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NIH-Funded Cardiac Arrest Research: A 10-year Trend Analysis

Running title: *Coute et al.; NIH-Funded Cardiac Arrest Research*

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Abstract

Background: Cardiac arrest (CA) is a leading cause of death in the U.S., claiming over 450,000 lives annually. Improving survival depends on the ability to conduct CA research, and the translation and implementation of research findings into practice. Our objective was to provide a descriptive analysis of annual NIH-funding for CA research over the past decade.

Method and Results: A search within NIH RePORTER for the years 2007-2016 was performed using the terms: *"cardiac arrest" or "cardiopulmonary resuscitation" or "heart arrest" or "circulatory arrest" or "pulseless electrical activity" or "ventricular fibrillation" or "resuscitation"*. Grants were reviewed and categorized as CA research (yes/no) using predefined criteria. The annual NIH funding for CA research, number of individual grants and principal investigators were tabulated. The total NIH investment in CA research for 2015 was calculated and compared to other leading causes of death within the U.S. Inter-rater reliability between three independent reviewers for FY2015 was assessed using Fleiss's Kappa. The search yielded 2,763 NIH-funded grants, of which 745 (27.0%) were classified as CA research (Kappa = 0.86 [95%CI 0.80-0.93]). Total inflation-adjusted NIH funding for CA research was $35.4 M in 2007, peaked at $76.7M in 2010, and has decreased to $28.5 M in 2016. Per annual death, NIH invests ~$2,200 for stroke, ~$2,100 for heart disease, and ~$91 for cardiac arrest.

Conclusions: This analysis demonstrates the annual NIH investment in cardiac research is low relative to other leading causes of death in the United States, and has declined over the past decade.

Key words: cardiac arrest, research funding, National Institutes of Health (NIH)

Clinical Perspective

What is new?

- We performed a descriptive analysis of NIH-funded cardiac arrest research over the past decade.
- The results demonstrate the annual NIH investment in cardiac arrest research is low relative to other leading causes of death in the U.S., and has declined over the past decade.

What are the clinical implications?

- These results should help inform the debate regarding optimal funding for cardiac arrest research in the U. S.

Introduction:

Cardiac arrest is the third leading cause of death in the United States (U.S.),[1, 2] claiming the lives of over 450,000 individuals annually.[3-5] The estimated survival rates of those treated for in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) with any initial rhythm are approximately 24% and 11%, respectively.[3] In order to improve outcomes for this lethal condition and decrease its burden on society, funding for cardiac arrest research and translation of findings into clinical practice is critical.[2, 6] Yet, the number of cardiac arrest randomized controlled trials (RCT), a marker of research and innovation in the field, is low with less than 5 published yearly throughout the world over the past two decades.[7]

Unlike other diseases (e.g., stroke and heart failure) cardiac arrest research rarely receives external funding from pharmaceutical or cardiovascular device manufacturers and instead relies heavily on funding from governmental agencies, such as the National Institutes of Health (NIH).[6] The NIH research portfolio, which provides support details for more than 250 disease areas and is updated annually, includes no data specific to cardiac arrest funding.[2] Therefore, data on the NIH investment in cardiac arrest research and number of funded cardiac arrest principal investigators are largely unknown.

In an effort to fill this knowledge gap, we performed a simple descriptive analysis of NIH-funded cardiac arrest research over the past decade. The overall goal was to understand the trend in cardiac arrest research funding over time and compare the NIH investment in cardiac arrest research to that of other leading causes of death in the U.S.

Methods:

NIH Funding for Cardiac Arrest Research

A search within the NIH Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) database[8] for the years 2007-2016 was performed using the following search term string: *"cardiac arrest" or "cardiopulmonary resuscitation" or "heart arrest" or "circulatory arrest" or "pulseless electrical activity" or "ventricular fibrillation" or "resuscitation*." All grants from non-NIH funding sources including the U.S. Food and Drug Administration (FDA), U.S. Department of Veterans Affairs (VA), and the Agency for Health Care Research and Quality (AHRQ) were excluded from the analysis. Grants were individually reviewed and categorized as cardiac arrest research (yes/no) using predefined inclusion/exclusion criteria.

