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Heredity Links Natural Hazards and Human Health: Apolipoprotein E Gene Moderates the Health of Earthquake Survivors

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Objective: This study aimed to investigate the role of the apolipoprotein ε4 allele in moderating the influence of an exogenous stressor, an earthquake, on health. ***Design:*** A "natural experiment" design was used where the interaction between the presence of the apolipoprotein ε4 allele and the level of subjective and objective exposure to a devastating earthquake was examined in a population-based cohort of elderly Taiwanese ($N = 718$). ***Main Outcome Measures:*** The cognitive-affective dimension of health was assessed by measures of perceived control and depression and functional limitations were assessed using measures of instrumental activities of daily living and mobility. Overall health status was gauged using a single-item measure of self-rated health. ***Results:*** Those who experienced damage to their property or were forced to move from their homes (high objective exposure) demonstrated low levels of self-rated health and somewhat lower perceived control a year later, only if they were apolipoprotein ε4 carriers. Similarly, those who found the earthquake severely distressing (high subjective exposure) were shown to have low levels of functioning and low self-rated health a year later, only if they possessed the ε4 allele. ***Conclusion:*** Our findings suggest that genetic variation in the apolipoprotein E gene may modify the health effects of the exogenous stress of natural disaster exposure.

Keywords: apolipoprotein E, gene × environment interaction, trauma, natural experiment

The concept of gene × environment interaction is central to diathesis-stress models of disease and psychological disorder. Such models aim to explain people's varied responses to stress as a product of both genetic endowment and environmental stressors that interact to produce resilience and thriving or distress and illness. However, until recently such models have tended to be descriptive rather than explanatory. Developments in the assessment of variation in highly specific aspects of the human genome have made it possible for researchers in behavioral science to show gene × environment interactions using measured genes (Moffitt, Caspi, & Rutter, 2006). This study aimed to test the idea that genetic factors may not necessarily directly affect health; rather our genetic endowment can interact with environmental stressors to change physical and mental health. To do this, we examined the effects of exposure to a devastating earthquake that occurred in Taiwan in 1999 using data from the 2000 Social Environment and Biomarkers of Aging Study (SEBAS). The "Chi-Chi" earthquake, measuring 7.3 on the Richter scale, caused more than 2,400 deaths, collapsed over 100,000 homes, and sent thousands of aftershocks through the region in the weeks that followed (Lin et al., 2002).

We sought to measure the interaction between the impact of the Chi-Chi earthquake and the presence of variation in the apolipoprotein E gene (APOE) and test if this interaction appeared to influence the health of elderly Taiwanese people. The APOE gene consists of three alleles (ε2, ε3, ε4) that code for protein isoforms involved in lipid metabolism and neuronal maintenance. The ε4 allele has been shown to interact with physical injury to produce detrimental effects. For instance, the head trauma experienced by boxers, American football players, and those with a traumatic brain injury hastens cognitive decline in those with the ε4 allele (Savitz, van der Merwe, Stein, Solms, & Ramesar, 2007; Teasdale, Nicoll, Murray, & Fiddes, 1997). Evidence from human subjects and mouse models suggests that in addition to regulation of the response to physical trauma, the APOE gene is implicated in the regulation of emotional trauma (Lee et al., 2008; Raber, 2007). For instance, when compared with those possessing the ε3/ε3 genotype, healthy carriers of the ε4 allele have been shown to be at elevated risk of depression following the psychological stress of caregiving (Gallagher-Thompson, O'Hara, Simmons, Kraemer, & Murphy, 2001). The available evidence is thus suggestive of a link between elevated reactivity to stressors and the APOE ε4 allele. However, further research is needed to verify the robustness of the adverse reactivity observed among ε4 carriers and to elucidate the physiological mechanisms underpinning this reactivity.

It may be possible that the reactivity linked to those possessing the APOE ε4 allele could be partially explained by neuropathological changes induced in the amygdala, as demonstrated in mice expressing the APOE ε4 allele and human brain atrophy studies of ε4 carriers (Basso et al., 2006; Cherbuin, Leach, Christensen, & Anstey, 2007; Raber, 2007). Augmentations in amygdala functioning could disrupt the regulation of the hypothalamic-pituitary-adrenal axis, resulting in the prolonged release of glucocorticoids in response to stress that can have detrimental health effects (Peavy, 2008). In support of this idea elevated concentrations of

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the hormone cortisol have been found in stressed older human carriers of the ε4 allele (Peavy, 2008) and transgenic mice expressing the ε4 allele were shown to have an impaired capacity to suppress corticosterone levels after receiving dexamthasone, indicating potential hypercorticolism (Robertson et al., 2005).

