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Longitudinal Average Attributable Fraction as a Method for Studying Time-Varying Conditions and Treatments on Recurrent Self-rated Health: The Case of Medications in Older Adults with Multiple Chronic Conditions

Heather G. Allore, PhD^{1,2}, Yilei Zhan, MS², Mary Tinetti, MD^{1,3}, Mark Trentalange, MD, MPH¹, and Gail McAvay, PhD¹

¹Yale School of Medicine, Department of Internal Medicine, Section of Geriatrics, New Haven, Connecticut, USA

²Yale School of Public Health, Department of Biostatistics, New Haven, Connecticut, USA

³Yale School of Public Health, Department of Chronic Disease, New Haven, Connecticut, USA

Abstract

Purpose—The objective is to modify the longitudinal extension of the average attributable fraction (LE-AAF) for recurrent outcomes with time-varying exposures and control for covariates.

Methods—We included Medicare Current Beneficiary Survey participants with two or more chronic conditions enrolled from 2005-2009 with follow-up through 2011. Nine time-varying medications indicated for nine time-varying common chronic conditions and 14 out of 18 forward-selected participant characteristics were used as control variables in the generalized estimating equations step of the LE-AAF to estimate associations with the recurrent universal health outcome self-rated health (SRH). Modifications of the LE-AAF were made to accommodate these indicated medication-condition interactions and covariates. Variability was empirically estimated by bias-corrected and accelerated bootstrapping.

Results—In the adjusted LE-AAF, thiazide, warfarin and clopidogrel had significant contributions of 1.2%, 0.4%, 0.2% respectively to low (poor or fair) SRH; while there were no significant contributions of the other medications to SRH. Hyperlipidemia significantly contributed 4.6% to high SRH. All the other conditions except atrial fibrillation contributed significantly to low SRH.

Conclusions—Our modifications to the LE-AAF method apply to a recurrent binary outcome with time-varying factors accounting for covariates.

Corresponding author: Heather Allore, Yale University, Program on Aging, 300 George St, Suite 775, New Haven, CT 06511 USA, Office: 203-737-1892, fax: 203-785-4823, Heather.Allore@Yale.edu.

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Keywords

aged; chronic disease; epidemiologic methods; longitudinal study

Introduction

Almost three quarters of persons 65 years have multiple chronic diseases or conditions (MCC) [1]. Individuals with MCCs are at greater risk of ineffective care and complications of medications [2, 3]. Despite the growing prevalence of MCCs and associated complications, existing medication guidelines largely do not address individuals with MCCs [4, 5]. One reason is the dearth of evidence on harms and benefits of medications in complex patients. Determining the contribution of medications to an outcome is more complex in individuals with MCC than in individuals with a single condition.

The first challenge is how to measure the contribution of a medication or compare across medications for conditions where multiple medications may be indicated and there are coexisting conditions. Condition-specific outcomes are inadequate to assess medications in those with MCC [6].

The sheer number of possible combinations of conditions and medications is a second challenge [7]. Sorace reported over 2 million combinations of conditions in a cohort of 32 million Medicare beneficiaries [8]. Furthermore, not only are there often multiple recommended medications for each condition, these medications may change over time. Thus, estimating the contribution of a medication to an outcome in persons with MCC is daunting.

A third challenge is that as a person's health changes, their response to medications may change. Methods that account for changes in medications and outcomes over time are needed to determine the contribution of common medications to outcomes important to patients.

One approach to measuring the effect of medications in persons with MCC is the use of cross-condition, universal health outcomes [9, 10]. Self-rated health (SRH) is one such universal health outcome that has been shown to be affected MCC [10-12].

The remaining two challenges require analytical techniques that can handle many variables that may change over time. Recently we modified the average attributable fraction for a time-to-event outcome with time-varying medical conditions [13-15]. To address recurrent outcomes and time-varying conditions and their indicated medications, additional methodological changes are required. Our objective is to present an expansion of the longitudinal extension of the average attributable fraction (LE-AAF) to estimate the contribution of recommended medications to recurrent measures of a universal outcome, SRH, in a cohort of older adults with MCC.

Methods

Study Design and Sample

We choose a well-characterized, nationally-representative cohort of older adults with longitudinal data on chronic conditions and medications. The study sample included Medicare Current Beneficiary Survey (MCBS) participants enrolled from 2005-2009 with follow-up data available through 2011. Each cohort completes a baseline interview and is followed at yearly in-person interviews for up to three years. MCBS is a sample of Medicare beneficiaries obtained using stratified multi-stage sampling from the Centers for Medicare and Medicaid Services enrollment file [16, 17]. Eligibility included participants aged ≥ 65 years; with one inpatient or 2 other type claims (outpatient, physician, skilled nursing, home health) during the first two years of MCBS enrollment for ≥ 2 of nine chronic conditions described below. Follow-up was up to three years or until death. Of the 20,026 participants aged ≥ 65 , 4,817 were excluded due to death, non-response or lack of medication data, 2,298 lacked claims data, 4,333 had <2 chronic conditions and 61 were missing SRH, for a final sample size of 8,517.

Data

The nine common chronic conditions studied included atrial fibrillation, coronary artery disease (CAD), chronic kidney disease, depression or anxiety, diabetes mellitus, heart failure, hyperlipidemia, hypertension, pulmonary embolism and venous thrombosis. Depression was defined by a claim for depression or self-reported depression or loss of interest.