Grants were classified as cardiac arrest research if they met any of the following criteria: (1) studies designed to improve the treatment/outcomes of prehospital or in-hospital cardiac arrest (2) use of a cardiac arrest model; (3) use of a global ischemic brain injury model; (4) study of the mechanism of ventricular fibrillation (VF), pulseless ventricular tachycardia (pVT), pulseless electrical activity (PEA) or asystole; (5) study of the mechanism of therapeutic hypothermia for cardiac arrest; or (6) funding for resuscitation centers or group collaborations that list cardiac arrest research as a specific aim.

Grants were classified as not cardiac arrest research according to the following guidelines: (1) study of channelopathies or arrhythmia research other than VF, pVT, PEA, or asystole; (2) cardioplegia research; (3) implantable cardioverter defibrillator research; (4) trauma unless traumatic arrest is specifically mentioned; or (5) not cardiac arrest research.

The data was directly exported from the NIH RePORTER search to a Microsoft Excel file. The data available included: the grant title, contact principal investigator, investigator affiliation, award amount, funding agency (i.e. NHLBI, NINDS, etc.), award type (i.e. newly funded, competing renewal, and non-competing renewal grants), and funding mechanism. As a measure of the cardiac arrest research *pipeline*, the number of individual trainee grants were also tabulated and defined as K awards (K01, K08, K22, K23, and K99), F awards (F30, F31, and F32) and R awards (R00). The data used in this analysis includes publicly available grant information from NIH RePORTER, thus did not require approval by the University of Michigan Institutional Review Board.

NIH Research Investment for Leading Causes of Death

Data for the top ten leading causes of death in the U.S. were obtained from the *National Center for Health Statistics 2015 Health Report*.[9] The annual NIH Categorical Spending Report is available online and is titled, *Estimates of Funding for Various Research, Conditions, and Disease Categories (RCDC)*.[10] NIH research funding data for the leading causes of death were obtained from the RCDC for funding year 2015.[10] Estimates for the number of deaths due to cardiac arrest (both IHCA and OHCA) were extrapolated from the *AHA Heart Disease and Stroke Statistics—2015 Update*.[11] Using this information, the NIH research investment, expressed as dollars per annual death, was calculated for each disease.

Primary Data Analysis

The data were analyzed descriptively. The primary outcome measure was inflation-adjusted annual funding of cardiac arrest research in millions of dollars. Inflation adjustment was performed for funding years 2007-2015 using the consumer price index (CPI) inflation calculator provided by the U.S. Bureau of Labor Statistics.[12] Secondary outcome measures included: number of individual principal investigators funded per year (defined as contact principal investigator), total number of funded grants per year, and the NIH investment in cardiac arrest research (defined as dollars per annual death) compared to other leading causes of death. For funding year 2015, we estimated inter-rater reliability (IRR) between three independent reviewers using Fleiss' kappa for multiple raters using the MAGREE macro in SAS (SAS 14.1, 2015). The MAGREE macro is based on methods developed by Fleiss et al.[13]

Results:

The NIH RePORTER database search yielded a total of 2,845 grants, 82 of which were excluded due to a non-NIH funding source. Of the remaining 2,763 NIH-funded grants, 745 (27.0%) met study inclusion criteria and were classified as cardiac arrest research (Figure 1). Of the total search result, 73% of NIH grants were excluded from the evaluation. Fleiss' kappa for IRR was 0.86 (95%CI 0.80-0.93), indicating good inter-rater agreement.

The total cardiac arrest funding in the index year of 2007 was $30.5M (inflation-adjusted $35.4 M), and declined to $28.5M in 2016 (Figure 2). Maximum annual funding during the study period occurred in 2010 ($69.7M; inflation-adjusted $76.7M), with $42.9M supporting the Resuscitation Outcomes Consortium (ROC) Data Coordinating Center. Of particular note, a decrease of over $12M was observed from 2015 to 2016, 80% of which can be attributed to the cessation ROC funding. A nearly 10-fold increase in pediatric cardiac arrest research was observed from 2007 ($0.95M; inflation-adjusted $1.1M) to 2016 ($9.6M).

The NIH investment in cardiac arrest research for the 2015 funding year ($40.8M) represents approximately 0.19% of the total NIH research grant funding for 2015 ($21.2B),[14] while stroke and heart disease represent 1.4% and 5.9%, respectively. As illustrated in figure 3, the NIH investment per annual death, equates to ~$2,200 for stroke, ~$2,100 for heart disease, and ~$91 for cardiac arrest.

