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No Man is an Island: living in a disadvantaged neighborhood influences chronic pain development after motor vehicle collision, and this effect is moderated by common genetic variation influencing HPA axis function

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Abstract

Living in a lower socioeconomic status neighborhood has been shown to alter stress system function and is associated with a number of adverse health outcomes, but its influence on musculoskeletal pain (MSP) outcomes after traumatic stress exposures such as motor vehicle collision (MVC) has not been assessed. We performed a multicenter, prospective study that enrolled 948 European-American individuals within 24 hours of MVC who were discharged home

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after ED evaluation. Follow-up evaluations were completed via telephone or internet survey six weeks, six months, and one year after MVC on 91%, 89%, and 91% of participants, respectively. A robust aggregate measure of census tract neighborhood disadvantage was derived, and individual-level characteristics assessed included socioeconomic and demographic characteristics, pain prior to MVC, litigation status, and opioid use. MSP was assessed in the ED, MSP and pain interference with daily activity were assessed at six weeks, six months, and one year. After adjustment for individual-level factors, living in more disadvantaged neighborhoods was associated with increased MSP ($p=0.0009$) and increased pain interference with daily function ($p<0.0001$). The relationship between neighborhood disadvantage and MSP was moderated by a common single nucleotide polymorphism, *rs2817038*, 5' of the gene encoding FKBP5, a functional regulator of glucocorticoid receptor sensitivity (interaction p-value=0.0015). These data support the hypothesis that low nSES increases the likelihood of worse MSP outcomes after traumatic stress exposures such as MVC, and that this influences is mediated in part via its influence on stress system function.

Keywords

musculoskeletal pain; motor vehicle collision; neighborhood effects; FKBP5; gene by environment interaction

1. INTRODUCTION

Motor vehicle collisions (MVCs) are among the most common life-threatening experiences, resulting in 50 million injuries worldwide and almost four million US emergency department (ED) visits each year [45; 55]. Approximately 90% of individuals presenting to US EDs for care after MVC are discharged home after ED evaluation [47]. Persistent musculoskeletal pain (MSP) after MVC in this population is a common and costly public health problem in the US and other industrialized nations [19; 25].

Available evidence suggests that individuals seen in the ED after MVC who live in a lower socioeconomic status neighborhood may experience worse pain outcomes [7; 12; 20; 24; 42]. Lower neighborhood socioeconomic status (nSES) has been associated with a range of adverse health outcomes [16; 21; 33-35; 38; 51], and studies of patients with pain conditions suggest that those living in lower socioeconomic status areas have worse pain severity and pain-related disability [7; 12; 20; 24]. However, these studies were cross-sectional and/or had only limited ability to adjust for individual-level characteristics.

In this study, we investigated the influence of nSES on chronic MSP severity and MSP-related disability in a large cohort of European Americans enrolled in the ED in the early aftermath of MVC and followed longitudinally for one year. We hypothesized that individuals in low SES neighborhoods would have more severe MSP and MSP-related disability after MVC. In addition, we also hypothesized that this effect is due in part to the influence of low nSES on stress system function, and therefore that living in a disadvantaged neighborhood environment would have a particularly deleterious effect on pain outcomes among those with stress system-related genetic vulnerability factors. We hypothesized that this is because lower nSES has been shown to cause alterations in stress system function

[43; 50] (e.g., dysregulated cortisol levels [15; 28]) and because increasing evidence indicates that stress systems are involved in the pathogenesis of persistent MSP after traumatic events such as MVC [2; 6; 40]. To test this hypothesis, we investigated common genetic variation in the locus of the gene coding for co-chaperone FK506 binding protein 51 (*FKBP5*), because this protein is known to influence hypothalamic-pituitary adrenal (HPA) axis function [48; 59] (an important component of the stress response system), and because *FKBP5* variants have been shown to predict persistent neck and overall pain severity after MVC [6].

2. METHODS

2.1. tudy population and design

2.1.1. Design and setting—This prospective longitudinal study enrolled patients presenting to the ED within 24 hours of MVC. Data were collected at eight EDs in four no-fault MVC litigation/insurance states (Michigan, Massachusetts, New York, and Florida) between February 2009 and October 2011. Participants were not required to reside in the enrollment state. The study was approved by the Institutional Review Boards of all participating hospitals, and each participant provided written informed consent. Complete information regarding study design, procedures, and methods has previously been described [6; 41; 46].

