PHARMACOEPIDEMIOLOGIC STUDIES: AN INTERRUPTED-TIME SERIES ANALYSIS ON DRUG UTILIZATION AND EVALUATION OF BENEFICIAL OR ADVERSE DRUG EFFECTS

by

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ABSTRACT

Background: Pharmacoepidemiologic research is a valuable tool to enable one to understand medication utilization patterns, beneficial/harmful outcomes of drug therapy, and to evaluate the impact of other interventions on outcomes of drug therapy in "real-world" settings.

Objectives: This dissertation aimed to apply pharmacoepidemiologic methods to examine (1) changes in utilization patterns of cholesterol-lowering medications following the release of the guidelines and evidence-based data, (2) the associations between statin use and gait speed decline in older adults, and (3) the associations between aspirin, non-aspirin nonsteroidal anti-inflammatory drugs or acetaminophen and risk of ovarian cancer.

Methods: The study samples were from two sources including (1) community-dwelling older adults in the Health, Aging and Body Composition Study, and (2) 902 women with ovarian cancer and 1,802 controls in a population-based case-control study. An interrupted time-series analysis, multivariable generalized estimating equations, and multivariable logistic regression were used to examine our three objectives, respectively.

Results: First, the use of cholesterol-lowering medication increased substantially over a decade in older adults, but was not related to a change in level or trend following the release of the evidence-based guidelines. Secondly, statin use had a decreased risk of gait speed decline. Thirdly, risk reductions of ovarian cancer were observed with the use of aspirin or selective COX-2 inhibitors.

Conclusion: These findings suggest that further studies are needed to investigate risk-benefit balance of cholesterol-lowering therapy and the potential benefits/barriers of the treatment among adults aged ≥ 80 years. Moreover, further investigations are warranted to confirm the risk-benefit balance of statin use and physical function decline in older adults. Future research on the associations between aspirin use and the risk of ovarian cancer should better characterize accompanying medical conditions, health and lifestyle behaviors, genetic susceptibility, and the overall risk-benefit balance. The ***public health relevance*** of these findings is that understanding the utilization patterns of cholesterol-lowering therapy and potential benefits of statins on physical function may prevent cardiovascular disease and disability in older adults. In addition, aspirin or COX-2 inhibitors may be potential agents for the prevention of ovarian cancer, the second leading gynecologic cancer in the US.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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1.0 INTRODUCTION

1.1 PHARMACOEPIDEMIOLOGY

Pharmacoepidemiology is the application of epidemiologic knowledge, methods, measurements, analysis, and reasoning to study the uses, beneficial and adverse effects of drugs (including biologics, vaccines, and therapeutic devices) in defined human populations.[1] It is an applied field bridging between clinical pharmacology (including pharmacokinetics and pharmacodynamics) and epidemiology.[2] Moreover, pharmacoepidemiology integrates with therapeutic risk management to minimize risks throughout the whole life cycle of a drug (i.e., from the time when it is first discovered or synthesized until it is no longer sold as a drug), and optimize its benefit/risk balance.[1,3]

In the United States (US), the current drug approval process includes preclinical testing followed by three phases of clinical testing. Phase I trials are generally conducted in a few healthy volunteers to determine the pharmacologic and pharmacokinetic actions, a safe dosage range of a drug, and to exclude any extremely common toxic reactions which are unique to humans. The goals of Phase II trials are to obtain more information on the pharmacokinetics, common adverse reactions, initial possible efficacy, and to determine daily dosage of a drug in a small number of patients (typically up to 300). The goals of Phase III trials are to rigorously

evaluate and confirm earlier efficacy studies and identify common adverse effects in a much larger number of patients (approximately 500-3,000).[1,2] To meet Food and Drug Administration (FDA) standards, at least one (traditionally two) of the Phase III trials needs to be a randomized clinical trial (RCT). However, the pre-marketing studies are inherently limited to detect a drug's long-term effects, uncommon or delayed adverse effects, adverse drug withdrawal events, relative effectiveness in special populations (e.g., children, pregnant women or elderly), modifiers of efficacy (i.e., with concurrent drugs, disease severity, and lifestyle), and consequences due to misuse of the drugs by prescribers or patients.[1] Once marketing approval of a drug is granted, phase IV studies (or post-marketing surveillance), which are usually non-experimental epidemiologic studies, play a role to monitor its use and effectiveness in the usual clinical care conditions.

The traditional field of pharmacoepidemiology primarily focuses on the study of adverse drug effects and drug utilization. During the past two decades, the field of pharmacoepidemiology has increasingly shifted to study beneficial or harmful effects, pharmacoeconomics, pharmacogenetics, quality of life, meta-analysis of drug use, and health service research on studying if interventions improve drug use. The potential contributions of pharmacoepidemiology include: (1) supplemental information to premarketing studies and better quantifying the incidence of known adverse and beneficial effects in certain populations not studied prior to marketing (e.g., elderly, children, or pregnant women), (2) new types of information not available from premarketing studies (e.g., undetected adverse and beneficial effects, patterns of utilization), and (3) reassurances about drug safety and fulfillment of ethical

and legal obligations.[2] In summary, questions that pharmacoepidemiologic studies can answer include: [4]

(1) How and why is drug therapy being used/misused or prescribed?

(2) What are the beneficial and harmful outcomes of drug therapy?

(3) What interventions are effective in modifying the use and outcomes of drug therapy?

1.2 STUDY DESIGNS USED IN PHARMACOEPIDEMIOLOGY

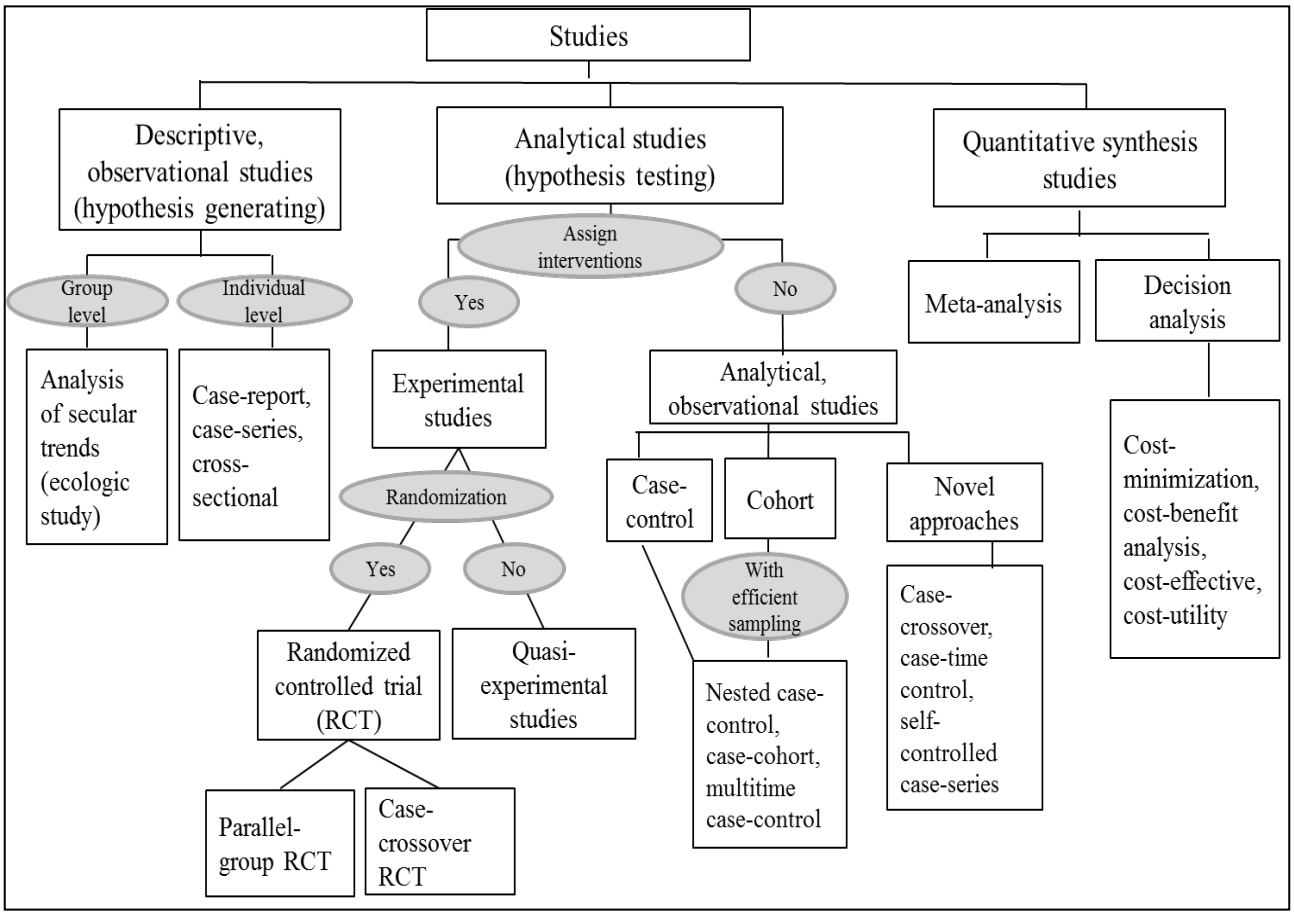

Figure 1. Study Designs Used in Pharmacoepidemiology

The types of study designs applied in pharmacoepidemiology differ with respect to several dimensions including direction of outcome measurement (e.g., prospective or retrospective), the unit (individual or group), number (one or more) of observations made, and methods and timing of data collection.[5] In **Figure 1**, case report, case-series, secular trend analysis (also called

ecologic study), cross-sectional, case-control and cohort studies are observational studies.[6,7] In observational studies, investigators do not control the therapy, but simply observes and evaluates the results of ongoing medical care. Case reports, case series, analyses of secular trends and cross-sectional studies are also referred to as descriptive studies. Through the use of descriptive study designs in pharmacoepidemiology, investigators may establish drug utilization patterns and quality of drug use in a population and provide data to be used not only for health policy and planning, but also as preliminary information to consider possible associations between exposure and outcome.[7] Due to intrinsic limitations that are described later, descriptive studies are sometimes called "hypothesis generating" studies, in which the proposed association will need to undergo further study.[7] Case-control studies, cohort studies, and RCTs all have control groups, and are considered to be analytic studies (i.e., hypothesis testing). Randomized clinical trials (RCTs) are experimental studies in which investigators control the therapy to participants.[8] In addition to the applications of traditional epidemiologic study designs, methodological advances in the design and analysis (e.g., nested case-control, case-cohort, multitime case-control, cross-over design) were developed to solve specific challenges in the conduct of research on drug effects during the past two decades. Moreover, quantitative synthesis studies including meta-analysis and decision analysis takes part of the medical literature or clinical experience, attempt to create an answer to a defined problem, resolve uncertainty and facilitate decision making in health care.[9]

In order to clarify different study designs used in pharmacoepidemiology, each study design and its characteristics, advantages, disadvantages and examples will be discussed in turn

and summarized in **Table 1**. The details of bias and confounding in pharmacoepidemiology will be discussed in **Section 1.5**.