The selected classes of medications are in national disease guidelines for the nine chronic conditions and were used by at least 20% of those with a given indication. The nine medication classes include renin angiotensin system blockers (RAS blockers); thiazides; beta blockers; calcium channel blockers; selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitors (SSRI/SNRI); metformin; warfarin; and clopidogrel. These medications were ascertained by direct observation during in-person interviews. Some medications may be indicated for more than one condition (Table 1).

The study outcome of SRH was coded as 0 = (fair or poor; hereafter referred to as low) versus 1 = (excellent, very good or good; hereafter referred to as high) and was recorded at baseline and yearly interviews. Socio-demographic, behavioral, and functional data were obtained from the annual in-person interviews (Table 1) [16, 17]. Cognitive impairment was considered present if there was a claim for dementia or cognitive disorder or self-reported memory loss plus either trouble concentrating or difficulty making decisions that interfered with daily activities. The Elixhauser comorbidity scale consisting of 23 conditions was computed based on the International Classification of Diseases-9 codes from claims, excluding the nine study conditions and was dichotomized at ≥ 2 [18, 19].

Statistical Methods

Baseline characteristics were summarized using means and standard deviations or frequencies, as appropriate.

We examined year-specific medications, conditions, medication by indicating condition interactions while controlling for covariates by estimating their associations with the recurrent dichotomous outcome SRH using generalized estimating equations (GEE) approach with the logit link function. We modeled the probability of high SRH. The GEE model for recurrent SRH estimates population-averaged response of the *a priori* factors of interest time-varying condition-indicated medications and conditions. We included interaction terms between a medication and each condition for which the medication is indicated according to national disease guidelines. We did not include medication main effects or interactions among conditions because the purpose of the analyses was to determine the effect of the indicated-condition medication usage on self-rated health.

To provide adjusted estimates for *a priori* participant characteristics previously found to be associated with either SRH or the chronic conditions a forward-selection process was used. However, in settings where there are not *a priori* factors of interest or control variables, we recommend selection techniques such as LASSO or Least Angle Regression [21, 22]. To address within-participant correlation across time, compound symmetry structure and first-order autoregressive structure were tested. The Quasi-likelihood under the Independence model Criterion (QIC) was used to select covariates and suitable covariance structure [20]; the model with the smaller QIC is generally preferred. We fit models all models with year specific effects with and without covariates to contrast their effect on the LE-AAF estimates. We implemented the GEE modeling using SAS Version 9.3 (SAS Institute Inc., Cary, NC) [23].

The LE-AAF achieves additivity and symmetry (e.g. the estimate is independent of the order the conditions occur) by averaging the contributions of a medication in all possible orders of co-existing medications and their co-occurrences, known as the average of the sequential attributable fractions (SAF) [13-15]. The input used GEE point estimates for the conditions, condition-indicated medications, and selected covariates. The total contribution of multiple factors combined equals the sum of the measures of contribution of the separate factors. The LE-AAF of a factor (condition-indicated medications and conditions) is its fractional contribution to the timed occurrence of the recurrent outcome in the presence of multiple co-existing medications. The LE-AAFs allocate the overlapping effects among co-existing medications to individual medications. The LE-AAF method allows quantification of the contribution of the time-varying medications to SRH.

The calculation of LE-AAF requires an enumeration of all the permutations of a combination of study medications and conditions. Given the 18 factors in the dataset, this process could involve calculating 2^{18} permutations, which is not computationally efficient. An approach to address the high-dimensional computational burden is to restrict evaluation to only combinations of factors observed in the dataset [14]. Hence, a data-centric design matrix is formed by all unique observed combinations of factors; next, a subsets lookup table is determined by the largest number of factors through all rows in the design matrix. For each row of the design matrix, the subsets lookup table is used to calculate SAFs for each factor from the partial difference of attributable fractions from each overlapping pair of subsets of this row. The year-specific attributable fraction is the average of all SAF calculated for each row of design matrix using prevalence of medications and conditions in

year-specific subset [14]. The LE-AAF is the weighted average of all the time year-specific attributable fractions, with person-year as the weights.

We further improved upon this computational approach using MATLAB Version 8.1 (The MathWorks Inc., Natick MA) [24] by incorporating covariates in the design matrix (code is in Appendix A). The inclusion of covariates increases the number of observed combinations and the number of variables in each row, thus expanding the design matrix in two dimensions. For instance, the design matrix without covariates contains 18 columns of variables and 5,925 rows of unique combinations; the design matrix with covariates increases to 32 columns and 15,177 rows of unique combinations. However, the subsets lookup table remains the same, because the covariates were used only for adjustments and the subsets of covariates are irrelevant to calculation for SAF. When calculating the SAF for a specific row of the design matrix, we inspect for the presence of each covariate and treat this combination of covariates as a constant portion similar to an intercept using estimates from the GEE model. We ran the LE-AAF with and without covariates.

Furthermore, to address the sampling variability of the LE-AAF estimates for a recurrent outcome, we used a bias-corrected and accelerated bootstrap method [25]. We generated 300 bootstrap pseudo-samples of study participants. The empirical distribution of the pseudo-sample mean of SRH and each condition were examined for normality. We checked the quartiles of the pseudo-samples and compared them with the original data.

Results

Characteristics of the study population are in Table 1. The most common dyads of conditions at baseline were hypertension and hyperlipidemia with 71.3% followed by diabetes and hypertension with 36.6%. The three medications with the highest prevalence at baseline were RAS blockers, statins, and thiazide. 4.5% of persons took no medications at baseline although they had 2 conditions. As shown in Figure1, multiple medication use increased with the number of conditions. On average 11.3% (range 7-17%) of the sample discontinued a medication over the three year follow-up period, while 6.9% (range 2-12%) started a new medication.