2.1.2. Participant eligibility criteria and study sites—In brief, patients aged 18 to 65 who presented to the ED within 24 hours after a MVC and were unlikely to require hospitalization were screened for eligibility. Patients who were admitted to the hospital, had fractures other than phalangeal fractures, had more than 4 lacerations requiring sutures or a single laceration more than 20 cm in length, or had intracranial or spinal injuries were excluded. Enrollment was also limited to non-Hispanic whites (the most common ethnicity at study sites) because the study included the collection of genetic data and genetic analyses are potentially biased by population stratification [14]. Patients who were not alert and oriented were also excluded, as were pregnant patients, prisoners, patients unable to read and understand English, patients taking a β-adrenoreceptor antagonist, or patients taking opioids above a total daily dose of 20 mg of oral morphine or equivalent.

2.2. Study procedures

Eligible and consenting participants completed ED interview evaluations regarding pre-MVC health status, the details of the MVC, and current symptoms. Research assistants conducted interviews at the time of the ED visit using a web-based survey with explicit definitions of variables. Injury characteristics and medications administered in the ED were obtained by data extraction from the ED medical record. Follow-up time points were six weeks, six months, and one year after the MVC. At each follow-up, participants completed an interview online, by telephone, or via mail. Participants were compensated $50 for completing the ED interview, $60 for completing each of the 6-week and 6-month interviews, and $70 for completing the one-year interview.

2.2.1. DNA collection and genotyping—Research assistants collected blood samples from participants at the time of enrollment using PAXgene DNA tubes. Following DNA purification (PAXgene blood DNA kit, QIAGEN), genotyping was performed using the Sequenom platform; two Hapmap samples and two repeat samples were included in each genotyping batch (96 samples) to ensure accuracy and reliability. All SNPs out of Hardy-Weinberg equilibrium were discarded ($p < 0.05$). Fifteen FKBP5 tag SNPs previously identified using the Tagger procedure in Haploview [3] ($r^2 \geq 0.8$ [13]) were selected for gene by environment interaction analyses.

2.2.2. Outcome variables—At each follow-up interview, participants responded to a question about their overall pain level during the week prior on a 0-10 numeric rating scale (NRS) where 0 was defined as no pain and 10 was defined as pain "as bad as it can possibly be" [58]. Additionally, participants were asked to respond to questions from the Brief Pain Inventory (BPI) [11] about how much pain related to the motor vehicle collision interfered with their daily lives during the past week. In particular, they were asked on a 0-10 NRS, where 0 is no interference and 10 is complete interference, how much this pain during the past week interfered with their general activity, mood, walking ability, normal work (including both work outside the home and housework), relations with other people, sleep, and enjoyment of life. The seven items were summed to obtain a total interference score. Participants were also asked at each interview whether they had been seen by a physician for MVC-related complaints since their ED visit.

2.2.3. Individual-level variables—Pain during the month prior to the MVC (0-10 NRS), acute pain in the ED (0-10 NRS), and sociodemographic variables were obtained from participant self-report during the ED interview. Participant age, sex, height, weight, and opioid receipt at discharge were obtained from a medical record abstraction completed within two weeks of discharge. Mental health status prior to the MVC was determined from participant response in the ED to the Short-Form 12 (SF-12) and scored as previously described [57]. Similarly, at risk drinking was determined from response in the ED to the TWEAK and scored as previously described [10]. Patient injuries were scored using the Abbreviated Injury Scale [1]. At each follow-up interview, participants were asked if they were working with a lawyer to pursue damages or compensation related to the MVC.

2.2.4. Neighborhood-level variables—Participant addresses at time of the ED visit were geocoded using the University of South Carolina's Desktop Geocoder [23]. Census tracts were matched to data in the 2010 American Community Survey (ACS) 5-year estimates [8]. The socioeconomic position (SEP) index was chosen to assess neighborhood socioeconomic environment because it includes key theoretical domains (occupational class, educational attainment, income and entitlements, wealth, and relative social ranking) [33; 34] and has been well validated [31-35]. A SEP index score was derived for each census tract by averaging the standardized scores of the following deprivation measures: percent unemployed, percent below the US poverty line, percent with high school education or less, percent expensive homes (owner-occupied homes worth ≥ $300,000) in the neighborhood, and median household income [33]. SEP index values were subsequently split into quartiles. The 3rd and 4th quartiles (highest levels of nSES, termed "not disadvantaged") were

combined into a referent group to maintain power to assess the effect of living in a disadvantaged neighborhood. Neighborhoods in the first and second quartiles were termed “most disadvantaged” and “moderately disadvantaged”, respectively.

