Title

Age-Period-Cohort (APC) Effects on Atherosclerotic Cardiovascular Disease Risk: the NHLBI Pooled Cohorts Study

Writing Group

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Introduction

The Pooled Cohorts Equations (PCEs) for 10-Year Atherosclerotic Cardiovascular Disease (ASCVD) Risk, released in 2013 (1), are now commonly used in the clinical setting to guide decisions regarding statin, aspirin, and anti-hypertensive therapy. This is notwithstanding a large number of studies showing that the PCEs are poorly calibrated with respect to ASCVD risk outside of the derivation cohorts (2). Overall, the PCEs have been found to overestimate 10-year ASCVD risk by 60-90% and to yield widely divergent estimates based upon specification of African-American race (2, 3). Some have argued that statistical shortcomings, such as overfitting of sparse data in the original modeling approach, may explain these problematic features (3). Nonetheless, secular trends are another major consideration.

ASCVD incidence and mortality have fallen precipitously since the mid-20th century, when some of the original PCE derivation cohort was recruited (1). There are certainly multiple reasons for this positive trend. These include changes in the relative contributions of risk factors resulting from secular trends, including increased obesity and decreased smoking, increasing uptake of effective medical therapies (e.g., statins), as well as differences in living conditions that may be harder to quantify but no less important (4). In addition to major technological, medical, and environmental changes that have been experienced since the original Framingham Heart Study participants were recruited, there have also been major social changes, with successive birth cohorts sharing distinct “norms” for behaviors potentially relevant to ASCVD risk.

We therefore propose to apply age-period-cohort (APC) analysis (5, 6) to examine the extent to which PCE mis-calibration may be attributable to differences in birth-cohort and/or period effects in the context of the NHLBI Pooled Cohorts Study (7), which includes nine cohorts recruited and followed up over the past four decades.

Hypothesis

There are period and cohort effects that contribute to mis-calibration of 10-year ASCVD risk.

Data

Sample: The NHLBI Pooled Cohorts Study harmonized and pooled data from the following prospective, observational epidemiologic cohorts:
1. Atherosclerosis Risk in Communities (ARIC) Study
2. Coronary Artery Risk Development in Young Adults (CARDIA) Study
3. Cardiovascular Health Study (CHS)
4. Framingham Heart Study – Offspring Cohort (FHS-O)
5. Health Aging and Body Composition (Health ABC) Study
6. Hispanic Community Health Study/Study of Latinos (HCHS/SOL)
7. Jackson Heart Study (JHS)
8. Multiethnic Study of Atherosclerosis (MESA)
9. Strong Heart Study (SHS)

Notably, four of these cohorts (ARIC, CARDIA, CHS, and FHS-O) were derivation cohorts for the 2013 PCE. Most of the required data has already been harmonized and pooled at Columbia University, where the proposed analyses will be performed.

**Inclusion criteria:**

- **Primary analysis:** identical to the 2013 PCE derivation (1)
  
  - Age 40-79 at time of observation
  - No history of myocardial infarction (MI), stroke, heart failure, percutaneous coronary intervention, or atrial fibrillation, at time of observation
  - White or black race
  - No baseline statin use

- **Secondary analyses:**
  
  - Retaining all race/ethnicities
  - Excluding participants who started statin therapy over follow-up

**ASCVD endpoint:** identical to the 2013 PCE derivation (coronary heart disease mortality, non-fatal MI, fatal or non-fatal stroke) (1).

**Estimated 10-year ASCVD risk:**

- **Primary definition:** calculated by original 2013 PCE using race- and sex-stratified equations incorporating current age, treated or untreated systolic blood pressure (measured), current tobacco smoking (self-reported), total cholesterol (measured), high-density lipoprotein cholesterol (measured), and diabetes (calculated, not self-reported) (1).

- **Secondary definition:** revised sex-stratified PCE including African American race as a predictor, but otherwise the same risk factors (3).

**Mis-calibration parameter:** ratio of expected-to-observed ASCVD risk using 2013 PCE (expected) and 10-year ASCVD incidence (observed) (2).

**Analysis plan**

The optimal APC analytic approaches remain controversial (8, 9), therefore this work will apply and compare several prominent methods to address the inherent identification problem (i.e., exact linear dependency, Cohort = Period – Age) (5, 6).

To explore the data, the following will be plotted graphically to assess time-based variations:
a) Median predicted 10-year risk according to 2013 PCE
b) Unadjusted incidence density rates (IDRs) for ASCVD
c) Mis-calibration parameter (expected-to-observed ratio)

These will also be tabulated by age group, period, and birth cohort, all categorized in 5-year bands, as well as by study cohort.

Then, we will compare the goodness-of-fit for models predicting mis-calibration (c) by age and period (AP), age and cohort (AC), and period and cohort (PC). If there is evidence that period and cohort are independent predictors, we will continue with APC analyses. We will also use these data to determine whether log-transformation of the mis-calibration parameter (c) is appropriate.

First, we will use the median polish approach (5). This method allows second-order effects to be estimated and interpreted without imposing strong a priori assumptions beyond the conceptualization of cohort effects as an interaction between age and period effects. In other words, this approach tests whether the effect of age and period interact to produce an effect that is more than what would be expected given their additive influences by estimating a two-factor model (age and period); hence, no constraints are necessary.

Using contingency tables for mis-calibration (c), stratified by age and period, we will iteratively subtract the median value of each row and column until we obtain row and column medians equal to zero. These residuals will be regressed on indicator variables for birth-cohort membership to determine the presence of a cohort effect independent of age and period effects.

For comparison, we will also estimate and interpret first-order effects of age, period, and cohort by an intrinsic estimator (IE) approach (10), which leverages principal components analysis, and hierarchical APC models (11), if appropriate.

The extent to which study cohort effect may be explained by estimated first-order age, period, and cohort effects will be evaluated.

Secondary analyses will evaluate for APC effects in alternative samples (inclusion of all race/ethnicities; exclusion of participants starting statins over 10-year follow-up) and using revised PCEs.
References