Table 1 presents data on the number of total grants funded, cardiac arrest principal investigators, newly funded grants, and trainee grants by year. Comparing 2007 to 2016, an increase was observed in the number of pediatric cardiac arrest grants (from 5 to 17) and individual trainee cardiac arrest grants (from 5 to 15). Little to no growth was observed in the number of funded investigators (from 54 to 60), newly funded grants (from 12 to 17), and overall grants funded (from 70 to 65).

Discussion:

In this evaluation, when adjusted for inflation, the total NIH funding for cardiac arrest research in 2016 was nearly 7 million dollars less than a decade previous in 2007. Although cardiac arrest is the third leading causes of death in the U.S.,[1] annual NIH funding for research to improve outcomes is relatively low. There were influxes of funding at different times in the decade in support of the Resuscitation Outcomes Consortium (ROC) with a large decrease in funding in fiscal year 2016 when ROC funding was discontinued. In 2015, the annual NIH investment in cardiac arrest research was $91 per annual U.S. cardiac arrest death.

The results of this analysis are consistent with previous assessments of NIH funding for cardiac arrest research. Ornato et al. reviewed cardiac arrest grants funded by the NIH National Heart Lung Blood Institute between 1985-2009. During this time period, they noted 257 funded grants in NIH RePORTER through a primary keyword search of "heart arrest and resuscitation".[6] They reported a large disparity in the number of funded projects per 10,000 annual deaths when compared to other cardiovascular diseases, with myocardial infarction having 439 grants, stroke with 294 grants, heart failure with 349 grants and cardiac arrest with only 8 funded grants.[6] More recently, an estimate of total cardiac arrest research funding was made as part of the Institute of Medicine (IOM) report using NIH RePORTER. Utilizing the search terms of "cardiac arrest" and "resuscitation science", NIH grants were identified with an estimated total funding in 2013 of $107.7 million.[2] In both of these studies, the calculated amount of funding was likely overestimated.[2, 6] These evaluations used nonspecific search terms (i.e resuscitation) identifying both cardiac arrest grants and those not studying cardiac arrest. In the current analysis, when strict inclusion and exclusion criteria were used requiring inspection of the individual grant descriptions, only 27% percent of all grants identified by initial search terms were cardiac arrest grants. These grants account for the overall funding of 28.5 million dollars for cardiac arrest in 2016.

Our analysis indicates that NIH cardiac arrest research funding is low per annual death compared to other leading causes of death (Figure 3). Cardiac arrest funding as calculated in this evaluation was $91 per death in 2015. This is significantly lower than other leading causes of death (Figure 3). For example, the investments in diabetes, kidney disease, and cancer are approximately $13,000, $12,000, and $9,000 per annual death, respectively. Another time sensitive condition, stroke has an investment of $2200 per annual death. Using total NIH funding for 2016, assuming no change in the incidence of cardiac arrest, we expect the NIH investment in cardiac arrest research to further drop to $63 per death.

It is important to note that the number of individual training grants increased from 5 (7% of all grants) in 2007 to 15 (23% of all grants) in 2016. Although this suggests a growing pipeline of early career investigators, it has yet to translate into an increased number of funded principal investigators or funded grants. Another area where a steady increase in funding was noted was grants related to cardiac arrest in pediatrics. The number of funded grants that had a pediatric focus increased steadily over the last decade from 5 (7% of all grants) in 2007 to 17 (26% of all grants) in 2016 (Table 1).

Limitations

Our study does not answer important questions about the cause of relatively low and declining funding for cardiac arrest research. Importantly, our results do not include numbers of grant applications submitted and funding rates. Unfortunately, this data is not publically available and is not released by the NIH. The lack of growth in number of PIs funded by NIH to perform cardiac arrest research does suggest an inadequate pool of investigators focused on this disease. Furthermore, we also did not evaluate funding from other federal sources, foundations or industry. We focused on NIH funding because NIH is the primary governmental funder of biomedical research in the U.S. However, there is no evidence that funding of cardiac arrest research from other sources is different for cardiac arrest compared to other diseases.

NIH funding per annual death may not be the best metric for cardiac arrest research funding since it is the final common pathway of death and overlaps with many other disease states. However a similar argument could be made about the overlap between other leading causes of death such as diabetes and heart disease or chronic respiratory disease and pneumonia, all of which are reported independently by CDC as causes of death. An alternative approach would be to compare funding per disability adjusted life year (DALY). However, to our knowledge, a reliable estimate of the annual DALYs lost due to cardiac arrest in the United States is currently not available.

