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Associations Between Vitamin D Deficiency/Insufficiency and Depression Expose Health Disparities in Older Rural West Texans: A Project FRONTIER Study

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ABSTRACT

Objective: *To determine associations between Vitamin D (VD) levels and clinical depression through the Geriatric Depression Scale (GDS) and its questions and subdomains, stratified by demographics and Hispanic/Latino ethnicity (HLE).* ***Design, setting, and participants:*** *A cohort of 299 Project FRONTIER participants aged 62.6 ± 11.7 years old, 70.9% female, and 40.5% HLE were used. Standard correlation and regression analyses were employed.* ***Measurements:*** *The main outcome measures were VD (serum 25(OH)-VD) level, GDS-30 (30-item questionnaire), GDS-30 subfactors and questions, and HLE status. VD categories were defined as VD deficiency (VDD; ≤20 ng/mL), VD insufficiency (VDI; 21–29 ng/mL), VD sufficiency (30–38 ng/mL) and high VD sufficiency (>38 ng/mL).* ***Results:*** *The majority (61.5%) of samples fell into VDD/VDI categories. A significant negative association was found between VD level and GDS-30 total score. VD level was negatively correlated with Dysphoria and Meaninglessness GDS-30 subfactors. Although GDS subfactors were similar between HLE and non-HLE groups, VD levels were significantly lower in HLE samples. Finally, HLE/non-HLE groups were differentially stratified across VD*

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categories. Only 4% of HLEs fell into the high VD sufficient category, suggesting low VD supplementation. ***Conclusion:*** *A significant negative association between VD level and depressive symptoms was revealed in our aging Project FRONTIER participants. HLE individuals were overrepresented in VDD/VDI samples, and VDD/VDI was associated primarily with the Dysphoria GDS subdomain. Regression analysis predicted high VD sufficiency (95.5 ng/mL) to be associated with no depressive symptoms (GDS=0). Our results underscore troubling disparities in VD-related depressive symptoms between HLE and non-HLE populations.* (Am J Geriatr Psychiatry 2024; 32:808−820)

Editorial accompaniment, please see page 821.

Highlights

- **What is the primary question addressed in this study?**
  Using the 30-question Geriatric Depression Scale (GDS-30), we tested the hypothesis that Vitamin D (VD) status was associated with self-reported depressive symptoms in a multiethnic aging sample in rural West Texas.
- **What is the main finding of this study?**
  A significant negative association between serum 25-hydroxyvitamin-D levels and depressive symptoms was revealed, spanning both Dysphoria and Meaninglessness GDS subfactors. Hispanic/Latino ethnicity (HLE) populations were overrepresented in VD deficiency (VDD) and VD insufficiency (VDI) categories, and less likely to use VD supplements compared to non-HLE populations.
- **What is the meaning of the finding?**
  Based on widespread VDD/VDI in our HLE sample, use of VD supplementation at high sufficient doses is predicted to reduce depressive symptoms. A subset of GDS Dysphoria questions were highly sensitive to VD status, providing important knowledge for VD screening in the clinic.

INTRODUCTION

By 2030, major depression is projected to rise in prevalence in the aging population.[1,2] The elderly exhibit more moderate to severe depressive symptoms compared to younger individuals, accompanied with a higher risk of suicidality, work-life disability, psychosis, substance abuse, and mood disorder comorbidities.[3,4] Specifically, vitamin D (VD) status is implicated in the development of new-onset depression.[5,6] VD deficiency (VDD) or VD insufficiency (VDI) are worldwide conditions affecting nearly 1 billion people. Nearly half of older adults may be in VDD or VDI categories.[7−9] Age-dependent reduction in the ability to synthesize and/or absorb VD contributes to low VD status.[10,11] Seasonal Affective Disorder, a type of depression, is associated with changes in sunlight exposure.[12] Underrepresented minorities that have high density of melanin in skin, including African Americans and those with Hispanic/Latino ethnicity (HLE), are at a higher risk for VDD and VDI compared to the general population.[13] Overall, a combination of age, skin tone, latitude, and seasonal variation in daylight are emerging factors that likely contribute to VD status.[10,14]

Depressive symptoms can be used to predict with 70-84% sensitivity the diagnosis of specific types of neurodegenerative disease.[15] The Geriatric Depression Scale (GDS) is a valid screening test used in primary care consultations to investigate clinical depression due to its high sensitivity and negative predictive value. GDS was created, first in a version of 30 items (GDS-30) and later of 15 items (GDS-15).[16,17] They present a dichotomous response format (Yes/No) that makes them easy to administer.[18] The GDS questions are structured into four different subfactor domains: Dysphoria, Meaninglessness, Apathy, and Cognitive Impairment (DMAC). The GDS screening tool has recently been validated in Mexican Americans.[19]

O'Bryant and colleagues[20] observed higher cognitive impairment scores in HLE groups, particularly with immediate and delayed memory, which were associated with GDS subcategories of Dysphoria and Meaninglessness. In addition, a previous study[21] established that depression in HLE individuals collectively increases the risk for mild cognitive impairment and Alzheimer's disease (AD). In general, increasing evidence suggests that VDD and VDI are associated with age and depression in older adults, both of which are risk factors for AD.[22–24] Despite emerging evidence of racial/ethnic disparities in health outcomes, few studies have explicitly examined the association between VD status and depression in the context of aging. A previous study observed VD supplementation provides no significant impact on depressive symptoms.[25] However, only 11% of the sample size fell into the VDD category, suggesting that VD supplementation may be more effective in subpopulations that exhibit both VDD/VDI and depressive symptoms. Therefore, it is important to identify populations at risk for VDD/VDI.

