

Article

Genotype-by-Environment Interactions in Nonalcoholic Fatty Liver Disease and Chronic Illness among Mexican Americans: The Role of Acculturation Stress

Eron G. Manusov ^{1,2,*} , Vincent P. Diego ¹ , Marcio Almeida ^{1,2}, David Ortiz ³, Joanne E. Curran ^{1,2} , Jacob Galan ^{1,2} , Ana C. Leandro ^{1,2} , Sandra Laston ^{1,2} , John Blangero ^{1,2}  and Sarah Williams-Blangero ^{1,2}

¹ Department of Human Genetics, University of Texas Rio Grande Valley, Brownsville, TX 78520, USA; joanne.curran@utrgv.edu (J.E.C.)

² South Texas Diabetes and Obesity Institute, School of Medicine, University of Texas Rio Grande Valley, Brownsville, TX 78520, USA

³ School of Medicine, University of Texas Rio Grande Valley, Edinburg, TX 78539, USA; david.ortiz04@utrgv.edu

* Correspondence: eron.manusov@utrgv.edu

Abstract: This study examines the complex interplay of genetic and environmental interactions that shape chronic illness risk. Evidence is mounting for the role of genetic expression and the immune response in the pathogenesis of chronic disease. In the Rio Grande Valley of south Texas, where 90% of the population is Mexican American, chronic illnesses (including obesity, diabetes, nonalcoholic liver disease, and depression) are reaching epidemic proportions. This study leverages an ongoing family study of the genetic determinants of risk for obesity, diabetes, hypertension, hyperlipidemia, and depression in a Mexican American population. Data collected included blood pressure, BMI, hepatic transaminases, HbA1c, depression (BDI-II), acculturation/marginalization (ARSM-II), and liver health as assessed by elastography. Heritability and genotype-by-environment ($G \times E$) interactions were analyzed, focusing on the marginalization/separation measure of the ARSM-II. Significant heritabilities were found for traits such as HbA1c ($h^2 = 0.52$), marginalization ($h^2 = 0.30$), AST ($h^2 = 0.25$), ALT ($h^2 = 0.41$), and BMI ($h^2 = 0.55$). Genotype-by-environment interactions were significant for HbA1c, AST/ALT ratio, BDI-II, and CAP, indicating that genetic factors interact with marginalization to influence these traits. This study found that acculturation stress exacerbates the genetic response to chronic illness. These findings underscore the importance of considering $G \times E$ interactions in understanding disease susceptibility and may inform targeted interventions for at-risk populations. Further research is warranted to elucidate the underlying molecular pathways and replicate these findings in diverse populations.

Keywords: $G \times E$; NAFLD; Mexican Americans; acculturation stress; marginalization



Citation: Manusov, E.G.; Diego, V.P.; Almeida, M.; Ortiz, D.; Curran, J.E.; Galan, J.; Leandro, A.C.; Laston, S.; Blangero, J.; Williams-Blangero, S. Genotype-by-Environment Interactions in Nonalcoholic Fatty Liver Disease and Chronic Illness among Mexican Americans: The Role of Acculturation Stress. *Genes* **2024**, *15*, 1006. <https://doi.org/10.3390/genes15081006>

Academic Editor: Clifford J. Steer

Received: 24 May 2024

Revised: 23 July 2024

Accepted: 30 July 2024

Published: 1 August 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Background

Hispanics are one of the largest and fastest-growing minority groups in the United States and are burdened with a disproportionately high prevalence of chronic illnesses [1]. In regions such as the Rio Grande Valley of south Texas, the prevalence of nonalcoholic fatty liver disease (NAFLD) approaches epidemic proportions (60%) in the Mexican American population [2–5]. NAFLD is the leading cause of liver disease in the world [6–10], and risk for the condition is associated with diabetes [11–13], depression [14,15], and obesity [8]. The heritability of NAFLD [16] ranges from 25% to 75%, with genetic loci related to hepatic fat accumulation, lipid metabolism, and insulin resistance [17]. Obesity [18], depression [19–22], and diabetes are also highly heritable [23,24] and influence the prevalence of NAFLD, as well as the progression of liver disease.

Previous research on NAFLD identified $G \times E$ interaction effects with depression, socioeconomic status, physical exercise, social stress, and the social determinants of

health [25–28]. As communities on the US–Mexico border grow and change in size, acculturation stress affects individuals as they assimilate into the US population. South Texas is unique compared to many areas of the United States because of its proximity to the US–Mexico border, high rates of poverty, increased immigration, and rapid growth. However, it shares similarities with other areas that experience high migration rates [29]. The population of the Rio Grande Valley region is predominantly of Mexican ancestry and is home to families that have been established for generations, new Mexican immigrants, families that only speak Spanish, bilingual families, and families that only speak English. The counties of the Rio Grande Valley (Cameron, Hidalgo, Starr, and Willacy) rank among the poorest in the nation. Cultural integration in the region is influenced by English language fluency, occupation, income status, and health insurance coverage [30].

The acculturation phenomenon occurs when individuals from one culture come into continuous first-hand contact with a predominant culture, subsequently changing cultural beliefs, values, identity, language, customs, diet, or social relationships [31,32]. The acculturation process, specifically acculturation stress, may result in depression, substance abuse, and less healthy dietary behaviors. Although there are over one hundred models of acculturation, a prominent accepted model is the “four-fold model” that assesses integration, assimilation, marginalization, and separation [33]. This model attempts to explain acculturation in terms of goodness-of-fit into society that can be mediated by acculturation stress and is described in the development of the Acculturation Rating Scale for Mexican Americans-II (ARSMA-II) [34,35]. The ARSMA-II contains two scales, one that measures acculturation as orientation (Mexican or Anglo) (13 items with a coefficient alpha of 0.83) and a second scale that measures marginality and separation (17 items with a coefficient alpha of 0.88). Each scale can be used independently.

Our goal is to assess the gene-by-environment interaction effects of acculturation stress on chronic illness, obesity, depression, diabetes, and NAFLD in Mexican Americans of the Rio Grande Valley. We theorize that genes underlying chronic illness interact with marginalization (acculturation stress) to worsen disease.

2. Materials and Methods

The University of Texas Rio Grande Valley IRB approved the study protocol. All participants provided informed consent before participating in the study. The Rio Grande Valley (RGV) is 90% Hispanic, with a high prevalence of diabetes (32%), obesity/overweight (60%), and NAFLD (60%). As described in earlier publications, our ongoing genetic epidemiological study recruits probands who are 18 years of age or older, have a family history of diabetes, and have five family members each having four Mexican-origin grandparents who are eligible to participate [3].

We recruited 547 participants into the RGV Family Study belonging to large families [16]. Community health workers (research assistants) interfaced with local community sites and contacted the family members identified by the proband. They obtained informed consent and scheduled each participant for assessment by the investigators at a community health clinic [36]. Information gathered included blood pressure, body mass index (BMI), liver transaminases (AST, ALT), HbA1c, an assessment of depression (BDI-II), a measure of acculturation (The Acculturation Rating Scale for Mexican Americans-II (ARSMA-II), and a measure of liver health (vibration-controlled transient elastography and controlled attenuation parameter measured by the FibroScan device) [37,38]. The recruitment strategy is further described in previous publications [16,25].

The Beck Depression Inventory-II (BDI-II) was used to assess the degree of depressive symptoms over the past two weeks [16,39]. The BDI-II is a reliable screening tool for assessing the severity of depression. The BDI-II assesses the severity of depression and is an acceptable screening instrument for depression when administered either in Spanish or English [40–42].

The Acculturation Rating Scale for Mexican Americans-II (ARSMA-II) was designed to quantify the acculturation construct and is the basis of many available acculturation

scales. The scale comprises two subscales (orientation and marginalization) that can be analyzed individually. Since we are interested in the role of acculturation stress and $G \times E$ effects on NAFLD, we analyzed the marginalization/separation measure of the ARSMA-II.