Additional limitations include the fact that data were extracted from the NIH RePORTER software, and depends on the accurate reporting of the grants funded per fiscal year by the NIH.

Data associated with the burden of disease and the funding associated with each of the leading causes of death are from the CDC and NIH research portfolios and depend on accuracy of these reports. The funding for Resuscitation Outcomes Consortium (ROC) supported both trauma and cardiac arrest research trials. NIH RePORTER does not provide details to delineate funding specific to cardiac arrest for ROC grants. With this in mind, the final estimates of total annual funding may be overestimated. The inclusion criteria used in this evaluation were liberal to enable capture of all research associated with cardiac arrest. Included in our criteria were global ischemia models and asphyxia models of cardiac arrest. We limited our evaluation of IRR to a single funding year. Although we utilized three reviewers in this evaluation and the IRR demonstrated good reliability, extraction errors in data collection are possible.

Conclusion:

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. This analysis demonstrates the annual NIH investment in cardiac research is low relative to other leading causes of death in the United States, and has declined over the past decade. Although these results do not elucidate the cause of this apparent funding disparity, they should inform the debate regarding optimal funding for cardiac arrest research in the United States.

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Figure Legends:

Figure 1. Flow diagram of grants extracted from NIH RePORTER database

Figure 2. NIH Annual Funding of Cardiac Arrest Research

◆ $42.9M ROC Data Coordinating Center, which supported both trauma and cardiac arrest studies. Proportion that specifically supported cardiac arrest studies is not reported in the RePORTER database

◆◆ $21.9M ROC Data Coordinating Center, which supported both trauma and cardiac arrest studies. Proportion that specifically supported cardiac arrest studies is not reported in the RePORTER database.

◆◆◆ Cessation of ROC funding accounts for ~80% of the decrease in 2016 funding

Individual training grants defined as: K awards (K01, K08, K22, K23, and K99), F awards (F30, F31, and F32) and R awards (R00).

Data for funding years 2007-2015 are adjusted for inflation.

ROC = Resuscitation Outcomes Consortium Epistry.

Figure 3. 2015 NIH Investment for Leading Causes of Death.

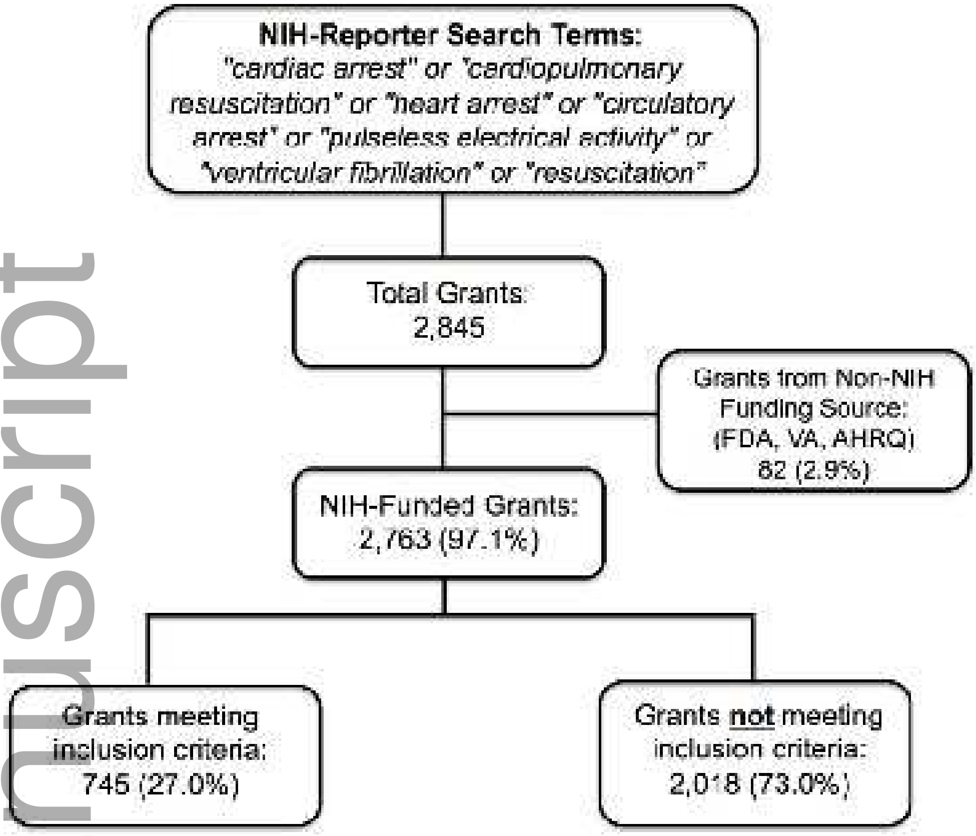
Data for leading causes of death obtained from *National Center for Health Statistics 2015 Health Report*, Table 19.[9] Data for NIH research funding obtained from the NIH portfolio on *Research, Condition, and Disease Category (RCDC) for 2015*.[10]