In a previous pilot study, Johnson and colleagues[26] examined the relationship between VD levels and depressive symptoms, as measured by GDS-30, in 68 rural-dwelling individuals (18 males and 50 females) enrolled in Project FRONTIER (PF). The original study determined that 50% of the individuals had sufficient VD levels, 33% had VDI, and 17% had VDD.[26] A significant negative relationship between VD level and GDS score was reported. VD status was negatively associated with the Dysphoria subfactor scale, while the other three subfactors (Meaninglessness, Apathy, and Cognitive Impairment) were not significantly correlated. However, due to the limited sample size, variables such as HLE and sex were not explored.

Here, we revisited the relationship between VD levels and GDS for an expanded multi-ethnic cohort of 298 individuals enrolled in PF. The increased sample size allowed us to overcome some limitations of the previous study, enabling a more comprehensive and detailed investigation of the relationship between VD status and GDS.

METHODS

Study Population and Sample

The sample consisted of 299 aging individuals from PF, a continuous ongoing longitudinal study in rural West Texas[27] (approved by TTUHSC IRB, Number L06-028). PF participants had the following demographics: 62.6 ± 11.7 years old, 70.9% female, and 40.5% Hispanic/Latino ethnicity (HLE). The analysis focused on data obtained at baseline (Visit 1, 2009-2011), for participants living in Parmer County, which was the only county where VD measurements (*bw_vitd*) were available. Samples were deidentified and exported from Qualtrics into Excel format. VD level was subcategorized into VD sufficiency (30−38 ng/mL), VD insufficiency (VDI; 21−29 ng/mL) and VD deficiency (VDD; ≤ 20 ng/mL).[28] Based on evidence for additional VD benefits beyond the health benefits associated with VD sufficiency,[29] we established a "high sufficient" VD category (>38 ng/mL). Finally, due to possible concerns regarding VD toxicity, we also established a category of >150 ng/mL as toxic.[11]

Ascertainment of Depressive Symptoms

Depressive symptoms were assessed using the GDS and corroborated with the consensus diagnosis for depression variable (*cdx_psya*), a variable that is informed by GDS score, current medications, and patient health history. The variable "GDS Total" (*gds_sumt*), ranging from 0 to 30 points, was subcategorized into Dysphoria (*gds_sumd)*, Meaninglessness (*gds_summ)*, Apathy (*gds_suma)*, and Cognitive Impairment (*gds_sumc)*.[30] Evidence of antidepressant medication was identified, parsed within *med* variables, and stored as a new variable (*med_antidepressants*). Of 299 participant samples, GDS scores were available for 298. GDS Total scores were categorized as Not Depressed (<10); Mild Depression 10-19), and Severe Depression (20-30). For logistic regression, GDS < 10 was coded as 0 and GDS ≥ 10 was coded as 1 to indicate mild/severe depression.

Ascertainment of Self-Reported Ethnicity

The study sample included participants who identified as HLE in status, as described as the categorical variable self-reported Hispanic ethnicity (*ds_16_3*). This variable initially described categorical values: Mexican, Mexican American, or Chicano (114, 38.3%), Puerto Rican (1, 0.34%), and Other Hispanic Origin (6, 2.0%). The remaining were categorized as non-HL White/Caucasian (177, 59.4%). Due to limited

samples in several categories, we combined all subgroups in one HLE subgroup, creating a binary HLE variable (non-HLE = 0; HLE = 1; *ds_16_3-JL*). None of the participants had entries in Don't Know or Refuse to Answer categories.

Assay of Serum 25-Hydroxyvitamin-D

Project FRONTIER was conducted under an IRB approved protocol at Texas Tech University Health Center. As described in the original study,[26] variables were collected using a standardized medical examination, fasting blood work at a local, CLIA certified hospital, detailed interview where medical history and GDS was conducted, and neuropsychological testing. Serum 25-hydroxyvitamin D measurements were taken with the fasting blood work and were part of Visit 1 which was conducted in 2010. Visits were not aligned to a specific season or time of year.

Baseline Characteristics

Demographics (age, sex, and HLE) are described above. There were no exclusion criteria in this observational study, other than the absence of a VD measurement.

Cross-Sectional Analysis of Serum 25(OH)-VD Level and GDS

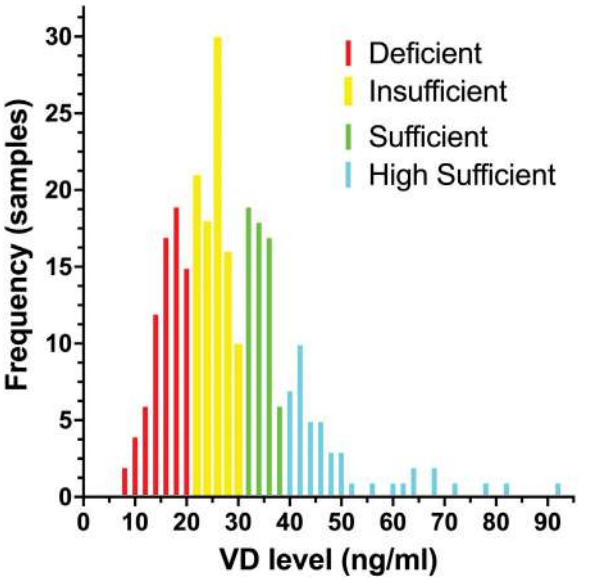
Statistical comparisons and graphics were generated with Graphpad Prism 10. For serum 25(OH)-VD level GDS Total, and HLE status, a normality test (Shapiro-Wilk test) first was performed. The distributions consistently failed normality tests; therefore, we used nonparametric analyses for statistical comparisons. Spearman's correlation and regression analyses were used. The Mann-Whitney U test was employed for statistical comparisons. Cross-sectional analysis of serum 25(OH)-VD level and GDS constructs. For bivariate analyses, we created correlation matrices. A Chi squared test was performed to compare HLE vs. non-HLE proportions across VD subcategories.

