Letters

RESEARCH LETTER

Scientific Publications on Firearms in Youth Before and After Congressional Action Prohibiting Federal Research Funding

In January 1996, Congress passed an appropriations bill amendment prohibiting the US Centers for Disease Control and Prevention (CDC) from using "funds made available for injury prevention . . . to advocate or promote gun control."[1] This provision was triggered by evidence linking gun ownership to health harms,[1] created uncertainty among CDC officials and researchers about what could be studied,[2] and led to significant declines in funding.[3] We evaluated the change in the number of publications on firearms in youth compared with research on other leading causes of death before and after the Congressional action. We focused on children and adolescents because they disproportionately experience gun violence and injury.[4]

Methods | We identified 10 leading causes of death among children and adolescents aged 1 to 17 years using CDC data on mortality between 1991 and 2010.[5] Each cause was then matched to a Medical Subject Heading, and PubMed was searched from 1991-2010 using causes of death and child or adolescent to determine the annual number of publications. Publications of all types and on all outcomes were included for each cause. To explore funding trends, we identified federal and private or nonfederal funding sources for firearms studies as reported by PubMed.

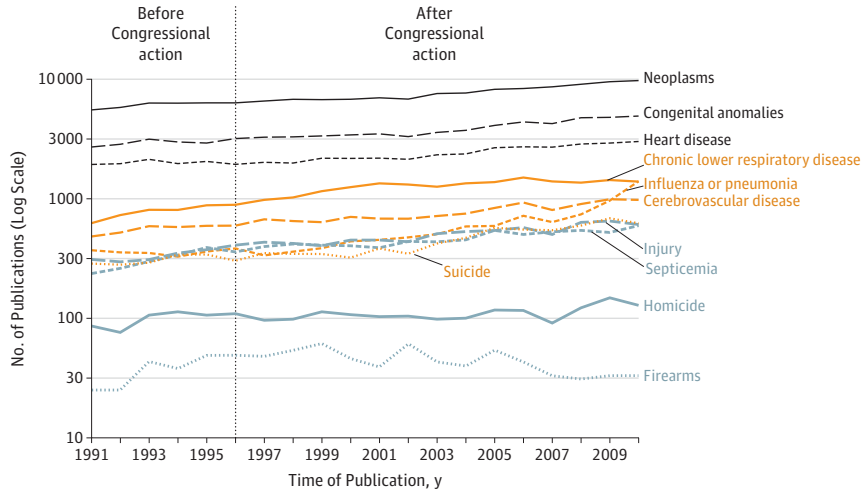
To quantify the change in annual publications, we used a quasi-experimental differences-in-differences design implemented with log-linear regression models.[6] This approach assessed change in the volume of firearms publications before and after a year, relative to the change in volume of publications on other causes before and after the same cut-point year. The null hypothesis was that the percentage change in volume of firearms publications would have been the same as the percentage change in volume of nonfirearms publications despite the events of 1996.[6]

Because the Congressional action may have had a delayed effect on publications, we allowed for a lag between the amendment and changes in annual firearms publications of 1 to 6 years. For each year, our model was specified as: publication volume = *f*(causes of death, firearms, post-cut-point year, firearms × post-cut-point year), in which post-cut-point year is an indicator variable for whether the data were drawn from before or after the year in question. The interaction term coefficient was the parameter of interest. Funding trends were categorized into prelag, perilag, and postlag periods.

Analyses were conducted using Stata version 12.0 (StataCorp Inc). Two-tailed *P* value of less than .05 was considered significant.