It must be recognized that the current human and animal literature examining the biological and psychological effects of stress reactivity among APOE ε4 carriers is limited and requires further extensive neuroimaging, transgenic mice, and clinical studies. However, the available evidence tends to suggest that when carriers of the APOE ε4 allele encounter stressors they often incur detrimental physical and mental health outcomes. A key initial step in furthering this literature would be to demonstrate that when a population of ε4 carriers are highly exposed to stressors the negative health effects observed are more pervasive than those seen among other groups.

The current evidence suggesting that the APOE ε4 allele may lead to a dysfunctional health response to stressors is limited as existing studies rarely consider the possibility that the ε4 allele may confer an elevated likelihood of encountering the stressors examined (e.g., accident exposure, caregiving for sick relative) (Moffitt et al., 2006). Previous gene × environment interaction (hereafter G × E) studies have incorporated novel methods to statistically control for potential correlations between genetic vulnerability and environmental risk, such as adjusting for parental disposition (e.g., Caspi et al., 2003). However, as yet few G × E studies have examined the effect of exposure to an exogenous shock (e.g., earthquake, tsunami, terror attack) that cannot be attributed to one's genetic makeup.

As exogenous shocks are difficult to predict, longitudinal data that allows G × E effects to be studied are often unavailable. In the absence of longitudinal data, the natural variation in the level of exposure to an exogenous stressor is an important determinant of postdisaster health that can act as a substitute method of testing G × E effects (Norris et al., 2002). Those highly exposed to the stressor can be contrasted with the less severely exposed. For instance, Kilpatrick and colleagues (2007) showed that when combined with low social support the low-expression serotonin transporter genotype (5-HTTLPR) predicted an increased risk of posttraumatic stress disorder among those highly exposed to a hurricane in Florida. Similarly, in two studies polymorphisms in the RGS2 gene were shown to modify the risk of posttraumatic stress disorder (Amstadter et al., 2009) and generalized anxiety disorder (Koenen et al., 2009) contingent on participants' level of exposure to a severe hurricane in Florida. In the context of a G × E study, as both the level of exposure to an exogenous stressor and the assortment of alleles at the time of gamete formation are likely to be randomly assigned and uncorrelated with each other or with health before the earthquake, this design can be considered a "natural experiment" (Giltay et al., 2009; Moffitt et al., 2006).

The Current Study

The SEBAS dataset is unique in that it contains genetic information and detailed self-reported data specifying both the personal impact of the Chi-Chi earthquake and the health of participants 1 year later. Thus, it provides unique data for a natural experiment to test to see if the presence of the APOE ε4 allele might interact with exposure to an exogenous stressor to produce its effect on health. Adults aged from 54 to 74 were examined as this group, with available data, fell within the age bracket where genetic factors have been deemed to have their greatest effect on health ratings (Harris, Pedersen, McClearn, Plomin, & Nesselroade, 1992; Svedberg, Lichtenstein, & Pedersen., 2001). To test the G × E hypothesis, we utilized an objective measure of earthquake exposure that was likely to be uncorrelated with health before the earthquake. Objective exposure was defined as those who had experienced damage to their home or had to move from their home as a result of the earthquake. Subjective ratings of the immediate fear in response to the earthquake were also used as an index of the severity of exposure and to test for a potential G × E effect.

We utilize several measures of health to specify which aspects of health likely to be affected by the interaction between the APOE ε4 allele and stressors in the current study. Two measures were used to gauge the cognitive-affective component of health: perceived control and the presence of depression. Participants' current level of functioning was assessed using a measure of self-reported mobility and a second instrument gauging the capacity to engage in the instrumental activities of daily living. Participants also rated their overall level of health. Each aspect of health was expected to be particularly detrimentally affected by earthquake exposure among ε4 allele carriers.

Method

Participants

The potential sample ($N = 755$) consisted of a cohort of older adults aged 54 to 74 drawn from the 2000 SEBAS survey (for detailed information on sampling and recruitment strategy see Goldman et al., 2003). The Chi-Chi earthquake occurred on September 21, 1999 and the self-reported information on health and earthquake experiences was collected as part of the SEBAS survey between June and December the following year. The average duration from the earthquake to participant assessment was approximately 12 months (e.g., Seplaki, Goldman, Weinstein, & Lin, 2006). In total, 27 participants were lost from analyses because of incomplete questionnaire, anthropometric, or blood data, leaving 718 participants (57.2% men, mean age = 64.5 [$SD = 6.2$]) in the final sample. Approximately 29% of participants had no formal education, while a further 45.2% had primary education only. Twenty percent had completed secondary school education and 6.5% had attended college. Ethnicity was classified into Fukien (73.3%), Mainlander (13%), and Hakka (13.7%).