RESULTS

The Majority of PF Participants Were Classified as VD Deficient or Insufficient

On average, the mean VD level was 28.6 ± 12.4 ng/mL (n=298; mean ± SD). VD level was not normally distributed (Shapiro-Wilk test for Normality, W = 0.8981; p <0.0001). Samples were stratified across all VD categories, ranging from 7.2 − 91.0 ng mL. VD values are plotted in a histogram (Fig. 1) that was asymmetrically distributed (skewness:1.56, kurtosis 4.19). Stratification across VD categories was as follows: VDD (75, 25.0%), VDI (109, 36.5%), VD sufficient (67, 22.4%), and high VD sufficient (48,16.1%; Fig. 1, colors). Overall, 184/299 (61.5 %) were classified as VDD or VDI. Although high VD sufficiency suggested the use of VD supplements, no individual had VD levels extending into the toxic range (>150 ng/mL).[11]

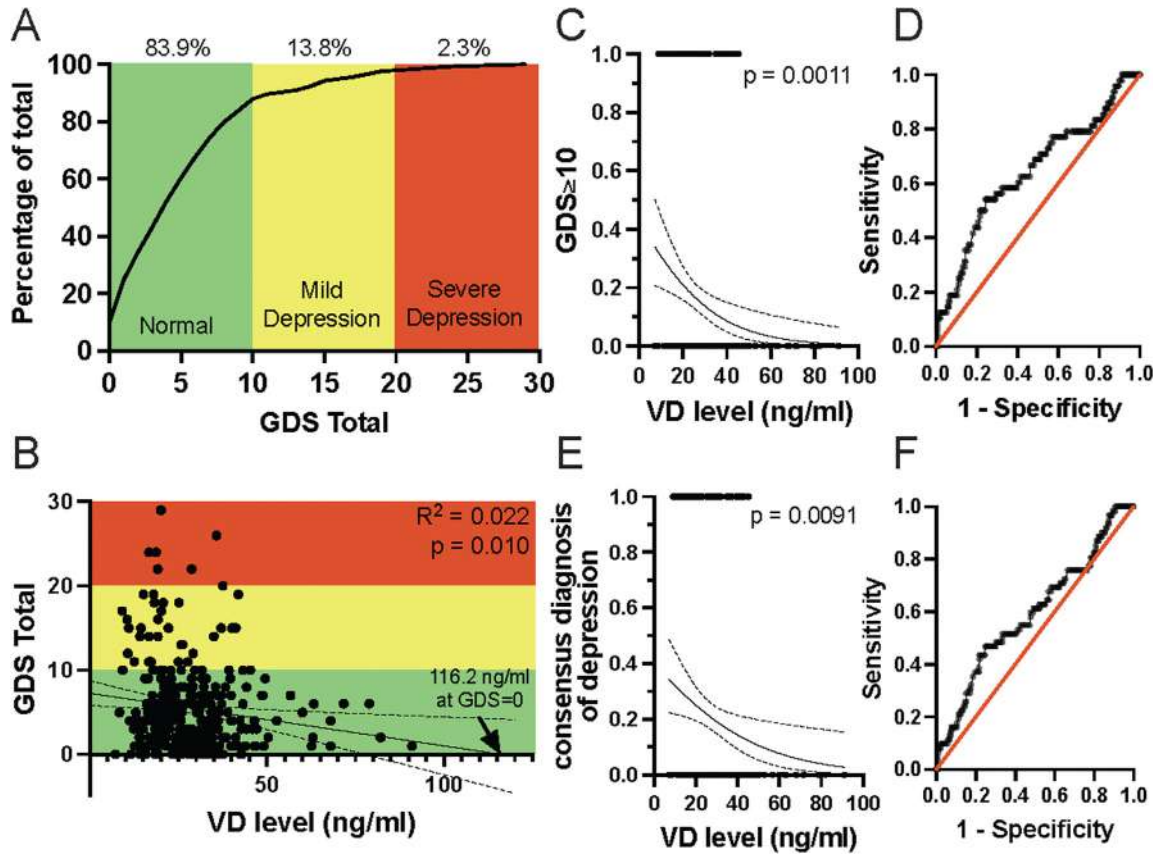
FIGURE 1. Vitamin D levels among 299 PF participants. Histogram of frequency vs. VD levels, parsed into Deficient (red, 75/299), Insufficient (yellow, 109/299), Sufficient (green, 67/299), and High Sufficient (cyan, 48/299) categories (bin width: 2 ng/mL).



Negative Associations Between *VD Status and GDS Total Score*

The mean GDS total score was 5.5 ± 5.2 (n = 298; Skewness:1.61, Kurtosis:3.07). The GDS scores were not normally distributed (Shapiro-Wilk test for Normality, W = 0.8495; p <0.0001). While 250/298 (83.9%) of participants fell into the normal category, 41/298 (13.8%) and 7/298 (3.2%) were classified with

FIGURE 2. Relationship between VD status and depression. (A) Cumulative probability plot of GDS total scores for PF sample (n = 298). Colors indicate GDS classification (normal = 0-9, green, mild depression = 10−19, yellow, severe depression ≥ 20, red). (B) Simple linear regression of VD level vs. GDS total scores. XY intercepts, linear regression line (dashed line) and 95% confidence intervals (thinner dotted lines) are shown. The estimated equation is Y = -0.0625*X + 7.263. Colors indicate the same GDS classification as in A. (C) Simple logistic regression of VD level vs. depression (GDS ≥ 10, p = 0.0011). The estimated equation is log odds = -0.2946−0.05154*X. (D) ROC curve for C (area = 0.642 ± 0.046; p = 0.0018). (E) Simple logistic regression of VD level vs. consensus diagnosis of depression (p = 0.0091). The estimated equation is log odds = -0.3985 -0.03479*X. (F) ROC curve for E (area = 0.593 ± 0.042, p = 0.0248).



demonstrating mild or severe symptoms of depression, respectively (Fig. 2A). Consistent with a previous study,[26] we found a significant negative correlation between VD level and GDS total score (n = 298; Spearman r = -0.1333, p = 0.0214). Simple linear regression demonstrated that the relationship differed significantly from zero (Fig. 2B; n = 298; $F_{(1,296)}$ = 6.723, p = 0.010). The X-intercept where GDS = 0 was 116.2 ng/mL (77.7−392.8 ng/mL, 95% confidence interval). The Y-intercept (at VD level = 0) was 7.62 ± 0.75 (5.79−8.74, 95% confidence interval), suggesting that VD level accounts for a large (~75%) fraction of total GDS score needed to reach a clinical diagnosis of mild depression (GDS ≥ 10), but only accounts for ~37.5% of the fraction of total GDS score required to achieve a diagnosis of severe depression (GDS ≥ 20).

