The causal impact of stress on inflammation over the long-term: Evidence from exposure to a natural disaster

Elizabeth Frankenberg, UNC Chapel Hill
Ralph Lawton, Duke University
Teresa Seeman, UCLA
Cecep Sumantri, SurveyMeter, Indonesia
Duncan Thomas, Duke University

September 2018

Acute levels of stress have been linked to elevated inflammation which, in turn, has been identified as a risk factor for cardio-metabolic and other diseases. Studies have established links between elevated inflammation and low socio-economic status (Alley et al, 2006), childhood adversity (Slopen et al, 2013), acute stress arising from work and economic insecurity (Niedzweidz et al, 2017) as well as stress associated with interpersonal or caregiving demands (Shivpuri et al, 2012). Moreover, well-established biological pathways link exposure to stress to activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis which results in hormone secretion and the initiation of an acute-phase inflammatory response (McEwan, 1988).

There are at least two important unresolved issues in this literature. First, it is unclear how much of the observed associations between stress and inflammation in human populations are driven by the causal impact of stress exposure on inflammation rather than other factors that affect both stress and inflammation. (See, for example, Das 2016.) Second, whereas the biological responses to stress are well understood, there is a paucity of evidence on the longer-term consequences of stress exposures on levels of inflammation and subsequent human health. This research is designed to address both of these challenges.

Data are drawn from a special wave of the Study of the Tsunami Aftermath and Recovery (STAR) which was specifically designed for this research. STAR is a large-scale population-representative longitudinal study of survivors of the 2004 Indian Ocean tsunami who were, at the time of the tsunami, living along the coast of Aceh at the northern tip of the island of Sumatra in Indonesia. The study area bore the brunt of the impact of the tsunami which reached across the entire Indian Ocean. In Aceh, over 160,000 people (5% of the total population) were killed by the tsunami and some communities in the study area were completely destroyed while others were left untouched by the tsunami. (Frankenberg et al, 2011).

There are two features of the study that are key to identify the causal impact of stress on inflammation. First, the tsunami was completely unanticipated. Prior to the 2004 tsunami, the Indian Ocean was not thought to be prone to tsunami waves and archaeological evidence indicates there has not been a tsunami in that area for over 200 years. At the time, there were no early warning buoys deployed in the Indian ocean which is in sharp contrast with the Pacific. The tsunami waves, which were spawned by the largest earthquake in recorded history and resulted in the North Pole shifting 2cm, hit the coastline of Aceh about 30 minutes after the earthquake at 8 am on Sunday 26 December, 2004. The people on the island of Sumatra were in no way prepared for the tsunami and pre-tsunami data collected from the study respondents indicates that none had taken actions to avoid the threat of a tsunami.

Second, the communities that were destroyed by the tsunami were not ex ante predictable. Specifically, the damage caused by the tsunami depended on the wave direction and wave height (which, in turn, depended on the topography of the seabed and location of the epicenter of the earthquake) as well as the topography of the land. Coastal communities that were otherwise essentially statistically exchangeable had completely different experiences because, for example, they faced different directions on a promontory and were separated by elevated land. The natural and built environments in communities that endured the full force of the water were devastated: waves reached 15m in height with mud and debris being pushed 6 kms inland. Other, nearby communities were spared the direct effects of the waves.

This research leverages the natural experiment design of the unanticipated tsunami in combination with biomarker data collected as part of STAR to isolate the causal effect of exposure to stress related to the tsunami on later like health. STAR is uniquely well-suited for this research for three reasons.

First, precisely because most natural disasters are unanticipated, few studies have information about the population before the event. STAR is one of very few studies that have successfully collected information on a population-representative sample of survivors both before and after the event. The baseline for STAR was conducted ten months before the tsunami and is representative at the district (*kabupaten*) level.

Second, we determined the survival status of over 98% of the baseline sample (>30,000) and we have interviewed over 96% of the tsunami survivors in at least one follow-up wave. Detailed information was collected immediately after the tsunami from each survivor about their own experience during the tsunami and its aftermath. This includes, for example, struggling in the water, watching family and friends perish and or struggling in the water, the loss of homes and loss of livelihoods. Detailed information about exposures at the community level, including wave heights, death and destruction in the community, are measured by interviews with respondents and local leaders as well as derived from remote-sensed imagery (Gillespie et al, 2007).

Third, we tracked and interviewed respondents for 17 years and in the most recent wave, we have collected biomarkers from a purposively-selected sub-sample of respondents that represents all tsunami survivors. The biomarkers, which span inflammation, lipids and glucose dysregulation, have been collected using point of care monitors that we have rigorously validated in the field; data collection is conducted in a climate-controlled mobile mini-lab we developed for this research. Biomarker data are complemented with anthropometry and body composition.

We compare C Reactive Protein (CRP), an acute phase marker of inflammation measured 13 years after the tsunami among nearly 7,000 survivors who were age 20 or older at the time of the measurement. About one-third of the respondents, who were age 7 and older at the time of the tsunami, were living along the coast of Aceh and were directly exposed to the devastation of the tsunami. They are compared with respondents who were living along the Acehnese coast but were not directly affected by the tsunami. Adjusting for age and gender as well as differences in socio-economic status, we find respondents who were exposed to the tsunami are significantly more likely to present with elevated rates of CRP (measured by CRP$\geq$3mg/dl conditional on CRP being less than 10mg/dl to exclude the small fraction with acute inflammation which is likely transitory).