We measured hepatic fibrosis, which was reported as the Liver Stiffness Measurement LSM Youden Index (kPa), steatosis (controlled attenuation parameter dB/m CAP), and the FAST (FibroScan-AST) (the most predictive model for risk of fibrosis that combines LSM, CAP, and AST). CAP identifies steatosis with an AUROC of 0.87 (95% confidence interval [CI] 0.82–0.92) for $S \geq S1$, 0.77 (95% CI 0.71–0.82) for $S \geq S2$, and 0.70 (95% CI 0.64–0.75) for $S = S3$. Youden cutoff values for $S \geq S1$, $S \geq S2$, and $S \geq S3$ were 302 dB/m, 331 dB/m, and 337 dB/m, respectively. LSM identified patients with fibrosis with AUROCs of 0.77 (95% CI 0.72–0.82) for $F \geq F2$, 0.80 (95% CI 0.75–0.84) for $F \geq F3$, and 0.89 (95% CI 0.84–0.93) for $F = F4$. Youden cutoff values for $F \geq F2$, $F \geq F3$, and $F = F4$ were 8.2 kPa, 9.7 kPa, and 13.6 kPa, respectively (Echosens, Paris, France) [37,43–45]. Exclusion criteria included pregnancy, implant, or a cardiac pacemaker. Participants presented fasting for at least 3 h prior to the exam. The participants lay supine, face-up on the exam table, and fully abducted their right arm. The FibroScan automatically chooses the correct probe size (M/XL). Ultrasound conduction gel was applied to the abdomen at the 8th–10th intercostal rib space at the mid-axillary line. Measurements were performed by scanning the right liver lobe through the intercostal space. CAP is an average estimate of ultrasound attenuation at 3–5 MHz (dB/m). Liver stiffness measurements (LSMs) are an average stiffness measurement at a shear wave frequency of 50 Hz (kilopascals). The median value of successful measurements with at least ten validated measurements and a success rate of at least 30% were selected to represent the LSM [44,46–48].

Additional measures included body mass index (BMI), aspartate aminotransferase (AST) ($AST > 37$), alanine aminotransferase (ALT) ($ALT > 40$ U/L in males or AST or $ALT > 31$ U/L in females), and the AST/ALT ratio (AST/ALT ratio > 1) [49]. The FibroScan-AST score (FAST), to evaluate progression of liver disease, was calculated for each participant [44].

2.1. Statistical Analysis

Using a variance components approach, we estimated heritabilities (h^2) and genotype $\times$ environment interaction effects (SOLAR. <https://solar-eclipse-genetics.org/about-brief-overview>). Each liver-related phenotype (AST, ALT, AST/ALT, CAP, FAST, and kPa), as well as hemoglobin A1C (HgA1C), BMI, and the ARSMA-II Marginalization Scale, was regressed against age, sex, age-squared, sex-by-age, and sex-by-age-squared. The regression residuals derived for each trait were then normalized using an inverse normal transformation [50].

2.2. Genotype-by Environment ($G \times E$) Interaction Model for Continuous Environments

The process is a multi-step analysis that begins with a standard additive polygenic model used to obtain estimates of liver trait heritabilities and that serves as a reference model for more complex model development. The polygenic model postulates that the phenotypic covariance can be decomposed into additive genetic and residual environmental variance components. The inter-individual covariances are defined by the additive genetic variance weighted by the genetic relatedness coefficient, assuming (for genetic covariance) that the pairwise genetic correlation across environments is unity and that the additive genetic variance is homogeneous.

The second step is to fit a $G \times E$ model to the data. To capture any potential interaction between the genetic effects (either the additive genetic variance and/or genetic correlation) and the specific environment (marginalization), we express both the additive genetic variance and genetic correlation as continuous functions of the environment (marginalization). If the expression of the aggregate of all genotypes underlying a phenotype (polygenotype) is dependent on a specific environment, this implies that the genotype–phenotype map for the trait (NAFLD) is a function of the environment. The $G \times E$ interaction variance is zero if the following two conditions are simultaneously true: (1) homogeneity of the

additive genetic variance across environments: $\sigma^2_{g1} = \sigma^2_{g2} = \sigma^2_g$, where σ^2_{g1} and σ^2_{g2} are the additive genetic variance in environments 1 and 2, respectively; (2) complete positive pleiotropy (i.e., the same genes are active across environments) in which the genetic correlation ($\rho_g = 1$) is one across environments: $\rho_g = 1$. There is $G \times E$ evidence if either null hypothesis is rejected [51]. Rejection of either or both of these statistical null hypotheses is evidence that the phenotypic response to the environment has a genetic basis.

We modeled the genetic variance and cross-environment genetic correlation as functions of “marginalization”, where the quantitative measure of marginalization is the total score on the marginalization survey. Since it is likely that our focal “environment” is also influenced (directly or, more likely, indirectly) by genetic factors, we first tested for genetic factors underlying the ARSMA-II measure of marginalization and observed a significant heritability of 0.30 ($p < 3.8 \times 10^{-5}$). We can account for additive genetic and environmental covariances among relatives in a known pedigree structure—using best linear unbiased prediction (BLUP) [52]. We then subtract the BLUP genetic values for the marginalization variable to obtain a BLUP-computed marginalization variable that reflects primarily environmental effects [52]. This lattermost variable is the focal (genetically corrected) environment in our $G \times E$ model.

We then model the genetic variance function (and model the environmental variance) using an exponential function of marginalization, where the exponential function maintains positivity, which is required of a variance [53]. Taking the natural logarithm of the exponential function, the variance homogeneity null hypothesis holds for a slope term equal to 0: $\gamma_g = 0$. The genetic correlation was modeled using the exponential decay function of the pairwise differences in marginalization scores.

We carried out model evaluations and hypothesis testing in two stages. In stage one, we determine which model (overall $G \times E$ interaction model or the polygenic model) provided a better fit to the data by way of a likelihood ratio test (LRT). It is important to note that the polygenic model is fully nested within the $G \times E$ interaction model and that relative to the polygenic model, the $G \times E$ interaction model has three additional parameters (γ_g , γ_e , and λ ; α_g and α_e are re-parameterized versions of the variances). The LRT statistic for this comparison is distributed as a 50:50 mixture of chi-squares with 2 and 3 degrees of freedom (df) [50,51,54].

We examine the more specific $G \times E$ interaction hypotheses in the second stage. The full $G \times E$ model with all parameters estimated was compared with models when either gamma (γ) or lambda (λ) was constrained to 0 to test, respectively, the hypotheses of additive genetic variance homogeneity and a genetic correlation equal to one. The distributions of the LRT statistics are a chi-square with 1 df, and a 50:50 mixture of a chi-square with a point mass at 0 and a chi-square with 1 df [51,54]. As part of this stage, we determined if each of the three additional parameters in the full $G \times E$ interaction model (γ_g , γ_e , and λ) should even be included at all by comparing its maximum likelihood estimate (MLE) to its standard error (S.E.). A parameter is roughly significant if its MLE is greater than twice its S.E. based on likelihood theory. Therefore, if a parameter S.E. was greater than its MLE, we judged that parameter to be statistically unimportant. We formally tested additional parameters by the same tests. If any of the three additional parameters were found to have S.E.s greater than their MLEs and if these were found to be formally insignificant, we then compared a reduced version of the $G \times E$ interaction model to the polygenic model, excluding the insignificant parameters.

3. Results

The characteristics (age, HbA1c, marginalization, AST, ALT, AST/ALT, BDI-II, BMI, CAP, FAST, kPa) of the sample by sex are listed in Table 1. Two-sample independent *t*-tests tested sex differences. There were significant differences by sex for AST, ALT, AST/ALT, BDI-II, and FAST. There were no significant differences between males and females for HbA1C, marginalization, BMI, CAP, and kPa.

Table 1. Characteristics of the sample showed significant differences by sex for AST, ALT, AST/ALT, BDI-II, and FAST.

