

tein synthesis. Although a small number of proteins appeared toxic (Fig. 3, inset), the vast majority had only a limited effect on cell growth. Overexpression levels do not correlate with—and hence cannot be predicted by—obvious sequence characteristics such as codon usage, protein size, hydrophobicity, and number of transmembrane helices (table S2). The C-terminal His₆ tag and the tobacco etch virus (TEV) protease site present in the GFP fusions (8) make it possible to use an efficient, standardized purification protocol for the whole clone collection; yields of purified fusion protein are typically ≥ 1 mg per liter of culture (25). This sets a lower limit for what can be expected for individual proteins expressed, for example, without a GFP tag or using other expression vectors and growth conditions (26).

In conclusion, by analyzing a library of *E. coli* inner membrane proteins fused to PhoA and GFP, we have derived an experimentally based set of topology models for the membrane proteome and provide a large-scale data set on membrane protein overexpression. Our results provide an important basis for future functional

studies of membrane proteomes and will facilitate the identification of well-expressed targets for structural genomics projects.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/308/5726/1321/DC1

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13 January 2005; accepted 14 March 2005
10.1126/science.1109730

Firearm Violence Exposure and Serious Violent Behavior

Jeffrey B. Bingenheimer,^{1*} Robert T. Brennan,² Felton J. Earls²

To estimate the cause-effect relationship between exposure to firearm violence and subsequent perpetration of serious violence, we applied the analytic method of propensity stratification to longitudinal data on adolescents residing in Chicago, Illinois. Results indicate that exposure to firearm violence approximately doubles the probability that an adolescent will perpetrate serious violence over the subsequent 2 years.

Within the past few decades, the popular notion that violence begets violence has come under scientific scrutiny. Early research by psychologists, criminologists, and others focused on the impact of being physically abused as a child on subsequent delinquency, community violence, and spouse and child abuse. Simple comparisons of violent offenders and nonoffenders showed that the former were more likely to report having been abused during childhood (1, 2). More carefully controlled prospective studies comparing abused and nonabused children confirmed these basic relationships (3) and provided insights into the cognitive and neurological mechanisms involved (4, 5).

Recently, interest has expanded to encompass exposure to violence occurring in community settings such as neighborhoods and schools. This change was spurred in part by elevated rates of violent crime, including firearm homicide, in American cities in the early 1990s (6, 7). In several studies conducted around that time, urban children and adolescents reported alarmingly high levels of exposure to community violence, both as witnesses and as victims (8–10). These findings raised troubling questions about the possible developmental ramifications of such widespread experience with violence.

Numerous recent investigations have revealed statistical associations between children's and adolescents' self-reports of exposure to community violence and concurrent or subsequent assessments of violence and aggression (11–14). Available estimates of these associations, however, do not adequately control for the possibility that a common set of personal characteristics and environment circumstances may jointly influence who is ex-

posed to community violence and who becomes a perpetrator of violent acts. The extent to which these statistical associations are attributable to cause-effect relationships therefore remains uncertain (15).

The randomized experiment is the scientific gold standard for causal inference, but in the instance of community violence is neither technically nor ethically feasible. We used the method of propensity score stratification (16–18) to approximate a randomized experiment in which exposure to firearm violence was the treatment variable and subsequent perpetration of serious violence was the outcome. This method is based upon counterfactual thinking and the framework of potential outcomes described by Rubin (19) and others (20). Investigators in economics (21), medicine (22), and other fields (23) are increasingly using propensity score matching and stratification to improve the credibility of estimates of cause-effect relationships obtained from observational data.

Propensity stratification views exposure allocation as a process involving both systematic and random components. First, personal and environmental characteristics of the individual determine systematically her or his probability π of exposure, called the propensity score. The individual then participates in a lottery in which the exposure is assigned with probability π , or nonexposure is assigned with probability $1 - \pi$. In theory, comparing individuals with identical propensity scores but different realized exposures is analogous to conducting a randomized experiment, and therefore provides a valid basis for measuring a cause-effect relationship between expo-

¹Department of Health Behavior and Health Education, 1420 Washington Heights, University of Michigan School of Public Health, Ann Arbor, MI 48109–2029, USA. ²Department of Social Medicine, Harvard Medical School, 1430 Massachusetts Avenue, 4th Floor, Cambridge, MA 02138, USA.

