

Prospective Cohort Studies – An Endangered Species?



CV Epidemiology Seminar, April 10, 2018

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Disclosures

- Research funding support from NHLBI and NIA

Cohort studies in cardiovascular (CV) epidemiology

- Large cohort studies have been the workhorse in cardiovascular (CV) epidemiology
- They contributed to the identification of modifiable CV risk factors, and arguably to the remarkable decline in CV morbidity and mortality in the US
- Between 1960 and 2000, life expectancy in the US increased by 7 years, with 70% of the increase attributable to fewer cardiovascular deaths

Cohort studies in CV epidemiology

Improved cardiovascular health may be attributed to:

- Innovations in specialized medicine (acute care, revascularization, defibrillators);
- “Low-technology” medicine (management of blood pressure and cholesterol levels in clinical settings);
- Behavioral changes (cigarette smoking, diet).
For each, cohort studies followed by clinical trials played critical roles

Cohort studies in CV epidemiology

Against this record of remarkable success, what has CV epidemiology done for us? “Much and not enough”

- Why do CV and respiratory diseases still account for 41% of all deaths? Why do evident disparities in CV health still exist by race, SES, geographic area?
- Concerns about innovation and costs

Lauer MS. Time for a creative transformation of epidemiology in the United States. JAMA. 2012;308(17):1804–1805.

Cohort studies in CV epidemiology

This conversation is focused on the role of large cohort studies in CV epidemiology, and their place in addressing the next generation of CV health questions.

Longitudinal data:

- Allow us to determine whether the presence of an exposure more likely precedes the hypothesized outcome (or a change in the former precedes a change in the latter)
- Help capture within-individual dynamics and between individual differences over time
- Help exercise better control over some common sources of bias
- Indispensable for identifying etiologic factors for disease

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The value of cohort studies is being questioned, however. Criticisms: Expense, small incremental knowledge, limited innovation, failure to address the questions of greatest impact

Typical timeline of CV cohort exams and follow-up



Funding of Cohort studies in CV epidemiology

- Investigator-initiated research (primarily R01 awards) makes up ~80% of the NHLBI extramural budget
- Historically, the NHLBI cohort studies have been funded as contracts with a high level of control by the institute over these large projects

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- At the start of a new cohort study, the initial proposals for field centers, laboratories, and a coordinating center are all selected on the basis of rigorous peer review. Once funded, these cohort studies undergo periodic contract renewals, also peer reviewed

Conduct of cohort studies in CV epidemiology

- Cohort re-examinations typically include (expensive) hypothesis-driven examination components, such as imaging.
- For all CV cohorts, these clinic visits have also incorporated additional, hypothesis-driven examination components funded by investigator-initiated, mostly as NIH peer-reviewed R01 applications (“ancillary studies”)

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- Over time, this mix of contract-funded and investigator-initiated components accumulates valuable scientific resources that are accessible to investigators not affiliated with the cohort

What has CV epidemiology done for the public's health?

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“Much and not enough”

Specifically: Is the NIH investment in CV cohort studies warranted?

Setting the research agenda for CV epidemiology

- As in any field of work, successes (or otherwise) prompt questions of “what is next” for CV epidemiology. How do we identify the important unanswered questions for cardiovascular health?
- A short answer: CV disease and its risk factors are preventable. CV health can be promoted and preserved. While important etiologic research is still of great importance, a major shift from etiologic research to preventive research is needed

Setting the research agenda for CV epidemiology

Answers to these questions need to draw on:

- Innovative, hypothesis driven thinking;
- Subject-matter expertise;
- Methodologic sophistication.

Input is needed from individual stakeholders, the public, the community of researchers, funding agencies, and more

Setting the research agenda for CV epidemiology

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- One forum: NIH institutes conduct strategic visioning cycles to identify scientific priorities to guide the institute in advancing its research that enhances public health
- The strategic visioning informs investments in institute-initiated solicitations (requests for applications (~20% of extramural research funds). NOTs that reflect an institute's research portfolio influence investigator initiatives to foster research in “important but unexplored” areas

Setting a research agenda for CV epidemiology

NHLBI used a crowdsourcing approach to engage the community on the scientific opportunities and challenges to be addressed through initiatives led by the institute. (Challenges to Epidemiology; <http://www.nhlbi.nih.gov/forum/epi/>)

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Questions put to the community of researchers by NHLBI staff:

- 1) How can we avoid wasting resources on studies that provide little incremental knowledge?
- 2) How can we assure that resources are applied towards innovative science?
- 3) How can we be nimble, responding quickly to new opportunities?
- 4) How can we identify prospectively the most meritorious research questions?