Health Measures

Cognitive-affective measures. The cognitive-affective aspect of participants' health was assessed using a measure of perceived control and a measure of depression. The Pearlin and Schooler (1978) mastery scale was used to index participants' perceived control over important life events. The scale is composed of seven items reflecting either perceptions of personal control (e.g., "What happens to me in the future mostly depends on me") or lack of control (e.g., "There is little I can do to change many of the important things in my life"). Participants rated each item using a 5-point scale from 1 = Strongly agree to 5 = Strongly disagree. The scores were combined to form a scale (Cronbach's

$\alpha = .61$) that ranged from 8 to 35 with a mean of 22.67 ($SD = 4.38$), with higher scores indicating greater perceived control.

The presence of depression was assessed using a 10 item version of Centre for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). Participants responded to the CES-D by rating their experience of depressive symptoms in the past week on a 4-point scale (0 = No, 3 = Often (>4 days)). The CES-D produces an index ranging from 0 to 30 (Cronbach's $\alpha = .766$), with scores of 10 and over deemed indicative of depression (Andresen, Malmgren, Carter, & Patrick, 1994). The mean score was 5.16 (Min = 0, Max = 28, $SD = 4.92$) and 17.36% of participants were classified as depressed. Depression scores were significantly negatively correlated with levels of perceived control ($r = -.3$, $p < .005$).

Functioning. Participants reported their ability to perform nine different physical movements on a four-point scale (0 = No difficulty, 1 = Some difficulty, 2 = Great difficulty, 3 = Unable to do it). Specifically, participants rated the difficulty they had standing for 15 min, standing for 2 hr, squatting, raising both hands over their head, grasping objects with their fingers, lifting 11–12 kg, running 20–30 m, walking 200–300 m, and walking up 2–3 flights of stairs. Most participants had few mobility restrictions and could complete most of these tasks without difficulty (M = 3.79, Min = 0, Max = 23, $SD = 5.16$, $\alpha = .86$). However, as some participants had severe mobility difficulties this variable was positively skewed and was therefore normalized via square root transformation.

Six Instrumental Activities of Daily Living (IADL) were also measured (i.e., ability to buy personal items, manage money, ride public transport alone, do light housework or physical work at home, make phone calls) and rated on the same four-point scale as mobility restrictions (0 = No difficulty, 1 = Some difficulty, 2 = Great difficulty, 3 = Unable to do it) (Lawton & Brody, 1969). The scale showed satisfactory reliability (Cronbach's $\alpha = .754$). However, as only a small portion of the sample indicated they experienced difficulties in completing these activities which resulted in a positively skewed distribution of instrumental activities. This variable was therefore normalized via square root transformation. Instrumental activity limitations were closely related to mobility difficulties ($r = .642$, $p < .005$).

Self-rated health. Self-rated health was measured using a noncomparative measure (comparative measures request participants to contrast current health with previous health or the health of others) that asked participants to rate their current health on a scale from 1 = poor to 5 = excellent (Eriksson, Undn, & Eloffson, 2001). The single-item measure has been shown to be a reasonable alternative to multi-item measures, producing comparable predictions of mortality, hospitalization, and other aspects of health care utilization (DeSalvo, Fan, McDonnell, & Fihn, 2005). The scores on the self-rated health measure were found to be normally distributed and centered close to the scale midpoint (M = 2.91, $SD = .97$).

Earthquake exposure. Participants indicated their subjective level of exposure to the earthquake by rating their level of fear in response to the event on a scale from 1 = not scared to 5 = extremely scared. Subjective exposure scores were normally distributed around the scale midpoint (M = 2.93, $SD = 1.27$). 37.5% of participants indicated they were "very" or "extremely" scared by the earthquake. This group was classified as highly exposed to earthquake trauma for inclusion in a "total exposure" composite variable.

Participants were categorized as having experienced a high level of objective exposure to the earthquake if they reported that their home had been damaged by the earthquake and/or if they had reported that they had to move from their home as a result of the earthquake (18.1% of the sample). A dummy variable was produced for regression analyses with those highly exposed to the earthquake coded as 1 and with the remaining portion coded as 0. There was a small but statistically significant correlation between the subjective and objective exposure variables ($r = .17$, $p < .01$).