Trait	Females		Males		<i>p</i> -Value for Difference
	Mean (N = 406)	S.D.	Mean (N = 141)	S.D.	
Age	44.13	14.61	46.18	15.69	0.1739
Marginalization	24.21	10.96	24.43	12.02	0.8543
BDI-II	6.79	8.14	4.59	6.51	1.4×10^{-3}
BMI	32.49	7.07	32.25	6.97	0.7272
HbA1C	6.60	1.96	6.62	2.13	0.9318
AST	19.91	15.78	25.69	19.83	2.0×10^{-3}
ALT	22.30	23.73	33.35	31.98	1.2×10^{-4}
AST/ALT	1.16	0.65	0.99	0.63	6.4×10^{-3}
CAP	284.24	64.94	289.64	59.21	0.4919
kPa	6.64	4.49	7.02	4.11	0.4808
FAST	0.14	0.20	0.22	0.26	8.4×10^{-3}

Heritability: Individuals with a complete data set (547) were analyzed. Heritabilities of the traits are significant and reported in Table 2 HbA1c ($h^2 = 0.52$, $p = 2.5 \times 10^{-6}$), Marginalization ($h^2 = 0.30$, $p = 3.8 \times 10^{-5}$), AST ($h^2 = 0.25$, $p = 0.029$), ALT ($h^2 = 0.41$, $p = 6.9 \times 10^{-3}$), AST/AST ($h^2 = 0.27$, $p = 1.9 \times 10^{-3}$), BDI-II ($h^2 = 0.36$, $p = 1.5 \times 10^{-5}$), BMI ($h^2 = 0.55$, $p = 8.0 \times 10^{-7}$), Steatosis CAP ($h^2 = 0.34$, $p = 3.6 \times 10^{-4}$), FAST ($h^2 = 0.35$, $p = 2.3 \times 10^{-3}$), hepatic fibrosis kPa ($h^2 = 0.37$, $p = 0.01$) and steatosis ($h^2 = 0.33$, $p = 4.3 \times 10^{-3}$). We formally compared the full G×E interaction model to the polygenic model for HbA1c, AST, ALT, AST/ALT, BDI-II, BMI, CAP, kPa, FAST (Table 3).

Table 2. Significant heritabilities with *p*-values.

Trait	Heritability	Standard Error	<i>p</i> -Value
HbA1C	0.52	0.11	2.5×10^{-6}
Marginalization	0.30	0.08	3.8×10^{-5}
AST	0.25	0.14	2.0×10^{-2}
ALT	0.41	0.13	6.9×10^{-3}
AST/ALT	0.27	0.10	1.9×10^{-3}
BDI-II	0.36	0.10	1.5×10^{-5}
BMI	0.55	0.11	8.0×10^{-7}
CAP	0.34	0.10	3.6×10^{-4}
FAST	0.35	0.13	2.3×10^{-3}
kPa	0.33	0.13	4.3×10^{-3}

From likelihood theory, a parameter's maximum likelihood estimates (MLEs) should be at least two times its standard error (S.E.) to indicate significance. When we found that the S.E. of a parameter was larger than its MLE, and if formal testing revealed it to be insignificant, we then elected to use a reduced version of the G×E model (Red. G×E). The results of comparing the polygenic model to either a reduced or full version of the G×E model are reported in Table 3. We found that the G×E model fit the data significantly better than the polygenic model for A1C, AST/ALT, BDI-II, BMI, and CAP.

Table 3. Testing the $G \times$ Marginalization interaction model against the polygenic model demonstrating $G \times E$ interaction.

Trait	Model	Ln Likelihood	Chi-Square	p-Value
HbA1c	Polygenic	−261.838	9.72868	4.8×10^{-3}
	Reduced $G \times E$	−256.973		
AST	Polygenic	−261.088	2.503294	0.199821
	Full $G \times E$	−259.836		
ALT	Polygenic	−264.444	2.952168	0.157147
	Full $G \times E$	−262.968		
AST/ALT	Polygenic	−265.081	14.65585	3.9×10^{-4}
	Full $G \times E$	−257.753		
BDI-II	Polygenic	−247.356	20.96177	1.6×10^{-5}
	Full $G \times E$	−236.876		
BMI	Polygenic	−260.745	12.40074	2.03×10^{-3}
	Reduced $G \times E$	−254.545		
CAP	Polygenic	−261.838	9.72868	7.7×10^{-3}
	Reduced $G \times E$	−256.973		
FAST	Polygenic	−226.611	1.992278	0.263703
	Full $G \times E$	−225.615		
kPa	Polygenic	−275.19	0.375754	0.684301
	Full $G \times E$	−275.002		

Results of the hypothesis tests for variance homogeneity (additive genetic and/or residual environment) and for the genetic correlation are presented in Figure 1a–c (Addendum Table 1). For HbA1c, we found that the genetic correlation significantly decays from one with increasing differences in marginalization (that is, $G \times E$ interaction due to the genetic correlation is indicated). For AST/ALT ratio, we found evidence of $G \times E$ interaction due to both additive genetic variance heterogeneity and a genetic correlation less than one. Moreover, for this trait, there was significant residual environmental variance heterogeneity. For BDI-II, the additive genetic variance was significantly increasing, whereas the residual environmental variance was significantly decreasing, with increasing marginalization. In other words, BDI-II comes to be increasingly dominated by genetic effects with increasing marginalization. For BMI, we found evidence of $G \times E$ interaction due to additive genetic variance heterogeneity (decreasing with increasing marginalization). For CAP, we found significant heterogeneity for both the additive genetic variance (evidence of $G \times E$ interaction) and the residual environmental variance. This evidence confirms that genetic factors interact with marginalization to influence the expression of the AST/ALT ratio, as well as risk for diabetes (HbA1c), depression, and obesity (BMI).

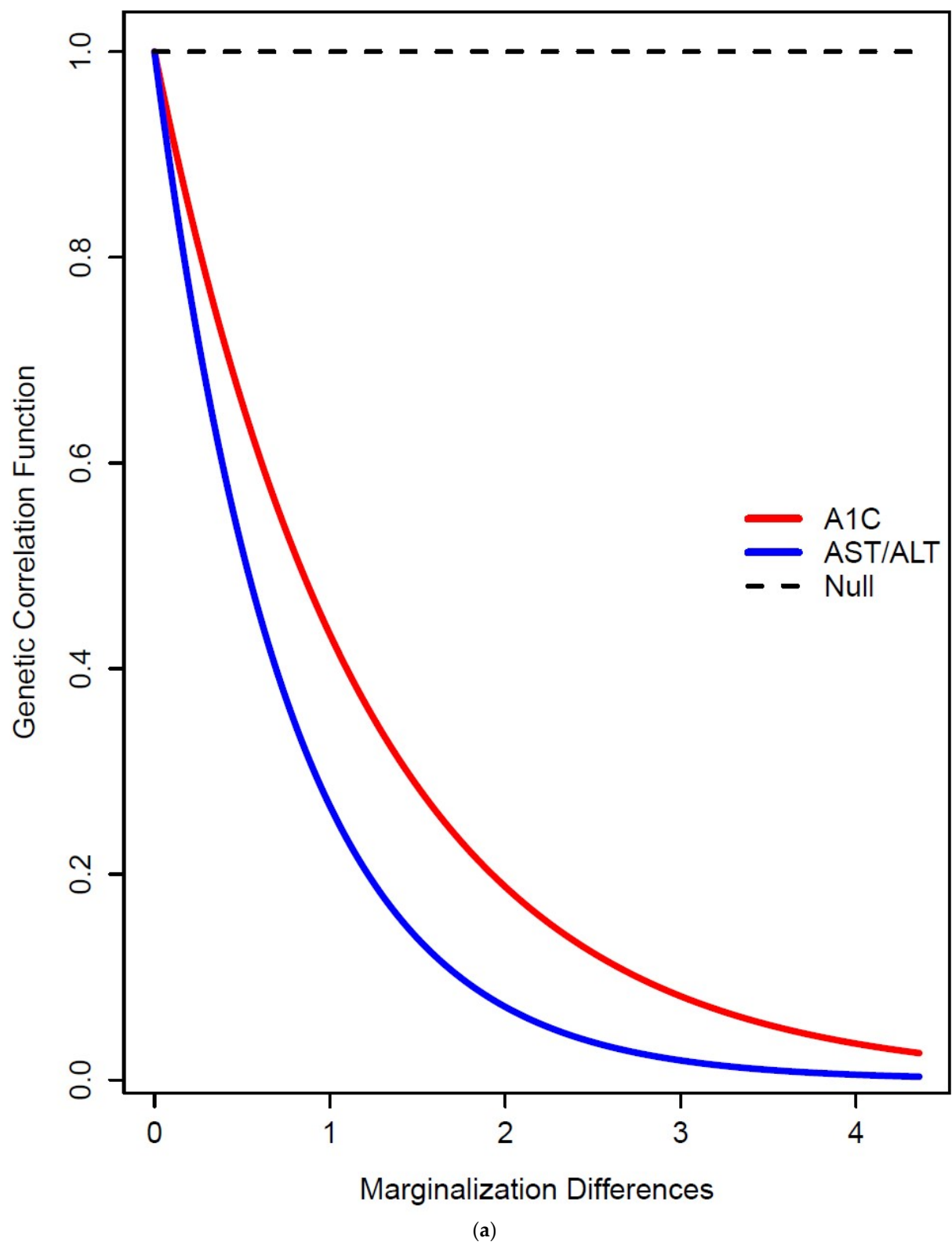


Figure 1. Cont.