2.3. Statistical methods

All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Mixed models were used to model MSP outcomes (0-10 NRS). Each model contained random intercepts and slopes over time points for each participant as well as random effects for county of residence to account for clustering by county. In the first model, fixed effects for the nSES quartiles, time after MVC, and an interaction between time and nSES quartile were included in the model. In the second model, participant sex, age, highest level of educational attainment, annual family income, and full time employment status were included as fixed effects. P-values were reported for testing the null hypothesis that no differences exist in mean MSP outcomes between nSES categories, both overall (across all timepoints) and also by follow-up timepoint. Least-squares (LS) means with 95% pointwise confidence intervals (CIs) were reported for each level of nSES at each time point. Pain recovery in statistical models was defined as the interaction of nSES and time.

Gene by environment interactions were evaluated by adding the main effects of each SNP and the SNP by nSES quartile interaction term to the second model. LS-means with 95% confidence intervals are reported. We also performed hypothesis tests in this model on the interaction between *FKBP5* genotypes and nSES on MSP outcomes over all timepoints and quartiles, and separately within each nSES quartile. Gene by environment interaction P-values in the overall model were adjusted by Bonferroni correction (15 hypothesis tests; Bonferroni-adjusted significance level=0.0033).

3. RESULTS

3.1. Participant characteristics

3.1.1. Follow-up—Among 10,629 patients screened in the ED, 1,416 were eligible, 969 consented (69%), and 948 were enrolled. The median time between MVC and ED presentation was 1.2 hours. Consistent with eligibility criteria, all patients were discharged home after ED evaluation and did not have life-threatening injury. Ninety-nine percent of participants had an Abbreviated Injury Scale score of one. Retention rates at six weeks, six months, and one year were 859/948 (91%), 840/948 (89%), and 861/948 (91%), respectively.

3.1.2. Genotyping—Blood was obtained from each of the 948 participants, and DNA was extracted from 946/948 (99.8%). Call rates for genotyping were > 99%. Selected repeated genotyping demonstrated greater than 98% call agreement, and all SNPs were in HWE.

3.1.3. Geocoding—Geocoding participants to their corresponding census tract from the ACS 2010 5-year estimates was initially successful in 824/948 participants (86.9%). Addresses which were not immediately coded to their specific census tract were individually investigated, re-cleaned, and re-submitted for geocoding. Using these methods, a total of

935/948 (98.6%) addresses were successfully matched with their census tract (Fig 1). The great majority of participants (890/935, 95%) lived in one of the enrollment states.

3.1.4. Individual and neighborhood characteristics—Individual and neighborhood characteristics are reported in Table 1. In general, the cohort was relatively wealthy ($64,015 v. $52,762 median household income) and educated (87.4% v 85.4% high school graduates) compared to the US population. Approximately half of participants (441/858, 51.4%) reported moderate or severe overall pain at six weeks, 335/837 (40.0%), and 358/857 (41.8%) reported moderate or severe overall pain at six months and one year, respectively. BPI pain interference in the study sample at six weeks, six months, and one year were 16.8 (SD 18.1), 10.9 (SD 16.5), 9.6 (SD 15.6), respectively.

3.2. Association between neighborhood socioeconomic status and overall pain

In initial mixed models controlling for nSES but not individual-level effects, decreased nSES was significantly associated with mean overall pain across timepoints ($p<0.0001$), and there was marginal evidence that rates of overall pain recovery were different according to nSES quartile (nSES-by-timepoint interaction $p=0.082$) (eTable 1). Differences in mean overall pain amongst nSES quartiles were observed at the ED time point ($p=0.0044$), at six weeks ($p<0.0001$), and at six months ($p=0.0003$), with a similar, although non-significant trend observed one year after MVC ($p=0.0526$).

