the lower limit of the therapeutic reference range and only one concentration (9.0%) was found below the lower limit. In contrast, in the vitamin D group above median, six concentrations (50%) each were found below and above the lower limit of the therapeutic reference range, resulting in a significant test statistic: χ² (1) = 4.54; P = .033. In other words, patients exhibiting vitamin D levels above the median showed a significantly higher proportion of drug concentrations below the lower limit of the therapeutic reference range.

4 | DISCUSSION

In the present study, we assessed the impact of vitamin D levels on antipsychotic drug concentrations and psychopathology in a sample of 80 patients diagnosed with schizophrenia according to DSM 5 criteria. In general, vitamin D levels and dose-adjusted serum concentrations (C/D) of antipsychotic drugs showed a negative correlation. However, we observed a significant impact of the drugs’ affinity to CYP3A4 on this relationship: drugs that are primarily metabolized by this enzyme (aripiprazole and quetiapine) indeed exhibited the strongest anti-correlation with vitamin D levels, whereas those with negligible CYP3A4 involvement showed the weakest negative correlation. As a complementary finding, the metabolite to parent compound ratios (MPRs) of the antipsychotics drugs with a high CYP3A4 involvement exhibited a positive correlation with vitamin D levels, indicating increased metabolism.

A path analysis suggested that vitamin D might have a direct relieving effect on the symptomatology of schizophrenia which is, however, counteracted by its negative impact on antipsychotic drug levels. Finally, patients exhibiting above median vitamin D levels had a significantly higher proportion of insufficiently low dose-normalized drug levels of aripiprazole and quetiapine, illustrating the therapeutic relevance of our findings.

The steroid hormone vitamin D exerts its multiple physiological functions by activation of the vitamin D receptor which acts as a direct modulator of gene transcription. Besides the classical vitamin D responsive organs (intestine, bone, kidney and parathyroid gland), vitamin D receptors are also expressed in many other organs, including the liver, muscle, skin, immune system, pancreas as well as the brain. In this context, it is assumed that reduced vitamin D receptor signalling in the brain may increase the risk of schizophrenia as well as the burden of symptomatology, which is also compatible with the findings of the present study. As the present study points out, however, clinicians who consider vitamin D supplementation in this patient group should be aware of the potential negative influence of vitamin D on antipsychotic drug exposure.

To the best of our knowledge, the first evidence for vitamin D’s effects on drug metabolism came from in vitro studies demonstrating a CYP3A4 induction by vitamin D in different cell lines including primary human hepatocytes. The first human in vivo evidence was obtained from a study which revealed that vitamin D supplementation leads to an increased clearance of atorvastatin, a known substrate of CYP3A4. Subsequently, Lindh et al. demonstrated that blood concentrations of the CYP3A4 substrates tacrolimus and sirolimus exhibit a cyclic seasonal variation which is anti-correlated with ultraviolet light exposure and vitamin D levels. In contrast, this phenomenon was not observed for mycophenolic acid, which is devoid of CYP3A4-mediated metabolism. Similarly, another study demonstrated a seasonal variation of intestinal CYP3A4 expression and identified genetic polymorphisms of the vitamin D receptor as significant predictors of CYP3A4 expression.

Accordingly, we assume that our pharmacokinetic findings reflect vitamin D’s impact on CYP3A4 gene expression, with higher vitamin D levels leading to higher gene expression and thus reduced drug concentrations of CYP3A4 substrates such as aripiprazole and quetiapine. Interestingly, we also observed a seemingly CYP3A4-independent influence of vitamin D on drug concentrations as reflected by the significant main effect of vitamin D in the generalized linear model and—on a descriptive level—the negative correlation between vitamin D and C/D levels observed for each individual drug. Indeed, in vitro studies have also suggested the induction of CYP2B6 and CYP2C9 by vitamin D, albeit to a lesser extent than CYP3A4. However, neither of the two isoenzymes are considered to be involved in the metabolism of the antipsychotics assessed in this study. More surprisingly, we also observed a negative relationship between vitamin D and amisulpride which is predominantly eliminated chemically unchanged via the kidneys. Indeed, there is converging evidence for a vitamin D-mediated induction of P-glycoprotein (P-gp), which serves as renal and cerebral efflux pump of xenobiotics and several antipsychotics including amisulpride have been identified as substrates of P-gp so far.

4.1 | Limitations

A major limitation of the present study is the limited amount of therapeutic drug monitoring (TDM) data available for some of the antipsychotic drugs. Sample size is particularly critical for SEM analyses. While our main SEM analysis of the pooled data exhibits a satisfying power of approximately 89% for the χ²-test of model fit, the power of our multi-group analysis was only 38%, which we therefore only consider as exploratory analysis. Future studies on larger samples for each drug are necessary to assess differences between drugs within the SEM framework more reliably. However, it is noteworthy that the signs of most path coefficients are consistent for most of the drugs. An obvious exception is observed for the impact of drug
concentration on negative symptoms which might be explained by the drugs’ different effectiveness on negative symptoms\textsuperscript{25} and their different propensity for inducing secondary negative symptoms.\textsuperscript{26,27} The latter phenomenon might also explain the weakly positive path coefficient observed for our pooled analysis.