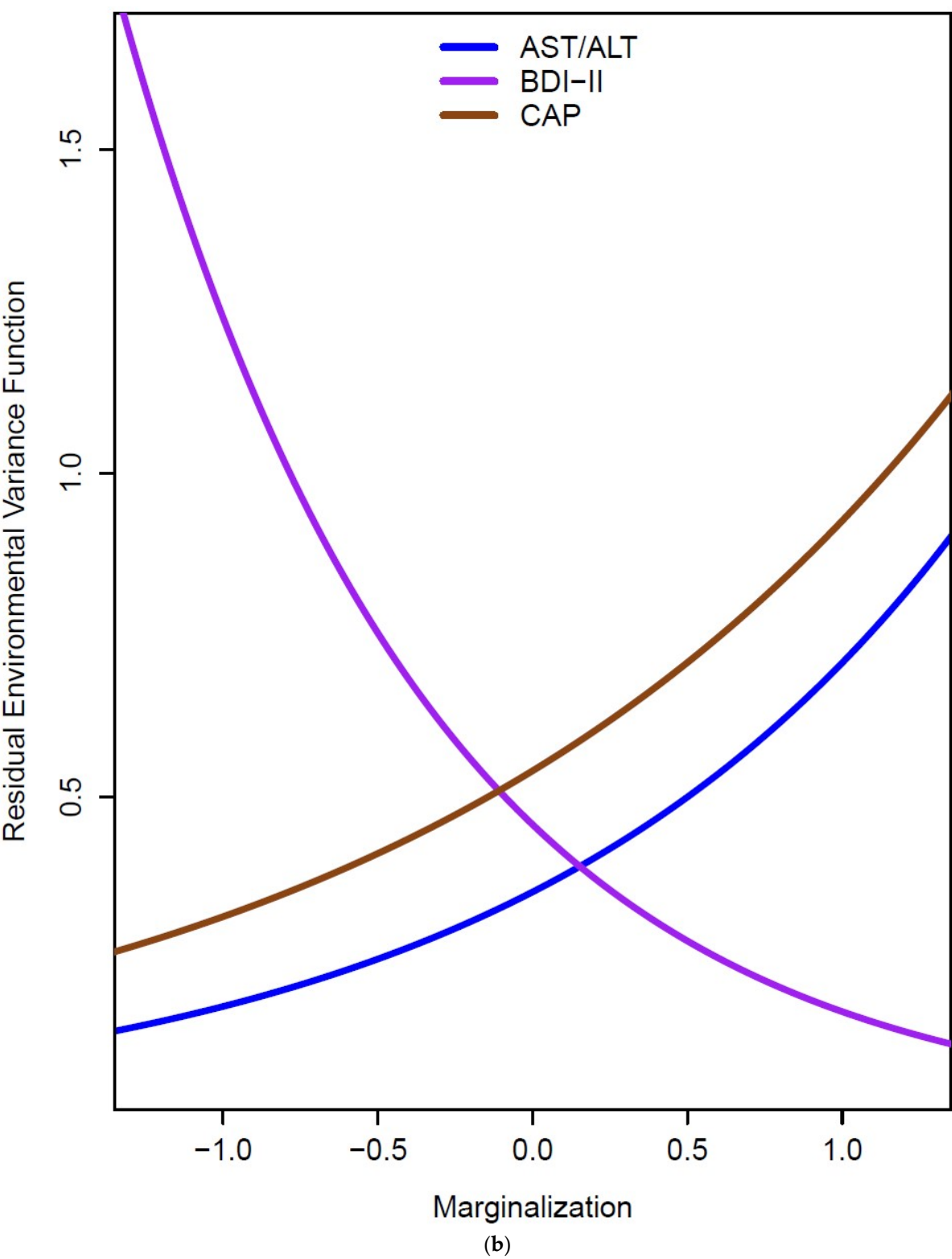


Figure 1. Cont.

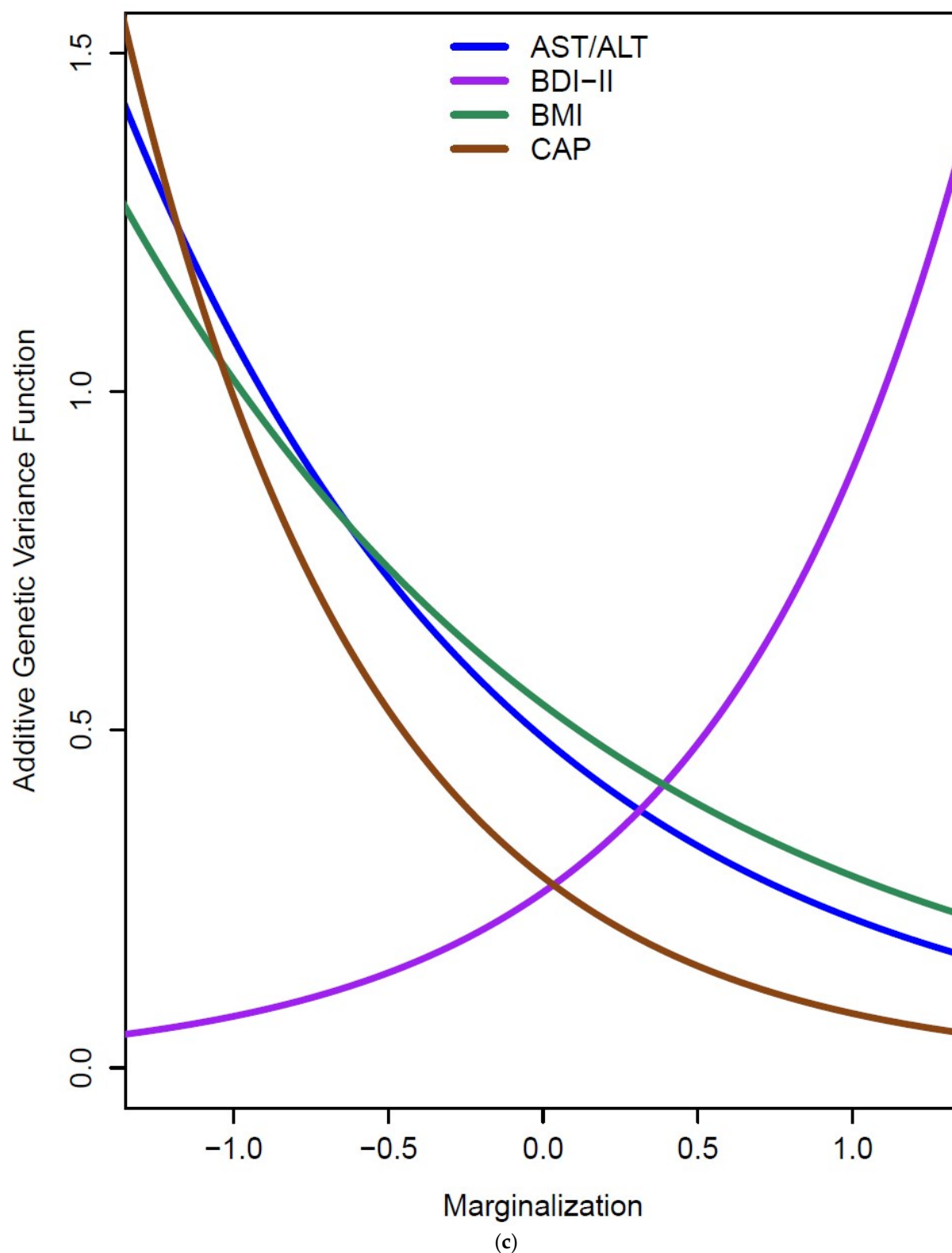


Figure 1. (a) The additive genetic variance function AST/ALT, BDI-II, BMI, CAP; (b) the residual environmental variance function for AST/ALT, BDI-II, CAP; (c) the genetic correlation function for A1C and AST/ALT.