Table 1. Summary of Study Designs Used in Pharmacoepidemiology Research

Study Design	Characteristics	Measures of Association	Advantages	Disadvantages	Main Applications/Examples (Ex)
Case series, case reports	• Observational, descriptive • Participants identified based on outcome • Generate information on natural history of disease and case definition	Not available	• Identifying new/rare disease/condition • Cheap and easy method for generating hypothesis	• No control group • Rates or measures of association cannot be calculated	• Monitor or capture adverse drug events or drug-drug interactions after marketing or in specific populations • Post-marketing spontaneous pharmacovigilance report • Ex: SSRIs induced serotonin syndrome in children[10,11] • Ex: Moxifloxacin-wafarin drug interaction[12]
Analyses of secular trends (ecological studies)	• Observational, descriptive • Trends in drug use and outcomes coinciding overtime for groups	Correlation	• Can provide rapid answers • Relatively quick and inexpensive	• No control of confounding • Ecologic fallacy • Changes in diagnosis, coding systems overtime	• Correlations between drug use and outcome overtime for groups • Ex: MMR immunization and autism occurrence among young children in California, US [13]
Cross-sectional	• Observational, descriptive • Study the distributions of drug use and disease in a populations	Prevalence	• Relatively quick and inexpensive • Valuable to estimate prevalence of drug use and disease	• Temporal association cannot be established • Limited generalizability if choosing a convenience sample	• Drug utilization study or snap-shot of the possible beneficial/harmful effects of drugs • Ex: Whether statin use was associated with a higher prevalence of musculoskeletal pain using NHANES data [14]
Case-control	• Observational, analytic • Participants identified based on outcome • Can study rare outcomes or outcomes with long latency periods	OR	• Can study multiple exposures • Logistically easier and faster, cheaper than RCTs	• Problematic control selection • Possibly biased exposure data • Recall limitation, recall bias, selection bias, temporal bias	• Study relative rare outcome related to certain medication use • Ex: Use of diethylstilbestrol in pregnant women and the risk of vaginal cancer in the off-spring[15]

Table 1 (Continued)

Study Design	Characteristics	Measures of Association	Advantages	Disadvantages	Main Applications/Examples
Cohort	• Observational, analytic • Participants identified based on exposure • Can study relatively rare exposures	Absolute risk (NNT/NNH), RR,	• Can study multiple outcomes • Temporal association established • Unbiased exposure data • Generally cheaper than RCTs	• Immortal-time, loss-to-follow-up biases, misclassification • Time-consuming if done prospectively	• Post-marketing surveillance studies or study potential effects of drugs use or factors to influence medication use • Ex: statin use and cholesterol associations with incident dementia and mild cognitive impairment [16]
Nested case-control	• Efficient sampling designs within a cohort • A type of case-control study • Controls are matched by certain variables and time of enrollment of cases	Allow to estimate absolute risk (NNT/NNH) and RR	• Minimize recall or selection bias (baseline data were obtained on exposure status) • Cost-intensive tests of biological samples can be carried out in a subset of cohort	• Loss-to-follow-up • May not be representative of all controls if outcome of interest is not rare • Drug use may change over time	• Ex: Whether statin use was associated with risk of cancer using 574 UK general practices cohort [17]
Case-cohort (case-base)	• Efficient sampling designs within a cohort • A type of case-control study • Controls are randomly selected from the rest of cohort	Allow to estimate absolute risk (NNT/NNH) and RR	• Same as nested case-control studies, plus • Controls may be used for multiple case groups	• Loss-to-follow-up • May need to select more controls since some controls who develop the diseases of interest may enter the study as cases • Drug use may change over time	• Ex: Associations of maximum prescribed daily opioid dose and dosing schedule with the risk of opioid overdose death among patients with cancer, chronic pain, substance use disorders using Veteran Health Administration Database[18]
Multitime case-control	• Efficient sampling designs within a cohort • A type of case-control study • Measure drug exposure at different time points to increase "numbers of observations per control"	Allow to estimate absolute risk (NNT/NNH) and RR	• Improve the precision of the RR and power without additional controls and cost	• Not suitable for chronic or cumulative drug exposure • Must correct for within-subject correlation	• For acute/transient drug exposure • Antibiotic use associated AMI 1:1 case-control: OR=2 (95% CI: 1.16–3.44); 1: 10 case-control: OR=2.13 (95% CI: 1.48-3.05); multitime case-control: OR=1.99 (95% CI: 1.36-2.90)[19]

Table 1 (Continued)

Study Design	Characteristics	Measures of Association	Advantages	Disadvantages	Main Applications/Examples
Case-crossover	• Assess the exposed versus unexposed periods of a drug in the same individuals • Study a transient exposure and acute events	OR	• Control for time-invariant confounders since each person serves as his/her control • Statistically efficient (require less sample size)	• Recall or selection bias • Not feasible for curative or rapid changing conditions • Inefficient if exposure does not shift frequently • Limited use in claim data • Need to specify the length of the effect period	• Examine the effects of drug use in patients with disease that worsen over time, various disease severity among patients, or the intermittent drug use • Ex: Study the association between sumatriptan and MI[20]
Case-time control	• Extension of case-crossover design • Controls are selected from a cohort with similar synchronization with cases	OR	• Similar to case-crossover • Situations where trends that may change overtime may be adjusted	• May not be valid when time-dependent confounders exist	• Control the time-trend in drug use and indication for drug use or disease severity • Ex: Examine the use of inhaled β-agonists and asthma death.[21]
Self-controlled case series	• Study a transient exposure and acute events • Drug exposure distribution doesn't need to be stationary • Adjust time-invariant confounders by self-controlled method	RR	• Efficient and cheaper • Allow temporal confounders (e.g. season), multiple risk periods and repeat exposures • Able to handle automated data, indefinite exposure (timeline is not censored at end-point)	• Would fail if outcome only occur at a determined age • May bias results if reporting strongly depend on the time interval between exposure and event	• Mainly use in vaccine surveillance • Ex: Study the influenza vaccine and acute asthma exacerbations in the 2 weeks following exacerbation[22]
Randomized clinical trial	• Experimental study • Investigator controls the exposure or therapy • A gold standard among all study designs • Also useful in post-marketing surveillance	Absolute risk (NNT/NNH), RR	• Only design which can control for unknown or unmeasured confounders	• Most expensive • Limited generalizability • Logistically most difficult • Ethical objections for proven therapies	• Can be used for post-marketing RCTs or comparative effectiveness research • Ex: A prospective study, ALLHAT, compared the four antihypertensive medications in those with hypertension and multiple comorbidities.[23]

Table 1 (Continued)

Study Design	Characteristics	Measures of Association	Advantages	Disadvantages	Main Applications/Examples
Quantitative Synthesis study: Meta-analysis	• Aims to resolve uncertainty and facilitate decision making • Systematically assess and combine the results of previous studies in order to draw conclusions about the body of research	For RCTs: Absolute risk (NNT/NNH), RR; For observational studies: RR or OR	• Increasing sample size and power to detect benefits and harms • Good source for evidence-based clinical decision making • Ability to assess subgroups effects and rare events • Save time/resources/ money	• Susceptibility of the original studies to bias • Publication bias, dissemination bias • Practical difficulties of combining results • May have paradoxical results • Potential biased results from manipulation of study selection and analytic strategies	• A meta-analysis on the effectiveness and safety of atypical antipsychotic medications for off-label uses in adults[24]
Quantitative Synthesis study: Decision analysis	• Aims to resolve uncertainty and facilitate decision making • 4 types of economic decision analyses: cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses.	ICER for cost-effectiveness analysis; ICUR for cost-utility analysis	• Assist health care professionals having a better understanding the risk-benefit trade-off of different treatment options • May incorporate patients' values into decision when utilities are obtained from patients (e.g., visual analog)	• Difficult to represent all choices and chance occurrences in the model • Patients cannot experience multiple outcomes at the same. • May require some events only occur for a set and limited amount of time • Obtaining utilities from patients can be challenging • The assumptions which were made from the diverse and imprecise data influence the quality and results	• A cost-utility analysis of the effects of aspirin therapy, statin therapy, combination therapy with both drugs, and no pharmacotherapy for the primary prevention of CHD events in men [25]

Abbreviation: **AMI**: acute myocardial infarction; **ALLHAT**: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **CHD**: coronary heart disease; **CVD**: cardiovascular disease; **ICER**: Incremental cost-effectiveness ratio; **ICUR**: incremental cost-utility ratio; **MI:** myocardial infarction; **MMR**: measles-mumps-rubella; **NHANSE:** National Health and Nutrition Examination Survey; **NNH**: number needed to harm; **NNT**: number needed to treat; **OR**: odds ratio; **RCT**: randomized clinical trials; **RR**: relative risk; **SSRI**: selective serotonin reuptake inhibitors

1.2.1 Case Report or Case Series and Post-Marketing Spontaneous Pharmacovigilance Reporting Systems

Recently, pharmacovigilance has been widely used to denote post-marketing safety activities and is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems."[26] The goal of a post-marketing spontaneous pharmacovigilance reporting system (briefly called spontaneous reporting systems) is to identify drug-related adverse events or adverse drug reactions (ADRs) that were not identified prior to approval, to refine knowledge of the known adverse effects of a drug, and to better understand the conditions under which the safe use of a drug can be assured.[27]

A case report or case series describes one or a number of interesting clinical cases who were exposed to a particular drug(s), usually having an adverse outcome, and observed by health care professionals from a single hospital or a specific geographic region.[5,6] Case reports or case series provide clinical descriptions after patients receive a particular drug. All voluntary case reports of adverse events or ADRs from health care professionals, patients/consumers or manufacturers that are received by regional or national monitoring systems are called spontaneous reports.[27,28] Once reports are received and entered into adverse events or ADR databases, these databases can then be inspected for drug safety signals, which form the basis of further study, necessary regulatory action or both. In the US, the individual spontaneous reports of ADRs, medication errors and product quality problems are sent directly to the FDA

through the MedWatch program or to the manufacturer, and then indirectly from the manufacturer to the FDA.[28] In addition, two international reporting and database systems are available: EudraVigilance in the European Union (run by the European Medicines Agency, EMA)[29] and WHO VigiBase, which pools data from the approximately 100 member countries of the WHO International Drug Monitoring Program (run by the Uppsala Monitoring Centre, UMC).[30]

Assessment of the drug-adverse event causality for a particular case report or series in the databases can be quite challenging. Useful factors for assessing causality between a drug and reported adverse events include: (1) chronology of administration of a drug (including beginning and ending of treatment and adverse event onset), (2) course of adverse event when the suspected agent continued or discontinued, (3) etiologic roles of agents and diseases in relation to adverse event, (4) response to re-challenge of agent, (5) laboratory test results, and (6) previously known toxicity of agent.[28,31] Naranjo's ADR causality algorithm is the method commonly used in clinical pharmacy to evaluate the probability of ADRs.[31] Rarely, definitive inference about causality can be made base on case reports or case series or from a spontaneous reporting database. In the absence of a control group, one cannot determine with certainty which features in the description of the patients are unique to the drug exposure. Measures such as incidence or prevalence rates cannot be calculated, as complete counts of all cases and/or the population at risk are usually not available.[5]

Reports detected from spontaneous reporting databases have several advantages including their large-scale, inexpensiveness, coverage of the population represented (including special subgroups), ability for signal detection, hypothesis generation, providing an opportunity

for healthcare professionals or the public to report adverse events/ADRs, and lack of interference with prescribing habits[27,32,33] Some limitations of spontaneous reporting include difficulties with adverse event recognitions, quality of reports (e.g., require detailed clinical information for a thorough case evaluation), under-reporting due to voluntary systems, inability to calculate population-based incidence of adverse events/ADRs (reporting ratio is used), non-uniform temporal trends in reporting (i.e., the frequency of adverse events/ADR reports per unit of drug utilization is not likely to be constant over time), and duplicated reports.[27,28,33] Due to the above limitations, interpretation of spontaneous reports always requires careful analysis and clear communication of results, conclusions, and limitations.