At baseline 71.3% of participants reported SRH as high. Among these participants, 15.3%, 18.4% and 20.4% reported a decline to low SRH at the first, second and third annual follow-up interviews, respectively. Among the 28.7% of participants who reported SRH as low at baseline, 35.3%, 38.1% and 39.0%, respectively, reported improvement to high SRH across the three annual follow-up interviews.

Model selection found 14 out of 18 *a priori* patient characteristics previously associated with SRH or a chronic condition significant and were included in the final GEE model as control variables, as well as being included as adjustments in calculation of LE-AAF for medications and conditions. Guided by QIC criterion, the first-order autoregressive structure provided the best fit in the fully adjusted model.

The parameter estimates for the conditions and condition-medication interactions from the GEE model are listed in (Table 2). The estimates for year were nearly identical indicating a

stable time effect. All the conditions except atrial fibrillation are associated with poorer SRH; pulmonary embolism/venous thrombosis are of borderline significance. Hyperlipidemia is associated with higher odds of reporting high SRH.

There are four significant condition-medication interaction terms: hypertension and RAS blockers, hypertension and thiazide, hyperlipidemia and statin, coronary artery disease and clopidogrel. Regarding participants with hypertension, the odds of high SRH for people who take RAS blockers are higher than those who do not take it (i.e. joint odds ratio of 0.94 versus marginal odds ratio of 0.82), controlling for all other variables. Conversely, the odds of high SRH for people who take thiazide for hypertension are lower than those who do not take thiazides. The odds of reporting high SRH for people taking statins is higher than those not taking statins within the hyperlipidemia subpopulation. The odds of high SRH among people who have coronary artery disease is lower in those who take clopidogrel than those who do not take clopidogrel.

We used the coefficient estimates from Table 2 with the design matrix to calculate the LE-AAFs for each medication and condition. The unadjusted and adjusted LE-AAFs are in Table 3. Regarding chronic conditions, hyperlipidemia significantly contributed 4.6% to high SRH in the adjusted model. All the other conditions contributed significantly to low SRH, as noted by the negative LE-AAFs, but the adjusted estimate for atrial fibrillation was not significant.

The unadjusted LE-AAF estimates show significant contributions for four of the nine medications to SRH. Thiazide, SSRI/SNRI and clopidogrel had significant contributions of 1.3%, 0.4%, 0.2% respectively to low SRH (indicated by a negative LE-AAF estimate); while RAS blockers had a significant 0.7% contribution to high SRH. In the adjusted model, only thiazide, warfarin and clopidogrel had significant contributions of 1.2%, 0.4%, and 0.2% respectively to low SRH. There were no significant contributions of other medications to SRH. (See above)

The LE-AAF estimates are additive. Thus, adding the adjusted -1.2% contribution of thiazide to the -5.1% contribution of hypertension is combined contribution of -6.3% to SRH. This is interpreted as thiazides increasing the negative effect of hypertension on SRH. Similarly, warfarin's -0.4% contribution accentuated the negative effects of atrial fibrillation's contribution of -0.7% for a combined effect of -1.1%, and pulmonary embolism/venous thrombosis contributions of -0.5% for a combined effect of -0.9% (Table 3).

The normality testing results suggest that the distribution of the pseudo-samples are normally distributed for both the SRH outcome and each condition. The interquartile range of the empirical distribution is <0.01 and the absolute difference between the original sample mean and the median of the empirical distribution is <0.001.

Discussion

We present a modification of the LE-AAF methodology to address the inherent complexity of estimating contributions of medications to a recurrent outcome in a cohort of older adults

with 2 chronic conditions; however, related clinical questions, such as the contribution of multiple medications indicated for persons with a single condition for a variety of universal health outcomes could use this methodology. Additionally, this methodology could be applied to persons with pre-specified combinations of conditions. The LE-AAF provides a population-level evaluation of the proportional contribution from risk factors; it is affected by the prevalence of the factors and their relative effects. The LE-AAF calculations are based on the adjusted GEE model but include information on the combinations of condition-indicated medications and covariates used as control variables in the design matrix. Hence, the LE-AAF provides information about the additive contributions of medications to a recurrent outcome, while the GEE provides marginal and joint odds ratios.

Most medications showed minor to non-significant contributions towards SRH. Nevertheless, the approach does quantify effects, both beneficial and harmful, of individual medications in a heterogeneous population with numerous combinations of medications and conditions. The findings presented pertain to the population level and should not be interpreted as suggesting the benefit or harm of any medication at the patient level.

With the exception of metformin and warfarin, we found that in the unadjusted model the majority of medications and all conditions showed stronger contributions to SRH than the adjusted model indicating that patient characteristics from the literature accounts for some of the contributions. Thus, the modification of the LE-AAF to account for covariates may control for some bias. Neither the unadjusted nor adjusted LE-AAFs absolute values sum to 100, which would indicate not all contributing factors were modeled.

Regarding sampling variability we applied bias-corrected and accelerated bootstrap method to construct 95% confidence intervals. The formula provided by Eide and Gefeller [26] is for calculation of the asymptotic variance estimate of a non-recurrent average attributable fraction rather than for recurrent variance and covariance. Thus, their formula does not apply for recurrent outcomes.

Although our modifications allow for time-varying medications, their indicating conditions and covariates for a recurrent dichotomous outcome, LE-AAF is not appropriate to situations where a time-varying outcome is recurrent within individual time intervals. Pichlmeier and Gefeller [27] have developed a concept called recurrent attributable risk estimator applicable to recurrent events within a time interval. Incorporating Pichlmeier and Geller's methods into LE-AAF may contribute to further methodological improvement for time-varying recurrent outcomes. Additionally, if the phenomena of interest is nonlinear or changes over time then modifications of the recurrent outcome model should consider a growth model or appropriate higher order terms, which in turn would require modification to the LE-AAF.