In mixed models that also controlled for individual-level characteristics, decreased nSES remained associated with the mean overall pain across all timepoints ($p=0.0009$), and with overall pain at specific outcome timepoints including in the ED ($p=0.038$) and six weeks ($p<0.0001$) and six months ($p=0.0065$) after MVC (eTable 1). Differences were not significant at one year ($p=0.21$), although a similar trend was observed. Mean overall pain for nSES quartiles at each time point with 95% CIs are reported in Fig 2A. Full details of these models are in eTable 1, and results did not change appreciably when prior pain was not included as a covariate (eTable 3), nor when participants not living in one of the four enrollment states were excluded from analysis (eTable 4). Results also remained significant after adjustment for opioid receipt in the ED, time dependent litigation status, body mass index (BMI), at risk drinking habits prior to the MVC, and mental health status prior to the MVC (eTable 4 and 5). Additionally, inhabitants of the most disadvantaged neighborhoods were more likely to visit a physician for MVC-related complaints (eTable 6).

3.3. Association between neighborhood socioeconomic status and pain interference

In both mixed models controlling for nSES alone and in models controlling for both nSES and individual-level effects, decreased nSES was associated with increased mean pain interference across timepoints ($p<0.0001$), and with overall pain at specific outcome timepoints including at six weeks ($p<0.0001$), at six months ($p<0.003$), and at one year ($p<0.001$) (Fig 2B, eTable 2). These associations remained significant when prior overall pain was removed as a covariate, when participants not living in one of the four enrollment states were excluded, when analyses were adjusted for opioid receipt or time-dependent litigation status, and when adjusted for BMI, at risk drinking habits prior to the MVC, and mental health status prior to the MVC (eTables 3, 4, and 5).

3.4. Gene by environment interactions between *FKBP5* and neighborhood socioeconomic status on overall pain

Fifteen *FKBP5* SNPs were investigated for interaction effects with nSES on overall pain. Two SNPs (rs17614642 and rs2817038) initially had significant interactions ($p<0.05$) with nSES on pain across all time points, while only one SNP (rs2817038) remained significant after Bonferroni correction (Table 3). Interestingly, we only found evidence of an association between mean overall pain and rs2817038 genotypes in the most disadvantaged quartile of nSES ($p < 0.0001$; Fig 3). In this quartile, participants with two copies of the G allele had the lowest pain, while participants with two copies of the A allele had the most pain. Results remained significant after adjustment for opioid receipt in the ED and time dependent litigation status (eTable 4).

4. DISCUSSION

Using robust area-based socioeconomic measures and outcomes data from a prospective longitudinal study with high retention, this study provides evidence that individuals living in more disadvantaged neighborhoods experience increased MSP in the early aftermath of MVC and that these differences persist during the first year after trauma. Inhabitants of disadvantaged neighborhoods also experience increased interference from pain with daily life functions such as general activity, work, and sleep six weeks, six months, and one year after MVC. These results remained robust after controlling for potential confounding by individual-level demographic characteristics, measures of socioeconomic status, opioid receipt, and litigation involvement.

Individuals living in disadvantaged neighborhoods have been hypothesized to experience a greater burden of traumatic and stressful events and to have worse health outcomes because of the chronic stress caused by these experiences [42]. Consistent with this hypothesis, lower nSES has been shown to alter stress system function [15; 28; 43; 50]. However, previous studies have not been able to directly test the hypothesis that low nSES affects adverse health outcomes by altering stress system function. In this study, a common genetic polymorphism near *FKBP5*, a gene known to influence the function of the HPA axis [4; 6; 27; 39; 49; 56], moderated MSP outcomes among those living in the lowest quartile of nSES, but not among individuals in less disadvantaged environments. Indeed, although average differences in pain across all time-points between the least and most disadvantaged quartiles of nSES (decrease of 0.6 points on 0-10 NRS or 14% decrease) did not exceed clinical significance (decrease of 1.7 points or 28% decrease [17]), differences according to SNP rs2817038 allele in the most disadvantaged nSES quartile (2.0 points on NRS or 42% decrease) were clinically significant. This finding supports the above hypothesis, and suggests that individuals experiencing an increased burden of chronic stress are most vulnerable to increased MSP after traumatic events such as MVC. If this is the case, then post-traumatic interventions that alter stress response function (e.g., pharmacologic interventions which reduce glucocorticoid resistance or non-pharmacologic interventions such as mindfulness-based mediation) might be efficacious in improving pain outcomes.