Results | Between 1991 and 2010, there were 310 203 deaths among youth from the 10 leading causes and 301 475 publications. Firearms accounted for 12.6% of deaths, but less than 0.3% of publications. There were 25 publications on firearms in 1991, 61 in 1999, and 33 in 2009 (**Figure**). In contrast, publications on neoplasms, which are responsible for approximately the same number of deaths, increased from 5519 to 9707. Using the differences-in-differences model and 1999 as the cut point, the volume of publications on firearms was 24.5% (*P* = .001) lower than it may have otherwise been compared with publications not on firearms (**Table**). Using different lag times did not significantly alter the results. The estimate was

Figure. Publications About Firearms and 10 Leading Causes of Death Among Children and Adolescents



The annual number of firearms publications was 25 in 1991 and 25 in 1992, 43 in 1993, 38 in 1994, 49 in 1995, 49 in 1996, 48 in 1997, 54 in 1998, 61 in 1999, 46 in 2000, 39 in 2001, 61 in 2002, 43 in 2003, 40 in 2004, 54 in 2005, 43 in 2006, 33 in 2007, 31 in 2008, 33 in 2009, and 33 in 2010.

Table. Average and Percentage Change in Annual Volume of Firearms Publications

Model[a]; Cut-Point Year[b]	Publication Topic	No. of Publications by Publication Year					Regression Model Estimates for Annual Volume of Publications[c]				P Value
		1991	1995	2000	2005	2010	Average From 1991 to Cut-Point Year	Average From Cut Point Year to 2010	Actual Change, %[d]	Relative Change (95% CI), %[e]	
1; 1997	Firearms	25	49	46	54	33	38	44	13.6	−15.4 (−30.1 to 2.4)	.09
2; 1998	Firearms						40	44	9.1	−19.3 (−32.5 to −3.4)	.02
3; 1999	Firearms						41	43	4.7	−24.5 (−36.3 to −10.5)	.001
4; 2000	Firearms						44	41	−7.3	−30.7 (−41.1 to −18.3)	<.001
5; 2001	Firearms						44	41	−7.3	−32.5 (−42.5 to −20.7)	<.001
6; 2002	Firearms						43	41	−4.9	−32.2 (−42.2 to −20.5)	<.001
3; 1999	Unintentional injury	310	374	450	541	607	363	524	30.7		
3; 1999	Neoplasms	5519	6320	6774	8202	9707	6230	7988	22.0		
3; 1999	Homicide	86	106	107	117	128	99	112	12.0		
3; 1999	Suicide	286	341	321	570	622	317	488	35.0		
3; 1999	Congenital anomalies	2701	2916	3410	4094	4902	3038	3998	24.0		
3; 1999	Heart disease	1930	2046	2168	2664	3004	1994	2516	20.7		
3; 1999	Influenza or pneumonia	370	361	439	591	1395	355	657	45.9		
3; 1999	Chronic lower respiratory disease	623	879	1247	1374	1378	841	1341	37.3		
3; 1999	Septicemia	236	390	403	542	594	337	479	29.7		
3; 1999	Cerebrovascular disease	482	592	703	835	975	584	799	26.9		

[a] Model 3 uses a cut-point year of 1999 (the approximate midpoint of a period at which the US Centers for Disease Control and Prevention funding for firearms research decreased sharply) and is the primary model. Models using other cut-point years (models 1-6) are presented for comparison.

[b] The cut-point year separates the before and after periods, taking into account a likely lag between the events of 1996 and changes in publication volume. The cut-point year is the first year of the after period.

[c] Models used a log-linear differences-in-differences design with cause-of-death fixed effects.

[d] This represents the average annual change in publications comparing the period before the cut-point year with the period after the cut-point year.

[e] This represents the average annual change in firearms publications after the cut-point year, relative to the average annual change in publications not on firearms during the same period. It assumes that the change in firearms publications would have been the same as the change in publications not on firearms during the same period, despite the events of 1996.

similar when considering only publications associated with a single cause of death (87%; differences-in-differences estimate, −19.9%; $P = .03$). In 1991-1996, 1997-2002, and 2003-2010, 33, 43, and 41 firearms publications reported federal funding, respectively; 25, 63, and 86 reported private or nonfederal funding.

Discussion | We only found modest increases in the number of scientific publications on firearms between 1991 and 2010, in contrast to other leading causes of death in youth. The change in number of publications on firearms was lower than anticipated compared with publications not on firearms. There was not a discrete point identified at which the pattern of publications changed. Therefore, whether the Congressional action or other events were responsible is unclear. Important limitations include use of a single database (PubMed) and lack of information on study inception. The effect on publications after President Obama's January 2013 memorandum directing the CDC to conduct or support research on the causes of gun violence and approaches to prevent it should be evaluated.