Next, we categorized participants based on whether or not they met the criteria for a high level of subjective and/or objective exposure to the earthquake. In total, 44.3% of participants were classed as highly exposed and were coded as 1 with the remaining 55.7% classed as experiencing a low level of exposure and coded as 0.

Genotyping. APOE was genotyped using the polymerase chain reaction amplification refractory mutation system (PCR-ARMS) and polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) techniques (see Goldman et al., 2003). Dummy coding was used, with those possessing at least one copy of the APOE ε4 allele coded as 1 (14.4% of the sample) contrasted with the remaining base group of noncarriers (85.6%) who were coded as 0. The distribution of the APOE alleles in the sample examined was found to resemble that found previously in other populations (e.g., Hallman et al., 1991) and to meet the criteria for Hardy-Weinberg equilibrium. The prevalence of the APOE ε4 did not differ as a function of ethnicity ($\chi^2 = 1.4$, $p = .49$).

Potentially confounding variables. The ε4 allele has been shown to predict a number of potentially confounding variables that were included as covariates in the analyses. For instance, as the ε4 allele has been implicated in Alzheimer's disease we adjusted for participants' memory functioning to ensure that a link between the ε4 allele and detrimental health outcomes could not be attributed to the negative effects of memory dysfunction. It is also possible that the ε4 allele could be linked to adverse health outcomes through its association with smoking or chronic illness (e.g., coronary heart disease, stroke) (Stengard, Pekkanen, Ehnholm, Nissinen, & Sing, 1996). Thus, we adjusted for these variables.

Memory. Each participant's average score on the Rey Auditory Verbal Learning Test (Lezak, 1983) and the Digits Backward test (Wechsler, 1981) were standardized and combined to produce a normally distributed metric of cognitive functioning.

Chronic illness and smoking. To estimate the number of chronic illnesses a participant had been diagnosed with each person indicated if their doctor diagnosed them with: heart disease, hypertension, stroke, cancer, arthritis, diabetes, lower respiratory tract disease, hip fracture, gastric ulcer, liver disease, kidney disease, cataracts, gout, and spinal or vertebral spurs. The number of illnesses a participant had been diagnosed with was summated across the 14 illnesses detailed above. In addition, participants indicated if they were taking medication for any of the long-term illnesses above. The mean number of chronic illnesses experienced was found to be 1.62 ($SD = 1.46$) and 59.7% of participants were found to be using a medication for a long-term illness. As the number of chronic illnesses experienced was positively skewed

this variable was transformed via a square-root transformation. The degree to which each chronic condition interfered with functioning was rated on a 3-point scale from 0 = No inconvenience to 2 = Much inconvenience (M = 1.12, *SD* = 1.56). Illness interference scores were also positively skewed and were transformed by a square-root transformation. Participants also indicated their smoking status (24.4% current smokers).

Statistical Analysis

Before analyses data were inspected for accuracy, and all study variables were examined for normalcy. First, we tested to see if the relationship between earthquake exposure and the set of health measures varied as a function of whether or not participants possessed the APOE ε4 allele. Then a regression framework was used to test if genotype moderated the association between level of exposure to the earthquake and health. The main effects of genotype and the level of exposure to the earthquake were first explored and then the G × E interaction term was entered into the model. For the binary objective exposure and total exposure variables, the product of the genotype and exposure variables formed the interaction terms for analyses. As the subjective exposure measure was continuous it was converted into a standardized Z-score and the product of this score and the genotype dummy variable was then used for the analysis of the genotype × subjective exposure interaction. All analyses were adjusted for the inclusion of demographic factors (age, sex, education, and ethnicity) and potentially confounding variables (cognitive function, smoking, and chronic illness).

Results

Preliminary Analyses

A series of logistic regression analyses were used to test if carriers of the APOE ε4 allele possessed characteristics that differed from noncarriers. There were no significant differences between APOE genotype groups on any of the demographic characteristics, as shown in Table 1. Although there were no differences between the APOE genotype groups in terms of the majority of the potentially confounding variables, there was some evidence that smokers were more likely to possess the ε4 allele (b = .059, SE = .027, $p < .05$). Importantly, the APOE ε4 allele was unrelated to the chances of being highly exposed to the earthquake on the subjective ($b = -.01$, SE = .1, p = .92), objective (b = .22, SE = .25, p = .39), and total exposure variables (b = .08, SE = .21, p = .7).