The *FKBP5* SNP that showed the strongest moderating effect and survived Bonferonni correction, rs2817038, has not been previously associated with pain outcomes. Nor was it in

strong LD ($r^2 \geq 0.8$) with any of the other *FKBP5* SNPs investigated in this cohort or with any variants in the CEU population of the 1000 Genomes project [6; 22]. Although not investigated in this study, one possible mechanism by which variants in the *FKBP5* locus such as rs2817038 moderate pain persistence in disadvantaged neighborhoods is via DNA demethylation. Mice undergoing corticosterone-induced hypercorisolemia have been shown to demonstrate behavioral and physiological changes corresponding to *FKBP5* DNA demethylation and increased *FKBP5* mRNA expression [36; 37]. Specific polymorphisms in *FKBP5* known to interact with childhood trauma on stress-related psychiatric disorders have recently been shown to influence epigenetic pathways resulting in DNA demethylation [30]. Such *FKBP5*-mediated differential epigenetic modification may be systemic [61], providing the opportunity to explore these potential mechanisms in studies examining *FKBP5* genetic variants, *FKBP5* blood mRNA expression levels, DNA methylation levels, and patient outcomes after traumatic events such as MVC.

A number of limitations should be considered when interpreting our results. First, in order to avoid confounding by population stratification in genetic analyses our study was limited to European Americans [9]. Furthermore, while we attempted to control for most individual level measures of socioeconomic status, we did not collect detailed data on the occupations of individuals enrolled in this study. Therefore the effect of specific occupation type on pain outcomes or on our association between nSES and pain outcomes is unknown. In addition, childhood trauma exposure was not assessed, although in previous studies recalled child trauma has been shown to interact with variants in *FKBP5* on stress-related disorders [5; 60]. Our study instead measured two different, but directly measurable, environmental stress exposures: 1) the MVC event itself and 2) lower nSES environment. A related limitation is that, while low nSES has been linked to increased experiences of trauma and stress [42] and altered stress system function [15; 28; 43; 50], we were unable to distinguish between the timing of such exposures relative to the MVC (e.g., during childhood, during adulthood prior to the MVC, and/or after the MVC). We chose to perform study analyses using linear mixed models, but there is considerable debate in the epidemiological community regarding the choice of standard regression, mixed, or marginal models for hierarchical data [26; 29; 44; 54]. Although estimates from marginal models are easier to interpret than mixed models for both longitudinal [18] and neighborhood effects [26; 53], mixed models are better equipped to handle variation within neighborhoods and thus were used in the present analysis [52; 54]. Finally, the vast majority of participants in this cohort lived in Michigan, Massachusetts, New York, or Florida, thus our results are not generalizable to all areas of the US.

In conclusion, individuals living in disadvantaged neighborhoods were found to experience more severe pain and pain-related interference during the first year after MVC. These findings persisted after adjustment for individual-level factors. The influence of low nSES on pain outcomes varied according to genetic polymorphisms in the *FKBP5* locus, supporting the hypothesis that low nSES affects pain outcomes via its influence on stress system function. Further studies are needed to better understand mechanisms by which low nSES contributes to worse chronic pain outcomes after MVC and other forms of trauma/stress exposure. Such studies could not only lead to a better understanding of adverse health

sequelae from living in low nSES, but could also contribute to an improved understanding of chronic pain pathogenesis.

Pain recovery after trauma is influenced by neighborhood socioeconomic characteristics. These findings are independent of individual characteristics, and moderated by genetic variation in *FKBP5*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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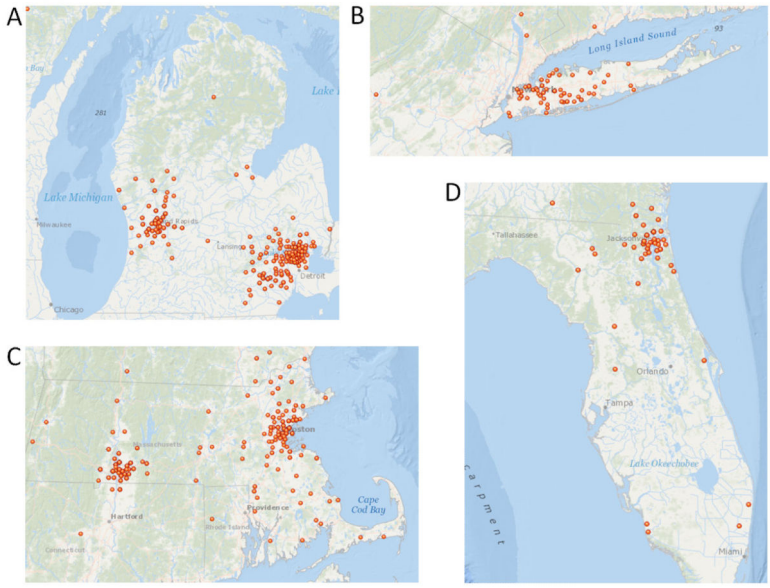

Fig 1.