Limitations

There are limitations of the LE-AAF method. First, one assumes averaging SAF over all possible removal orders is feasible and equally likely [24]. The complexity of causal ordering of medications and their indicating conditions in the MCBS cohort of older adults makes LE-AAF an attractive methodology to study contributions to our dichotomous

outcome. However, casual relationships are undetermined and extremely complex for at least two reasons. With the existence of a large number of risk factors and potential confounders including medications, chronic conditions and covariates, there are no conclusive causal relations among medications and covariates, or among conditions and covariates. Moreover, some medications are used for more than one condition. Although medication is usually received because of an indicating condition, the various combinations of multiple medications and conditions make it impossible to unveil the causal pathway. While we have adjusted for demographic, psychosocial, indications for medication usage, and other factors, we cannot eliminate the possibility of other unmeasured covariates that may bias results of the GEE model.

There are other limitations as follow-up is limited to 3 years prohibiting us from evaluating long-term outcomes. As initiation dates of the condition and medications are lacking, we are unable to create an inception cohort for medication use or determine duration of use. Studying an inception cohort would not be feasible regardless as we are studying multiple medications for multiple conditions with variable initiation dates and durations. Although better than administrative data because of the generalizability of MCBS, we cannot completely disentangle disease and medication effects, as well as some medications depend on disease severity or type, which were not recorded. Lastly, it does not incorporate causal patterns among the various contributing factors, although future work that incorporates causal models or casual patterns would provide a greater range of application and is warranted.

Conclusions

The initial LE-AAF method has methodological limitations in handling computational complexity, recurrent outcomes, and controlling for adjusting variables. Murphy and co-workers' data-centric approach [14] expanded the applicability of this method to high-dimensional situations. Our modifications to the LE-AAF apply to even broader settings with a binary recurrent outcome and where a large number of time-varying factors, as well as confounders are taken into account. Indeed, many vexing issues facing public health concern the amount of contribution a wide array of time-varying factors make to a time-varying outcome. The current adaptation to LE-AAF adds to the methodological armamentarium available to public health investigators.

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Appendix A

MATLAB code for longitudinal extension of the average attributable fraction (LE-AAF).

```
% matlab initialization
close all
```



```

clear all
% clc
fclose('all');
tic
% cd c:/username; path to data, code (function, numNZs2subsetsB.m), and output
% specify output file name
Outputfile = 'output.txt';
outputbyYearfile = 'outputbyYear.txt';
% read datasets: original data, design matrix, coefficients
load originaldata.txt;
% variable list of originaldatamatrix.txt by order: 9 medications, 9 conditions, 0 covariates, 1 stop (time), 1 health
(outcome) listed as below,
% ace_arb statin thiazide beta_blocker calcium_channel ssri_snri metformin warfarin clopidogrel
% afib cad chf diabetes hypertension hyperlipidemia kidneydisease depression thromboembolic
% stop
% fairpoor
load designmatrix.txt;
% variable list of designmatrix_BslhealthCondMed.txt by order: 9 medications, 9 conditions, 14 covariates listed as
below,
% ace_arb statin thiazide beta_blocker calcium_channel ssri_snri metformin warfarin clopidogrel
% afib cad chf diabetes hypertension hyperlipidemia kidneydisease depression thromboembolic
load outbeta.txt;
% variable list of outbeta.txt by order: 1 intercept, 9 conditions, 14 covariates, 22 interactions (no medication main
effects) listed as below,
% intercept
% afib cad chf diabetes hypertension hyperlipidemia kidneydisease depression thromboembolic
% ace_arb*cad ace_arb*kidneydisease ace_arb*diabetes ace_arb*chf ace_arb*hypertension
% statin*cad statin*hyperlipidemia statin*diabetes
% thiazide*hypertension
% beta_blocker*afib beta_blocker*cad beta_blocker*chf beta_blocker*hypertension
% calcium_channel*afib calcium_channel*cad calcium_channel*hypertension
% ssri_snri*depression
% metformin*diabetes
% warfarin*afib warfarin*thromboembolic
% clopidogrel*afib clopidogrel*cad
% list number of covariates, conditions, medications, and interactions between conditions and medications
NMed = 9;
NCond = 9;
NMandC = NMed+NCond;
NCov = 14;
NX = NMed+NCond+NCov;
NInter = 22;
X = originaldata(:,1:NX);
Year = originaldata(:,NX+1);