4. Discussion

This study investigates the gene-by-environment interactions and the response to acculturation stress (marginalization) that shape chronic disease (obesity, diabetes, depression,

and liver disease) risk. The impact of an environmental factor (such as marginalization) on a trait (such as obesity, diabetes, depression, and liver disease) can vary depending on the genetic makeup of an individual. G×E interaction findings increasingly support how genes underlying chronic illness respond to different environments. Our recent studies demonstrate the joint effects of socioeconomic status and genetics on risk for cardiovascular disease [25]. We used variance component models and likelihood-based statistical inference to examine the role of genes underlying hepatic fibrosis, steatosis, transaminases, and the FAST score that respond to the environment (depression). We found statistically significant moderate heritabilities for AST/ALT ($h^2 = 0.26$, $p = 0.004$), (3) FAST ($h^2 = 0.36$, $p = 1.5 \times 10^{-3}$) [3], fibrosis ($h^2 = 0.36$, $p = 0.01$), and steatosis ($h^2 = 0.33$, $p = 0.01$) [16]. We also reported G×E interaction between genes underlying the AST/ALT ratio, FAST, steatosis, fibrosis, and depression [3,16]. In this study, we found associations between marginalization, obesity, diabetes, depression, and NAFLD (in particular, the AST/ALT ratio and steatosis), further affirming the G×E effects at the molecular level.

Acculturation affects lifestyle habits among Hispanics in United States–Mexico border communities [50]. Less acculturated Mexican Americans are more likely to consume food items on the Healthy Eating Index [51]. Second-generation Mexican Americans who prefer English, compared to bilingual or Spanish language preference (especially women), more frequently report eating foods on the Unhealthy Eating Index. Mexican Americans born in Mexico report consuming more fruits and vegetables than Mexican Americans born in the US. Recent immigrants report healthier eating habits and fewer sugary drinks than second- and third-generation Mexican Americans. When controlled for sociodemographic factors, health, dietary intake, physical activity, and sedentary behavior, greater acculturation was associated with higher BMI and unhealthy dietary intake.

Older individuals demonstrate a greater likelihood of consuming foods on the Healthy Eating Index and of not consuming foods on the Unhealthy Eating Index. Acculturation and hypertension in Mexican Americans are associated (aOR = 1.71, 95% CI, 1.24–2.36) [52]. Our findings reproduce other research as the effects of a genetic risk score for increased BMI and female sex are worsened with higher levels of acculturation in Mexican Americans (controlled for relatedness, gender, principal components of ancestry, and gender) [53]. Acculturation is an effect modifier of family history on metabolic syndrome, correlating with the number of years living in the US. As the number of years in the United States increased, the effect of family history on metabolic syndrome increased, suggesting that gene-by-environment interaction may be more critical in metabolic syndrome traits compared to type 2 diabetes mellitus (T2DM) [54]. The length of residency in the United States is also one of the strongest predictors of obesity. A total of 16% of the variation in BMI can be attributed to the age of immigration, years since the first arrival to the US., and healthy diet [53]. For obesity, the environment may be more important than genetic factors [55].

The process of acculturation that mediates adverse physical and mental health outcomes [56] is explained by acculturation stress experienced from negotiating heritage and host cultures. Age, female sex, acculturation stress, and emotional support are related to chronic illness, while ethnic pride, coping, social support, and individual resilience buffer adverse health outcomes [57]. Our findings support significant genetic variation for BMI and diabetes in response to acculturation.

NAFLD is highly prevalent in both American-born and Mexican-born individuals. Individuals of Mexican ancestry are carriers of risk alleles for metabolic syndrome, diabetes, and depression [28,58–60]. Immigration status, length of stay in the United States, socioeconomic status, education, and chronic illness affect the prevalence of NAFLD and progression to fibrosis and hepatocellular carcinoma. Perceived stress, differences in experiences, and personal resilience mediate the stress response and are also NAFLD risk factors [61]. The odds of NAFLD are higher for Mexican-origin adults with an Anglo orientation, and the odds are lower for Mexican-origin individuals with a Mexican orientation, both reflecting the role of stress associated with acculturation.

Patients with NAFLD have a higher prevalence of depression than patients without NAFLD (R.R.: 2.83, $p < 0.001$) [14,62], and patients with depression have a higher prevalence of NAFLD [3,16]. Our current findings support the $G \times E$ interaction between NAFLD, depression, and acculturation and support the role of acculturation in the phenotypic expression of other chronic illnesses (obesity and diabetes) [63]. NAFLD is a complex condition influenced by genetic, environmental, and social factors. The immune inflammatory response is to be a mediator of chronic illnesses such as diabetes, obesity, depression, and liver disease. Our findings suggest that the interplay of NAFLD and acculturation stress (marginalization) occurs at the cellular or molecular level [57,64–68]. Stress may activate behavioral, psychological, and physical reactions. Pro-inflammatory pathways are involved in translating sociocultural stress (socioeconomic status and low education levels) into mental and physical health disparities. There is evidence that many chronic illnesses upregulate pro-inflammatory gene expression. The reactions are mediated by the hypothalamus–pituitary–adrenal axis (corticotropin-releasing hormone, adrenocorticotrophic hormone, and glucocorticoids) and the sympathetic–adrenal–medullary axis. The pathways are mediated by the immune response (chemokines, cytokines, and growth factors), including interleukin 6 (IL6), interferons (IFNs), and tumor necrosis factors (TNFGs) [69]. Job stress has been associated with seven serum factors (CCL27 CCL27/CTACK, CCL11/Eotaxin, CCL2/MCP-1, IL-17, IL-6, and BDNF) [69]. While the PNPLA3 polymorphism rs738409 C/G variant has been reliably associated with an increased prevalence of NAFLD and the progression of the disease to NASH and hepatocellular carcinoma [70], little is currently known about specific genes involved in NAFLD risk. Future gene identification and transcriptomic, proteomic, and network analysis will further highlight possible precision medicine approaches to the management of chronic illnesses.

5. Limitations

The cross-sectional nature of this study limits our ability to infer causality between acculturation stress, gene-by-environment interactions, and the prevalence of chronic illnesses such as NAFLD, obesity, diabetes, and depression. Longitudinal studies are needed to confirm these associations over time. While our study provides valuable insights into the gene–environment interaction between NAFLD and marginalization, it is essential to acknowledge certain limitations when interpreting the findings. The Acculturation Rating Scale for Mexican Americans-II (ARSMa-II) provides valuable insights but may not capture the full complexity of the acculturation process. Other dimensions of acculturation, such as cultural practices, social networks, and identity conflict, may also influence health outcomes and should be explored in future research. While we controlled for several environmental factors, other unmeasured variables, such as specific dietary components, occupational hazards, and detailed socioeconomic factors, could confound the observed relationships. Future studies should aim to include a broader range of environmental and lifestyle variables. Our sample of 547 participants is reasonable for a single-center study but may limit the generalizability of the findings. The population of the Rio Grande Valley region is predominantly of Mexican origin. A more extensive and diverse sample would provide a broader representation of the Mexican American population and more robust results. The study design was cross-sectional (data from a single time point) and limits, as mentioned, our ability to establish causal relationships or determine the directionality of the observed associations. Longitudinal studies can elucidate the temporal dynamics of the gene-by-environment interactions and their impact on NAFLD, depression, obesity, diabetes, and depression. Our focus is on Mexican Americans, and future research will determine whether the finding of genotype-by-environment interaction effects between chronic illness and acculturation is replicated in other populations. Finally, we did not evaluate the role of alcohol in the $G \times E$ interaction of NAFLD and marginalization. Alcohol consumption may affect the interaction, but that is also true for many chronic and acute illnesses. Self-reported alcohol intake is not a sensitive measure of alcohol use. However,

future studies could include biomarkers such as ethanol, ethyl glucuronide, ethyl sulfate, phosphatidyl ethanol, fatty acid ethyl esters, and acetaldehyde.

6. Conclusions

This study investigates the gene-by-environment interactions that influence the prevalence and progression of chronic illnesses such as obesity, diabetes, depression, and nonalcoholic fatty liver disease (NAFLD) among Mexican Americans in the Rio Grande Valley. The findings highlight the significant role of acculturation stress, particularly marginalization, in exacerbating these conditions. The research underscores the heritability of these traits and the complex interplay between genetic predispositions and environmental factors. While the study provides valuable insights, it also acknowledges limitations such as the need for larger, more diverse sample sizes and longitudinal studies to establish causality. Future research should aim to explore additional dimensions of acculturation and include a broader range of environmental and lifestyle variables to enhance our understanding of these interactions. Addressing these factors is crucial for developing targeted interventions to mitigate the high prevalence of NAFLD and associated comorbidities in this population. Future directions will focus on identifying the nature of the interactions and the specific genes involved.