		Funding Year									
		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Grants	Total, n	70	64	67	79	86	82	72	79	81	65
	Pediatric Specific, n (%)	5 (7.1)	5 (7.8)	9 (13.4)	10 (12.7)	13 (15.1)	16 (19.5)	14 (19.4)	17 (21.5)	16 (19.8)	17 (26.2)
Funded Investigators*, n		54	58	53	68	77	74	62	72	75	60
Funding Institute, n (%)	NHLBI	37 (52.9)	37 (57.8)	35 (52.2)	44 (55.7)	46 (53.5)	47 (57.3)	39 (54.2)	45 (57.0)	46 (56.8)	33 (50.7)
	NINDS	21 (30.0)	15 (23.4)	21 (31.3)	24 (30.4)	23 (26.7)	22 (26.8)	21 (29.2)	22 (27.8)	24 (29.6)	25 (38.5)
	Other	12 (17.1)	12 (18.8)	11 (16.4)	11 (13.9)	17 (19.8)	13 (15.9)	12 (16.7)	12 (15.2)	11 (13.6)	7 (10.8)
Research Setting, n (%)	University	65 (92.9)	60 (93.8)	64 (95.5)	75 (94.9)	83 (96.5)	76 (92.7)	70 (97.2)	74 (93.7)	78 (96.3)	64 (98.5)
	Industry	5 (7.1)	4 (6.3)	3 (4.5)	4 (5.1)	3 (3.5)	6 (7.3)	2 (2.8)	5 (6.3)	3 (3.7)	1 (1.5)
Grant Type, n (%)	Newly Funded Grants	12 (17.1)	13 (20.3)	14 (20.9)	15 (19.0)	16 (18.6)	11 (13.4)	11 (15.3)	16 (20.3)	16 (19.8)	17 (26.2)
	Continuing	58 (82.9)	51 (79.7)	53 (79.1)	64 (81.0)	70 (81.4)	71 (86.6)	61 (84.7)	63 (79.7)	65 (80.2)	48 (73.8)
Individual Trainee Grants**, n (%)		5 (7.1)	6 (9.4)	7 (10.4)	13 (16.5)	15 (17.4)	17 (20.7)	16 (22.2)	15 (19.0)	16 (19.8)	15 (23.1)
Study Model, n (%)	Human Subjects	29 (41.4)	24 (37.5)	20 (29.9)	34 (43.0)	36 (41.9)	39 (47.6)	35 (48.6)	37 (46.8)	39 (48.1)	32 (49.2)
	Non-human Subjects	41 (58.6)	40 (62.5)	47 (70.1)	45 (57.0)	50 (58.1)	43 (52.4)	37 (51.4)	42 (53.2)	42 (51.9)	33 (50.8)

Table 1. Funded grants and associated types and descriptions summarized from 2007-2016.