Demographic and control variables were used to predict exposure to the earthquake in regression analyses to identify nonrandom variation in earthquake exposure. We found that younger adults were more likely than older adults to experience earthquake exposure, indicating a nonrandom component to exposure, as shown in Table 1. More educated participants were more likely to experience high levels of objective earthquake exposure when contrasted with less educated participants. In addition, women were more likely than men to report experiencing high levels of fear in response to the earthquake. No other demographic or control factors significantly predicted measures of exposure to the earthquake.

Earthquake exposure and health as a function of APOE genotype. Next, we examined the link between objective and subjective exposure to the earthquake and health metrics for carriers and noncarriers of the APOE ε4 allele. These analyses demonstrated that noncarriers of the ε4 appeared to show little or no ill-effects of earthquake exposure. However, ε4 carriers who had to move from their house or experienced damage to their home showed reduced levels of perceived control ($b = -1.77$, SE = .89, $t = -1.99$, $p < .05$) and self-rated health ($b = -.54$, SE = .18, $t = -3$, $p < .01$) 1 year after the earthquake, as outlined in Table 2. Similarly, those without the APOE ε4 allele who felt scared (high subjective exposure) at the time of the earthquake did not experience detrimental health effects on any of the measured examined. For ε4 carriers feeling scared during the earthquake was related to increased mobility problems (b = .16, SE = .08, t = 2, $p < .05$) and low self-rated health ($b = -.2$, SE = .08, $t = -2.5$, $p < .05$) 1 year after the earthquake. The likelihood of depression (b = .61, SE = .34, t = 1.79, $p < .1$) and problems in completing instrumental activities (b = .14, SE = .08, t = 1.75, $p < .1$) were found

Table 1
Results of Regression Analyses Testing the Relationship Between Demographic Characteristics and Potentially Confounding Variables and the APOE ε4 Allele and Objective, Subjective, and Combined Earthquake Exposure

		Measure of exposure		
Predictor	APOE ε4 allele *B* (SE)	Objective *B* (SE)	Subjective *B* (SE)	Combined *B* (SE)
Age	−.00 (.02)	−.005† (.003)	−.012* (.006)	−.04** (.02)
Women	.42 (.26)	.05 (.04)	.52** (.09)	1.1** (.19)
Education	−.11 (.15)	.04* (.02)	−.03 (.05)	−.064 (.12)
Mainland[a]	−.28 (.32)	−.02 (.04)	.18† (.1)	.23 (.23)
Hakka[a]	−.21 (.37)	−.06 (.05)	−.06 (.12)	−.29 (.28)
Chronic illnesses	.14 (.14)	−.01 (.02)	−.00 (.05)	−.04 (.11)
Illness inconvenience	−.05 (.14)	.03† (.02)	.04 (.05)	.18† (.1)
Cognitive functioning	.09 (.14)	−.03 (.02)	−.04 (.05)	−.03 (.11)
Medication	−.1 (.27)	−.03 (.04)	−.00 (.09)	−.02 (.21)
Smoking	.59* (.27)	−.00 (.04)	−.11 (.09)	−.11 (.21)

Note. [a] Base category for ethnicity analysis refers to those of Fukien origin.
† $p < .1$. * $p < .05$. ** $p < .01$.

Table 2
Summary of Regression Analyses of the Association of Objective, Subjective, and Combined Earthquake Exposure With Outcome Variables as a Function of Possession of the Apolipoproetein E ε4 Allele

	Measure of exposure								
	Objective			Subjective			Combined		
Predictor	ε4 *B* (SE)	no ε4 *B* (SE)	G × E *B* (SE)	ε4 *B* (SE)	no ε4 *B* (SE)	G × E *B* (SE)	ε4 *B* (SE)	no ε4 *B* (SE)	G × E *B* (SE)
Depression	−.8 (.67)	−.24 (.3)	−.29 (1.36)	.61† (.34)	.16 (.13)	.36 (.31)	1.55* (.7)	.22 (.25)	1.27* (.64)
Locus of control	−1.77* (.89)	−.64 (.45)	−.96 (1.06)	−.54 (.4)	−.23 (.18)	−.16 (.44)	−1.48† (.78)	−.4 (.36)	−.45 (.86)
Mobility difficulties	.05 (.09)	.18 (.18)	.07 (.21)	.16* (.08)	−.05 (.03)	.21* (.09)	.28† (.15)	−.02 (.07)	.23 (.17)
IADL[a] difficulties	.04 (.18)	.02 (.08)	−.00 (.18)	.14† (.08)	−.05† (.03)	.18* (.08)	.21 (.15)	−.04 (.06)	.24 (.15)
Self-rated Health	−.54** (.18)	−.14 (.09)	−.38† (.22)	−.2* (.08)	−.02 (.04)	−.19* (.09)	−.54** (.16)	−.02 (.07)	−.5** (.18)

Note. [a] IADL = Instrumental Activities of Daily Living.
† $p < .1$. * $p < .05$. ** $p < .01$.

to be marginally increased among ε4 carriers who experienced a high level of subjective exposure to the earthquake.