For example, numerous case reports of serotonin syndrome, a potentially life-threatening condition, in children being treated with selective serotonin reuptake inhibitors triggered the need to study the safety of antidepressants in children.[10,11] Furthermore, an example of a case series is the description of five cases of moxifloxacin-warfarin drug interaction, which resulted elevated international normalized ratios, prolonged hospitalization in two cases and clinically significant hemorrhage in one case. This case series helped health professionals detect this potential interaction, which was not indicated in the moxifloxacin product monograph at that time, and subsequently prevent this interaction in future patients.[12]

1.2.2 Analyses of Secular Trends (or Ecological Studies)

Analyses of secular trends (or ecological studies) examine trends in exposure (drug use) and outcomes when they coincide over time for groups (i.e., communities, counties or population

level) or across geographic boundaries.[6,34] One of the best-known sources of data on drug utilization is Intercontinental Marketing Services (IMS), tracking more than 80% of global pharmaceutical sales activity.[35] Vital statistics, such as National Death Index, are often used as a source of disease incidence in these studies.[6] The measure of association for an analysis of secular trends is correlation.[7] Analyses for secular trends are useful for rapidly providing evidence for hypothesis generation and preliminary research. However, a major limitation of this study design is "ecologic fallacy", a term used to represent the fact that associations observed at the level of the group or population may not represent the association at the individual level.[7] Thus, analyses of secular trends are unable to differentiate which factor is likely to be the true cause of the outcome of interest and establish a causal relationship between the drug exposure and the outcome of interest on an individual level.[6,7] Other potential problems using vital statistics include changes in diagnostic methods or terminology, coding systems, and population demographics overtime.[36]

For example, Dales et al. conducted a study in California, US to determine if a correlation exists between measles-mumps-rubella (MMR) immunization coverage among young children and autism occurrence between 1980 and 1994.[13] The study did not find a positive correlation between MMR immunization and autism occurrence among young children.

1.2.3 Cross-Sectional studies

Cross-sectional studies (also called **prevalence studies**) are useful when investigators are interested in gathering information on drug use and the extent of disease in a particular

population or in characterizing or comparing populations.[5] Information on drug use and/or disease are usually collected in a single visit or through a survey.[37] Cross-sectional studies are often quick, easy, inexpensive, and can be effectively estimate the prevalence of disease and/or drug exposures. They provide information on distributions of drug use and diseases in populations and can allow clinicians, public health professionals, and health policy makers to design and implement appropriate interventions or to allocate resources effectively. However, major limitations include the inability to establish a temporal association and sometimes the necessary restriction to studying rare diseases or diseases with short duration.[5,7] In addition, investigators sometimes elect to study a convenience sample, which may limit the reliability and generalizability of the study results.[7]

An article published in 2008 provides an example of a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002.[14] Investigators sought to evaluate whether statin use was associated with a higher prevalence of musculoskeletal pain in a nationally representative sample. In this study, statin users were significantly more likely to report musculoskeletal pain.

1.2.4 Case-Control Studies

Case-control studies are analytic observational studies that compare cases with a disease (or an adverse event) to controls without the disease, looking for differences in preceding drug(s) use.[34] The common sources for selecting cases with the outcome of interest include case-control surveillance and registries.[36] It is critical to select representative controls that have the same risk

of exposure as cases. Poor choice of controls can lead to both wrong results and possible medical harm. Controls can be recruited from known or unknown study populations (or study group or base). In general, when a study population is known, a sample of the population can be used as controls by using a population roster or techniques such as random-digit dialing. If study population is unknown, hospital controls, neighborhood controls, and friend, associate, or relative controls can be used.[38-42] However, it is challenging to define the group or population from which controls should come. For example, since endometriosis needs an operation for the diagnosis, investigators frequently select women having laparoscopy or laparotomy without diagnosis of endometriosis. But women having operations are unlikely to be representative of all those at risk of developing endometriosis, since operations do not occur at random.[43]

Case-control studies are advantageous to assess relatively rare outcomes (e.g., ovarian cancer), outcomes with long latency periods, or multiple possible causes of a single outcome.[7,34] Other advantages of case-control studies include being less expensive and quicker to complete than RCTs. Potential biases while conducting case-control studies may include selection, recall, and/or temporal biases.[44] One of the common limitations in case-control studies is the validity of retrospectively collected drug use information, which is mainly obtained by administering questionnaires or interviews. In addition, selecting cases and controls properly can be challenging and inappropriate control selection can lead to a selection bias and invalid results.[6,34] However, when case-control studies are done well, subsequent well-designed cohort studies or RCTs can generally confirm their results.[6] In case-control studies, one cannot determine the size of either the populations with or without drugs exposure (i.e., denominators) from which the cases and controls were drawn. Therefore, incidence rates of disease among individuals with or

without drugs exposure are not calculable. Thus, the measure of association obtained from a case-control study is an odds ratio (OR).[7] In addition, attributable risk cannot be directly calculated from a case-control study since incidence rates are not available.

One of the seminal case-control studies was conducted by Herbst et al., who examined the association between the use of diethylstilbestrol (DES) in pregnant women (for the prevention of spontaneous abortion) and the risk of vaginal cancer in the off-spring.[15] This study included 8 cases and 32 age-matched controls. The association between DES and vaginal cancer was very strong (7 of the 8 cases, but none of the 32 controls were prenatally exposed to DES). Even this small sample size provided sufficient power to reach statistical significance.

1.2.5 Cohort Studies

Cohort studies are essential to pharmacoepidemiology since they form the basis for the quantification of drug risk and benefit assessments. Cohort studies are studies that identify subsets of a defined population, based on the presence or absence of a particular drug use, and follow them over time, looking for differences in the outcome of interest.[6,34] Cohort studies generally are used to compare drug-exposed patients to unexposed patients, but they can be used to compare one drug use to another drug or treatment. The major sources of information about drug exposures are billing claims or automated databases, physicians (e.g., sent questionnaires in the prescription event monitoring in UK), pharmacies (e.g., pharmacy-based surveillance), and self-reports from patients.[36]

Cohort studies can be performed prospectively, retrospectively or ambispectively.[34] Prospective cohort studies have fewer problems with validity compared to retrospectively collected drug data.[6] Retrospective cohort studies use historical data to reconstruct an individual's past drug use status at baseline (or time zero) and subsequent outcomes that have occurred and have been recorded prior to the study.[45] The ambispective cohort design is a blend of the retrospective and prospective designs; retrospective data are used to determine drug status, and participants are then followed into the future to obtain outcome status.[45] Retrospective and ambispective cohort studies require reliable historical drug use data in order to be considered effective.

Cohort studies are particularly useful to study multiple possible outcomes and relatively infrequent drug use. They can be used in post-marketing drug surveillance studies to look at any possible effect of a newly marked drug.[6] However, they are not practical to study rare outcomes as the sample size needed to detect such outcomes would be extremely large.[46] In addition, prospective cohort studies can require a prolonged time period to study delayed drug effects.[6] Further, cohort studies may be susceptible to immortal-time bias, loss-to-follow-up bias, and misclassification of drug use (especially drug use changes during a period of follow-up duration).[45,46] Incidence rates can be calculated within a cohort study which enables estimation of risks such as the relative risk and attributable risk (also called risk difference or excess risk). The relative risk is the ratio of the incidence rate of an outcome in the drug exposed group to that in the unexposed group. The relative risk is more important in considering questions of causation. The attributable risk is more important in considering the public health impact of an association, as it represents the absolute increased rate of disease due to the drug exposure. It is

simply the arithmetic difference between the risk in the treatment group and the risk in the control group. A statistic that is directly related to the absolute risk but that offers a different prospective is the number needed to treat (NNT) or number needed to harm (NNH). NNT tells us how the many persons would have to be given a beneficial intervention to prevent 1 case of disease. NNH tells us how many people would have to be given a harmful intervention to cause 1 excess of disease. The NNT or NNH is equal to the inverse of the absolute risk difference.[47,48] For example, treating 10,000 women with estrogen plus progestin for 1 year yields 8 excess cases of breast cancer. Thus, one would need to treat 10,000/8 = 1,250 women for 1 year to cause a single excess case. Although the risks to a given women are small, the overall public health impact could be large if many women were taking hormone therapy.

For example, Beydoun et al. examined statin use and cholesterol associations with incident dementia and mild cognitive impairment using the data from Baltimore Longitudinal Study of Aging (a prospective cohort study).[16] 1604 and 1345 eligible participants were followed after age 50 for a median time of 25 years to examine the incidence dementia and mild cognitive impairment. The authors found that statin users had about 60% risk reduction of developing dementia, but not mild cognitive impairment, when considering "time-dependent" statin use with propensity score model adjustment. This association remained significantly independently of serum cholesterol levels. The authors suggest statins may have multifactorial effects on dementia.

1.2.6 Efficient Sampling Designs within a Cohort Study

Conducting a cohort study in pharmacoepidemiology is constrained by the following challenges: (1) expensive and time-consuming to collect data on all cohort members; (2) may require additional and validated data to control the confounding when using automated databases; (3) technically infeasible in data analysis of a cohort with multiple and time-dependent drug exposures, particularly if the cohort size and number of outcome events are large.[49] To overcome these difficulties, three sampling designs within a cohort (i.e., **nested case–control, case–cohort designs, and the multi-time case–control**) have been proposed and applied successfully in pharmacoepidemiology. Different from the traditional case-control and cohort studies, these sampling designs within a cohort permit the precise estimation of relative risk measures with negligible losses in precision.[50,51]

In **nested case-control studies**, cases are usually matched by certain variables such as sex, age, and "time of enrollment" into the cohort.[44,50] Matching on calendar time is crucial in studies where the drug prevalence and outcome incidence both vary substantially over time, which is not uncommon in pharmacoepidemiology.[51] A control may later become a case, however, this does not typically occur when the outcome of interest is uncommon.[50] A major advantage of this study design is that since baseline drug use and other clinical data were obtained, certain biases such as recall and selection biases may be minimized.[52] The design of nested case-control allows for the estimation of absolute and relative risk.[53] Limitations with this study design may arise; for example, if controls are samples at the end of the study period, issues such as loss to follow-up and representation of all controls may need to be considered.[53] In

addition, it is challenging when subjects are possibly selected more than once in the sample when the drug exposure and covariate factors are time-dependent, particularly when the data are obtained by questionnaire where the respondent would have to answer questions regarding multiple time points in their history.[49] An example of nested case-control studies is a series of studies conducted covering 574 UK general practices investigating the effect of statins on cancer incidence.[17] Within the cohort, cases were patients with primary cancers diagnosed between 1998 and 2008. Each case was linked to 5 controls alive and registered with the practice at the time of diagnosis of the case and matched by age, sex, and practice and calendar time. The study showed that prolonged use of statins was not associated with an increased risk of cancer at any of the most common sites, except for colorectal cancer, bladder cancer and lung cancer, while there was a reduced risk of hematological malignancies.