*To whom correspondence should be addressed. E-mail: bartbing@umich.edu

sure and outcome. The analytic strategy, then, has four stages: (i) Use all available preexposure information to derive an estimate $\hat{\pi}$ of each subject's propensity score; (ii) divide subjects into strata on the basis of $\hat{\pi}$; (iii) within each stratum, confirm that exposed and unexposed subjects are balanced on all measured preexposure covariates; and (iv) compute the mean difference between exposed and unexposed subjects on the outcome measure within these strata. This produces an unbiased estimate of the average causal effect of exposure under the assumption, termed "strongly ignorable treatment assignment" (16), that no measured or unmeasured preexposure characteristic predicts both exposure and outcome independent of estimated propensity scores. The greater the quantity and quality of preexposure information available to the analyst, the more precisely $\hat{\pi}$ will estimate π , and the more plausible the strongly ignorable treatment assignment assumption will become. Sensitivity analyses (24) enable the investigator to study the robustness of results to plausible violations of this assumption.

We analyzed data from a longitudinal cohort study of adolescents residing in 78 neighborhoods of Chicago, Illinois (Fig. 1) (25). The subjects ($N = 1517$) were aged 12 or 15 years at the beginning of the study (table S1). Subjects and their primary caregivers were each interviewed on three occasions over a period of 5 years. At Assessment 1, subjects and their caregivers provided detailed information about themselves. From these data we derived measures of 139 preexposure covariates falling into 10 domains: demographic background, family history and home environment, temperament, health and physical development, social support, peer influences, vocabulary and reading proficiency, school-

related factors, behavioral patterns, and previous exposure to violence (25) (table S2). Additionally, 14 neighborhood social and economic characteristics were quantified by means of census data and an independent survey of a probability sample of adult residents (26, 27), bringing the total number of preexposure covariates to 153 (25) (table S2).

At Assessment 2, subjects ($n = 1239$, 81.7% of the original sample) who could be located and who agreed to continue participating answered a series of questions regarding their exposure to firearm violence in the previous 12 months (25) (table S1). They were classified as exposed if they reported that they had been shot or shot at, or if they had seen someone shot or shot at, during that period. Those who reported none of these experiences were classified as unexposed. Fourteen subjects could not be classified due to missing or inconsistent data. Of those who could be classified, the majority ($n = 942$, 76.9%) were unexposed, and the remainder ($n = 283$, 23.1%) were exposed (25).

Subjects who reported exposure to firearm violence at Assessment 2 differed from unexposed subjects on many Assessment 1 covariates at the $\alpha = 0.01$ statistical significance level (Table 1; for more details see table S2). Compared with unexposed subjects, exposed subjects were more aggressive and reported committing more violent offenses. They tended to be non-white, male, from single-parent households, and receiving public assistance. In terms of temperament, exposed subjects were more impulsive and emotional and less inhibited than unexposed subjects. They were more likely to report having engaged in alcohol and drug use, truancy, general delinquency, and property crimes. Exposed subjects were more likely than unexposed subjects to

have family members with criminal records or legal problems. They were also more likely to have been corporally punished and physically abused and to have witnessed domestic violence in their households. Their peer groups were characterized by higher levels of aggressive and delinquent behaviors compared with the peer groups of unexposed subjects. Exposed subjects had lower scores on standardized tests of vocabulary and reading proficiency. Their neighborhoods of residence were characterized by more anomie, physical and social disorder, perceived violence, and concentrated disadvantage, and by lower levels of informal social control and satisfaction with policing, compared with the neighborhoods in which unexposed subjects resided. Many of these correlates of exposure to firearm violence are also well-established predictors of violent behavior (28, 29), substantiating the possibility that statistical associations between violence exposure and perpetration may be attributable in part to the joint influence of these factors on exposure and outcome status.

We used a maximum-likelihood logistic regression model to obtain an estimated propensity score $\hat{\pi}$ for each subject whose Assessment 2 exposure status was available. The model was constructed by an iterative stepwise selection procedure. The 153 Assessment 1 covariates, plus squared terms for the 92 covariates that were measured on continuous metrics, comprised the pool of candidate predictors. At each iteration, the procedure either (i) added to the model the single covariate that was most strongly associated with firearm violence exposure conditional upon the covariates already in the model, provided that the conditional association was statistically significant at the $\alpha = 0.10$ level, or (ii) removed from the model any covariate whose conditional association with gun violence exposure was no longer statistically significant at that level. The resulting model included 37 covariates. We modified this model by adding a squared term for each first-order continuous covariate selected by the procedure, and by adding a first-order term for each squared continuous covariate selected, bringing to 48 the total number of covariates included in the final model (25) (table S3).