An examination of the combined exposure variable demonstrated a similar pattern of results: high earthquake exposure predicted significantly raised levels of depression ($b = 1.55$, $SE = .7$, $t = 2.21$, $p < .05$) and reduced levels of self-rated health ($b = -.54$, $SE = .16$, $t = -3.38$, $p < .01$) as well as marginally reduced perceived control ($b = -1.48$, $SE = .78$, $t = -1.9$, $p < .1$) and increased mobility difficulties ($b = .28$, $SE = .15$, $t = 1.87$, $p < .05$). In summary, we found little evidence that high levels of earthquake exposure had a detrimental effect on the majority of the study sample which consisted of non-ε4 carriers. In contrast, for the smaller portion of the sample consisting of ε4-carriers, earthquake exposure was significantly or marginally significantly related to poor health in 10 of the 15 analyses conducted.

G × E moderation analyses. We next sought to identify if the pattern of results showing a relatively consistent relationship between earthquake exposure and diminished health only among APOE ε4-carriers would be evident as statistical interaction effects. Thus, the next set of analyses tested if genetic vulnerability to stress moderated the association between the level of objective exposure to the earthquake and current levels of health. Self-rated health was the only health variable that showed a statistically significant interaction between objective earthquake exposure and the possession of the APOE ε4 allele. An unadjusted analysis identified the hypothesized interaction ($b = -.5$, $SE = .25$, $t = -2.01$, $p < .05$) and after adjusting for demographics and potentially confounding variables this interaction remained as a marginal effect ($b = -.38$, $SE = .22$, $t = -1.72$, $p < .1$), as shown in Table 2.

The self-rated health G × E interaction identified in the objective exposure analysis was replicated in both the unadjusted subjective exposure analysis ($b = -.23$, $SE = .1$, $t = -2.19$, $p < .05$) and in the regression model which adjusted for demographic factors and potentially confounding variables ($b = -.19$, $SE = .09$, $t = -2.03$, $p < .05$). Similarly, there was evidence that high levels of subjective earthquake exposure interacted with the presence of the ε4 allele to predict both mobility ($b = .21$, $SE = .09$, $t = 2.33$, $p < .05$) and instrumental activities ($b = .18$, $SE = .08$, $t = 2.25$, $p < .05$). Subjective earthquake exposure was negatively related to self-rated health and positively related to mobility difficulties for APOE ε4 carriers but not for noncarriers. Subjective exposure predicted a marginally increased level of difficulties in instrumental tasks for ε4 carriers ($b = -.14$, $SE = .08$, $t = -1.75$, $p < .1$) and a marginally reduced level of difficulty for non-ε4 carriers ($b = .05$, $SE = .03$, $t = -1.68$, $p < .1$).

Objective and subjective exposure variables were then combined into a single metric, which classified 43.2% of participants as highly exposed to the earthquake. The hypothesized G × E was highly significant for self-rated health ($b = -.5$, $SE = .18$, $t = -2.78$, $p < .01$). As in the subjective and objective analyses, this interaction showed that high levels of exposure to the earthquake appeared to have a greater detrimental influence on self-rated health for APOE ε4 than for noncarriers, as illustrated in Figure 1. Similarly, the combined high exposure metric interacted with the presence of the ε4 allele to predict the presence of depression ($b = 1.27$, $SE = .64$, $t = 2$, $p < .05$), with high levels of exposure predicting depression only among ε4 carriers ($b = 1.55$, $SE = .7$, $t = 2.21$, $p < .05$).

Discussion

Although previous research has shown that unfavorable health outcomes can result from a combination of genetic vulnerability and early maltreatment or physical injury (e.g., Teasdale et al., 1997), little is known about the role of genetic factors in moderating how people respond to natural disaster situations. The exogenous shock of a disaster situation is by definition unrelated to a person's genetic makeup and thus offers a suitable opportunity to examine G × E interactions. The present investigation assessed the level of exposure to the 1999 Chi-Chi earthquake in a cohort of elderly Taiwanese people using both objective and subjective measures.