We also performed a logistic regression to determine whether a significant relationship existed between VD level and the probability of depressive symptoms considered clinically significant. Of 298 participants, 48 (16.1%) met the binomial criteria of GDS ≥ 10. There was a significant negative relationship between VD level and the probability of depression (Likelihood ratio test, G^2 = 10.57, p = 0.0011; Fig. 2C). The receiver operating characteristic (ROC) curve demonstrated a positive relationship between

VD level and depression (ROC area: 0.642 ± 0.047, p = 0.0018; Fig. 2D). For VD deficiency (<20 ng/mL), the odds ratio (OR) was 1:3.76, decreasing to 1:6.33 at VD sufficiency (30 ng/mL). Interestingly, the odds continued to fall (to 1:9.66) with high VD sufficiency (38.3 ng/mL). At the highest recorded VD level (91 ng/mL), the odds ratio was 1:146. VD toxicity (>150 ng/mL) was not present in any of the samples. Therefore, high sufficient VD levels may be safe and provide protection against depressive symptoms.

We next examined consensus diagnosis for depression (*cdx_psya,* see Methods). Logistic regression between VD level and cdx_psya revealed a similar negative association (Likelihood ratio test, R^2 = 6.805, p = 0.0091, Fig. 2E; ROC area: 0.59 ± 0.042, p = 0.025, Fig. 2F). Moreover, the depressed group was associated with lower VD levels (25.1 ± 1.2 ng/mL, n = 62) than the non-depressed group (29.4 ± 0.8 ng/mL, n = 237; U = 5987, p = 0.025, Mann-Whitney U test, data not shown).

Finally, we asked whether a relationship existed between antidepressant medication and VD levels. As expected, GDS scores were significantly lower in the antidepressant group (8.8 ± 1.0, n = 45) than the depressed group not taking antidepressants (13.9 ± 0.8, n = 36, U = 338.5, p <0.0001, Mann-Whitney U test, data not shown). Interestingly, participants taking antidepressant medications had higher VD levels (31.5 ± 1.9 ng/mL, n = 46) compared those that were clinically depressed yet were not taking antidepressant medications (23.2 ± 1.6 ng/mL, n = 36; U = 508, p = 0.0025, Mann-Whitney U test, data not shown).

In summary, using a ~4-fold larger sample size than in the original study by Johnson and colleagues,[26] we validated the finding of a negative association between VD status and depressive symptoms.

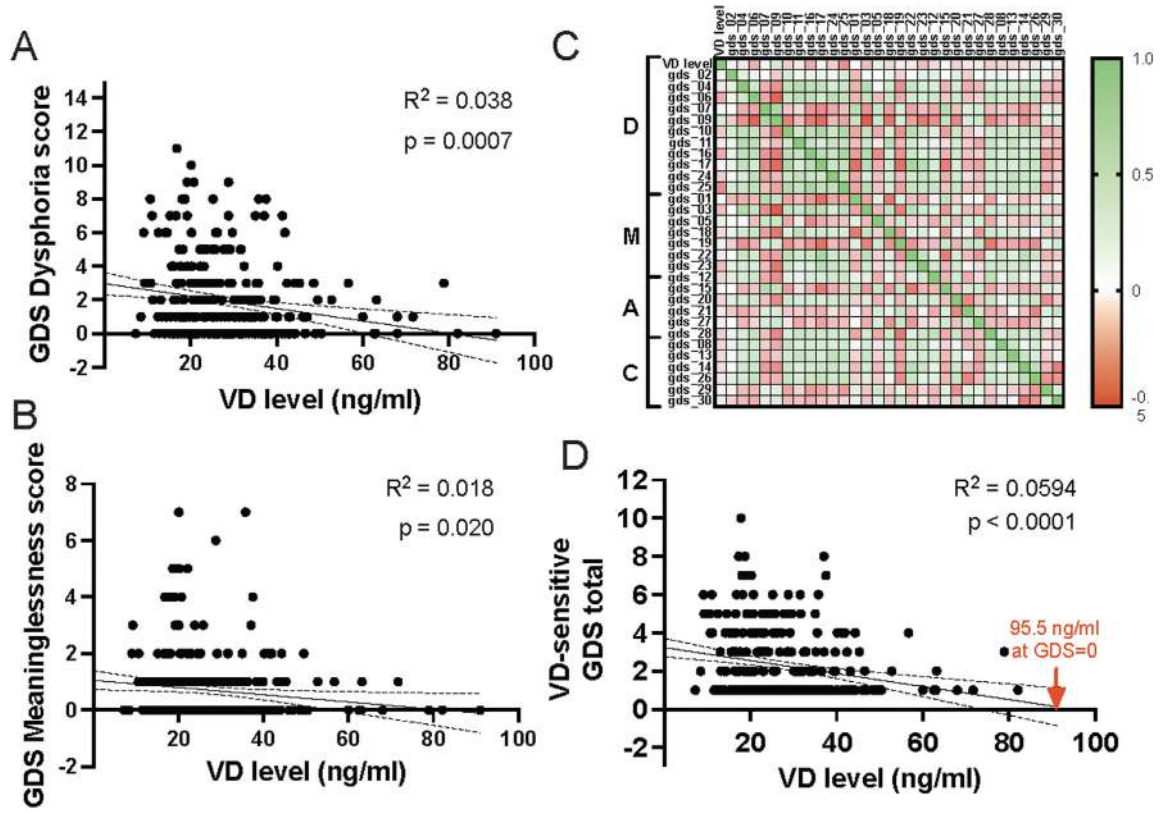
VD Sensitivity Across GDS Subfactor Domains