Author Contributions: Conceptualization E.G.M., J.E.C., S.L., J.B. and S.W.-B.; Methodology J.B.; Formal Analysis—V.P.D. and M.A.; Investigation—E.G.M. and S.L.; Data curation—V.P.D., M.A. and S.L.; Original Draft—E.G.M., V.P.D., M.A., A.C.L. and D.O.; Review and Editing—E.G.M., V.P.D., M.A., D.O., J.G., J.B. and S.W.-B.; Visualization—J.G.; Supervision—E.G.M., J.E.C., J.B. and S.W.-B.; Project Management—J.E.C. and S.L.; Funding Acquisition—S.W.-B. All authors have read and agreed to the published version of the manuscript.

Funding: The research leveraged state-of-the-art instrumentation and capabilities established as part of the Valley Baptist Legacy Foundation-supported Project THRIVE. The research was supported by a grant from the Knapp Community Care Foundation, NIH grant U54 HG013247 to S.W.-B., and R01 MD912564 to J.B.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Texas Rio Grande Valley.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Wanat, K.A.; Kovarik, C.L.; Shuman, S.; Whitaker, R.C.; Foster, G.D.; O'Brien, M.J. The association between obesity and health-related quality of life among urban Latinos. *Ethn. Dis.* **2014**, *24*, 14–18. [[PubMed](#)]
2. Manusov, E.G.; Diego, V.P.; Smith, J.; Garza, J.R., 2nd; Lowdermilk, J.; Blangero, J.; Williams-Blangero, S.; Fernandez, F. UniMóvil: A Mobile Health Clinic Providing Primary Care to the Colonias of the Rio Grande Valley, South Texas. *Front. Public Health* **2019**, *7*, 215. [[CrossRef](#)] [[PubMed](#)]
3. Manusov, E.G.; Diego, V.P.; Abrego, E.; Herklotz, K.; Almeida, M.; Mao, X.; Laston, S.; Blangero, J.; Blangero, S. Gene-by-Environment Interaction in Non-Alcoholic Fatty Liver Disease and Depression: The Role of Hepatic Transaminases. *Med. Res. Arch.* **2023**, *11*, 1–9. [[CrossRef](#)] [[PubMed](#)]
4. Manusov, E.; Reininger, B.; Ulloa-Aguirre, A.; Williams-Blangero, S. Editorial: The biology and management of chronic diseases in Mexican Americans. *Front. Med.* **2022**, *9*, 1095203. [[CrossRef](#)] [[PubMed](#)]
5. Heredia, N.I.; Xu, T.; Lee, M.; McNeill, L.H.; Reininger, B.M. The Neighborhood Environment and Hispanic/Latino Health. *Am. J. Health Promot.* **2022**, *36*, 38–45. [[CrossRef](#)] [[PubMed](#)]
6. Vilar-Gomez, E.; Vuppalanchi, R.; Mladenovic, A.; Samala, N.; Gawrieh, S.; Newsome, P.N.; Chalasani, N. Prevalence of High-risk Nonalcoholic Steatohepatitis (NASH) in the United States: Results From NHANES 2017–2018. *Clin. Gastroenterol. Hepatol.* **2023**, *21*, 115–124. [[CrossRef](#)]
7. Makri, E.; Goulas, A.; Polyzos, S.A. Epidemiology, Pathogenesis, Diagnosis and Emerging Treatment of Nonalcoholic Fatty Liver Disease. *Arch. Med. Res.* **2021**, *52*, 25–37. [[CrossRef](#)] [[PubMed](#)]

8. Sabotta, C.M.; Kwan, S.Y.; Petty, L.E.; Below, J.E.; Joon, A.; Wei, P.; Fisher-Hoch, S.P.; McCormick, J.B.; Beretta, L. Genetic variants associated with circulating liver injury markers in Mexican Americans, a population at risk for non-alcoholic fatty liver disease. *Front. Genet.* **2022**, *13*, 995488. [CrossRef] [PubMed]
9. Young, K.A.; Palmer, N.D.; Fingerlin, T.E.; Langefeld, C.D.; Norris, J.M.; Wang, N.; Xiang, A.H.; Guo, X.; Williams, A.H.; Chen, Y.I.; et al. Genome-Wide Association Study Identifies Loci for Liver Enzyme Concentrations in Mexican Americans: The GUARDIAN Consortium. *Obesity* **2019**, *27*, 1331–1337. [CrossRef] [PubMed]
10. Younossi, Z.M.; Golabi, P.; de Avila, L.; Paik, J.M.; Srishord, M.; Fukui, N.; Qiu, Y.; Burns, L.; Afendy, A.; Nader, F. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J. Hepatol.* **2019**, *71*, 793–801. [CrossRef] [PubMed]
11. Stefan, N.; Cusi, K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol.* **2022**, *10*, 284–296. [CrossRef] [PubMed]
12. Tanase, D.M.; Gosav, E.M.; Costea, C.F.; Ciocoiu, M.; Lacatusu, C.M.; Maranduca, M.A.; Ouatu, A.; Floria, M. The Intricate Relationship between Type 2 Diabetes Mellitus (T2DM), Insulin Resistance (IR), and Nonalcoholic Fatty Liver Disease (NAFLD). *J. Diabetes Res.* **2020**, *2020*, 3920196. [CrossRef] [PubMed]
13. Muzica, C.M.; Sfarti, C.; Trifan, A.; Zenovia, S.; Cuciureanu, T.; Nastasa, R.; Huiban, L.; Cojocariu, C.; Singeap, A.M.; Girleanu, I.; et al. Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: A Bidirectional Relationship. *Can. J. Gastroenterol. Hepatol.* **2020**, *2020*, 6638306. [CrossRef] [PubMed]
14. Xiao, J.; Lim, L.K.E.; Ng, C.H.; Tan, D.J.H.; Lim, W.H.; Ho, C.S.H.; Tan, E.X.X.; Sanyal, A.J.; Muthiah, M.D. Is Fatty Liver Associated With Depression? A Meta-Analysis and Systematic Review on the Prevalence, Risk Factors, and Outcomes of Depression and Non-alcoholic Fatty Liver Disease. *Front. Med.* **2021**, *8*, 691696. [CrossRef] [PubMed]
15. Soto-Angona, Ó.; Anmella, G.; Valdés-Flrido, M.J.; De Uribe-Viloria, N.; Carvalho, A.F.; Penninx, B.; Berk, M. Non-alcoholic fatty liver disease (NAFLD) as a neglected metabolic companion of psychiatric disorders: Common pathways and future approaches. *BMC Med.* **2020**, *18*, 261. [CrossRef] [PubMed]
16. Manusov, E.G.; Diego, V.P.; Sheikh, K.; Laston, S.; Blangero, J.; Williams-Blangero, S. Non-alcoholic Fatty Liver Disease and Depression: Evidence for Genotype $\times$ Environment Interaction in Mexican Americans. *Front. Psychiatry* **2022**, *13*, 936052. [CrossRef] [PubMed]
17. Trépo, E.; Valenti, L. Update on NAFLD genetics: From new variants to the clinic. *J. Hepatol.* **2020**, *72*, 1196–1209. [CrossRef] [PubMed]
18. Locke, A.E.; Kahali, B.; Berndt, S.I.; Justice, A.E.; Pers, T.H.; Day, F.R.; Powell, C.; Vedantam, S.; Buchkovich, M.L.; Yang, J.; et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* **2015**, *518*, 197–206. [CrossRef] [PubMed]
19. Suppli, N.P.; Andersen, K.K.; Agerbo, E.; Rajagopal, V.M.; Appadurai, V.; Coleman, J.R.I.; Breen, G.; Bybjerg-Grauholm, J.; Bækvad-Hansen, M.; Pedersen, C.B.; et al. Genome-wide by Environment Interaction Study of Stressful Life Events and Hospital-Treated Depression in the iPSYCH2012 Sample. *Biol. Psychiatry Glob. Open Sci.* **2022**, *2*, 400–410. [CrossRef] [PubMed]
20. Zhao, M.Z.; Song, X.S.; Ma, J.S. Gene $\times$ environment interaction in major depressive disorder. *World J. Clin. Cases* **2021**, *9*, 9368–9375. [CrossRef] [PubMed]
21. Glahn, D.C.; Curran, J.E.; Winkler, A.M.; Carless, M.A.; Kent, J.W., Jr.; Charlesworth, J.C.; Johnson, M.P.; Göring, H.H.; Cole, S.A.; Dyer, T.D.; et al. High dimensional endophenotype ranking in the search for major depression risk genes. *Biol. Psychiatry* **2012**, *71*, 6–14. [CrossRef] [PubMed]
22. Gu, Y.; Zhang, W.; Hu, Y.; Chen, Y.; Shi, J. Association between nonalcoholic fatty liver disease and depression: A systematic review and meta-analysis of observational studies. *J. Affect. Disord.* **2022**, *301*, 8–13. [CrossRef] [PubMed]
23. Albuquerque, D.; Nóbrega, C.; Manco, L.; Padez, C. The contribution of genetics and environment to obesity. *Br. Med. Bull.* **2017**, *123*, 159–173. [CrossRef] [PubMed]
24. Virolainen, S.J.; VonHandorf, A.; Viel, K.; Weirauch, M.T.; Kottyan, L.C. Gene-environment interactions and their impact on human health. *Genes Immun.* **2023**, *24*, 1–11. [CrossRef] [PubMed]
25. Diego, V.P.; Manusov, E.G.; Mao, X.; Curran, J.E.; Göring, H.; Almeida, M.; Mahaney, M.C.; Peralta, J.M.; Blangero, J.; Williams-Blangero, S. Genotype-by-socioeconomic status interaction influences heart disease risk scores and carotid artery thickness in Mexican Americans: The predominant role of education in comparison to household income and socioeconomic index. *Front. Genet.* **2023**, *14*, 1132110. [CrossRef] [PubMed]
26. Arya, R.; Farook, V.S.; Fowler, S.P.; Puppala, S.; Chittoor, G.; Resendez, R.G.; Mummidi, S.; Vanamala, J.; Almasy, L.; Curran, J.E.; et al. Genetic and environmental (physical fitness and sedentary activity) interaction effects on cardiometabolic risk factors in Mexican American children and adolescents. *Genet. Epidemiol.* **2018**, *42*, 378–393. [CrossRef] [PubMed]
27. Choh, A.C.; Lee, M.; Kent, J.W.; Diego, V.P.; Johnson, W.; Curran, J.E.; Dyer, T.D.; Bellis, C.; Blangero, J.; Siervogel, R.M.; et al. Gene-by-age effects on BMI from birth to adulthood: The Fels Longitudinal Study. *Obesity* **2014**, *22*, 875–881. [CrossRef] [PubMed]
28. Ramos-Lopez, O.; Martinez-Lopez, E.; Roman, S.; Fierro, N.A.; Panduro, A. Genetic, metabolic and environmental factors involved in the development of liver cirrhosis in Mexico. *World J. Gastroenterol.* **2015**, *21*, 11552–11566. [CrossRef] [PubMed]
29. Barton, J.; Perlmeter, E.R.; Blum, E.S.; Marquez, R.R. Las Colonias in th 21st Century: Progress along the Texas-Mexico Border. Available online: <https://www.dallasfed.org/~media/microsites/cd/colonias/index.html> (accessed on 3 January 2024).
30. Alarcón, R.D.; Parekh, A.; Wainberg, M.L.; Duarte, C.S.; Araya, R.; Oquendo, M.A. Hispanic immigrants in the USA: Social and mental health perspectives. *Lancet Psychiatry* **2016**, *3*, 860–870. [CrossRef] [PubMed]