Specifically, using different indicators of exposure, ranging from the extent of damage in the respondent's location at the time of the tsunami to individual-specific experiences, we find that the fraction of the population with elevated CRP is significantly higher among females and older males included in this biomarker study.

Key results are summarized in Table 1. The upper panel displays the fraction of study subjects with elevated CRP by gender and age among those who were not directly exposed to the tsunami and the difference for those who were directly exposed at the community level, adjusting for age and education. As shown in the first column, among female adults not directly exposed to the tsunami, 22.1% are measured to have elevated CRP but exposed females are 4.9% more likely to have elevated CRP (t statistic=2.9). Among males age 40 and older, 21.0% of those not exposed have elevated CRP and nearly 28% of those exposed have elevated CRP. (The t statistic on the difference, 7.8%, is 2.4.) The results are unchanged if the models do not adjust for education and if the small fraction of study subjects whose CRP>10mg/dl are included in the analyses.

Corroborating evidence that stress is implicated is provided by similar differences in adiposity as indicated by waist circumference which was measured for each respondent during the biomarker sub-study. As shown in the lower panel of the table, waist circumference is also significantly higher among females (by 2.2cm, t=3.2) and older males (1.6cm, t=2.0).

The same conclusions are drawn when exposure to stress is measured with individual-specific measures of tsunami exposures, even after taking into account all community-level variation including destruction. Exploring heterogeneity in the effects across pre-tsunami socio-economic status establishes that resilience and recovery differ by SES. Further analyses suggest that recovery is likely linked to the extent of post-tsunami reconstruction as well as social networks.

The evidence from STAR clearly establishes that exogenous increases in acute stress have sustained impacts on population health, as evidenced by significantly elevated rates of inflammation and adiposity over the long-term. These effects vary by age, gender and socio-economic status and indicate that the extent of resilience depends not only on individual-specific pre-existing characteristics but also on the availability of social and economic resources after the tsunami.

References

Alley, DE, TE Seeman, JK Kim, A Karlamangla, P Hu, EM Crimmins. (2006). Socioeconomic status and C-reactive protein levels in the U.S. population: NHANES IV. *Brain, Behavior and Immunity*, 20:498-504.

Das, A. (2016). Psychosocial distress and inflammation: Which way does causality flow? *Social Science and Medicine*, 170:1-8.

Frankenberg E, T Gillespie, S Preston, B Sikoki, C Sumantri and D Thomas. (2011). Mortality, family and the Indian Ocean tsunami, *Economic Journal*, 121:554:F162-82.

Frankenberg, E, J Friedman, T Gillespie, N Ingwersen, R Pynoos, B Sikoki, A Steinberg, C Sumantri and D Thomas. (2008). Mental health in Sumatra after the Indian Ocean tsunami. *American Journal of Public Health*, 98:1671:77.

Gillespie, T, J Chu, E Frankenberg and D Thomas. (2007). Assessment and prediction of natural hazards from satellite imagery. *Progress in Physical Geography*, 31.5:459-70.

McEwan, BS. (1988). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338.3:171-9.

Niedzwiedz, CL, SV Katikireddi, A Reeves, M McKee and D Stuckler. (2017). Economic insecurity diuring the Great Recession and metabolic, inflammatory and liver function biomarkers: Analysis of the UK Household Longitudinal Study. *Journal of Epidemiology and Community Health* 71:1005-13.

Slopen, N, LD Kubzansky, KA McLaughlin and KC Koenen. (2013). Childhood adversity and inflammatory processes in youth: A prospective study. P*sychoneuroendocrinology* 38:188-200.

Table 1
Effect of exposure to tsunami on inflammation and adiposity 12 years after tsunami

Respondent age at time biomarker measured:	Females			Males		
	>=20y	<40y	>=40y	>=20y	<40y	>=40y
% elevated CRP						
Community heavily damaged	4.9	5.1	4.7	1.5	-1.6	7.8
	[2.9]	[2.6]	[1.4]	[0.9]	[0.9]	[2.4]
Mean for not directly exposed	22.1	19.3	28.9	18.2	16.9	21.0
Waist circumference (cms)						
Heavily damaged	2.2	2.2	2.0	1.3	1.1	1.6
	[3.2]	[2.8]	[2.3]	[2.0]	[1.4]	[2.0]
Mean for not directly exposed	84.3	81.9	88.7	81.6	79.8	84.4
Sample size	3,555	2,425	1,130	3,352	2,236	1,116

Notes: [t statistics] take into account clustering and heteroskedasticitiy. Estimates are differences between living in community that was heavily damaged relative to community not directly exposed to tsunami, based on community of residence at time of tsunami. All models adjust for age, education and some damage to community. Elevated CRP is CRP>=3 conditional on CRP<10 mg/dL.