Johnson *et al.*[26] originally found that VD levels were related specifically to the Dysphoria subfactor score but not correlated with Meaninglessness, Apathy, and Cognitive Impairment subfactors. We determined whether this preference for the Dysphoria subfactor could be confirmed with our larger sample size. We first examined correlations between VD level and the different GDS subfactors. VD level was negatively correlated not only with Dysphoria (n=298; Spearman r = -0.19, p = 0.001) but also, to a lesser extent, with Meaninglessness (n = 298; Spearman r = -0.15, p = 0.011), but not Apathy (n = 298; Spearman r = -0.053, p = 0.36) or Cognitive Impairment (n=298; Spearman r = -0.030, p = 0.60) subfactors. To investigate the extent that VD levels were predictive of GDS subfactors, we also investigated relationships between VD levels and each of the GDS subfactors through simple linear regression (Fig. 3A,B). Consistent with correlation and an earlier study,[26] VD level was a significant predictor of the Dysphoria subfactor (R^2 = 0.038, $F_{(1,296)}$ = 11.8, p = 0.0007; Fig. 3A). However, the Meaninglessness subfactor was also significant (R^2 = 0.018, $F_{(1,296)}$ = 5.4, p = 0.020; Fig. 3B), which was not found in the original study by Johnson et al.[26] VD level predicted neither Apathy (R^2 = 0.003, $F_{(1,296)}$ = 0.83, p = 0.36) nor Cognitive Impairment (R^2 = 0.004, $F_{(1,296)}$ =1.13, p = 0.29). The X-intercept of the VD vs. Dysphoria subfactor relationship was 80.47 ng/mL (95% CI: 60.7−151 ng/mL), indicating that high VD sufficiency is associated with low GDS Dysphoria scores. Similarly, the X-intercept of the VD vs. Meaninglessness subfactor relationship was 82.66 ng/mL (95% CI: 56.7−375 ng/mL).

Overall, these findings overlap with Johnson et al. [26] in two ways. First, Dysphoria was the most significant VD-sensitive subfactor. Second, VD level was a significant predictor for neither Apathy nor Cognitive Impairment subfactors. However, in our study, we also detected that the Meaninglessness subfactor was a significant predictor of VD levels.

To determine the extent that VD sensitivity varied within and across DMAC subfactor domains, we generated a correlation matrix between VD level and each of the 30 GDS questions (Fig. 3C). As anticipated, many questions were sensitive to VD level within the Dysphoria subfactor category. Of 11 GDS Dysphoria questions, 6 were significantly correlated (p <0.05) with VD level (D, Fig. 3C, pink/red; Table 1). Of 7 GDS Meaninglessness questions, 3 were significantly correlated with VD level (M, Fig. 3C, pink/red; Table 1). Reflecting the overall Apathy and Cognitive Impairment subfactor scores, none of the Apathy or Cognitive Impairment GDS questions were significantly correlated (A, C, Fig. 3C; not shown in Table 1). Interestingly, the GDS question gds_25 "Do you frequently feel like crying?" was the most highly correlated (n = 299; Spearman r = -0.274, p = $1.55e^{-6}$; Fig. 3C, Table 1), which itself was

FIGURE 3. Relationship between VD level and GDS subfactor scores. Simple linear regression of the relationship between VD level and (A) Dysphoria and (B) Meaninglessness subfactors. The estimated equation for Dysphoria was Y = -0.03686*X + 2.966. The estimated equation for Meaninglessness was Y = -0.01278 + 1.056. (C) Correlation matrix VD level and all 30 GDS questions, ordered according to Dysphoria (D), Meaninglessness (M), Apathy (A), and Cognitive Impairment (C) subfactors. Positive and negative correlations are shown in green and red, respectively. (D) Linear regression of VD level vs. VD-sensitive GDS scores. The estimated equation is Y = -0.03404*X + 3.239.



more significant than GDS total (Fig. 2B), Dysphoria (Fig. 3A), or Meaninglessness (Fig. 3B) subfactor scores.