31. Brown, S.A.; Becker, H.A.; García, A.A.; Velasquez, M.M.; Tanaka, H.; Winter, M.A.; Perkison, W.B.; Brown, E.L.; Aguilar, D.; Hanis, C.L. Acculturation, Dietary Behaviors, and Macronutrient Intake Among Mexican Americans With Prediabetes: The Starr County Diabetes Prevention Initiative. *Sci. Diabetes Self Manag. Care* **2023**, *49*, 65–76. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Nelson, T.; Perez, A.; Alcaraz, J.; Talavera, G.; McCarthy, J.J. Family History of Diabetes, Acculturation, and the Metabolic Syndrome among Mexican Americans: Proyecto SALSA. *Metab. Syndr. Relat. Disord.* **2007**, *5*, 262–269. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Cuellar, I.; Arnold, B.; Maldonado, R. Acculturation Rating Scale for Mexican Americans-II: A Revision of the Original ARSMA Scale. *Hisp. J. Behav. Sci.* **1995**, *17*, 275–304. [\[CrossRef\]](#)
34. Jimenez, D.E.; Gray, H.L.; Cucciare, M.; Kumbhani, S.; Gallagher-Thompson, D. Using the Revised Acculturation Rating Scale for Mexican Americans (ARSMA-II) with Older Adults. *Hisp. Health Care Int.* **2010**, *8*, 14–22. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Suarez, L.; Pulley, L. Comparing acculturation scales and their relationship to cancer screening among older Mexican-American women. *J. Natl. Cancer Inst. Monogr.* **1995**, *18*, 4–47.
36. Hull, S.C.; Glanz, K.; Steffen, A.; Wilfond, B.S. Recruitment approaches for family studies: Attitudes of index patients and their relatives. *IRB Ethics Hum. Res.* **2004**, *26*, 12–17. [\[CrossRef\]](#)
37. Eddowes, P.J.; Sasso, M.; Allison, M.; Tsochatzis, E.; Anstee, Q.M.; Sheridan, D.; Guha, I.N.; Cobbold, J.F.; Deeks, J.J.; Paradis, V.; et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* **2019**, *156*, 1717–1730. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Siddiqui, M.S.; Vuppalandhi, R.; Van Natta, M.L.; Hallinan, E.; Kowdley, K.V.; Abdelmalek, M.; Neuschwander-Tetri, B.A.; Loomba, R.; Dasarathy, S.; Brandman, D.; et al. Vibration-Controlled Transient Elastography to Assess Fibrosis and Steatosis in Patients With Nonalcoholic Fatty Liver Disease. *Clin. Gastroenterol. Hepatol.* **2019**, *17*, 156–163.e152. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Lee, K.; Kim, D.; Cho, Y. Exploratory Factor Analysis of the Beck Anxiety Inventory and the Beck Depression Inventory-II in a Psychiatric Outpatient Population. *J. Korean Med. Sci.* **2018**, *33*, e128. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Penley, J.A.; Wiebe, J.S.; Nwosu, A. Psychometric properties of the Spanish Beck Depression Inventory-II in a medical sample. *Psychol. Assess.* **2003**, *15*, 569–577. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Wiebe, J.S.; Penley, J.A. A psychometric comparison of the Beck Depression Inventory-II in English and Spanish. *Psychol. Assess.* **2005**, *17*, 481–485. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Wang, Y.P.; Gorenstein, C. Psychometric properties of the Beck Depression Inventory-II: A comprehensive review. *Braz. J. Psychiatry* **2013**, *35*, 416–431. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Eilenberg, M.; Munda, P.; Stift, J.; Langer, F.B.; Prager, G.; Trauner, M.; Staufer, K. Accuracy of non-invasive liver stiffness measurement and steatosis quantification in patients with severe and morbid obesity. *Hepatobiliary Surg. Nutr.* **2021**, *10*, 610–622. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Newsome, P.N.; Sasso, M.; Deeks, J.J.; Paredes, A.; Boursier, J.; Chan, W.K.; Yilmaz, Y.; Czernichow, S.; Zheng, M.H.; Wong, V.W.; et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: A prospective derivation and global validation study. *Lancet Gastroenterol. Hepatol.* **2020**, *5*, 362–373. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Oeda, S.; Takahashi, H.; Imajo, K.; Seko, Y.; Kobayashi, T.; Ogawa, Y.; Moriguchi, M.; Yoneda, M.; Anzai, K.; Irie, H.; et al. Diagnostic accuracy of FibroScan-AST score to identify non-alcoholic steatohepatitis with significant activity and fibrosis in Japanese patients with non-alcoholic fatty liver disease: Comparison between M and XL probes. *Hepatol. Res.* **2020**, *50*, 831–839. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Cassinotto, C.; Boursier, J.; de Ledinghen, V.; Lebigot, J.; Lapuyade, B.; Cales, P.; Hiriart, J.B.; Michalak, S.; Bail, B.L.; Cartier, V.; et al. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. *Hepatology* **2016**, *63*, 1817–1827. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Mikolasevic, I.; Orlic, L.; Franjic, N.; Hauser, G.; Stimac, D.; Milic, S. Transient elastography (FibroScan((R))) with controlled attenuation parameter in the assessment of liver steatosis and fibrosis in patients with nonalcoholic fatty liver disease—Where do we stand? *World J. Gastroenterol.* **2016**, *22*, 7236–7251. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Xu, Y.; Liu, Y.; Cao, Z.; Wang, L.; Li, Z.; Sheng, Z.; Cai, W.; Wang, H.; Bao, S.; Xie, Q. Comparison of FibroTouch and FibroScan for staging fibrosis in chronic liver disease: Single-center prospective study. *Dig. Liver Dis.* **2019**, *51*, 1323–1329. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Grob, S.R.; Suter, F.; Katzke, V.; Rohrmann, S. The Association between Liver Enzymes and Mortality Stratified by Non-Alcoholic Fatty Liver Disease: An Analysis of NHANES III. *Nutrients* **2023**, *15*, 3063. [\[CrossRef\]](#)
50. Ghaddar, S.; Brown, C.J.; Pagán, J.A.; Díaz, V. Acculturation and healthy lifestyle habits among Hispanics in United States-Mexico border communities. *Rev. Panam. Salud Publica* **2010**, *28*, 190–197. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Delaney, C.L.; Spaccarotella, K.; Quick, V.; Byrd-Bredbenner, C. A Comparison of Weight-Related Behaviors of Hispanic Mothers and Children by Acculturation Level. *Int. J. Environ. Res. Public Health* **2021**, *18*, 503. [\[CrossRef\]](#)
52. McIntire, R.K.; Scalzo, L.; Doran, C.; Bucher, K.; Juon, H.S. Acculturation and Hypertension Diagnoses Among Hispanics in California. *J. Racial Ethn. Health Disparities* **2022**, *9*, 946–953. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Fernández-Rhodes, L.; McArdle, C.E.; Rao, H.; Wang, Y.; Martinez-Miller, E.E.; Ward, J.B.; Cai, J.; Sofer, T.; Isasi, C.R.; North, K.E. A Gene-Acculturation Study of Obesity Among US Hispanic/Latinos: The Hispanic Community Health Study/Study of Latinos. *Psychosom. Med.* **2023**, *85*, 358–365. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Liu, J.; Fulda, K.G.; Tao, M.H. Association between acculturation and metabolic syndrome in Hispanic adults mediated by fruits intake. *Public Health Nutr.* **2021**, *24*, 6472–6476. [\[CrossRef\]](#) [\[PubMed\]](#)