Unlike a nested case-control study where controls are usually matched to cases on time of entry into the cohort, in a **case-cohort study** (also called **case-base study**) every individual in the cohort has an equal probability of being a control since the control groups are randomly selected (or called **unmatched nested case-control design**).[50] Similar to nested case-control studies, case-cohort studies allow investigators obtain certain information for only a subset of all controls, potentially saving time and money and minimizing certain biases in traditional case-control studies.[44,50] The group of individuals serving as controls may be used for multiple case groups.[50] Controls that later develop the outcome(s) of interest may become cases; therefore, investigators have to select more controls for each case than they would in a traditional case-control study to attain the same level of statistical precision.[50] Potential limitations of case-cohort studies are loss to follow-up and the possibility of drug use changing over time.[44,50] The

analytic method must take into account the overlap of cohort members induced by the sampling strategy.[49] Bohnert et al. recently published a case-cohort study to examine the association of maximum prescribed daily opioid dose and dosing schedule (i.e., as needed, regularly scheduled or both) with the risk of opioid overdose death among patients with cancer, chronic pain, acute pain and substance use disorders.[18] In this study, 750 incident cases of unintentional prescription opioid overdose decedents in a Veteran Health Administration database from 2004-2008 were sampled, in addition to a random sample (n=154,684) who used medical services in 2004 or 2005 and received opioid therapy for pain from this same cohort. Among patients receiving an opioid prescription for pain, higher opioid doses were associated with an increased risk of opioid overdose death. The risk of opioid overdose should continue to be evaluated relative to the need to reduce pain and suffering and should be considered along with other risk factors.

The case–cohort design has some advantages over the nested case–control design: (1) simpler in sampling; (2) flexible to use the same sample to study several different types of events and each can be analyzed with the same "control" subcohort (whereas the nested case–control design requires different control groups for each type of event because the selection depends on event times); (3) case–cohort design allows one to change the primary time axis of analysis from calendar to disease time and vice versa; and (4) easier to perform external comparisons.[49,54] Conversely, the nested case–control design has some advantages over the case–cohort design: (1) easier to perform power calculation or equivalently sample size determination (whereas a case–cohort design requires more complicated calculation due to the overlap in risk-sets); (2) data on time-dependent exposure and covariates need only be collected up to the time of the risk-set

(while the collection must be exhaustive for the case–cohort); and (3) despite the accessibility of software for data analysis of case–cohort data, these can quickly become surpassed and even infeasible with larger sample sizes and time-dependent exposures. In this situation, the nested case–control design, with its single risk-set per case, is not only advantageous but also the only solution.[49,54]

Suissa et al. recently proposed the **multitime case–control design** as an alternative strategy to improve the precision of the OR in a case–control study with "acute or transient" time-varying exposures, especially when increasing the number of control subjects is too costly.[19] This approach measures drug exposure at many different points in time to increase "the number of observations per control subject", which must however be corrected for within-subject correlation.[19] Traditionally, case–control studies usually collect extensive data on time-dependent drug exposures, but only use a portion of these data in calculating OR. The advantage of a multitime case-control study is to improve the precision of OR and increase the power without adding additional controls and costs. However, the multitime case-control design is not suitable for chronic or cumulative drug exposure because the OR varies as a function of the duration of drug exposure. For example, in a nested case–control study within a cohort of 12,090 patients with chronic obstructive pulmonary disease, there were 245 incident cases of acute myocardial infarction (AMI) that occurred during follow-up, for whom 1 and 10 controls per case were identified. The OR of AMI associated with use of antibiotics in the month prior to the index date was 2.00 (95% CI: 1.16–3.44) with one control per case. The precision (as reflected in the confidence intervals) was improved by increasing to 10 controls per case with a rate ratio of 2.13 (95% CI: 1.48–3.05). Alternatively, keeping only one control patient per case,

but increasing the number of control time windows per subject from 1 to 10 (taken as 10 control exposure measures, one for each of the 10 months prior to the index date) also improved the precision with a rate ratio of 1.99 (95% CI: 1.36–2.90). [19]

1.2.7 Case-Crossover, Case-Time-Control, and Self-Controlled Case Series Studies

Pharmacoepidemiology is frequently faced with the assessment of the risk of acute adverse events resulting from transient drug effects. For example, this is the case in trying to study the risk of ventricular tachycardia, from hypokalemia and prolonged Q-T intervals, associated with the use of inhaled β-agonists in asthma.[51] Traditional study designs may be challenging because of the acuteness of the adverse event, difficulties in determining the timing of drug exposure, and possible confounding by indications. Three other study designs were devised to counter these complexities in pharmacoepidemiology: **case-crossover study**, **case-time-control study** and **self-controlled case series** study.[6,34,55]

A **case-crossover study** is similar to an experimental study in that the same individual is assessed during the periods of a specific drug exposure and periods without that exposure (control period).[56-58] In other words, the case has the outcome of interest and serves as its own control. Two assumptions need to be held for the case-cross over study, including: (1) the effect of the drug exposure is not cumulative nor does not extend beyond the risk period, and (2) the outcome of interest is without a preclinical stage that may influence the exposure.[55,57,59,60] In addition, the outcome of interest must be a discrete event, a risk period (between drug exposure and outcome) should be specified, and the data on the usual drug use pattern are necessary to

determine the typical probability of exposure during the time window of effect.[49,55,57] The design is particularly useful for examining the effects of drug use in patients with diseases that worsen over time or vary in severity from patient to patient or require intermittent drug use.[56,59] Another advantage of this design is that it eliminates the problem of time-invariant measurable (e.g., gender, race) or unmeasurable confounders (e.g., genetic factors). Limitations of case-crossover studies include selection bias (if case selection is related to the drug exposure), information bias (if differential quality of recent and past drug exposure data is present), restrictions of using automated data due to logistical issues, confounders that change over time that cannot be controlled for, and having the assumption of the absence of a time trend in the drug exposure prevalence.[34,51,55,57] Ottervanger et al. conducted a case-crossover study to examine the association between sumatriptan and myocardial infarction (MI) in the Netherlands.[20] Sumatriptan is used to abort an acute migraine (transient basis) and has a relatively fast onset of action (12 minutes, injectable formulation) and about 2-4 hours duration of action.[61] The investigator asked the subjects whether they took sumatriptan during the 2-4 hours immediately before the MI (risk period). Then the subjects were asked if they took sumatriptan 1 week before the MI (control period). The investigators found that young age, hypertension, general complaints of abdominal pain, and a family history of myocardial infarction are associated with an increased risk of chest pain attributed to sumatriptan. Sex is an effective modifier of risk factors of sumatriptan-induced chest pain. In particular, hypertension is a strong risk factor in men.

The **case-time-control study** design is an extension of the case-crossover design. In 1995, this study design was proposed for controlling for confounding by indication (e.g., disease

severity), which was not measured because of the within-subject analysis.[21] It is used to examine associations that may exist between drug use and an outcome in situations where trends that may change over time (such as prescribing patterns or disease severity) could confound the association.[59,60] For example, a standard case-crossover study is not suitable for studying events related to drug use during pregnancy because drug use often changes during gestation. A control group is selected within a cohort and with an approximate synchronization with cases. Both cases and controls are examined for drug exposure status during the control period and during the time period corresponding to the outcome of interest.[57] As cases and controls were selected from approximately the same time period, changes in trends over time may be adjusted for, although this is not guaranteed and may itself introduce other bias.[57] An example of the use of a case-time-control design was the study to examine the use of inhaled β-agonists and its potential association with asthma death. In Spitzer et al's previous work, the used of inhaled β-agonists were associated with the increased risk of asthma death.[62] However, they argued that one potential explanation for the increase in deaths (despite adjustment of potential confounders) may be a natural increase in the use of inhaled β-agonists overtime (e.g., due to increase in physician prescribing, more evidence of drug efficacy and better compliance with the drug). The same group of investigators conducted a case-time-control study and showed that inhaled β-agonists may not play the leading role attributed to the risk of fatal or near-fatal asthma, as was previously suspected.[21]

Self-controlled case series studies can be used to study the temporal association between a time-varying drug exposure and an adverse event using data on cases only.[55] Self-controlled case series studies require the following three key assumptions to be applicable: (1)

events arise in a non-homogeneous Poisson process; (2) the occurrence of an event must not alter the probability of subsequent exposure; and (3) the occurrence of the event of interest must not censor or affect the observation period.[55] Data are usually collected during a predefined study period given in terms of calendar time and possibly age boundaries, typically determined by the availability of database records. The main advantages are that it often has high efficiency relative to the cohort method and that is self-controlled for time-invariant confounders (such as gender, location, genetics, and underlying health status).[55] Time varying confounders such as age and season can be allowed for in the baseline incidence. For example, ages at vaccination are regarded as fixed, and the random variable of interest is the age at adverse event, conditioned on its occurrence within a pre-determined observation period.[55] The self-controlled case series method shares in all the benefits of the case-crossover method, but has two important advantages over the case-crossover method. The first is that there is no requirement of stationary or exchangeability of times of exposure (e.g., vaccination).[63] For example, the case-crossover method would not be appropriate for the seasonal influenza vaccination. Secondly, in conditions of high vaccine coverage, the method is nearly as powerful as a full cohort analysis.[63] This is because non-cases contribute very little information about the vaccine effect. However, it would fail in the unlikely event that the adverse event could only occur at a determinate age, since no within-individual variation would then be possible. If on the other hand vaccination times were determinate, then age and vaccine effects would be confounded, and an unvaccinated group of cases would be required to disentangle their independent effects. Generally, the greater the variability in vaccination ages within the observation period, the more powerful the study.[63] Kramarz et al. investigated whether administration of influenza vaccine to asthmatic children

(aged < 6 years) caused acute asthma exacerbations in the 2 weeks following vaccination in 1993-1996.[22] Using the self-controlled case series analysis, which automatically adjusts completely for underlying disease severity, the vaccine appears to be protective.