This study found that each of five measures examined (i.e., depression, perceived control, instrumental activities, mobility, self-rated health) provided some evidence of reduced levels of health among APOE ε4 carriers for whom the earthquake had personal objective consequences or for those who subjectively perceived the earthquake as severely disturbing. In the absence of the ε4 allele considerable exposure to the earthquake appeared to contribute little to a decline in health. The effect of exposure to the earthquake indicates that a traumatic event in itself or genetic susceptibility alone may not be enough to cause negative effects. Instead, our analysis suggests a complex relation between health

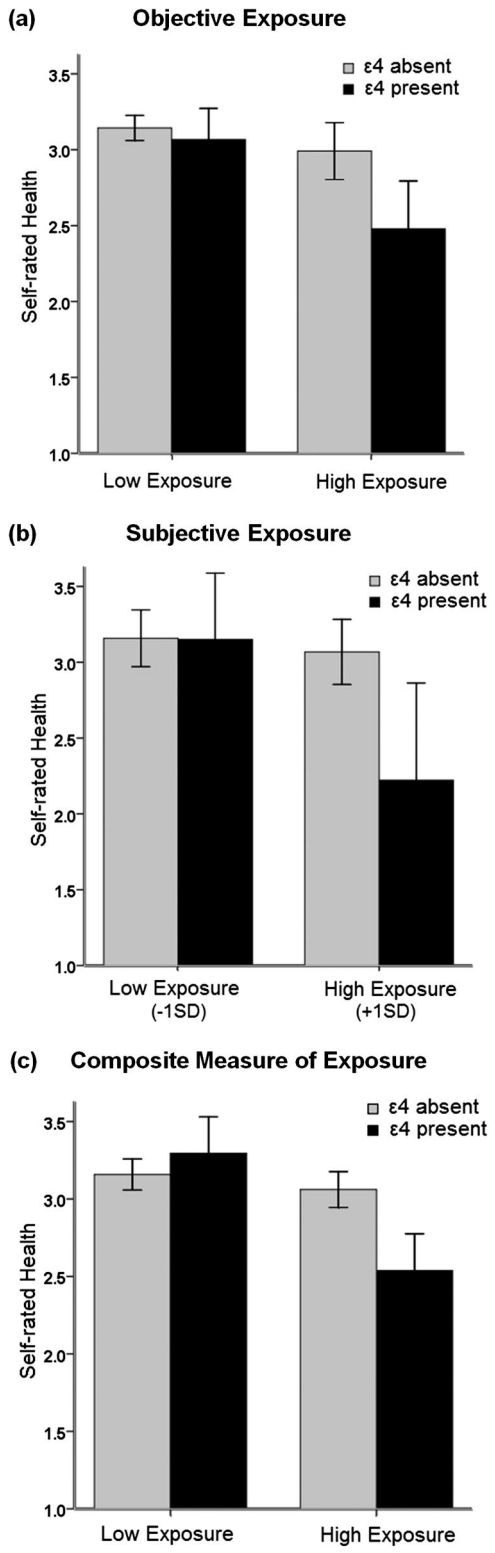

Figure 1. Self-rated health as a function of level of exposure to the earthquake by APOE genotype for (a) objective, (b) subjective, and (c) combined composite exposure variables.

and genetic factors where a person's genotype *only in combination* with the severity of their exposure to stressors may act to modify the risk of detrimental health outcomes.

The subjective exposure measure assessed the degree to which participants were afraid during the aftermath of the earthquake. Interestingly, carriers of the ε4 allele were equally as fearful as noncarriers. However, feeling afraid at the time of the earthquake predicted activity limitations, poor mobility, and low self-rated health a year later among ε4 carriers but not noncarriers. Several studies have shown that the effects of trauma unfold over many years (Ben-Zur & Zeidner, 2009). For instance, a separate study of survivors of the Chi-Chi earthquake showed suicidality to increase from 4.2% at 6 months after the earthquake to 6% at 3 years (Chou et al., 2007). It may be the case that a restricted capacity to respond to challenges to the central nervous system could lead to a worsening health status among APOE ε4 carriers (Gallagher-Thompson et al., 2001; Peavy, 2008). The current study suggests that functional rather than cognitive/affective aspects of health may be detrimentally affected by high subjective exposure to earthquake trauma.