```

```

outcome = 1-originaldata(:,NX+2); % recoding: outcome=1/0 means fairpoor=0/1
xMed = x(:,1:NMed);
xCond = x(:,NMed+1:(NMANDC));
N = length(x(:,1)); % number of observations from original dataset
% calculate 22 interactions
loc = cell(NMed,1);
loc{1} = [2,7,4, 3, 5];
loc{2} = [2,6,4];
loc{3} = 5;
loc{4} = [1,2,3,5];
loc{5} = [1,2,5];
loc{6} = 8;
loc{7} = 4;
loc{8} = [1,9];
loc{9} = [1,2];
% number of time intervals, for this specific data, maxyear=3, one time interval is one year
Maxyear = max(year);
DesMtx = designmatrix(:,1:NX);
LenDesMtx = length(DesMtx);
sumNonZeros = sum(DesMtx(:,1:NMANDC),2);
maxNonZeros = max(sumNonZeros);
% these are used later to add up contributions to AAF from each subset (instead of permutations)
nz2enum = cell(maxNonZeros, 1);
for i = 1:maxNonZeros
    nz2enum{i} = 0:(2i)-1;
end
% function (numNZs2subsetsB.m) generates all possible subsets for given
% number of nonZeros in bit vector of conditions this was written by Nick and Diana Carriero and is
% found in this same folder as the file numNZs2subsetsB.m (matlab)
% list number of covariates, conditions, medications, and interactions between conditions and medications
subsets = numNZs2subsetsB(maxNonZeros);
beta = outbeta;
beta0 = beta(1);
betaMed = zeros(1,NMed); % set betas of medications to zeros
betaCond = beta(2:NMANDC+1);
if NCov~ = 0
    betaCov = beta(NMANDC+2:NMANDC+NCov+1);
end
% betaInter contains 9 cells, each cell represents betas for pairwise interactions between a specific medication and all
related conditions
betaInter = beta(NMANDC+NCov+2:end);
N1 = zeros(maxyear,1); % number of occurrences(outcome=1) in each time interval
% create templates of matrices used in loop-based computations
AAFbyYearMtx = zeros(maxyear, NMANDC); % AAF values in year (row) by medication (column) arrangement

```

```

NskByYearMtx = zeros(maxyear, LenDesMtx); % 3 years (rows) by Number of Design Combinations (columns)
Nyr = zeros(maxyear,1);
% below looping across all years to calculate yearly AAF for each medication
for yr=1:maxyear
N1 (yr)=sum(outcome(year==yr));
% below calculating Nsk for each row of design matrix
% using the number of observations per year for the weight of that year;
xmat = x(year==yr,:);
Nyr(yr) = length(xmat(:,1));
for i=1:LenDesMtx
    xmat2 = zeros(Nyr(yr),NX);
    xmat2(xmat==repmat(DesMtx(i,:),Nyr(yr),1)) = 1;
    temv = sum(xmat2,2);
    NskByYearMtx(yr,i) = sum(temv==NX);
end
% completes calculation of Nsk
% below looping by row of design matrix
xPs0v = zeros(NMandC,1);
for r=1:LenDesMtx
    row = DesMtx(r,:); % call out each individual row of design matrix
    rowMandC = row(1:NMandC);
    numNonZeros = sum(row,2);
if numNonZeros ~= 0
    if NCov~=0
        rowCov = row((1+NmandC):NX);
sumCov = sum(betaCov(rowCov~=0));
    else
        sumCov=0;
    end
    nzsloc = find(rowMandC);
    numNzs = length(nzsloc);
    subs = subsets(numNzs);
    % precalculated by function in file 'numNZs2subsetsB.m' in this folder
    numSubs = length(subs); % # of subsets in cell corresponding to nzsloc
    Ps0vector = zeros(numSubs,1);
    % below calculating ps0 for all the variables in the particular order;
    for j=1:numSubs
        if isempty(subs{j})
            Ps0vector(j) = 1./(1+ exp(-beta0 - sumCov));
        else
            list=nzsloc(subs{j});
            rowsubMandC=zeros(1,NMandC);
            rowsubMandC(list)=1;

```

```

        rowsubMed=rowsubMandC(1,1:NMed);
        rowsubCond=rowsubMandC(1,NMed+1:NMandC);
        %calculate and store 22 interactions by medication
        rowInter=cell(1, NMed);
        for i=1:NMed
            rowInter{i}=rowsubCond(loc{i}).*rowsubMed(i);
        end
        rowInter=cell2mat(rowInter);
        Ps0vector(j) = 1./(1+ exp(-beta0 -sum(betaCond(rowsubCond~=0))-sumCov-sum(betaInter(rowInter~=0))));
    end
    % this end statement completes calculation of Ps0 for each different subset pertaining to nzslc
    end
    enum = nz2enum{numNzs};
    for i = 1:numNzs
        xk = nzslc(i);
        p = 2^(numNzs-i);
        combinedPs0v = (sum(Ps0vector(bitand(enum,p)==p)) - ...
        sum(Ps0vector(bitand(enum,p)~=p)))/(numSubs/2);
        combinedPs0v = NskByYearMtx(yr, r)*combinedPs0v/N1(yr);
        xPs0v(xk) = xPs0v(xk) + combinedPs0v;
    % this ends summation of Ps0v across all subsets of a given row of the design matrix
    end
    end % this ends operations for if statement
    end % this ends operations for each row of the design matrix
    % if there were no NonZeros then Ps0mtx(r,:) = 0, otherwise
    % from calculation immediately above
    AAFbyYearMtx(yr,:) = xPs0v';
end % this end statement ends looping of all operations across all years
FinalAAFbyYearMtx = AAFbyYearMtx;
fid1 = fopen(outputbyYearfile,'wt');
fprintf(fid1, '%12.6f',FinalAAFbyYearMtx);
fclose(fid1);
% below calculate LEAAF the weighted average of all the time year-specific attributable fractions, with person-year as
the weights.
Then adding up all the variable-specific LEAFs as the total attribution;
allaverage = sum(FinalAAFbyYearMtx.*repmat(Nyr, 1, NMandC))/N ;
sumLEAAF = sum(allaverage);
fid2 = fopen(outputfile, 'w');
fprintf(fid2,'%12.6f',allaverage, sumLEAAF);
fclose(fid2);
toc
% end of matlab program, LEAAF;
% function, numNZs2subsetsB, which should be placed as separate file in active folder;
function subsets = numNZs2subsetsB(maxNonZeros)