1.2.8 Randomized Clinical Trials (RCT)

A RCT is an experimental study in which investigators control the intervention and randomly allocate patients among the study groups. The major strength of this approach is random assignment, which is the only way to ensure that the study groups are comparable in potential unknown or unmeasurable confounding variables. RCTs are considered to be the most scientifically rigorous method for hypothesis testing and remain the "gold standard" against which other studies are judged.[6,64] However, investigators may be limited in their ability to use a RCT design because of issues related to feasibility, sample size, length of follow-up, ethics, or cost.[64] If the incidence of an adverse event is very rare or if the adverse event only arises in the long term, this potential safety issue will not be detected through RCTs. In addition, RCTs are more expensive and may not generalize to population. In the past, RCTs are used less after marketing; however, there is an increased concern about relying solely on non-experimental methods to study drug safety after marketing. Therefore, large RCTs are emerging as a part of post-marketing surveillance.[6]

Moreover, comparative effectiveness research (CER) has become the spotlight after the introduction of the American Recovery and Reinvestment Act, which provided $US1.1 billion over two years to support CER.[65] CER has two major components including the comparison of

two or more agents or interventions that are considered true therapeutic alternative, and the examination of effects (or outcomes) in actual practice.[66] CER may include prospective clinical trials (also called large simple clinical trials or pragmatic clinical trial), observational studies, or synthesis studies. A traditional phase III RCT, which is an explanatory trial, aims to establish the efficacy of a new drug in narrowly selected population in a controlled setting. They usually compares the new drug with placebo or an inferior treatment option rather than legitimate alternative treatment option. Explanatory RCTs often evaluate a single main measure of clinical outcomes, which are often short-term, surrogate or intermediate endpoints.[66,67]

In contrast, pragmatic clinical trials, which may be randomized or non-randomized, aim to demonstrate effectiveness of a drug in a diverse population and heterogeneous practice settings, and answer the questions faced by decision makers. Pragmatic clinical trials may use wide range of outcomes which are more informative for decision makers (e.g., participants, funders, communities, and healthcare practitioners).[66-68] For example, in trials of back pain, the Cochrane Collaboration recommends that outcomes should include pain, functional status, ability to work, and satisfaction with treatment. However, increasing the number of measures in a trial increases the probability that one will reach statistically significance on the basis of chance alone. This needs to be taken into account in the sample size calculation. In general, more subjects are needed when several outcomes are being measured.

An example of a comparative effectiveness trial is Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT study).[69] ALLHAT compared the effectiveness of four antihypertensive medications in general population with hypertension and multiple comorbidities. The primary outcome was combined fatal CHD or nonfatal myocardial

infarction, rather than surrogate measures. Findings of the ALLHAT have influential effects on the treatment of hypertension in current practice. For example, thiazide-type diuretics are superior in preventing one or more major forms of cardiovascular disease and are less expensive. They should be preferred for first-step antihypertensive therapy.[23]

1.2.9 Quantitative Synthesis Studies: Meta-analysis, Decision analysis, and Cost-Effectiveness Analysis

Meta-analysis and decision analysis have in common that they synthesized knowledge.[9] Each method takes parts of the medical literature or clinical experience and, based on this information, attempts to create a whole answer to a defined problem. In addition, they are quantitative, using statistical and numerical analysis, aims to resolve uncertainty and facilitate decision making. Each plays a prominent role in the formulation of clinical and public policy in health care.[9]

Meta-analysis is a qualitative and quantitative approach for systematically assessing and combining the results of previous studies in order to draw conclusions about the body of research.[9] Studies of a topic are first systematically identified, and inclusion and exclusion criteria are defined. In traditional meta-analysis, data from the eligible studies are abstracted or collected from the investigators of the study. The data are then analyzed and the heterogeneity of the results is tested. If the results are homogenous, a summary estimate of the size of the effect of treatment is estimated. If the results are heterogeneous clinically or statistically, the heterogeneity needs to be further explored.[70,71] Ideally, meta-analysis is applied most appropriately to RCTs and provides most powerful evidence. When in cases of RCTs are

impossible, meta-analysis of observational studies is useful to explore dose-response relationship, to understand reasons for discrepancies among the results of difference studies, and to assess the possibility of differences in the effects of the drug exposure in subgroups.[70] Another type of meta-analysis, **pooled analysis**, obtains and analyzes the "individual" data from participants in a systematically ascertained group of studies. Pool analysis of individual level data has the same concept and aim as traditional meta-analysis.[9] When systematic review and meta-analysis are used to compare alternative treatments from the standpoint of real-world health care decision, they are considered as secondary comparative effectiveness studies.[66]

The use of meta-analysis has been growing since 1987, the advantages of meta-analysis include increasing sample size and power to detect benefits and harms of a drug or treatment, good source for evidence-based clinical decision making, ability to assess subgroups effects and rare events, ability of indirect comparison and simultaneous evaluation of treatment therapies available for special conditions, and saving time, resources and money.[72] In addition, cumulative meta-analysis could be as a tool to detect safety signal earlier. The disadvantages of meta-analysis include susceptibility of the original studies to bias (garbage in and garbage out), publication and dissemination bias, practical difficulties of combining results from different studies (i.e., variations in study designs, subject characteristics, drug exposures, and outcomes), paradoxical results due to combining different studies, potential biased results from manipulation of study selection and analytic strategies, and challenges of including advanced study designs (e.g., case-crossover, clustered randomized trials).[72]

For example, Maher et al. performed a systematic review and meta-analysis on the effectiveness and safety of atypical antipsychotic medications for off-label uses in adults.[24] The

authors found that benefits and harms vary among atypical antipsychotic medications for off-label use. For global behavioral symptom scores associated with dementia in elderly patients, small but statistically significant benefits for global behavioral symptom scores associated with dementia in elderly patients were observed for aripiprazole, olanzapine, and risperidone. Quetiapine was associated with benefits in the treatment of generalized anxiety disorder, and risperidone was associated with benefits in the treatment of obsessive-compulsive disorder; however, adverse events were common.

Decision analysis is a quantitative approach that assesses the relative value of different decision options.[9] It is a method of probabilistic reasoning and decision-making under conditions of uncertainty.[73] In other words, when some uncertainty about the appropriate clinical strategy for patients with a given health state and there is a meaningful tradeoff in the problem, it is appropriate to conduct a decision analysis.[74] Decision analysis always requires comparison of at least two clinical strategies with advantages and countervailing disadvantages.[74] The results from decision analysis are used to decide how to manage an individual patient and to formulate policy recommendations about a group of similar patients. Briefly, performing a decision analysis involves (1) defining a specific question, (2) creating a model (usually a decision tree or MarKov model) to frame the question, (3) assessing utilities or values to outcomes in the model, (4) assigning probabilities to chance events in the model based on direct assessment, literature or expert opinion, (5) identifying the best strategy within the model, (6) sensitivity analysis (to determine the robustness of the results), and (7) model refinement based on the internal, external, between-model consistency and predictive validity of the model.[9,74]

When an economic perspective is assumed, values of the outcome are assigned in terms of their monetary cost. Economic decision analysis research is increasingly used to inform funding decisions for new therapies (e.g., incorporation as part of phase III trials), and deliver high-quality care within the constraints of limited budgets or reduced fee schedules.[75] Types of economic decision analyses in pharmacoeconomic research considering both costs and utilities of outcome include **cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analyses** (**Table 2**).[73,75] **Cost-minimization analysis** (or **cost-identification** analysis) assumes that alternative treatment result in the same outcome, and value or decision is assigned entirely based on the lowest cost. It is appropriate only if treatment outcomes or benefits are equivalent among the therapies being evaluated.[75] **Cost-benefit analysis** remains a less common used technique in economic assessments of health care in the US, because it is difficult to translate all outcomes into monetary measures.[9] **Cost-effectiveness analysis** assumes that cost and the effectiveness of interventions vary, and uses natural units as outcome measures. Consequently, value is assigned by the cost per unit improvement of a health status, such as dollars per years of life saved. **Cost-utility analysis,** a type of cost-effectiveness analysis, often presents the outcome as cost per quality-adjusted life-year. The advantage of cost-utility analysis is that the utility assignment can be generalized to all health states.

For example, Pignone et al. performed a cost-utility analysis of the effects of aspirin therapy, statin therapy, combination therapy with both drugs, and no pharmacotherapy for the primary prevention of CHD events in middle-aged men.[25] Compared with no treatment, aspirin is less costly and more effective for preventing CHD events in middle-aged men with a 10-year risk for CHD ≥ 7.5%. The addition of a statin to aspirin therapy becomes more cost-effective (an

incremental cost-utility ratio of 42,500 dollars per quality-adjusted life-year gained) in men with a 10-year CHD risk ≥ 10% at baseline.

The main advantage of decision analysis is that it assists health care professionals having a better understanding the risk-benefit trade-off of different treatment options. Another advantage is that decision analysis incorporates patients' values into decision when utilities are obtained from patient populations (e.g., visual analog, stand gambling, or time trade-off methods).[76] The decision analysis has inherent limitations. Oftentimes, the tree may need to be simplified to show only major choices and outcomes rather than all choices and chance occurrences.[77] For example, treatments vary among physicians and that heterogeneity may not be easily represented. In addition, the decision tree is limited that in that patients cannot experience multiple outcomes at the same.[77] Furthermore, many decision tree analyses require that some chance events occur for a set and limited amount of time. Eliciting utilities can be challenging, even using the most reliable methods such as time trade-off and standard gamble methods.[73] Lastly, using the assumptions made from the diverse and imprecise data in the decision analysis may heavily influence the quality and conclusions of the results.

Table 2. Overview of Types of Decision Analyses in Pharmacoeconomic Research

Type of Analysis	Measurement of Costs	Measurement of Outcome	Common Presentation for the Results	Characteristics and Other Comments	Example
Cost-minimization (or cost-identification)	Monetary units	None	Cost per unit or service provide	• Outcome is assumed to be the same • Not often used due to outcomes are usually different • Appropriate only if treatment outcomes or benefits are equivalent among the therapies being evaluated	Evaluation of brand-name vs. generic drugs (with same outcome or indication)
Cost-benefit	Monetary units	Monetary units	Net benefits or cost-benefit ratios	• More commonly used in economics and policy than in health care (due to difficulties in assigning a cost to many outcomes)	Pharmacist-managed clinic for a disease vs. cardiac rehabilitation program
Cost-effectiveness	Monetary units	Natural units (e.g., life-years gained, disability-days saved, reduction of blood pressures)	ICER is presented (e.g., $100,000 dollars per life saved)	• Same outcome measured for the drugs/services being compared • Can be challenging to compare different outcome measures across different studies	Cost/mmHg decrease in blood pressure treatment
Cost-utility	Monetary units	Utility or healthy years (typically measured as QALY)	ICUR is presented (e.g., $100,000 dollars per QALY gained)	• Combine quantity and quality of life • A type of cost-effectiveness analysis	Cost/QALY gained for aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men

Abbreviations: ICER: incremental cost-effectiveness ratio; **ICUR**: incremental cost-utility ratio; **QALY**: quality-adjusted life-year;

1.2.10 Summary

Each study design described above can be applied in pharmacoepidemiology research. In general, science proceeds from the case reports toward RCTs. Case reports and case series are useful for suggesting an association, while analyses of trends and case-control studies are useful for exploring these associations. Observational study designs are important approaches to identify and evaluate of drug effects that would not be ethical to conduct in experimental studies. Observational studies also allow one to examine drug effects in more diverse or special populations (e.g., elders or children), assess drug effects that are uncommon or latent, or that are the result from drug over-dose or off-label use.[34] Case-crossover, case-time-control, and self-controlled case series methods are increasingly used in pharmacoepidemiology, particularly in vaccine safety studies. These methods are typically used to evaluate the association between a transient exposure and acute event. Decision analysis provides a way to quantify preferences, and when it is evaluated in conjunction with cost data, this analytic tool may provide additional evidence for clinical decision making. In summary, traditional study designs can generally optimize the conduct of research in pharmacoepidemiology, and further enhancements of novel approaches or tools have been developed specifically to solve challenges in pharmacoepidemiology. The common aim of using an appropriate study design in pharmacoepidemiology is to investigate the optimal use of therapeutic agents and contribute to evidence-based decision-making in clinic settings and for overall public health.