Setting a research agenda for CV epidemiology

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Sorlie PD, Bild DE, Lauer MS. Am J Epidemiol. 2012 Apr 1;175(7):597-601

- The community of researchers did not engage however, and its response to the Epid forum enabled by the NHLBI has been notoriously poor

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- With little input from the community NHLBI defined its goals in transforming HLB epidemiology as a **process to identify and tackle scientific challenges, accelerate the pace of research translation for maximum impact, and make population research more cost-efficient.**
- Some tension between these goals (best ideas vs pace of translation vs cost efficiency)

Some Remedies Recommended by NHLBI Leadership

Results-based accountability, as a principle for research

- Consideration of costs and impact seem to have motivated recent NHLBI cuts in funding of their contract-supported cohorts.

Estimation of returns on investment:

- Bibliometric analysis and econometric models used, with some difficulty

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Returns on investment – Example: **WHI E+P trial**:

- The WHI findings resulted in 4.3 million fewer combined HT users, 126 000 fewer breast cancer cases, 76 000 fewer cardiovascular disease cases, 263 000 more fractures, 145 000 more quality-adjusted life-years, and expenditure savings of \$35.2 billion. The corresponding net economic return of the trial was \$37.1 billion

Roth JA et al. Economic Return From the Women's Health Initiative Estrogen Plus Progestin Clinical Trial. Ann Intern Med. 2014 May 6; 160(9): 594–602.

Some Remedies Recommended by NHLBI Leadership

Return-on-investment evaluations are challenging. Consider:

- The choice of the set of metrics to assess attribution and contribution of cohort studies in a quantitative, scalable, and comparative way;
- The need to factor in the time lags between research and measurable health benefits;
- How to value health benefits vs research costs;
- How to evaluate societal benefits

STAR METRICS Consortium (US federal science agencies and research institutions to document the return on investment, research impact, and social outcomes of federally funded R&D).
<https://www.starmetrics.nih.gov/>

- Vasan RS, Folsom AR. Invited commentary: future of population studies—defining research priorities and processes. *Am J Epidemiol.* 2015;181(6):369–371

Some Remedies Recommended by NHLBI Leadership

Refocused Scientific Questions

- The determinants of most chronic diseases are complex systems; simple pathways do not adequately explain their incidence and population burden
- These insights emphasize the need for sophisticated study questions, well designed studies, high quality of data (none of which lead to cost savings)

Some Remedies Recommended by NHLBI Leadership

Centralized and Efficient Governance and Management

New ideas for the design and conduct of large cohort studies

- The UK Biobank investigators successfully enrolled and assessed in-depth phenotypes of more than 500 000 people at a cost of \$100 million (or \$200 per study participant)

Manolio TA. New Models for Large Prospective Studies: Is There a Better Way? Am J Epidemiol. 2012 May 1; 175(9): 859–866

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- Highlights the efficiencies from a centralized conduct of most or all aspects of a study, recruiting through multiple temporary assessment centers
- Time efficient phenotypic characterization, emphasizing the collection of biospecimen
- Non-fatal and fatal outcomes are ascertained through linkage to the UK National Health Service (NHS)

Some Remedies Recommended by NHLBI Leadership

Centralized and Efficient Governance and Management

A number of concerns:

- Collected in this fashion, biospecimens typically represent a narrow window of a limited number of exposures. Such biologic samples rarely contribute to public health initiatives or policy decisions that must consider lifestyle choices, or ambient exposure levels that can be regulated

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- Collected in this fashion, biospecimens typically represent a narrow window of a limited number of exposures. Such biologic samples rarely contribute to public health or policy decisions that must consider lifestyle choices, or ambient exposure levels that can be regulated
- Recruited study participants from areas that show demographic diversity, by mailing invitations to volunteer. Response: ~6% (1%-10%)
- It is posited that extreme selection bias will not affect internal validity, and that selection is of concern only for the estimation of disease frequency and not for investigations of risk associations

Some Remedies Recommended by NHLBI Leadership

Centralized and Efficient Governance and Management

- Calls for large study sizes (500,000 to 1 million ppts.), without a scientific or economic argument for cohort studies with “hundreds of thousands of participants.” In the absence of study questions or hypotheses, promoting optimal study sizes is not meaningful
- Favors agnostic, hypothesis-free research, an approach suitable for gene discovery but at variance with generalizable research for scientific, ethical and fiscal reasons

Some Remedies Recommended by NHLBI Leadership

Centralized and Efficient Governance and Management

- The proposed approach seems to target very rare exposures or outcomes, thus become remarkably inefficient and of limited impact
- It is proposed that “process expertise to maximize efficiency of high-throughput operations is as important as scientific rigor,” reflecting a perspective of population research as a data collection exercise