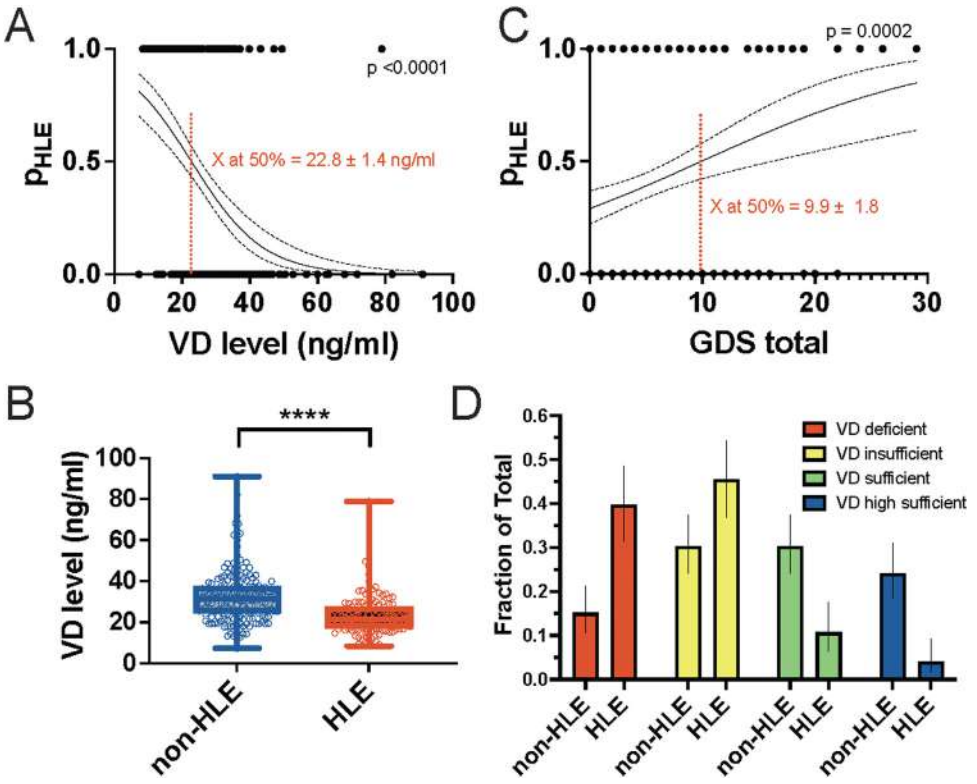
The above GDS question analysis suggested that the inclusion of VD-insensitive GDS questions confounded VD-sensitive GDS questions, thereby

TABLE 1. Vitamin D-sensitive Dysphoria and Meaninglessness GDS Questions

GDS Dysphoria Questions	PF Variable	Spearman r	p Value	Confidence Interval
Are you bothered by thoughts you can't get out of your head?	gds_06	−0.196	0.001*	−0.3059 to −0.08126
[a]Do you feel happy most of the time?	gds_09	0.196	0.001*	0.08156 to 0.3062
[a]Do you often feel helpless?	gds_10	−0.129	0.025*	−0.2423 to −0.01267
Do you feel downhearted and blue?	gds_16	−0.198	0.001*	−0.3072 to −0.08266
Do you frequently get upset over little things?	gds_24	−0.117	0.044	−0.2303 to 9.103e-5
Do you frequently feel like crying?	gds_25	−0.274	$1.55e^{-6}$*	−0.3784 to −0.1621
GDS Meaninglessness questions				
[a]Do you feel that your life is empty?	gds_03	−0.156	0.007*	−0.2682 to −0.04036
Are you hopeful about the future?	gds_05	0.115	0.047	−0.001854 to 0.2286
[a]Do you think that most people are better off than you are?	gds_23	−0.158	0.006*	−0.2698 to −0.04207

[a] Common VD-sensitive questions between GDS-30 and GDS-15.

FIGURE 4. Hispanic ethnicity is associated with lower VD levels and higher GDS scores. (A) Simple logistic regression analysis of the relationship between VD level and the probability of Hispanic ethnicity (p_{HLE}). The estimated equation is log odds = 2.153 - -0.09455*X. (B) VD level is significantly lower in HLE (open red symbols) than non-HLE (open blue symbols) populations (Mann-Whitney nonparametric test). Asterisks indicate p <0.0001. (C) Simple logistic regression of GDS total score vs. p_{HLE}. The estimated equation is log odds = -0.8973 + 0.09031*X. (D) Differences in the distribution of HLE and non-HLE groups across VD strata. Error bars indicate upper and lower limits. Dotted lines in A and C indicate 95% confidence bounds.



reducing VD sensitivity (see Fig. 2B). Therefore, on the basis of 9/30 (30%) statistically significant GDS question correlations, VD-sensitive scores were pooled into a "VD-Sensitive" GDS (VS-GDS) subfactor. A strong significantly negative association was found between VS-GDS and VD level (n = 299, Spearman r = -0.274, p < 0.0001). Linear regression analysis gave similar results ($F_{(1,297)}$ = 18.2, R^2 = 0.0577, p <0.0001; Fig. 3D). The Y intercept was 3.29; given that the average GDS score among all participants was 5.5 ± 5.2, this observation suggests that more than half of the GDS score within the sample is sensitive to VD status. The X intercept was 95.2 ng/mL (95% confidence intervals 73.8−151.2 ng/mL).

In summary, VD level was negatively correlated with GDS score, spanned solely Dysphoria and Meaninglessness subfactor domains, and accounted for >50% of the average GDS score. Finally, high VD sufficiency (~74-151 ng/mL) was predicted to be associated with low GDS scores.

Association of HLE Status With Lower VD Levels and Higher Depression Symptoms

To determine whether HLE status related to VD status, we first examined the relationship between VD level and probability of HLE (p_{HLE}) using logistic regression analysis. There was a highly significant negative association (Likelihood ratio test, G^2 = 53.5, p <0.0001; Fig. 4A). The X = 50% was 22.77 ng/mL, indicating that VD levels of <22.77 ng/mL are >50% likely to be from the HLE sample. The ROC curve indicated a positive association (AUC = 0.755 ± 0.282, p <0.0001) yielding sufficient predictive power. VD

levels were significantly lower in HLE (22.93 ± 0.85 ng/mL, n = 121) than non-HLE (32.36 ± 0.96 ng/mL, n = 178; U = 5280, p <0.0001, Mann-Whitney U test; Fig. 4B) samples. We then investigated whether the HLE group was at higher risk of depressive symptoms. Logistic regression between GDS total score and p_{HLE} revealed a significant positive association (Likelihood ratio test, G^2 = 14.85, p = 0.0001; AUC = 0.601, p = 0.0031; Fig. 4C). The X=50% value of 9.9 indicated that individuals who have a score that is nearly 10 (close to the range for a clinical diagnosis of depression, GDS ≥10), are >50% likely to be HLE status.