1.3 SOURCES OF DATA TO ASSESS SAFETY/BENEFIT OF DRUGS

While premarketing studies identify many aspects of drug safety, the full safety and benefit profiles can only be identified when the drug is used in large numbers of patients in "real world" settings. The major sources of data to assess safety or benefit of drugs include automated health data systems, field studies (or ad-hoc studies), and other special ad-hoc studies (e.g., case-control surveillance, prescription-event monitoring, and registries). Main medication use sources will be reviewed in this section. The details of each source/database are beyond the scope in this section. **Table 3** summarizes the characteristics, advantages, disadvantages and examples of these medication data sources. The US National Cancer Institute also provides some available pharmacoepidemiology sources (see http://riskfactor.cancer.gov/tools/pharmaco/epi/).

Table 3. Overview of Sources of Data to Access Safety/Benefit of Drugs

Sources	Characteristics	Advantages	Limitations / Biases	Examples
Automated Data Systems: Often considered as the gold standard for medication data				
Administrative claims databases (claims databases)	• Arises from a person's use of health care system and the submission of claims to insurance companies for payment (health insurer databases) • Uncommon outcomes can often be studied • Can study drugs and devices as used in real-world clinical practices • Include membership data, physician services, outpatient pharmacy claims, hospital services, laboratory services	• Large sample, quicker, less expensive • Very high-quality data on drug exposure • Minimize recall/interview bias • Usually have standard formats	• Uncertain validity on diagnosis data (especially outpatient) • Unavailable confounders • Limited medication coverage • Lack of information on clinical data, patient history, OTC drugs, outside of the insurance's plan, or uninsured population, patient's adherence • Instability of the population (e.g., job changes)	• US: HMO, Medicare, Medicaid, State blue cross/blue shield plans, commercial insurance (e.g., HealthCore, UnitedHealth group, Ingenix Research database) • Canada: Canadian provincial databases (e.g., BCLHD)
Electronic health records (EHRs), or Electronic medical records (EMRs)	• Used by healthcare professionals in the delivery of care to patients • Uncommon outcomes can often be studied • Can study drugs and devices as used in real-world clinical practices • Include patient data, activity, prescription, clinical/lab observations, orders (diagnosis and procedure codes)	• Large sample, quicker, less expensive • Better quality on diagnoses • Minimize recall/interview bias • Able to extract data from clinical text (e.g., through natural language processing method)	• Require data manipulation • Uncertain completeness of data from other physicians/sites • Unavailable confounders • Lack of information on clinical data, OTC drugs, patient's adherence • Complex and costly of computer hardware and software	• US: HMORN, VA data, PPD, Cerner's Health Facts Database • UK: GPRD, THIN • The Netherlands: PHARMO • Denmark: OPED, AUHD • Other: IMS Disease Analyzer
Ad-Hoc Studies				
De Novo: Field study	• Epidemiologic studies in which data are collected in the field for evaluating specific hypothesis • At least partially enroll the subjects and collect data • Mostly, self-reported data about medication use (recall or brown bag medication inventory)	• More rigorous defined outcomes • Feasible to enroll subjects with very rare conditions • Feasible to obtain information/confounders not collected in the pre-existing databases • Capture actual medication use (prescription, OTC medications and dietary/herbal supplements)	• Time-consuming • Relatively expensive • Logistic challenges • Completeness of ascertainment of drug exposure varies from different study designs: e.g., recall accuracy on drug exposure in case-control study • Potential biases influencing study validity	Studies in the elderly: CHS, EPESE, Health ABC, NSHAP, MrOS, SOF, WHAS, WHI

Table 3 (Continued)

Sources	Characteristics	Advantages	Limitations / Biases	Examples
Special Types of Ad-Hoc Studies				
Case-control surveillance (CCS)	• Started in 1976 at collaborating hospitals in Boston, Baltimore, New York and Pennsylvania, U.S, A • Multiple case-control studies are conducted simultaneously • Relies on self-reported of regular or long-term medication and dietary supplement use for 43 indications or medication categories	• Large sample size • Including OTC and dietary supplement • Ability to access the effect of a drug use that occurred in the distant past or long duration of exposure • Accurate outcome data from hospital discharge summary and pathology reports	• Selection bias due to hospital-based case-control studies • Difficulties in validating self-reported OTC medication and dietary supplements • Potential misclassification of drug use • Dose of drugs was not collected	Slone Survey
Prescription-event monitoring (PEM)	• Also called yellow-card system • Since 1981, PEM systematically monitors the safety of targeted medications in cohorts of 10,000-15,000 patients in England • Questionnaires are sent to general practitioners to request information on specific drug use and events • Single-cohort design	• Large sample size • Representativeness of patients treated in real-world clinical practices • Ability to examine adherence to prescribing guidelines • Examine drug utilization and safety in special populations • Medication exposures derived from dispensed prescriptions with validations from prescribers • Complete collections of outcome events	• Absence of data on an unexposed comparator • Selection bias from preferential prescribing • Unpredicted patterns of adoption of a new drug • Non-response questionnaires • Possible under-reporting of serious/fatal adverse events • Misclassification bias depend on patient's adherence, accuracy in physicians' diagnosis • Inability to control/adjust all the confounders • Cannot study drugs used in hospitals	Specifically refer to PEM in England

Table 3 (Continued)

Sources	Characteristics	Advantages	Limitations / Biases	Examples
Registry	• An organized system that uses observational study methods to collect uniform data to evaluate specified outcome of a population defined by a particular disease, condition or exposure • Used for monitoring public health intervention and systematic collections of data on people with shared characteristics • Uses extended to patient support effectiveness/safety evaluations, characterization of clinical presentation of diseases	• Ability to simultaneously collect detail clinical, administrative information • Flexibility to adapt over time to accommodate new research questions and purposes • Better representing the situations in real-world practices • Ability to follow patients over long periods of time	• Lack of pre-specified hypotheses if registries are designed to provide an adaptive framework for evaluating treatment • Difficulties in explaining the observed effects if lack of comparison groups • Selection bias if recruiting subjects preferentially • Discouraging reporting rate if data collection systems are hard-to-use	The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute in the US

Abbreviations: **AUHD**: Arhus University Prescription Database; **BCLHD**: British Columbia Linked Health Database; **CHS**: Cardiovascular Health Study, **EPESE**: Established Population for Epidemiological Studies of the Elderly, **FDA**: US Food and Drug Administration; **GPRD**: General Practice Research Database; **Health ABC**: Healthy, Aging and Body Composition Study, **HMORN**: Health Maintenance Organization Research Network; **IMS**: Intercontinental Marketing Services; **NSHAP**: National Social Life, Health and Aging Project, **MrOS**: Osteoporotic Fractures in Men, **OPED**: Odense University Phamacoepidemiological Database; **OTC**: over-the-counter; **PHARMO**: PHARmacoMOrbidity Linkage System Database; **PPD**: Premier Prospective™ Database; **SOF**: Study of Osteoporosis Fractures, **THIN**: The Health Improvement Network; **VA**: Department of Veterans Affairs Heath Care System; **WHAS**: Women's Health and Aging Study, **WHI**: Women's Health Initiative; WHO: World Health Organization

1.3.1 Automated Data Systems (or Computerized Healthcare Data)

Since 1980, automated databases (or computerized healthcare data) containing medical care data became an excellent source of data for pharmacoepidemiologic studies, especially for very rare adverse events (incidence rate <1 in 10,000).[78] Databases that contain health information can be generally divided into two categories: **administrative/claims database** and **electronic health records (EHR, or electronic medical records [EMR]).** Claims data arise from a person's use of the health care system (pharmacy, hospital, physician) and the submission of claims to insurance companies for payment.[78] EHRs are used by clinicians in the delivery of care to patients. They consist of pharmacy, primary care and hospital databases including information such as clinical observations, lab test results, and prescriptions.[78] Since claims data arise from a system not designed for research or clinical care, linking to EHRs improves the range of data for research purposes. A research study may link de-identified claims data from a population of patients diagnosed with a particular condition such as hypertension, with de-identified clinical data on everything from a patient's body mass index, blood pressure, symptoms and more, while maintaining patient privacy and full compliance with HIPAA standards. This linkage enables researchers to assess the effectiveness of medical treatments, prescription adherence, and disease management based on extensive clinical and administrative data including hospitalizations, ambulatory visits, filled prescription, cost, and reimbursements. The existing automated databases in the US available for pharmacoepidemiologic research include Health Maintenance Organization Research Network (HMORN), Kaiser Permanente Medical Care Program (KP-MCP), Group Health Cooperative (GHC), US government claims databases (e.g., Medicaid, Medicare), other commercial insurances (e.g., HealthCore, UnitedHealth group, Ingenix

Research database), and in-hospital databases (e.g., Pediatric Health Information System and Premier Prospective™ Database).[78-82] The General Practice Research Database (GPRD), the Health Improvement Network (THIN) in UK, the Department of Veterans Affairs (VA) Heath Care System in the US, and the Intercontinental Marketing Services (IMS) Disease Analyzer are the most well-known and widely used examples of EHRs.[83] Moreover, pharmacy-based medical record linkage systems, which integrate multiple autonomous databases with a primary pharmacy-based dispensing database into a single system, have been established in the Nordic countries (e.g., Danish Odense University Pharmacoepidemiologic Database [OPED] and Arhus University Prescription Database [AUHD]] and the Netherlands (PHARmacoMorbidity linkage system [PHARMO]).[84] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) provides a useful electronic index (digest) of 327 databases worldwide (119 in the US; available at http://www.ispor.org/DigestOfIntDB/CountryList.aspx). The Digest consists of key attributes of each health care database. It is grouped by country and allows both key word searches and searches by type of database.[85]

In general, automated databases are quite accurate representations of drug prescribing and are often considered the "gold standard" among medication data sources.[86,87] The major advantages of automated databases are their ability to provide very large sample sizes, relatively inexpensive, minimization of recall and interviewer biases, and ability to calculate incidence rates (mainly for claim database; some EHRs can only obtain prevalence).[88-90] Automated databases can also be used to assess clinician and patient adherence to evidence-based pharmacotherapy.[91] Grymonpre et al. showed the high concordance between the rates of prescription refills from and pill counts.[92] In addition, one may extract valuable, research-quality data from clinical texts in EHRs through developing methods (e.g., natural language processing

methods).[83] Several limitations of the automated databases include the uncertain validity of diagnosis data (especially for the claims databases and outpatient data), lack of information on some potential confounding variables (e.g., alcohol consumption, diet, physical activity), lack of information on non-prescription medications (e.g., non-steroidal anti-inflammatory drugs) or outside of the particular insurance carrier's prescription plan, instability of the population due to job changes or employment status (for claim-based data), restricted generalizability to certain population (e.g., patients without coverage or with insufficient insurance not included), expense or difficulty in obtaining permission to use the data, and lack of information on actual use by patients and adherence to treatments.[88-90] Although the size of most individual automated databases is quite large, a study using these might still be underpowered to detect very rare outcomes or outcomes that only occur a long time after drug exposure. The power can further be increased by combining data from different region- or country-specific databases into one analysis set through the unique linkage system. This is relatively new development within the field of pharmacoepidemiologic research. For example, this principle of database linkage is being used in studies of the potential teratogenic effects of a drug where a prescription database is linked to a pharmacy database and a birth registry.[93]

Research based on automated data plays an important role in pharmacoepidemiology. Automated data systems will become even more evaluable as larger, more effective records linkage systems are implemented. The ideal automated database would include records from both in- and outpatient care, emergency care, mental care, clinical measurements (laboratory, radiological, pathology tests), medication data (prescription, over-the-counter [OTC] medications, dietary/herbal supplements), and other potential confounders (e.g., smoking status, alcohol use, body mass index, disease severity marker, physical activity). Other requirements of

an ideal database are population-based, that all parts are easily linked by means of a patient's unique identifier, that the records are updated regularly, verifiable/traceable, and reliable.[78,89]

1.3.2 Field Study (or Ad Hoc Studies)

Epidemiologic studies in which data are collected in the field for the purpose of evaluating a specific hypothesis are known as "field" or "ad hoc" studies.[94] In contrast with studies using pre-existing data, field studies enroll the subjects and collect data (at least partially) to answer a specific research question. Several special types of ongoing field studies such as case-control surveillance, prescription event monitoring, and registries will be described in the next section.