*Includes only contact Principal Investigator

**Includes K awards (K01, K08, K22, K23, K99), F awards (F30, F31, F32), and R award (R00)



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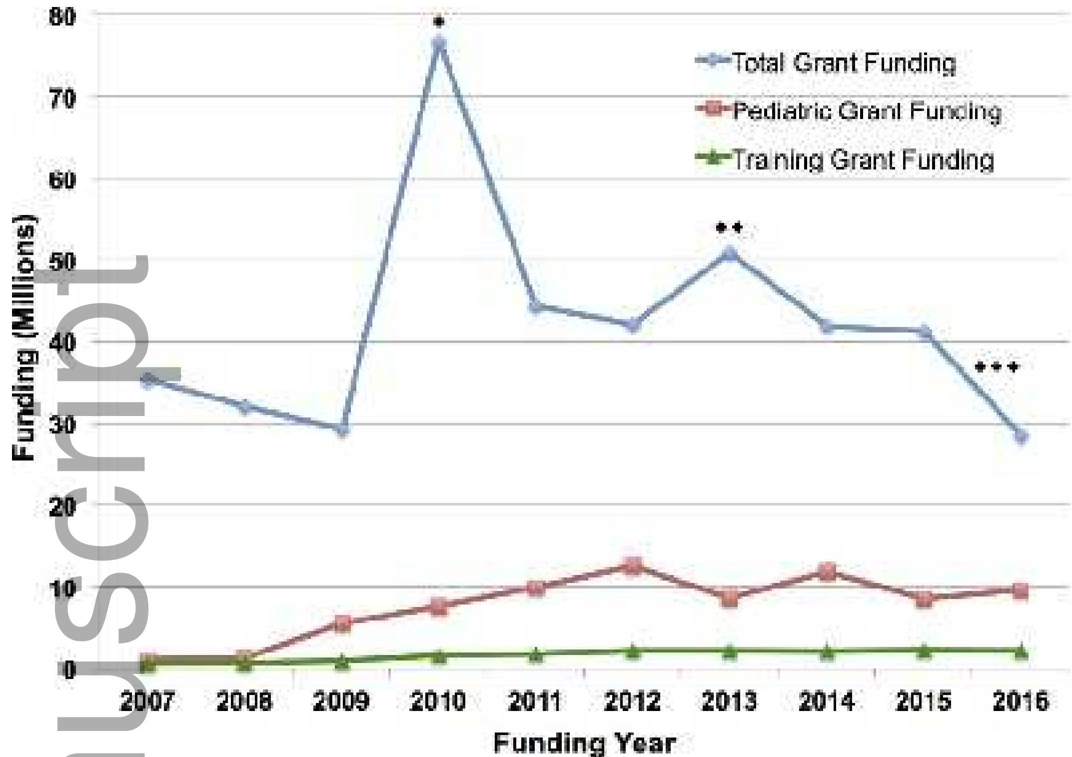

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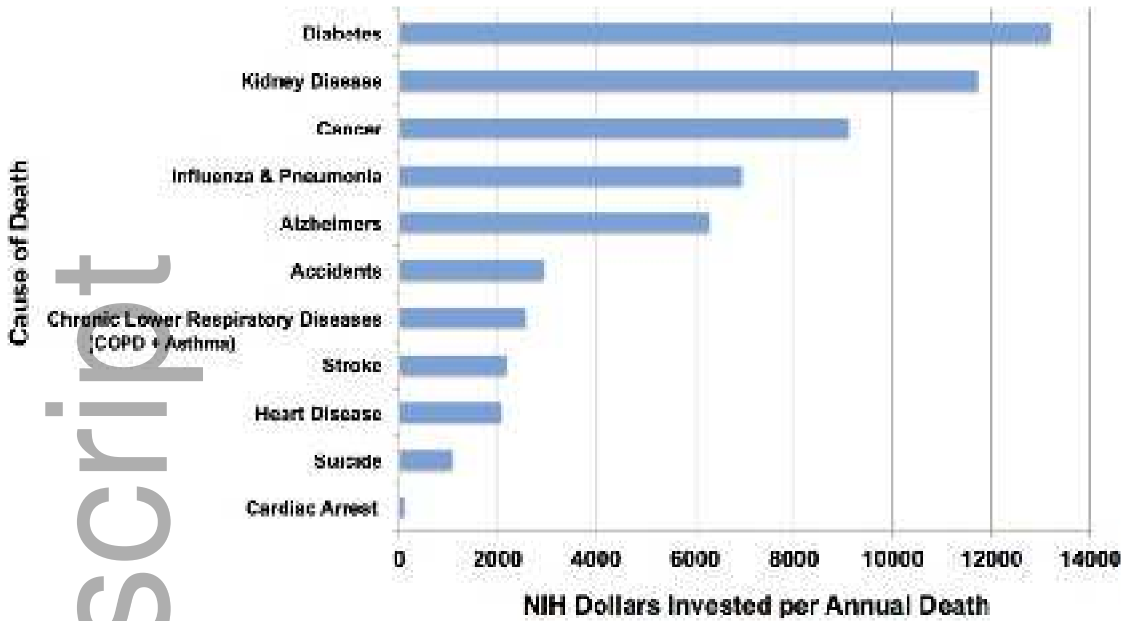

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