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Analysis and interpretation of data: Ladapo, Ryan, Trasande, Blustein.
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Administrative, technical, or material support: Trasande.

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COMMENT & RESPONSE

BRAF V600E Mutation and Papillary Thyroid Cancer

To the Editor The study by Dr Xing and colleagues[1] explored the association between the *BRAF* V600E mutation and mortality in patients with papillary thyroid cancer (PTC) in a large retrospective cohort of 1849 patients from 13 centers worldwide. The authors concluded that the *BRAF* mutation was significantly associated with cancer-related mortality.

However, this work actually demonstrates that the *BRAF* mutation is just a marker of aggressiveness and not a true prognostic factor because it was significantly associated with aggressive features and mortality in the bivariable analysis. When other clinical variables were entered in the analysis, the correlation disappeared. Therefore, the way the data were described and the conclusion may be misleading.

The conclusion that the *BRAF* mutation does not predict negative outcomes emerged from a recent study,[2] in which the *BRAF* mutation was analyzed in a sample of 47 patients with PTC with distant metastases, 26 of whom died because of the tumor. The *BRAF* V600E was not predictive of distant metastases or higher mortality because the frequency of this mutation was lower in the distantly metastatic group and within the subgroup of patients who died than in the control group (75 PTCs without distant metastases based on a minimum follow-up of 7 years). This evidence extends and confirms the results from the study by Xing et al[1] that the *BRAF* mutation is not a determinant of the metastatic potential of PTC.

Papillary thyroid cancers are generally nonaggressive tumors with low occurrence of metastases and death. This is a limitation for correlational prognostic studies. The series of PTC with distant metastases[2] and the sample described by Xing et al[1] are the largest ever analyzed. Xing et al[1] suggested that further studies are needed to determine the most appropriate use of the *BRAF* mutation as a clinical marker, whereas we believe that it is time to move forward and look for novel molecular determinants that may perform better in predicting outcome of patients with PTC.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Xing M, Alzahrani AS, Carson KA, et al. Association between *BRAF* V600E mutation and mortality in patients with papillary thyroid cancer. *JAMA*. 2013;309(14):1493-1501.

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In Reply I disagree with Dr Ciarrocchi and colleagues that *BRAF* V600E has no role in the aggressiveness of PTC because of its dependence on tumor behaviors, including local and distant metastases and invasion. It is clear that PTC would not cause patient death without aggressive tumor behaviors.

Our study demonstrated a strong synergism between *BRAF* V600E and aggressive clinicopathological behaviors, as reflected by the strong synergy indices and the fact that the association of mortality with *BRAF* V600E or clinicopathological behavior alone was only moderate but increased when the 2 were considered jointly. Thus, *BRAF* V600E does have a significant association with mortality, which likely occurs through promoting aggressive tumor behaviors and would be misleadingly lost using conventional multivariable models. Further efforts are needed to define how to specifically use the prognostic value of *BRAF* V600E clinically.

Some studies have not shown an association of *BRAF* V600E with aggressive behaviors of PTC. However, most have, as shown in large meta-analyses.[1,2] Many factors could bias the conclusion about the prognostic value of *BRAF* V600E. For example, in a large study of 631 patients with PTC that failed to show an association of aggressiveness of PTC with *BRAF* V600E,[3] many patients (41.5%) had only partial thyroidectomy, making thorough pathological characterization difficult. In addition, the majority of the patients in this study did not receive radioiodine ablation, potentially masking an effect of *BRAF* V600E on clinical outcomes given that *BRAF* mutation-negative PTC is more sensitive to radioiodine ablation.[1,2]

Ciarrocchi and colleagues' statement that a previous study[4] showing no aggressive role of *BRAF* V600E in PTC confirms our study is incorrect. However, the 2 studies are not comparable; the former was a single institution study focused on a small number of highly selected cases and the latter was a large multicenter study of consecutive cases.

The study by Sancisi et al[4] selected patients with distant metastases who only had well-differentiated primary cancer;