In contrast, there was some evidence that the perceived control of ε4 carriers was diminished as a result of objective earthquake exposure as assessed by participant ratings of earthquake damage or having to move home as a result of the earthquake. The self-rated health of ε4 carriers also appeared to be reduced as a result of objective earthquake exposure. This G $\times$ E relationship between earthquake exposure and self-rated health was amplified when the subjective and objective earthquake exposure variables were combined to form a composite variable, as illustrated in Figure 1. Taken together, the results suggest that the self-rated health measure provided the most consistent evidence that health levels may be reduced as function of earthquake exposure and the presence of the APOE ε4 allele. It may be the case that the broad self-rated health measure best captures the portion of variation in health that is influenced by adverse reactivity to stressors among ε4 carriers. Other more specific measures that focus on cognitive/affective or functionality dimensions of health may succeed in capturing only a smaller component of the G $\times$ E effect.

While the results in this study suggest that it is the exposure to trauma that has a detrimental effect on ε4 carriers, it must be recognized that the size of the main effects of exposure and the G $\times$ E interaction effects observed in the current study were small, yet not atypical (e.g., see Plomin & Davis, 2009). In addition, several limitations to the current study warrant comment. The retrospective assessment of participants' response to the earthquake may have been influenced by memory distortions, bias, and normal forgetting (Moffitt et al., 2006). Nonetheless, these potential confounds would impact on the results only if they produced estimates of exposure that varied by genotype which did not appear to be the case. The design of the present investigation was based on the idea that longitudinal data, while preferable, is not essential to examine a G $\times$ E effect on physical or mental health. This is because a natural experiment can be constructed if genetic variation (e.g., possession of the ε4 allele) and the level of exposure to an exogenous stressor (e.g., an earthquake, terror attack) are likely to be randomly assigned and uncorrelated with each other and with pre-earthquake health.

While the results suggest that the APOE genotype could be considered a quasi-experimental independent variable (Giltay et

al., 2009), there was some evidence of nonrandomness in exposure to the earthquake. Younger adults were more likely to experience objective exposure to the earthquake, potentially reflecting nonrandom factors other than pre-earthquake health, such as age-related trends in home occupancy. The possibility that less healthy female ε4 carriers experienced an elevated subjective impact of the earthquake is potentially more problematic for the results. However, as post hoc analyses revealed that the increased likelihood of high subjective exposure found among women did not differ by genotype this explanation is unlikely. Nonetheless, future multiwave studies will assist in providing essential tests for replication of the identified results and in demonstrating the within-person change in the health of ε4 carriers resulting from stress exposure (e.g., Munafo & Flint, 2009; Risch et al., 2009).

Future studies should also investigate pathways through which the identified trauma exposure × APOE genotype interaction may influence health. APOE ε4 carriers have demonstrated elevated levels of anxiety, a trait characterized by a propensity toward rumination and persistent physical hyperarousal (Grootendorst, de Kloet, Vossen, Dalm, & Oitzl, 2001; Raber, 2007). It is feasible that trauma could induce these psychological states that in turn may enhance sensitivity to physical symptoms and promote illness behavior (Schnurr & Jankowski, 1999). While a measure of anxiety was not available in the current study there was evidence that levels of depression were raised among ε4 carriers who were highly exposed to the earthquake (as gauged by combined high subjective and objective exposure). Thus, we suggest that psychological distress may be one clear outcome of traumatic events that could in turn lead to further decrements in health. For instance, the distress that is inherent in the threat to life that characterizes traumatic experiences could cause people to engage in riskier health behaviors such as excessive drinking (Ben-Zur & Zeidner, 2009). Trauma may also have effects on biological function and health, altering the body's response to stress by heightening noradrenergic function, influencing the hypothalamic-pituitary-adrenal axis and activating immune-mediated inflammation (Peavy, 2008; Schnurr & Jankowski, 1999).

Rather than supporting a model where genetic factors lead to poor health, the findings from this study suggest that exogenous stressors can interact with genetic vulnerability to explain trajectories of physical and mental health. When people experience potentially traumatizing events, those who carry risk polymorphisms, such as the APOE ε4 allele, may be susceptible to subsequent negative health outcomes. It is therefore important to examine the interaction between genetic and psychological factors in coping with traumatic exposure to disaster situations.

Our results suggest that while both carriers and noncarriers of the APOE ε4 allele experienced the Chi-Chi earthquake as equally fearful, those with the APOE ε4 allele appraised and/or reacted to the event in a way that produced lower health. A better understanding of whether the APOE ε4 allele is involved in psychological appraisal mechanisms and/or emotional and health-related reaction mechanisms would be helpful. This knowledge could be used to design randomized treatment experiments to both prevent post-exposure health decline in those at genetic risk and help extend the frontier of our understanding of the determinants of outcomes following adversity.

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