Census tracts represented in each of the four states with enrollment sites (**A-D,** Michigan, Massachusetts, New York, and Florida).

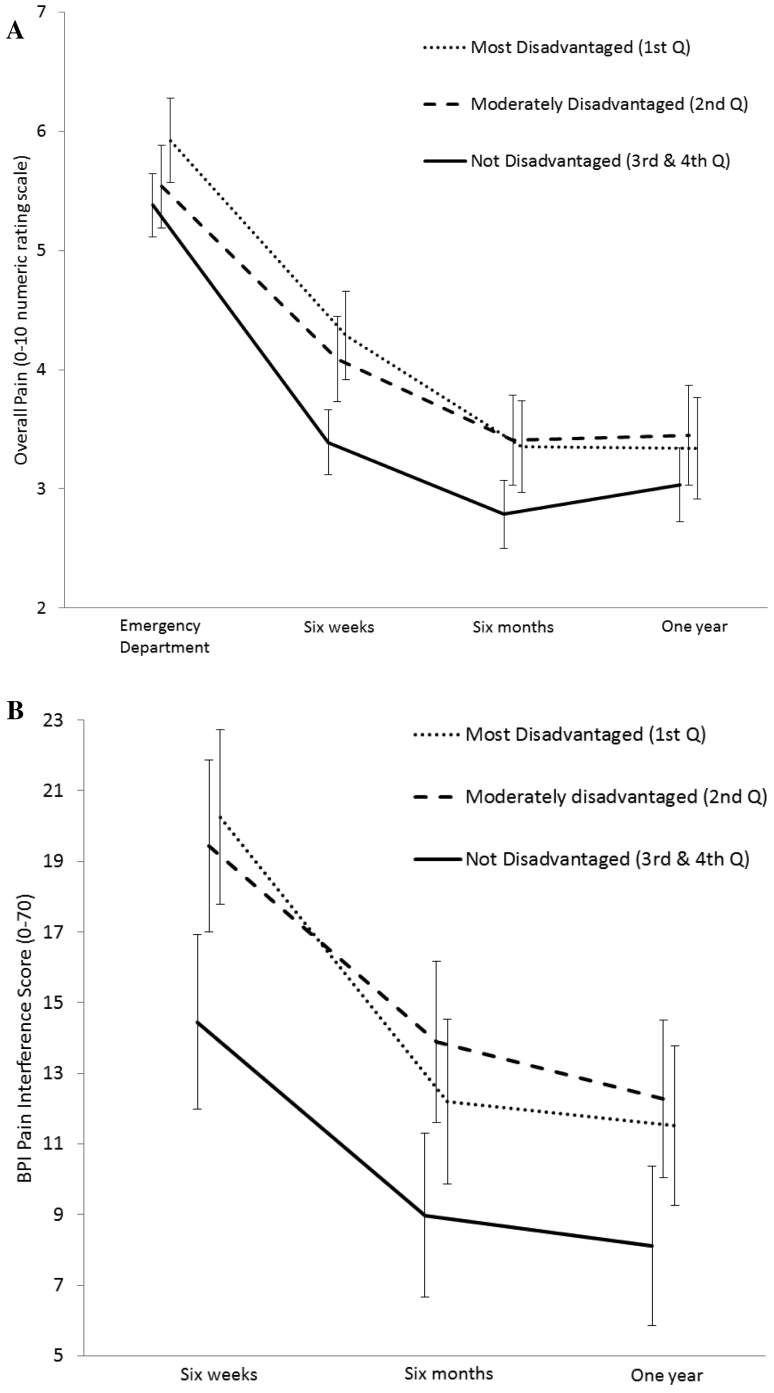

Fig 2.

A) Mean overall pain during the first year after motor vehicle collision amongst quartiles of socioeconomic disadvantage. **B)** Mean BPI pain interference during the first year after motor vehicle collision amongst quartiles of socioeconomic disadvantage. Pain interference is the sum of pain interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life each on a 0-10 NRS. Both 2A and 2B are adjusted for individual factors of annual household income, highest level of educational

attainment, full time employment status, sex, age, and prior overall pain prior to the MVC. Error bars represent 95% confidence intervals for the least squares mean estimates.