55. Isasi, C.R.; Ayala, G.X.; Sotres-Alvarez, D.; Madanat, H.; Penedo, F.; Loria, C.M.; Elder, J.P.; Daviglius, M.L.; Barnhart, J.; Siega-Riz, A.M.; et al. Is acculturation related to obesity in Hispanic/Latino adults? Results from the Hispanic community health study/study of Latinos. *J. Obes.* **2015**, *2015*, 186276. [[CrossRef](#)] [[PubMed](#)]
56. Hernandez, C.M.; Moreno, O.; Garcia-Rodriguez, I.; Fuentes, L.; Nelson, T. The Hispanic Paradox: A Moderated Mediation Analysis of Health Conditions, Self-Rated Health, and Mental Health among Mexicans and Mexican Americans. *Health Psychol. Behav. Med.* **2022**, *10*, 180–198. [[CrossRef](#)] [[PubMed](#)]
57. Gonzalez-Guarda, R.M.; McCabe, B.E.; Nagy, G.A.; Stafford, A.M.; Matos, L.; Lu, M.; Felsman, I.; Rocha-Goldberg, P.; Cervantes, R.C. Acculturative Stress, Resilience, and a Syndemic Factor Among Latinx Immigrants. *Nurs. Res.* **2023**, *72*, 249–258. [[CrossRef](#)] [[PubMed](#)]
58. Ray, M.; Wallace, M.K.; Grayson, S.C.; Cummings, M.H.; Davis, J.A.; Scott, J.; Belcher, S.M.; Davis, T.S.; Conley, Y.P. Epigenomic Links Between Social Determinants of Health and Symptoms: A Scoping Review. *Biol. Res. Nurs.* **2023**, *25*, 404–416. [[CrossRef](#)] [[PubMed](#)]
59. Balakrishnan, M.; Kanwal, F.; El-Serag, H.B.; Thrift, A.P. Acculturation and Nonalcoholic Fatty Liver Disease Risk Among Hispanics of Mexican Origin: Findings From the National Health and Nutrition Examination Survey. *Clin. Gastroenterol. Hepatol.* **2017**, *15*, 310–312. [[CrossRef](#)]
60. Kallwitz, E.R.; Daviglius, M.L.; Allison, M.A.; Emory, K.T.; Zhao, L.; Kuniholm, M.H.; Chen, J.; Gouskova, N.; Pirzada, A.; Talavera, G.A.; et al. Prevalence of suspected nonalcoholic fatty liver disease in Hispanic/Latino individuals differs by heritage. *Clin. Gastroenterol. Hepatol.* **2015**, *13*, 569–576. [[CrossRef](#)] [[PubMed](#)]
61. Maldonado, A.; Villavicencio, E.A.; Vogel, R.M.; Pace, T.W.; Ruiz, J.M.; Alkhouri, N.; Garcia, D.O. The association between perceived stress, acculturation, and non-alcoholic fatty liver disease in Mexican-origin adults in Southern Arizona. *Prev. Med. Rep.* **2023**, *32*, 102147. [[CrossRef](#)] [[PubMed](#)]
62. Tomeno, W.; Kawashima, K.; Yoneda, M.; Saito, S.; Ogawa, Y.; Honda, Y.; Kessoku, T.; Imajo, K.; Mawatari, H.; Fujita, K.; et al. Non-alcoholic fatty liver disease comorbid with major depressive disorder: The pathological features and poor therapeutic efficacy. *J. Gastroenterol. Hepatol.* **2015**, *30*, 1009–1014. [[CrossRef](#)] [[PubMed](#)]
63. Shea, S.; Lionis, C.; Kite, C.; Atkinson, L.; Chaggar, S.S.; Randeve, H.S.; Kyrou, I. Non-Alcoholic Fatty Liver Disease (NAFLD) and Potential Links to Depression, Anxiety, and Chronic Stress. *Biomedicines* **2021**, *9*, 1697. [[CrossRef](#)] [[PubMed](#)]
64. Serafica, R.; Lekhak, N.; Bhatta, T. Acculturation, acculturative stress and resilience among older immigrants in United States. *Int. Nurs. Rev.* **2019**, *66*, 442–448. [[CrossRef](#)] [[PubMed](#)]
65. Liem, A.; Renzaho, A.M.N.; Hannam, K.; Lam, A.I.F.; Hall, B.J. Acculturative stress and coping among migrant workers: A global mixed-methods systematic review. *Appl. Psychol. Health Well Being* **2021**, *13*, 491–517. [[CrossRef](#)] [[PubMed](#)]
66. Bekteshi, V.; Kang, S.W. Contextualizing acculturative stress among Latino immigrants in the United States: A systematic review. *Ethn. Health* **2020**, *25*, 897–914. [[CrossRef](#)] [[PubMed](#)]
67. Korbecki, J.; Bobiński, R.; Dutka, M. Self-regulation of the inflammatory response by peroxisome proliferator-activated receptors. *Inflamm. Res.* **2019**, *68*, 443–458. [[CrossRef](#)] [[PubMed](#)]
68. Lommel, L.L.; Thompson, L.; Chen, J.L.; Waters, C.; Carrico, A. Acculturation, Inflammation, and Self-rated Health in Mexican American Immigrants. *J. Immigr. Minor. Health* **2019**, *21*, 1052–1060. [[CrossRef](#)] [[PubMed](#)]
69. Polacchini, A.; Girardi, D.; Falco, A.; Zanutta, N.; Comar, M.; De Carlo, N.A.; Tongiorgi, E. Distinct CCL2, CCL5, CCL11, CCL27, IL-17, IL-6, BDNF serum profiles correlate to different job-stress outcomes. *Neurobiol. Stress.* **2018**, *8*, 82–91. [[CrossRef](#)]
70. Sohal, A.; Chaudhry, H.; Kowdley, K.V. Genetic Markers Predisposing to Nonalcoholic Steatohepatitis. *Clin. Liver Dis.* **2023**, *27*, 333–352. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.