Exposed and unexposed subjects had notably different probability densities of $\hat{\pi}$ (Fig. 2). The distribution for unexposed subjects was skewed sharply to the right, with nearly half ($n = 459$, 48.7%) having $\hat{\pi} < 0.10$ and none having $\hat{\pi} > 0.85$. In contrast, the probability density for exposed subjects was more nearly uniform, the only exception being that very few ($n = 3$, 1.1%) had $\hat{\pi} < 0.05$. We divided subjects into 12 strata on the basis of their estimated propensity scores (Table 2). Cut points were selected such that exposed and unexposed subjects had statistically indistinguishable mean estimated propensity scores

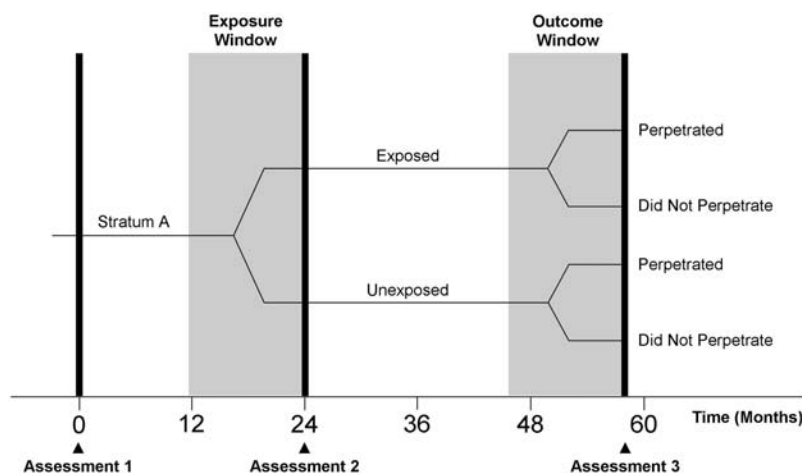


Fig. 1. Design of the propensity-stratified longitudinal study. This design was implemented for 12 propensity strata, 10 of which were used for estimating the cause-effect relationship between exposure to firearm violence (obtained at Assessment 2) and subsequent perpetration of serious violence (obtained at Assessment 3). Strata were defined on the basis of modeled probabilities of exposure at Assessment 2 conditional upon 153 covariates measured at Assessment 1. The placement of Assessments 2 and 3 on the horizontal axis is based upon the median time between interviews.

within each of the resulting strata. Satisfactory balance of unexposed and exposed subjects could not be achieved within the ranges $\hat{\pi} < 0.05$ and $\hat{\pi} > 0.75$. We therefore excluded the lowest and highest strata from the propensity-stratified analyses. Within each of the remaining 10 strata, exposed and unexposed subjects had nearly identical mean values of $\hat{\pi}$ [no statistical difference: $F(10,862) = 0.11, P = 0.9998$]. We also used statistical hypothesis tests to determine whether unexposed and exposed subjects had similar distributions of the Assessment 1 covariates within each of the 10 analytic propensity strata. We found no statistically significant ($\alpha = 0.01$) within-stratum differences between exposed and unexposed subjects on any of the 153 covariates (table S2), suggesting that our propensity model and stratification scheme adequately controlled selection on all measured preexposure covariates.

At Assessment 3, subjects who could again be located and who agreed to continue participating ($n = 984, 80.3\%$ of those whose Assessment 2 exposure status could be ascertained) answered questions about their perpetration of violent behavior in the previous 12 months (25) (table S1). Those reporting that they had carried a hidden weapon, attacked someone with a weapon, shot someone, shot at someone, or been in a gang fight in which someone was hurt or threatened with harm were classified as perpetrators of serious violence. Those reporting none of these five activities were classified as nonperpetrators. The majority of subjects ($n = 856, 87.0\%$) were classified as nonperpetrators, and a minority ($n = 122, 12.4\%$) were classified as perpetrators (25). A few ($n = 6, 0.6\%$) could not be classified due to incomplete or inconsistent responses.

We used a series of maximum-likelihood logistic regression models to obtain estimates of the statistical association and the cause-effect relationship between exposure to firearm violence and subsequent perpetration of serious violence (25). A model with no covariates revealed a strong statistical association; subjects who were exposed to firearm violence at Assessment 2 were much more likely than unexposed subjects to report perpetration of serious violence at Assessment 3 [odds ratio (OR) = 3.71, $\chi^2(1) = 41.99, P < 0.0001$]. Adjustment for race/ethnicity, age, sex, family socioeconomic index, and neighborhood of residence by regression methods attenuated this association only slightly (adjusted OR = 3.57, $t_{970} = 5.29, P < 0.0001$). Further adjustment for previous violence exposure, self-reported violent crime, and self- and caregiver-reported delinquency attenuated the association more substantially (adjusted OR = 2.47, $t_{966} = 3.64, P = 0.0003$).