Since we adhered to the routines established in our clinical laboratory in house, vitamin D levels were assessed using CLIA. For a more accurate assessment, future studies should employ LC–MS/MS which is considered as the gold standard.\textsuperscript{28} A further bias may have been introduced by our strategy to use drug concentrations from the hospital charts if blood samples withdrawn for the study did not meet the criteria for TDM. Since we accepted a temporal window of 2 months before or after the determination of vitamin D levels, the real vitamin D levels present at the time of the valid TDM may have been over- or underestimated in some of the patients. Among the different metabolites of vitamin D, in the present study, we focused on 25-OH-vitamin D which is the precursor of the more active form 1,25-(OH)\textsubscript{2}-vitamin D (calcitriol). Due to the relatively low concentrations of calcitriol, its short half-life and high intra-individual variation, it is generally not recommended for the assessment of vitamin D status—with the exception of diseases of the kidney and calcium homeostasis.\textsuperscript{29} Moreover, contrary to 25-OH-vitamin D and the two CYP3A4-metabolized drugs tacrolimus and sirolimus,\textsuperscript{9} no clear seasonal variation could be observed for calcitriol-levels,\textsuperscript{30} which is another reason why we focused on 25-OH-vitamin D in the present study. For a more comprehensive assessment, however, future studies should include calcitriol and potentially also 24,25-(OH)\textsubscript{2}-vitamin D.\textsuperscript{31} Surprisingly, risperidone concentrations were particularly low in our study sample with a significant proportion of the dose-adjusted concentrations (76\%) falling more than one standard deviation below the expected average, corresponding to a C/D-value < 0.34 ng/mL/mg/d (see Figure 1). However, concentrations of the active metabolite, 9-OH-risperidone, were still within the dose-related reference ranges for 64\% of these patients. One potential explanation for such increased metabolite to parent compound ratios may be a relatively high proportion of CYP2D6 ultra rapid metabolizers in our study sample. Unfortunately, pharmacogenetic testing was not performed within the framework of this study. When assessing the relationship between vitamin D levels and psychopathology, the direction of influence is still debatable. Furthermore, it may be difficult to distinguish pure vitamin D-related effects from psychological effects of sunlight exposure. For a comprehensive and unambiguous clarification, double-blind randomized controlled trials (RCTs) comparing vitamin D supplementation versus placebo are required. Besides one ongoing study,\textsuperscript{32} we are only aware of one open-label RCT addressing this issue. However, the study could not identify a significant treatment effect of vitamin D on psychopathology,\textsuperscript{33} taking into account that only psychopathologically stable patients under continued antipsychotic treatment were recruited for that study. Moreover, as our findings suggest, a vitamin D-mediated increase of drug metabolism may have diminished its beneficial effects. Hence, future trials should apply therapeutic drug monitoring to rule out this side effect.

5  |  CONCLUSION

The present study confirms prior evidence of vitamin D deficiency being a frequent phenomenon in schizophrenia, which may increase the burden of symptomatology. In addition, we show that patients with higher vitamin D levels were more likely to have therapeutically insufficient blood concentrations of antipsychotic drugs, particularly those metabolized by CYP3A4. Clinicians who consider supplementing vitamin D in schizophrenia patients should therefore apply TDM-guided dose adjustment to prevent re-exacerbation of symptomatology.

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COMPETING INTERESTS

M.P. has received speaker’s fees from Neurapharm and Lundbeck. G.G. has served as a consultant for Allergan (Dublin, Ireland), Boehringer Ingelheim (Ingelheim, Germany), Institute for Quality and Efficiency in Health Care (IQWIG, Cologne, Germany) Janssen-Cilag (Neuss, Germany), Lundbeck (Copenhagen, Denmark), Otsuka (Chiyoda, Japan), Recordati (Milan, Italy), Sage (Cambridge, USA), and Takeda (Osaka, Japan). He has served on the speakers’ bureau of Gedeon Richter (Budapest, Hungary), Janssen Cilag, Lundbeck, Otsuka, Recordati. He has received grant support from Boehringer Ingelheim, Lundbeck and Saladax (Bethlehem, USA). He is co-founder and/or shareholder of Mind and Brain Institute GmbH (Zornheim, Germany), Brainfoods GmbH (Zornheim, Germany), InMediCon GmbH (Pentling, Germany), OVID Health Systems GmbH (Berlin, Germany) and MIND Foundation gGmbH (Berlin, Germany).

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

CONTRIBUTORS

A.J.G., M.F.-P., G.G. and F.Sch. were responsible for the study design. The data was acquired by A.J.G., M.F.-P., S.L., S.S., P.E., F. St., E.R., L.W., P.K., L.L., M.A., J.H., L.S., E.S., F.K., M.P. and APIC Consortium. The data was analysed by A.J.G., M.F.-P. and K.M. A.J.G. wrote the manuscript and all authors contributed to its critical revision.

DATA AVAILABILITY STATEMENT

Data are stored at RWTH Aachen University hospital. The data are not publicly available due to privacy and ethical restrictions.

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