Bracken MB et al. New Models for Large Prospective Studies: Is There a Risk of Throwing Out the Baby With the Bathwater? American Journal of Epidemiology, 2013;177, 285–289

Some Remedies Recommended by NHLBI Leadership

Exposure and Outcome Measures

Epidemiologists are missing out on the digital revolution: Need to leverage the increasing digital connectedness and use of electronic health records by health systems

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Epidemiologists are missing out on the digital revolution: Need to leverage the increasing digital connectedness and use of electronic health records by health systems

- “Big data” resources are being used, yet the field needs to learn how to minimize bias associated with their use, and enable population-based research using such ad hoc data repositories
- Stringent harmonization (or standardization) is difficult, and more flexible harmonization does not ensuring inferential equivalence to allow for data synthesis
- Wearable technology/self collecting data: a potential to be realized

Some Remedies Recommended by NHLBI Leadership

Embedded Clinical and Policy Trials

- The expense and complexity of clinical challenge our ability to conduct
- Proposed: Conduct clinical trials embedded within preexisting observational cohorts and registries

Newman AB et al. Embedding clinical interventions into observational studies.

Contemporary Clinical Trials, 2016;46,100-105. DOI: 10.1016/j.cct.2015.11.017

- Several RCTs are now in the field, embedded in ongoing (observational) cohort studies

Recommendations from Scientific peers Advising the NHLBI

In 2013, the NHLBI assembled a working group on epidemiology and population sciences from its Advisory Council and Board of External Experts.

Its charge: make recommendations about how the NHLBI can take advantage of new scientific opportunities and delineate future directions for the epidemiology

Roger VL et al. Strategic Transformation of Population Studies: Recommendations of the Working Group on Epidemiology and Population Sciences from the National Heart, Lung, and Blood Advisory Council and Board of External Experts. *Am J Epidemiol*. 2015 Mar 15; 181(6): 363–368

Roger et al. Recommendations

Recommendation	Description
Create a scientific forum on population sciences	The NHLBI should convene a scientific forum to anticipate the major scientific questions and methodological needs in epidemiology and population science over 10–20 years
Launch electronic epidemiology, in collaboration with other organizations and agencies	The NHLBI should engage in studies to establish the validity, reliability, and scalability of electronic tools for primary data collection
Build the data-science workforce	The NHLBI should help establish an adequate workforce to conduct population sciences “of the future” (create multifaceted and complementary career development grants).

Roger et al. Recommendations

Recommendation	Description
Develop a dynamic compendium of epidemiologic resources	Create a compendium of large epidemiologic resources, including cohort studies, clinical trials data sets, registries, biorepositories, etc., to assist researchers in identifying and accessing existing resources & improve the return on the investment from these studies
Integrate epidemiology and clinical trials	Where genuine efficiencies can be created, encourage the integration of clinical trials and epidemiologic studies.
Create a cohort consortium	The NHLBI should create a cohort consortium to support large-scale collaborations and provide a coordinated, interdisciplinary approach to addressing scientific questions

Roger et al. Recommendations

Recommendation	Description
Implement competitive external evaluation of cohorts	The NHLBI should implement a competitive peer review–based model for its portfolio of large epidemiologic and population studies

Investigator-initiated grants should be the predominant driver of the research agenda

The Current Landscape

To increase hypothesis-driven, investigator-initiated research, the NHLBI recently revised its approach to funding cohorts:

- Contracts continue to fund infrastructure, which includes participant follow-up and health outcomes, contacts, exam facilities, and the management of data and stored biospecimens
- If applicants obtain NIH funding for investigator-initiated grants that include at least 1 major examination component, the institute will also fund a core clinic visit
- Peer review of investigator-initiated grants emphasizes innovation & impact. Failure to obtain NIH grant funding for an investigator-initiated examination component precludes funding of cohort clinic visits by the NHLBI

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At present:

- Rapid and successful adoption of the new funding model for NHLBI-supported cohorts (MESA, CARDIA, Framingham, ARIC, → SOL)
- The model requires active and nimble engagement by a large group of investigators, and a strong and flexible coordinating center

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At present:

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- The model requires active and nimble engagement by a large group of investigators, and a strong and flexible coordinating center
- A suite of strongly collaborative, innovative and cost efficient studies has resulted around the CV cohorts that have implemented this model. Rather than a qualitative change it represents growth in the number of investigator-initiated, ancillary studies and their temporal alignment
- Even more so than before, cohort-based ancillary studies provide ongoing, valuable research and career development opportunities for early career investigators

Fertile ground for innovative ancillary studies