Within the 10 analytic propensity strata, we found that subjects who were exposed to firearm violence at Assessment 2 were more

likely than unexposed subjects in the same stratum to report serious violence perpetration at Assessment 3 (common within-stratum OR = 2.43, $\chi^2(1) = 11.74, P = 0.0006$). Regression adjustment for race/ethnicity, age, sex, family socioeconomic index, and neighborhood of residence did not substantially alter this finding (adjusted common within-stratum OR = 2.62, $t_{677} = 3.039, P = 0.0025$), nor did further adjustment for previous violence exposure and violent and aggressive behaviors (adjusted common within-stratum OR = 2.76, $t_{673} = 2.721, P = 0.0067$). We also estimated a model in which the effect of firearm violence exposure was allowed to vary across the propensity strata, but comparison of this model with the original propensity-stratified model revealed that any heteroge-

neity in this effect was too small to be estimated reliably [no statistical difference: $\chi^2(9) = 15.12, P = 0.0877$].

Our estimate of the cause-effect relationship between firearm violence exposure and subsequent perpetration of serious violence represents an average treatment effect estimate. This estimate does not apply to individuals with very low or very high levels of propensity to be exposed. We did not estimate a cause-effect relationship outside the range $0.05 < \hat{\pi} < 0.75$ because of imbalance between exposed and unexposed subjects in the lowest and highest propensity strata.

Some sources of potential bias should also be noted. First, the subjects' exposure to firearm violence and subsequent perpetration of serious violence were both assessed by

Table 1. Comparison of exposed and unexposed subjects on select Assessment 1 covariates. Unless otherwise noted, covariates are measured on a continuous scale and standardized to unit variance; differences are standardized mean comparisons; and test statistics are $F(1,1223)$.

Preexposure covariate	Difference	Test statistic	P value
<i>Demographic characteristics</i>			
Male sex*	1.199	7.37	0.0066
Minority race/ethnicity†	–	38.55	<0.0001
Receiving public assistance*	1.664	24.34	<0.0001
Single-parent family structure†	–	28.52	0.0002
<i>Temperament</i>			
Impulsivity	0.298	19.63	<0.0001
Inhibitory control	0.218	10.43	0.0013
Sensation-seeking	0.341	25.91	<0.0001
Emotionality	0.203	9.00	0.0028
<i>Antisocial behaviors</i>			
Self-reported aggression	0.315	22.00	<0.0001
Caregiver-reported aggression	0.349	27.14	<0.0001
Violent offenses	0.619	89.19	<0.0001
Alcohol use*	1.540	19.31	<0.0001
Cigarette use*	1.508	15.48	<0.0001
Marijuana use*	2.550	39.41	<0.0001
Truancy	0.118	20.00	<0.0001
School drop-out*	0.977	12.14	0.0005
Self-reported delinquency	0.398	35.40	<0.0001
Caregiver-reported delinquency	0.471	50.27	<0.0001
Property crimes	0.375	31.36	<0.0001
<i>Family environment</i>			
Family members with criminal records*	1.407	12.98	0.0003
Family members with legal problems*	1.620	13.39	0.0003
Corporal punishment	0.244	13.10	0.0003
Physical abuse	0.299	19.80	<0.0001
Witnessing domestic violence	0.240	12.60	0.0004
<i>Peer group characteristics</i>			
Aggressive behaviors	0.567	74.13	<0.0001
Property crimes	0.358	28.52	<0.0001
Drug use	0.397	35.17	<0.0001
Drug selling	0.173	35.02	<0.0001
Sexual activity	0.373	81.76	<0.0001
<i>Indicators of intelligence</i>			
Vocabulary	–0.233	11.90	0.0006
Reading proficiency	–0.181	7.17	0.0075
<i>Neighborhood characteristics</i>			
Anomie	0.352	27.56	<0.0001
Social disorder	0.359	28.73	<0.0001
Perceived violence	0.265	15.45	<0.0001
Concentrated disadvantage	0.529	64.16	<0.0001
Informal social control	–0.190	7.95	0.0049
Satisfaction with policing	–0.269	15.92	<0.0001

*Measured dichotomously; differences are relative risks and test statistics are $\chi^2(1)$. †Measured nominally with more than two categories; reported differences are too complicated to tabulate here, but test statistics are $\chi^2(5)$ for race/ethnicity and $\chi^2(7)$ for family structure.

Fig. 2. Probability densities of estimated propensity scores.