```

```

tic
subsets = cell(maxNonZeros, 1);
for numNZs = 1:maxNonZeros
    bvs = ff2n(numNZs); % generate bit vector representations of the numbers from 0 to 2^N-1
    numbvs = size(bvs, 1);
    c = cell(1, numbvs); % a single column cell array. Each element is one % subset of the numbers from 1 to
    maxNonZeros.
    for bvx = 1:numbvs
        c{bvx} = find(bvs(bvx, :));
    end
    subsets{numNZs} = c;
end
return
toc
% end function, numNZs2subsetsB;

```

References

1. Anderson, G. [Accessed May 5, 2014] Chronic care: Making the case for ongoing care. Robert Woods Johnson Foundation Website. <http://www.rwjf.org/content/dam/farm/reports/reports/2010/rwjf54583>. Published March 7, 2010
2. Fortin M, Lapointe L, Hudon C, Vanasse A. Multimorbidity is common to family practice: is it commonly researched? *Can Fam Physician*. 2005; 51:244–5. [PubMed: 16926936]
3. Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med*. 2005; 3:223–8. [PubMed: 15928225]
4. Boyd CM, Darer J, Boulton C, Fried LP, Boulton L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005; 294:716–24. [PubMed: 16091574]
5. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older adults with multimorbidity. *J Am Geriatr Soc*. 2012; 60(10):E1–E25.10.1111/j.1532-5415.2012.04188.x [PubMed: 22994865]
6. Tinetti ME, Han L, McAvay GJ, Lee DSH, Peduzzi P, Dodson JA, et al. Anti-hypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Intern Med*. 2014; 174(4):588–95. [PubMed: 24567036]
7. Van den Bussche H, Koller D, Kolonko T, Heike H, Wegscheider K, Glaeske G, et al. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. *BMC Public Health*. 2011; 11:101.10.1186/1471-2458-11-101. [PubMed: 21320345]
8. Sorace J, Wong HH, Worrall C, Kelman J, Saneinejad S, Macurdy T. The complexity of disease combinations in the Medicare population. *Popul Health Manag*. 2011; 14:161–6. [PubMed: 21241184]
9. Tinetti ME, McAvay G, Chang SS, Ning Y, Newman AB, Fitzpatrick A, et al. Effect of chronic disease-related symptoms and impairments on universal health outcomes in older adults. *J Am Geriatr Soc*. 2011; 59:1618–27. [PubMed: 21883120]
10. Tinetti ME, McAvay G, Chang SS, Newman AB, Fitzpatrick AL, Fried TR, et al. Contribution of multiple chronic diseases to universal health outcomes. *J Am Geriatr Soc*. 2011; 59:1686–91. [PubMed: 21883118]
11. Fortin M, Bravo G, Hudon C, Lapointe L, Almirall J, Dubois MF, et al. Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual Life Res*. 2006; 15(1):83–91. [PubMed: 16411033]

12. Fortin M, Dubois MF, Hudon C, Soubhi H, Almirall J. Multimorbidity and quality of life: a closer look. *Health Qual Life Outcomes*. 2007; 5:52. [PubMed: 17683600]
13. Tinetti ME, McAvay GJ, Murphy TE, Gross CP, Lin H, Allore HG. Contribution of individual diseases to death in older adults with multiple diseases. *J Am Geriatr Soc*. 2012; 60(8):1448–56. [PubMed: 22734792]
14. Murphy TE, McAvay G, Carriero NJ, Gross CP, Tinetti ME, Allore HG, et al. Deaths observed in Medicare beneficiaries: average attributable fraction and its longitudinal extension for many diseases. *Stat in Med*. 2012; 31(27):3313–9. [PubMed: 22415597]
15. Lin H, Allore HG, McAvay G, Tinetti ME, Gill TM, Gross CP, et al. A method for partitioning the attributable fraction of multiple time-dependent coexisting risk factors for an adverse health outcome. *Am J Public Health*. 2013; 103(1):177–82. [PubMed: 22515873]
16. Medicare Current Beneficiary Survey (MCBS). [Accessed May 5, 2014] Centers for Medicare and Medicaid Services Website. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/index.html?redirect=/MCBS/> Published July 2013
17. Adler G. A profile of the Medicare current beneficiary survey. *Health Care Financ Rev*. 1994; 15(4):153–63. [PubMed: 10138483]
18. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998; 36:8–27. [PubMed: 9431328]
19. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005; 43(11):1130–39. [PubMed: 16224307]
20. Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics*. 2001; 57(1):120–25. [PubMed: 11252586]
21. Tibshirani, R. Regression shrinkage and selection via the Lasso. *J Royal Stat Soc Series B*. 1996; 58:267–288.
22. Efron B, Hastie T, Johnstone I, Tibshirani R. Least Angle Regression. *Ann Stat*. 2004;32, 407–499.
23. SAS Institute Inc. SAS/STAT® 9.3 User's Guide. Cary, NC: SAS Institute Inc; 2011.
24. The MathWorks Inc. MATLAB Version 8.1. Natick, MA: The MathWorks, Inc; 2013.
25. Efron, B.; Tibshirani, RJ. An Introduction to the Bootstrap. Boca Raton, Florida: Chapman &Hall/ CRC; 1993.
26. Eide GE, Gefeller O. Sequential and average attributable fractions as aids in the selection of preventive strategies. *J Clin Epidemiol*. 1995; 48(5):645–55. [PubMed: 7730921]
27. Picheier U, Gefeller O. Conceptual aspects of attributable risk with recurrent disease events. *Stat Med*. 1997; 16(10):1107–20. [PubMed: 9179977]

Figure 1.