Next, we investigated whether differences in GDS scores existed between HLE and non-HLE samples. HLE was associated with a significantly higher GDS score (6.89 ± 0.57, n = 120) compared to the non-HLE group (4.53 ± 0.30, n = 178; U = 8519, p = 0.0029, Mann-Whitney U, not shown). We also examined GDS subfactor scores in the HLE group compared to the overall study sample. The HLE group was associated with a significantly higher Dysphoria score (2.79 ± 0.26, n = 120) than non-HLE (1.32 ± 0.13, n = 178; U = 7472, p <0.0001, Mann-Whitney U, not shown). Similarly, HLE had a significantly higher Meaninglessness score (0.98 ± 0.13, n = 120) than non-HLE (0.49 ± 0.07, n = 178; U = 8615, p = 0.0012, Mann-Whitney U, not shown). However, neither Apathy (U = 10422, p = 0.715, Mann-Whitney U, not shown) nor Cognitive Impairment (U = 9740, p = 0.18; Mann-Whitney U, not shown) scores were significantly different between HLE and non-HLE groups. We interpret these results to suggest that the HLE group suffers more severe symptoms than the non-HLE group, but, consistent with the overall sample, GDS scores remain largely within Dysphoria/Meaninglessness subfactor domains. In summary, compared to the non-HLE group, the HLE group possessed lower VD levels and higher total GDS scores.

Finally, we tested the hypothesis that HLE and non-HLE groups are differentially stratified across categorical VD levels. We found that VD stratification was significantly different between HLE and non-HLE across VD strata ($X^2_{(3,\ 299)}$ = 52.09, p <0.0001; Fig. 4D). First, a greater fraction of the HLE group (85.1%) occupied VDD and VDI categories relative to the non-HLE group (45.5%). Second, a greater fraction of the non-HLE group occupied VD sufficient and high VD sufficient (54.5%) than HLE (14.9%) categories. The largest difference was observed in the VD deficient category, where 48/121(39.7%) of the HLE group were VDD, compared to only 27/178 (15.2%) of the non-HLE group. Finally, 43/178 (24.1%) of the non-HLE group but only 5/121 (4.1%) of the HLE group were in the high VD sufficient category. The relative absence of HLE in the high VD sufficient category suggests that only 4.1% of the HLE sample actively take VD supplements that would be required to achieve high VD sufficiency.

DISCUSSION

The present study provides new and significant information on VD and depression in rural West Texas communities compared to a previous report on the influence of VD status on depression in a smaller sample of 68 PF participants.[26] Although the data were generated exclusively in Parmer County, we feel it to be representative of a rural West Texas population based off similar demographics, educational attainments, health care access, and geographic setting. Here, we investigated identical GDS variables within a four-fold larger dataset. We report four notable findings. First, we validated that VDD/VDI is a major public health concern among PF participants in West Texas (Fig. 1). Second, we found a significant negative association between VD status and GDS score (Fig. 2). Third, this association spanned two GDS subfactor domains: Dysphoria and Meaninglessness (Fig. 3), but not Apathy and Cognitive Impairment. Moreover, we analyzed the VD sensitivity of specific GDS questions (Fig. 3C; Table 1). We found that 9 GDS-30 questions were VD-sensitive, 4 of which also appear on the GDS-15 test (Table 1). GDS question 25 was the most highly VD sensitive (Table 1).

Finally, we found that HLE groups had lower VD levels, which were also associated with higher depressive symptoms compared to their non-HLE counterparts (Fig. 4). GDS subfactors were similar but more severe for the HLE group. Although previous studies have shown VDD/VDI in HLE individuals[13,31] and HLEs in rural West Texas have been recognized to be at risk for depression previously,[32,33] to our knowledge, this is the first study to associate VDD/VDI with HLE in aging rural West Texans. Although a previous study in Mexican pregnant women had

shown VDI in both urban and rural HLE,[34] it is possible that there may be challenges to health care access in rural groups that could alter VD status. Our results identify at-risk communities that may have implications for VD treatment strategies to combat depression and depressive symptoms among individuals suffering from health disparities in rural West Texas. Moreover, we revealed new insights into the VD sensitivity of GDS subfactors and specific GDS questions.

Several previous studies have failed to yield significant results of VD supplements in treating clinical depression (i.e. [25,35,36]). Although it is possible that VD supplementation truly has no effect on some types of depression, previous studies may contain confounds that limit or obscure effect size, such as design effects in dose, duration, and/or administration that lead to floor or ceiling effects, inadequately defining thresholds that determine a beneficial effect, and VD intakes through sunlight exposure or food that may confound VD supplementation effects.[37,38] One clinical trial demonstrated, by measuring VD levels before and after intervention, that VD supplementation (50,000 IU/2 weeks) was effective in significantly reducing depression scores.[39] Such an experimental design is an attractive approach that could be applied to West Texas communities in future clinical trials.

We discovered that only a subset of GDS questions were associated with VD level (Fig. 3). The subdomain of depression must first be identified to determine the extent that it is associated with VD deficiency. Specifically, the Dysphoria and Meaninglessness subdomains offer insights into managing depression with VD. Conversely, depression specific to the Apathy and Cognitive Impairment subdomains may not benefit from VD supplementation, as these domains appear to be much less VD sensitive. Using the more conservative Bonferroni correction that controls for false positive ratio ($p = 0.0125$ to adjust for the 4 subdomains tested), we found that Dysphoria was still significant ($p = 0.0125$; Fig. 3A). Similarly, adjusting for the 30 GDS questions tested ($p=0.0016667$), 4/9 of the Dysphoria subdomain questions (Q6,9,16,25) remained significant. Indeed, the Dysphoria subdomain question 25 remained most sensitive to VD level (Table 1). Unfortunately, this question is not included in the GDS-15 test. Consistent with the weaker significance of the Meaninglessness subdomain (Fig. 3B), the Meaninglessness subdomain, as well as all three (gds_3,gds_5, gds_23) of the Meaninglessness GDS-30 subdomain questions, did not reach significance after Bonferroni correction. Therefore, on the basis of these results, we propose that Dysphoria GDS-30 questions gds_6, gds_9, gds_16, and especially gds_25, be considered as a rapid means of determining whether measuring VD level is advised. It would be interesting to validate the VD sensitivity of these GDS questions using additional published or publicly available datasets that measure both GDS-30 and VD levels in multi-ethnic cohorts.