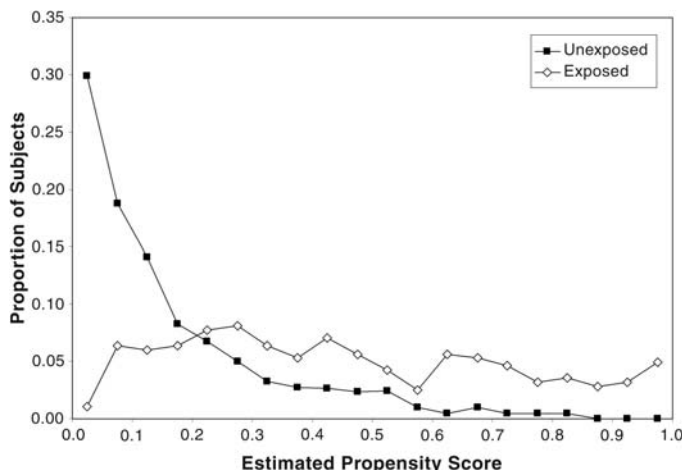


Table 2. Distribution of Assessment 3 serious violence perpetration, by propensity stratum and Assessment 2 firearm violence exposure status. Columns labeled "No" contain subjects who denied serious violence perpetration at Assessment 3; columns labeled "Yes" contain subjects who reported serious violence perpetration; columns labeled "?" contain subjects who were lost to follow-up or whose responses to Assessment 3 questions about violence perpetration were inconsistent.

Propensity stratum	Unexposed (N = 942)			Exposed (N = 283)		
	No	Yes	?	No	Yes	?
0.0000 – 0.0500*	224	12	46	3	0	0
0.0500 – 0.0875	96	5	24	8	3	2
0.0875 – 0.1250	85	10	17	4	0	7
0.1250 – 0.1625	82	5	16	7	3	6
0.1625 – 0.2000	35	0	13	8	1	4
0.2000 – 0.2500	44	6	14	10	9	3
0.2500 – 0.3375	58	8	9	19	3	9
0.3375 – 0.4375	31	8	10	25	6	10
0.4375 – 0.5375	26	6	13	20	6	4
0.5375 – 0.5875	6	1	5	2	3	2
0.5875 – 0.7500	12	3	4	22	9	15
0.7500 – 1.0000*	2	3	3	27	12	11
Total	701	67	174	155	55	73

*These strata are excluded from propensity-stratified analyses of covariate balance and treatment effects.

self-report, which implies that correlated misclassification on exposure and outcome status may have occurred, but the magnitude and direction of the resulting bias cannot be determined. Differential attrition of subjects between assessments is another potential source of bias. We found, however, that attrition was not strongly related to baseline covariates (25) (table S1), suggesting that any bias resulting from this may have been of minor importance.

Furthermore, we cannot rule out the possibility that unmeasured preexposure characteristics may have jointly influenced both exposure status at Assessment 2 and perpetration at Assessment 3. Yet, the omission of such variables from our analyses would constitute a violation of the assumption of strongly ignorable treatment assignment only to the extent that their influences were independent of estimated propensity scores. This would be most likely in the case of an omitted variable that was uncorrelated with the 153 covariates used in developing and testing our propensity model, but could occur under other circum-

stances as well. Sensitivity analyses (24, 25) (table S4) showed that these independent influences on both exposure and perpetration would need to be very strong to reduce substantially our estimate of the effect of firearm violence exposure on subsequent violent perpetration.

In conclusion, our focus on firearm violence exposure provided an operational definition of the treatment and control conditions and facilitated the assessment of each subject's exposure status. The longitudinal structure of the investigation established the temporal ordering of preexposure covariates, realized exposure status, and the behaviors comprising the focal outcome. We had access to a large and diverse set of well-measured preexposure covariates obtained from multiple sources, including subjects, their caregivers, neighborhood residents, and census data. We used this information to develop a model of how subjects' personal characteristics and environmental circumstances systematically influenced their probability of being exposed to firearm

violence. Stratifying on estimated propensity scores derived from this model provided statistical balance on all 153 measured preexposure covariates, suggesting that we succeeded in isolating the random part of the exposure allocation process, and thereby adequately approximated a randomized experiment. Our results thus provide a more credible basis for the conclusion that exposure to violence is causally related to violent behavior. Specifically, we estimate that being exposed to firearm violence approximately doubles the probability that an adolescent will perpetrate serious violence over the 2 subsequent years.

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30. We thank J. Brooks-Gunn, R. J. Sampson, and S. W. Raudenbush for insight and advice. This work was funded in part by grants from the John D. and Catherine T. MacArthur Foundation, the National Institute of Justice, and the National Institute of Mental Health.

Supporting Online Material
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24 January 2005; accepted 30 March 2005
 10.1126/science.1110096