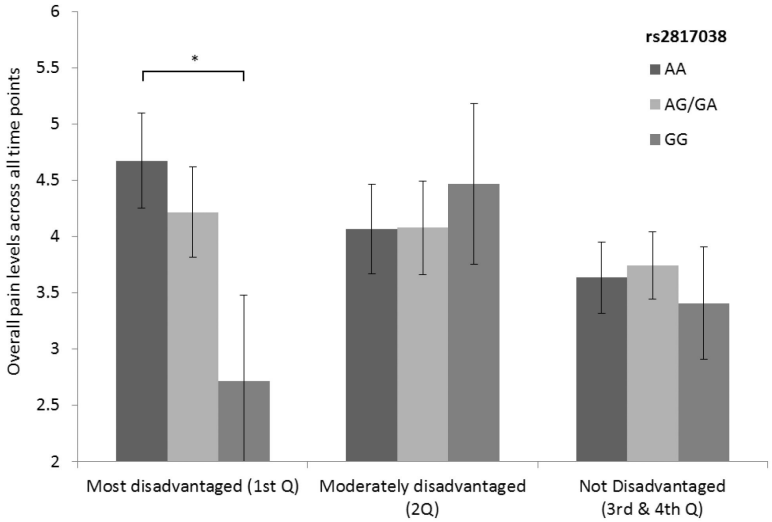

Fig 3.

Gene by environment interaction between FKBP5 SNP rs2817038 and the most disadvantaged quartile (1st quartile). Error bars represent 95% CIs of the least squares means. *Differences in overall pain amongst the genotypes is significant (p<0.0001). *MAF = minor allele frequency*.

Table 1

Individual and neighborhood characteristics of the MVC Cohort

Individual **(n, %)**	**n=948**
Sex	
Male	373 (39)
Female	575 (61)
Age	
18-27	315 (33)
28-41	302 (32)
42-65	331 (35)
Education	
High school or less	226 (24)
Some college or other training	369 (39)
College grad or post-grad	351 (37)
Income	
Below $20K	117 (12)
$20k to $40k	176 (19)
$40k to $80k	277 (29)
>$80k	273 (29)
Overall Pain in the ED	
None	38 (4)
Mild (0.5 to 3.5)	150 (16)
Moderate (4.0 to 6.5)	407 (43)
Severe (7.0 to 10.0)	344 (37)
Overall Pain prior to the MVC	
None	611 (65)
Mild (0.5 to 3.5)	142 (15)
Moderate (4.0 to 6.5)	111 (12)
Severe (7.0 to 10.0)	81 (9)
Neighborhood[*] *(mean, SD)*	
Percent unemployed	8.4 (4.2)
Percent below US poverty line	7.9 (8.3)
Percent high school education or less	12.6 (8.3)
Percent expensive homes	33.3 (33.6)
Percent working class	69.5 (11.8)
Median household income	64,015 (25,560)

[*] Neighborhood characteristics are weighted according to the percentage of the cohort residing within each census characteristic.

Table 2

FKBP5 SNP and their interactions with nSES on overall pain outcomes in a genotypic model.

SNPs*	Alleles	MAF	p-value
rs3800373	T:G	0.304	0.51†
rs7753746	A:G	0.207	0.29
rs3777747	A:G	0.474	0.52
rs10947562	C:T	0.110	0.57†
rs4713902	T:C	0.283	0.11†
rs17614642	T:C	0.070	0.017
rs9470079	G:A	0.169	0.50†
rs9380526	T:C	0.338	0.51†
rs10456432	T:C	0.174	0.24
rs9394314	A:G	0.305	0.54†
rs2766534	T:G	0.227	0.60†
rs12200498	G:A	0.149	0.54
rs2817032	T:C	0.290	0.36†
rs2817038	**A:G**	**0.354**	**0.0015**
rs2817040	G:A	0.261	0.62†

*15 tag SNPs were chosen from the 33 genotyped SNPs (rs10807151, rs3800373, rs992105, rs3798346, rs7753746, rs2395634, rs16878806, rs3777747, rs9368878, rs9380524, rs7748266, rs10947562, rs28675670, rs7751598, rs9348979, rs2143404, rs4713902, rs9394309, rs17614642, rs4713904, rs13192954, rs7762760, rs9470079, rs34110646, rs9380526, rs10456432, rs9394314, rs2766534, rs12200498, rs2817032, rs7751693, rs2817038, rs2817040).

†Models did not originally produce parameter estimates, so clustering by county were removed for these analyses.