The completeness of ascertainment of drug exposure varies across different study designs depending on how the participant is questioned and the specificity of the questions asked. In case-control studies, questions on medication use can range from open-ended (e.g., did you take any drugs in the last month?), to ask about the use of specific medications of interest by name, and to even showing the participants cards with specific drug names on them.[94] Mitchell et al. found that 0-45% of the use of a number of drugs was identified by asking an open-ended question, 35-81% by asking a structured list of selected indications, and 19-48% by asking a specific name.[95] A diary of life events is commonly used as a memory aid for obtaining drug exposure information. For obtaining recent medication use, requesting subjects to check the medication packages or using product photographs seems to be helpful.[96] However, case-controls studies may be more likely to have recall bias (e.g., cases are more likely to remember drug use than controls).

In cohort studies, a "brown bag" medication inventory through in-person interviews or phone surveys is used to collect actual medication use.[97,98] Typically, for prescription medications, interviewers will either read or ask the participant to read the name, strength, frequency of the medication and the direction for use of the labels from the original prescription bottle. Asking participants how many units or tablets/capsules they took over the previous day, week or month is helpful to assess consistency with the prescribed directions.[99] A similar technique is repeated for over-the-counter medications and dietary/herbal supplements, except that strength and directions for use are not usually queried because many of these drugs are taken as needed and having multiple ingredients. The correct coding and identification of dietary supplements can be difficult since many pharmacotherapy sources do not have complete information regarding these agents.[99] A common approach is for interviewers to ask the participants to identify the supplement's manufacturer so a further search may be conducted. Several studies show that the validity of self-reported medication use by older adults is reliable.[100-102] The recall accuracy for past medication use leads most surveys of older adults to limit the recall period to the recent past (e.g., 1-4 weeks).[99]

Compared to studies using information from pre-existing databases, the strengths of field studies include more rigorously defined outcomes (not only replying on diagnosis codes), increased feasibility of enrolling subjects with very rare conditions (unless using a large government databases or linking multiple databases for other sources), and increased feasibility of obtaining more comprehensive information (e.g., OTC drugs, herbals and other supplements, alcohol and tobacco consumption, and patient-reported quality of life).[94] The limitations of field studies include being time-consuming, relatively expensive, having logistical challenges in enrollment and data collections, and potential biases that can influence study validity. In

addition, many questions in pharmacoepidemiology are urgent in nature, especially if driven by regulatory concerns; thus, the long lead-time required to conduct field studies can be a significant barrier that must be balanced against the requirement for information that cannot be obtained by other approaches.[94]

1.3.3 Case-Control Surveillance, Prescription-Event Monitoring, and Registry

Case-Control Surveillance (CCS) was begun in 1976 and the data collection took place at collaborating hospitals in Boston, Baltimore, New York and Pennsylvania until 2009.[103] In CCS, multiple case-control studies are conducted simultaneously in order to monitor the effects of prescription and OTC medications and dietary/herbal supplements on the risk of various diseases, particularly cancers. CCS relies on self-report of regular or long-term medication and dietary supplement use (name, timing, frequency and duration) for 43 indications or medication categories (e.g., headache, cholesterol-lowering). CCS collects many factors that may confound or modify drug-disease association. The strengths of CCS include its large sample size and high statistical power, systematically assessing OTC medications and dietary/herbal supplements in addition to prescription medications, ability to assess the effect of drug use that occurred in the distant past or use with long duration of exposure, ability to control for potential confounders, and accurate outcome data (confirmed from the hospital discharge summary and pathology report). Several limitations of CCS include potential selection bias due to hospital-based case-control studies, difficulty in validating self-reported OTC medications and dietary/herbal supplement use, potential misclassification of drug use, and lack of dosage information.[32,103]

Since 1981, **Prescription-Event Monitoring (PEM, or yellow-card system)** systematically monitors the safety of targeted new medicines in cohorts of 10,000-15,000 patients in England. PEM is complementary to spontaneous reporting of suspected ADRs.[104] PEM selects new medicinal products which are expected to be widely used in general practice, or established products with a new indication or extending usage to a new population, and sends questionnaires to general practitioners to request information on specific medications use and medical events. PEM offers opportunities for better quantification of ADRs and identifies and characterizes some ADRs which were unrecognized during premarketing development and are not possible to quantify through spontaneous reporting.[104] The strengths of PEM include: (1) large sample size, (2) representativeness of patients treated in "real-world" clinical practices, (3) ability to examine adherence to prescribing guidelines and drug utilization and safety in special populations (e.g., children, elderly, pregnant women and with off-label use), (4) opportunities for following up subgroups of patients of interest and generating or strengthening signals of ADRs or diseases, (5) more accurate medication exposure data derived from dispensed prescriptions with validation from prescribers, and (6) complete collections of outcome events (regardless of recognized ADRs or unrecognized syndromes). Several limitations of PEM include: (1) absence of data on an unexposed comparator due to the single-group cohort design, (2) potential selection bias from preferential prescribing, (3) unpredicted patterns of adoption of a new drug, (4) non-response to questionnaires, (5) possible under-reporting of serious and fatal adverse event, and (6) misclassification bias depending on patients' adherence and the accuracy and thoroughness of the general practitioners in diagnosis. Furthermore, there is an inability to collect and control for all potential confounders, a restricted statistical power and sample size to detect very rare ADR, and an inability to study drugs used in the hospital.[104,105]

A **registry** is an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and serves a predetermined scientific, clinical or policy purpose.[106] Traditionally, registries were either population-based tools for monitoring public health interventions (e.g., records of receipt of childhood vaccines), collections of data on people with shared characteristics (e.g., disease registries, birth defects, HIV) or other systematic programs for case ascertainment and recruitment. Recently, registry methods extend to a variety of purposes such as patient support activities, evaluating safety and effectiveness of marketed products, health interventions, and characterizing clinical presentation and progression of diseases. The strengths of registries include: (1) the ability to simultaneously collect detailed information (e.g., clinical and medical data, paper/electronic health records, and administrative data), (2) flexibility to adapt over time to accommodate new research questions and purposes, (3) better at reflecting the safety and effectiveness of medical interventions in real-world practice than clinical trials, and (4) ability to follow patients over long periods of time. The limitations of registries include: (1) a lack of pre-specified hypotheses of registries that are designed provide an adaptive framework for evaluating new treatment, (2) having difficulties in explaining whether the observed effects are due to the intervention or are merely a characteristic of the type of people if lack of comparison groups, (3) selection bias if recruiting subjects non-randomly or preferentially, and (4) discouraging reporting rate if data collection systems are hard-to-use.[107] For example, the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute in the US provides statistics for monitoring of cancer disease burden since 1973, drawing on 18 cancer registries in 14 states that collectively represent 28% the US population.[108] In pharmacoepidemiology studies, with approval, researchers may be granted access to the

SEER-Medicare linked data files to obtain medication use information prior to, during, and following cancer diagnosis and treatment in the elderly.[109]

1.3.4 Summary

It is important to tailor the choice of pharmacoepidemiology data sources to the research question to be addressed. More than one data collection strategy or sources, in parallel or combination may be used. By considering the characteristics of pharmacoepidemiology resources available, as well as the characteristics of the research question to be addressed, choices of data resources that are best suited to addressing the question at hand can be made.

1.4 AVAILABLE DRUG CODING SCHEMES AND CLASSIFICATION SYSTEMS

Appropriate coding and classification of medications can make a major contribution to efficient data management and analyses. However, little is published reviewing and comparing different drug coding schemes and classification systems. In this section, major available drug coding schemes including the National Drug Code (NDC),[110] WHO Drug Dictionary (WHO-DD),[111] Iowa Drug Information System (IDIS)[112], the Slone Drug Dictionary,[113,114] Medi-Span®, Lexi-Data™ (or Cerner Multum's Lexicon),[90] First DataBank,[115] Veteran Health Administration (VA) National Drug File Reference Terminology (NDF-RT) and RxNorm/RxNav[116] will be described. **Table 4** summarizes the characteristics of each coding scheme and its classification system. These drug coding schemes integrated with the classification systems facilitate the identification and grouping of agents with similar pharmacologic properties and therapeutic uses. Two systems, the Anatomical Therapeutic Chemical (ATC) Classification System and American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification®, are commonly used in pharmacoepidemiologic studies. While no single classification system is comprehensive for all medications, both are well suited for coding most drugs used in Europe and the U.S, respectively and are proven practical useful.[112]

Table 4. Overview of Available Drug Coding Schemes

Coding Schemes (Abbreviations)	Characteristics	Coding Example (Simvastatin)	Example(s) Using the Coding Scheme
National Drug Code (NDC)[110]	• Maintain by the U.S Food and Drug Administration • Designed for inventory management and reimbursement • 10 digits (3 segment code):distributor/manufacturer/re-packager, product, and package size • Do not provide unique codes for drug ingredients	0006-0740-31 Manufacturer: Merck, Sharp & Dohme; Product: Zocor® 20mg/tablet; Package size: 30 tablets/bottle	Community and nursing home pharmacies
WHO Drug Dictionary (WHO-DD)[111]	• ATC classification system conjunction with the DDD method • ATC system: 5 hierarchical levels: a main anatomical group; 2 therapeutic subgroups, a chemical –therapeutic subgroup, and a chemical substance subgroup • Contains primarily European drug names and their ingredients • Contains an herbal dictionary based on the Herbal ATC system • Yearly updated	C10AA01 C: cardiovascular system; C10: Lipid modifying agents; C10A: Lipid modifying agents, plain; C10AA: HMG CoA reductase inhibitors	Italian group of pharmacosurveillance in the elderly study (Gruppo Italiano di Farmacovigilanza nell' Anziano GIFA) study[112]
Iowa Drug Information System (IDIS)[112]	• Modified version of AHFS Pharmacologic Therapeutic Classification • 4 hierarchical levels: 3 levels of therapeutic categories and one level of chemical ingredient category • Mostly US prescription drug names linked to their therapeutic class	24060205 24: Cardiovascular agents 2406: Antilipemic agents 240602: Antilipemic agents-HMG-CoA reducatase Inhibitors	Health ABC,[117] EPESE[112]
Slone Drug Dictionary[114]	• Use AHFS Pharmacologic Therapeutic Classification • Contains US and non-US drugs, and supplements and other non-prescription products • Multi-component products are cross-linked with their individual ingredients • Have "Coalitions", epidemiologist-defined groups	560622: Simvastatin, single component drug, under AHFS classification code 24:06:08:00 (cardiovascular/antilipemic/HMG-CoA reductase inhibitors), under coalition 790106 (HMG-CoA reductase inhibitors)	Studies using data from Slone Survey[96,118]
Medispan®[119]	• Use the Generic Product Identifier (GPI) system • Modified AHFS Pharmacologic Therapeutic Classification • Includes drug information, clinical decision support and disease suite modules, and application programming surface • Includes NDC, Universal product codes • Cross reference to RxNorm, uniform system of classification	GPI (14 digits): 394000750003XX 39 (drug group): cardiovascular agents; 3940 (drug class): HMG-CoA reductase inhibitors; 394000 (drug subclass): none; 39400075 (drug name): simvastatin; 3940007500 (drug name extension): none; 394000750003 (dosage form): Tablet 39400075000330 (strength): 20 mg	CHS[98]