Table 1
Baseline Characteristics of Participants: Medicare Current Beneficiary Survey (N=8,517)

	n	%
Characteristic:		
Age ≥ 80 years	3044	35.7
Female gender	4987	58.6
White race	7425	87.2
Hispanic ethnicity	494	5.8
Income < \$25,000	4697	55.2
Current smoker	720	8.5
Obesity	2277	26.7
Prescription drug insurance	5441	63.9
Incontinence	1663	19.5
Use of assistive device	2198	25.8
Hearing impairment	754	8.9
Vision impairment	687	8.1
Cognitive impairment	2134	25.1
Comorbidity score ^{2a}	3803	44.7
Chronic conditions:		
Atrial fibrillation	1633	19.2
Coronary artery disease	3364	39.5
Depression or anxiety	2200	25.8
Diabetes	3384	39.7
Heart failure	1728	20.3
Hyperlipidemia	6564	77.1
Hypertension	7855	92.2
Kidney disease	991	11.6
PE/Venous thrombosis	473	5.6
Number of Study Conditions:		
2	2861	33.6
3	2559	30.1
4-5	2458	28.9
6-9	639	7.5
Indicated Condition: Medication ^b		
Atrial Fibrillation:	1633	19.2
Beta Blocker	979	60.0
Calcium Channel Blocker	595	36.4
Clopidogrel	204	12.5
Warfarin	909	55.7

	n	%
Coronary artery disease:	3364	39.5
Beta Blocker	2116	62.9
Calcium Channel Blocker	1127	33.5
Clopidogrel	852	25.3
Renin Angiotensin System	1939	57.6
Statin	2039	60.6
Depression or Anxiety:	2200	25.8
SSRI/SNRI	1147	52.1
Diabetes:	3384	39.7
Metformin	1138	33.6
Renin Angiotensin System	2034	60.1
Statin	1953	57.7
Heart Failure:	1728	20.3
Beta Blocker	1096	63.4
Renin Angiotensin System	1050	60.8
Hyperlipidemia:	6564	77.1
Statin	4190	63.8
Hypertension:	7855	92.2
Beta Blocker	3782	48.2
Calcium Channel Blocker	2724	34.7
Renin Angiotensin System	4403	56.1
Thiazide	3824	48.7
Kidney Disease:	991	11.6
Renin Angiotensin System	566	57.1
PE/Venous Thrombosis:	473	5.6
Warfarin	280	59.2
Number of study medications		
0	387	4.5
1-2	3053	35.8
3-5	4606	54.1
6-9	471	5.5
Self-rated health high	6069	71.3
Declined at 1 st FUP ^c	930	15.3
Declined at 2 nd FUP ^c	796	18.4
Declined at 3 rd FUP ^c	632	20.4

PE=pulmonary embolism; SSRI/SNRI=selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor; FUP=Follow-up.

^a Comorbidity 2 indicates two or more comorbid conditions from the 23 item Elixhauser scale [18, 19] excluding the study conditions.

^b Number and percentages reflect the number of participants taking the medication among those with the indicated condition. Participants could have more than one of the indicated conditions.

^cPercentages based on participants with high self-rated at baseline who completed each follow-up. 1st follow-up N=6,069, 2nd follow-up N=4,321, 3rd follow-up N=3,104.

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Table 2
Odds Ratio Estimates of High Self-Rated Health from the Generalized Estimating Equations Model with Logit Link Function: Medicare Current Beneficiary Survey

Model Term ^a	b (SE)	P value	Marginal OR ^b	Joint OR ^c
Intercept	2.006 (0.128)	<.001		
Chronic Condition				
Atrial fibrillation	-0.13 (0.10)	.203	0.88	
CAD	-0.17 (0.09)	.048	0.84	
Heart failure	-0.26 (0.09)	.004	0.77	
Diabetes	-0.15 (0.07)	.045	0.86	
Hypertension	-0.21 (0.10)	.040	0.82	
Hyperlipidemia	0.23 (0.06)	<.001	1.25	
Kidney disease	-0.45 (0.09)	<.001	0.64	
Depression or anxiety	-0.53 (0.06)	<.001	0.59	
PE/Venous thrombosis	-0.23 (0.12)	.059	0.80	
Interactions ^d				
RAS × CAD	0.03 (0.08)	.751		0.86
RAS × kidney disease	0.06 (0.11)	.574		0.68
RAS × diabetes	-0.12 (0.08)	.130		0.76
RAS × heart failure	-0.08 (0.10)	.388		0.71
RAS × hypertension	0.15 (0.07)	.027		0.94
Statin × CAD	-0.10 (0.08)	.232		0.76
Statin × hyperlipidemia	0.14 (0.07)	.036		1.45
Statin × diabetes	-0.11 (0.08)	.149		0.77
Thiazide × hypertension	-0.21 (0.04)	<.001		0.66
Beta blocker × atrial fibrillation	0.04 (0.10)	.724		0.91
Beta blocker × CAD	0.07 (0.09)	.446		0.90
Beta blocker × heart failure	-0.05 (0.10)	.615		0.73
Beta blocker × hypertension	-0.05 (0.06)	.378		0.77
Calcium CB × Atrial fibrillation	0.14 (0.10)	.171		1.01
Calcium CB × CAD	-0.06 (0.09)	.472		0.79
Calcium CB × hypertension	-0.06 (0.06)	.322		0.77
SSRI/SNRI × depression or anxiety	-0.07 (0.07)	.309		0.55
Metformin × diabetes	-0.05 (0.07)	.431		0.82
Warfarin × atrial fibrillation	-0.16 (0.09)	.080		0.75
Warfarin × PE/Venous thrombosis	-0.27 (0.16)	.086		0.61
Clopidogrel × atrial fibrillation	0.07 (0.13)	.591		0.95
Clopidogrel × CAD	-0.18 (0.08)	.021		0.70

OR= odds ratio; CAD = coronary artery disease; PE = pulmonary embolism; CB = channel blocker; RAS= Renin angiotensin system; SSRI/ SNRI=selective serotonin reuptake inhibitor /serotonin norepinephrine reuptake inhibitor.