VD status is influenced by many environmental and metabolic factors, spanning VD consumption, absorption, and production. First, VD synthesis is directly influenced by UVB ray absorption via sunlight exposure. Despite West Texas having abundant sunshine throughout the year, VDD/VDI was detected in over half of participants. The underlying mechanisms for this observation are not clear because exposure to sunlight and/or being outdoors were not measured variables in the PF database. Second, skin melanin concentration influences VD absorption.[40,41] This barrier to VD synthesis[42,43] may explain, at least in part, decreased VD levels among HLE participants in this study.[42] Notably, we found that only 4.1% of our HLE sample possessed high VD sufficiency levels, which may suggest that VD supplementation is rare within the rural HLE population. Third, chronic diseases, which include obesity, cardiovascular disease, type 2 diabetes, and kidney disease, are highly prevalent in HLE communities across West Texas.[44] These disease processes increase inflammation and reactive oxygen species generation throughout the integumentary system, liver, and kidney, impairing their integral function in VD synthesis.[45,46] Mexican Americans were found to have 5−12 times higher rate of diabetes and depression comorbidity compared to their non-HL counterpart.[21] In addition, obesity is associated with low VD status, which may be explained by sequestration of VD in adipose tissue. Finally, chronic stress, possibly influenced by socioeconomic status, can reduce VD levels.[43] Therefore, comorbidities frequent in HLE communities may contribute to reduced VD levels and increased levels of depression in this sample. These variables have been investigated and are topics for future studies.

Currently, recommendations for VD supplementation vary widely. General recommendations were historically aimed to provide a VD threshold dose to prevent musculoskeletal diseases such as rickets,[8,47] yet effective doses to prevent non-musculoskeletal diseases such as depression have not been incorporated.[48] Current NIH guidelines recommend 600 IU of supplementation for 1- to 70-year-olds and 800 IU for >70-year-olds. However, the Endocrine Society recommends 1,500-2,000 IU for adults to maintain VD levels above >30 ng/mL.[28] A systematic review of 10 RCTs over 12 months with 3,336 participants showed high VD supplementation of 4,000 IU significantly decreased depressive symptoms regardless of participant's baseline VD level.[49] Notably, less than 4,000 IU supplementation failed to show any improvement in symptoms.[49] Further studies should investigate the maintenance level that provides the maximum VD therapeutic effects on depressive symptoms. Finally, depressive symptoms should be examined by considering its GDS subdomains. This study suggests that VD supplementation might be effective when treating individuals with Dysphoria and/or Meaninglessness-specific depressive symptoms. When accounting for only VD-sensitive GDS subdomains (Fig. 3D), a VD level of 95.5 ng/mL corresponded to a GDS of 0. On the other hand, a VD level of 0 ng/mL approached a GDS of 3.24, signifying risk for depressive symptoms.

Some limitations of our study should be considered. First, this is a cross-sectional, correlative study; therefore, we cannot infer causal relationships beyond speculation. Second, no PF variables exist that capture sunlight exposure, time spent outside, or skin pigmentation. Third, PF variables do not exist on VDR gene single nucleotide polymorphisms (SNPs) that would impact VD metabolism,[50] which spans across different ethnicities.[51,52] Fourth, we did not perform a detailed analysis of antidepressant medications and/or therapies, which could impact depressive symptom severity. Fifth, GDS and HLE are self-reported measures, which may signal differences in some social, cultural, and economic factors that were not explicitly included in this study. Therefore, misclassification bias cannot be ruled out. Sixth, in a deliberate effort to replicate the statistical analysis of an earlier study,[26] we only explored linear relationships between VD level and GDS. Seventh, we have not performed multiple linear regression or multivariate analyses on this dataset. Therefore, the possibility of chance findings cannot be excluded. Eighth, relative to the original study of 68 participants,[26] some group comparisons were associated with large effect sizes (Cohen's $d > 0.8$) and significance was still present after Bonferroni correction for false discovery rate. However, we still lack sufficient power and balance in the study design to fully address subgroup analyses (i.e. ethnicity and other demographics). Finally, because participant samples were obtained using a convenience sampling technique, these findings apply to the sample and may, or may not, be generalizable to the West Texas population.

In conclusion, sufficient VD levels is associated with reduced depression levels in our sample, suggesting that VD supplementation may hold promise for managing VD-sensitive depressive symptoms in future studies that use larger sample sizes. Treatment strategies should be tailored to target populations with VD-sensitive forms of depression established by a clinical diagnosis. HLE communities are more vulnerable to VDD and may be less likely to use VD supplements, though other factors need to be considered, as currently only 4.1% of HLE individuals in our sample fell into the high sufficient VD category. Proper diagnosis and treatment could potentially lead to improved quality of life in over 22.4 million individuals, especially HLE individuals in rural communities of West Texas, as identified in this study.

AUTHOR CONTRIBUTIONS

MP, JJL, FRV, AB, and AS made substantial contributions to the conception and design of the work. JJL, MP, and JK drafted the work. JJL, JC, GA, HK, and VN revised it critically for important intellectual content and interpretation of data for the work. All authors agree to be accountable for all aspects of the work.

DATA STATEMENT

The data from this study initially were presented in poster form at the regional Texas Alzheimer's Research

and Care Consortium (TARCC) Scientific Symposium in Austin, Texas on May 12th, 2022. A preliminary abstract was published on the TARCC web site. Data and statistical analyses will be made available upon reasonable request.

DISCLOSURES

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