^aEstimates are adjusted for the control variables: year, age, gender, race, ethnicity, income, smoking, obesity, prescription drug insurance, incontinence, use of assistive device, hearing impairment, vision impairment, cognitive impairment, and Elixhauser comorbidity score (2). A first-order autoregressive structure accounts for within-subject correlation of the recurrent observations.

^bMarginal OR for high self-rated health over the three year follow-up for the presence relative to the absence of the condition. For example, those with hypertension are 18% less likely (OR of 0.82) to report high self-rated health relative to those without hypertension controlling for all other variables over the 3 year follow-up.

^cJoint OR of high self-rated health over the three year follow-up for the presence of both condition and medication relative to absence of both condition and medication. These are obtained by adding the parameter estimates (b) for the condition and the appropriate interaction term. For example, for those with hypertension who take renin angiotensin system blockers the b estimates of -0.21 (hypertension) and 0.15 (RAS × hypertension) are added to obtain -0.06, which is then exponentiated for a joint OR of 0.94. This is interpreted as renin angiotensin system blockers improves the likelihood of high self-rated health for those with hypertension by increasing the 0.82 to a joint OR of 0.94. Thus, the odds of high self-rated health for people who take renin angiotensin system blockers for hypertension are higher than those who do not take renin angiotensin system blockers, controlling for all other variables over the 3 year follow-up.

^dWe included interactions between each condition-indicated medication and the condition.

Table 3
Longitudinal Extension of Average Attributable Fraction for High Self-Rated Health:
Medicare Current Beneficiary Survey

	LE-AAF ^a , %(95% CI ^b)	
	Unadjusted Model	Adjusted Model ^c
Condition		
Atrial fibrillation	-1.19 (-1.96, -0.53)	-0.67 (-1.41, 0.08)
Coronary artery disease	-3.51 (-5.06, -2.49)	-2.13 (-3.55, -1.06)
Heart failure	-3.50 (-4.40, -2.82)	-1.89 (-2.69, -1.22)
Diabetes	-3.63 (-4.63, -2.47)	-2.25 (-3.21, -1.05)
Hypertension	-8.48 (-11.95, -5.56)	-5.08 (-8.82, -1.77)
Hyperlipidemia	8.52 (6.46, 10.37)	4.58 (2.61, 6.56)
Kidney disease	-1.90 (-2.49, -1.42)	-1.56 (-2.15, -1.05)
Depression or Anxiety	-6.66 (-7.60, -5.80)	-4.25 (-5.24, -3.35)
PE and Venous thrombosis	-0.75 (-1.08, -0.47)	-0.50 (-0.85, -0.22)
Total for conditions:	-21.10	-13.74
Total for conditions absolute values:	38.14	22.91
Medication		
Renin-angiotensin system blocker	0.73 (0.18, 1.26)	0.49 (-0.08, 1.08)
Statin	0.17 (-0.44, 0.61)	0.08 (-0.66, 0.52)
Thiazide	-1.25 (-1.77, -0.75)	-1.17 (-1.74, -0.64)
Beta blocker	0.17 (-0.31, 0.73)	-0.12 (-0.59, 0.44)
Calcium channel blocker	-0.24 (-0.61, 0.15)	-0.22 (-0.58, 0.15)
SSRI/SNRI	-0.42 (-0.75, -0.17)	-0.15 (-0.47, 0.12)
Metformin	-0.08 (-0.32, 0.11)	-0.09 (-0.34, 0.11)
Warfarin	-0.16 (-0.42, 0.11)	-0.35 (-0.61, -0.08)
Clopidogrel	-0.23 (-0.43, -0.05)	-0.21 (-0.40, -0.05)
Total for medications:	-1.31	-1.74
Total for medications absolute values:	3.47	2.87
Overall total:	-22.41	-15.48
Overall total absolute values:	41.60	25.79

CI=confidence interval; LE-AAF=longitudinal extension of average attributable fraction; PE= pulmonary embolism; SSRI/SNRI = selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor.

^a LE-AAF is the longitudinal extension of the average attributable fraction where a positive values is the additive contribution to high self-rated health and negative values are the additive contributions to low self-rated health. For example, renin angiotensin system blockers have a 0.5% contribution to high self-rated health, while all of the conditions that indicate its use (coronary artery disease, heart failure, diabetes, hypertension and kidney disease) have negative contributions. Thus, renin angiotensin system blockers slightly ameliorate the effects of these indicating conditions. On the other hand, thiazide has a negative (-1.2%) contribution to high self-rated health as does its indicating condition hypertension (-5.1%) for a total of -6.3%, interpreted as a 6.3% contribution to low self-rated health.

^b 95% CI is the 95% confidence interval derived from 300 bias-corrected and accelerated bootstrap pseudo-samples.

^cEstimates are adjusted for the control variables: year, age, gender, race, ethnicity, income, smoking, obesity, prescription drug insurance, incontinence, use of assistive device, hearing impairment, vision impairment, cognitive impairment, and Elixhauser comorbidity score (2).

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