Table 4 (Continued)

Coding Schemes (Abbreviations)	Characteristics	Coding Example (Simvastatin)	Example(s) Using the Coding Scheme
Lexi-Data™ (or Multum®)[120]	• Use Multum's Therapeutic Categorizations that are organized into a 3-level hierarchy permitting classification at the therapeutic, pharmacological and drug category levels. • Modified AHFS Pharmacologic Therapeutic Classification • Monthly update the new drug availability and other drug information from FDA and pharmaceutical manufacturer announcements and publications to research findings • Can cross-link to NDC and therapeutic drug classes	• Simvastatin 20mg oral table: Multum Mediasource Lexicon (MMSL) numeric code: 3083; or MMSL with term type: CD3083, CD indicates as clinical drug; • Linked to 3-levels: level 1=358 (metabolic agents), level 2=019 (anti-hyperlipidemic agents), level 3=173 (HMG-CoA reductase inhibitors)	NHANES,[121] MEPS,[122,123] NSHAP[120], NAMCS and NHAMCS[124]
First DataBank (FDB)[115]	• Use FDB Enhanced Therapeutic Classification system, an 8-character numeric identifier (ETC_ID) • Aggregates drug information on indications, drug-disease contraindications, side effects, drug/drug and drug/food interaction, allergy	ETC_ID level 1: cardiovascular therapy agents: 00002553 (or 2553), ETC_ID level 2: antihyperlipidemic agents: 00000263 (or 263), and ETC_ID level 3: HMG-CoA reductase inhibitors: 00002747 (or 2747).	A data book of Medicare Part D Program from the MedPAC [125]
Veterans Health Administration (VA) National Drug File-Reference Terminology (NDF-RT)[126]	• Non-proprietary drug terminology system • NDF-RT includes drug knowledge (e.g., disease-based interactions) and classifies drugs, most notably by mechanism of action, physiologic effect, and therapeutic categories • Use five-character alpha-numeric codes for classify a drug	Simvastatin under drug class CV350 CV350: Antilipemic drugs; CV: Cardiovascular medication	Studies using VA medication data
RxNorm/ RxNav[116]	• Non-proprietary drug terminology system • NLM repository of standard names (active ingredient, strength, dose form) for clinical drugs and assign a concept unique identifier (CUI) • Generic and branded normalized forms are related to each other and to the names of their individual components by a well-defined set of named relationships • Link to First DataBank National Drug Data File Plus, Micromedex, Medi-Span®, Gold Standard, Multum, and VA NDF-RT • Does not include drug knowledge	Simvastatin 20 mg oral tablet [Zocor®] RXCUI: 104491	TEDDY[127]

Abbreviations: **AHFS:** American Hospital Formulary Service; ATC: Anatomic Therapeutic Chemical; **CHS:** Cardiovascular Health Study; **DDD**: defined daily dose; **EPESE:** Epidemiologic Studies of the Elderly survey; **Health ABC:** Healthy Aging and Body Composition Study; **MedPAC**: Medicare Payment Advisory Commission; **MEPS:** Medical Expenditure Panel Survey; **NAMCS:** National Ambulatory Medical Care Survey; **NHAMCS**: National Hospital Ambulatory Medical Care Survey; **NHANES:** National Health and Nutrition Examination Survey; **NLM:** National Library of Medicine; **NSHAP:** National Social Life, Health and Aging Project; **TEDDY:** The Environmental Determinants of Type 1 Diabetes in the Young; **WHO:** World Health Organization

1.4.1 National Drug Code (NDC) in the US

Most pharmacies in the U.S use computer systems that automatically convert alphabetically entered drug product names into corresponding NDC numbers. The NDC was designed for inventory management and reimbursement. The NDC is 10-digit-code consisting of three parts delimited by dashes: a manufacturer code, a product code and a package size code (e.g., 0006-0740-31: Merck Sharp & Dohme, Zocor® 20mg/tablet, 30 tablets/bottle).[110] It does not provide unique codes for drug ingredients. For example, any one drug product (e.g., simvastatin 20 mg tablet) can be represented by numerous codes since there may be various manufacturers (brand and generic) and package sizes (e.g., 100-count bottles, unit-dose packages). To avoid problems associated with numerous NDC codes for each drug, other drug coding schemes with hierarchical levels (e.g., WHO-DD or IDIS) can be combined with NDC codes to facilitate analytical process.

1.4.2 The Anatomical Therapeutic Chemical (ATC) Classification System and WHO Drug Dictionary (WHO-DD)

The WHO-DD includes drug names linked to the ATC Classification System, which is generally used in conjunction with the defined daily dose (DDD) method to standardize doses.[128] The WHO-DD contains primarily European drug names and their ingredients, and an herbal dictionary based on the Herbal ATC system (HATC) as well.[129] This is a five-level hierarchical system including a main anatomical group, two therapeutic subgroups, a chemical/therapeutic

subgroup, and a chemical ingredient (e.g., simvastatin: C10AA01). Products are classified according to the main therapeutic indication for the principal active ingredient. Most products are assigned only one ATC code. However, some active ingredients may have more than one ATC code, if the drug has different uses at different strengths (e.g., aspirin as a platelet aggregation inhibitor and as an analgesic–antipyretic), dosage forms (e.g., timolol to treat hypertension and to treat glaucoma) or both (e.g., medroxyprogesterone for cancer therapy and as a sex hormone).[130] Prednisolone is an example of a drug that has six different codes. Fixed dose combination products pose classification difficulties. For example, a combination product that contains and analgesic and a tranquilizer is classified as an analgesic, even though it also contains a psychotropic substance.[130] In addition, the ATC does not distinguish chemicals by dose-form or strength and assigns classes based on main therapeutic indication, so less common uses may be omitted.[131]

1.4.3 The American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification® and Related Coding Schemes

The AHFS Pharmacologic-Therapeutic Classification® was developed and is maintained by the American Society of Health-System Pharmacists (ASHP). The AHFS Pharmacologic-Therapeutic classification® allows the grouping of drugs with similar pharmacologic, therapeutic, and/or chemical characteristics in a 4-tier hierarchy. There are 31 classifications in the first tier, 185 in the second tier, 256 in the third tier, and 94 in the fourth tier.[132] For example, the AHFS classification number for aspirin is 28:08.08.24 (Central Nervous System Agents: 28:00; Analgesics and Antipyretics: 28:08; Nonsteroidal Anti-inflammatory Agents: 28:08.04;

Salicylates: 28:08.04.24).[133] A drug may have multiple classes (due to its indication, mechanism of action, or route of administration) and all classes for a drug are considered equally valid. For example, labetalol has AHFS classification numbers: 24:24 (β-Adrenergic Blocking Agents), 24:04.04.16 (Class II Antiarrhythmics), 24:08.04 (α-Adrenergic Blocking Agents), and 24:08.08 (β-Adrenergic Blocking Agents). In addition, combination products inherit all of the classifications of the individual active ingredients since the AHFS classification is assigned to the active ingredient.[132] In the next few paragraphs, coding schemes based on the modifications of AHFS Pharmacologic-Therapeutic Classification® will be briefly described.

The IDIS scheme represents a modification of the AHFS Pharmacologic Therapeutic Classification.[133] The IDIS scheme includes most of the US prescription drug names linked to their therapeutic class. The IDIS code has eight numeric digits, two digits per level. The first six digits of the drug code identify the hierarchical therapeutic class to which the drug term was assigned (e.g., simvastatin: 24060205).[112] The seventh and eighth digits are assigned by the IDIS and had no hierarchical meaning. The main difference between WHO-DD and IDIS scheme is that WHO-DD has specific codes for combinations of ingredients, while IDIS codes each ingredient separately.[112] The advantage of IDIS over the NDC and other coding systems is that it provides codes for OTC medications and dietary supplements.

The Slone dictionary developed and maintained by the Slone Epidemiology Center, is a computerized linkage system composed of single medication components and multi-component products. The Slone dictionary contains US and non-US prescription drugs, and in addition it includes OTC products, vitamins and dietary supplements.[113,134] Each product is assigned a unique number and links to its active ingredients; each active ingredient is classified by AHFS Pharmacologic Therapeutic Classification; the Dictionary includes “coalitions”, which are

epidemiologist-defined groupings of drugs and drug products that can be used in various analyses.[113] The Slone Survey was used in many pharmacoepidemiologic studies and the Slone Epidemiology Data Center published three annual reports (2004-2006) on medication use in the U.S.[135]

Other drug coding schemes use principles similar to those of AHFS and ATC classification systems and provide tables for mapping NDCs to their clinical drug codes, which offers increased flexibility or specificity for an individual drug product. These commercial coding schemes usually integrate with drug information or knowledge databases (e.g., pricing, adverse effects, dosing, and cross-references to NDC, RxNorm or other coding systems or schemes), clinical decision support and disease suite modules and other applications or programs. Other systems used in commercial drug coding schemes such as the Generic Product Identifier (GPI) system from Medi-Span® (Wolters-Kluwer Health, Inc., Conshohocken, PA),[119] Multum's Therapeutic Categorization in the Lexi-Data™ (Cerner Multum, Inc. Denver, CO),[90] and First DataBank Enhanced Therapeutic Classification™ System (First DataBank, Inc., San Bruno, CA)®.[115]

Medi-Span® incorporates the AHFS Pharmacologic-Therapeutic System and groups drugs with comparable compounds in the same therapeutic class through the GPI. [119] The GPI, a hierarchical classification scheme, is a 14-digit field consisting of seven subsets, each providing increasingly more specific information about the drug (i.e., drug group, class, sub-class, name, name extension, dosage form, and strength). [136] For example, the GPI for simvastatin tablet 20 mg is 39400075000330 (39: cardiovascular agents; 3940: HMG-CoA reductase inhibitors; 394000: no sub class; 39400075: simvastatin; 3940007503: tablet (PO); 394000750330: 20 mg). Products having the same 14-digit GPI are identical with respect to active ingredient(s), dosage

form, route of administration and strength or concentration.[136] The same drug may be classified in multiple therapeutic classes.

Lexi-Data™ incorporates four distinct therapeutic/chemical classification systems including Multum's Therapeutic Categorization, Lexi-Comp's Pharmacologic Category, Therapeutic Duplication Categorization, and Allergic Cross-Reactivity Categorization, to support different types of use.[137] In general, Multum's therapeutic categorizations are based on the AHFS therapeutic categories and are organized into a 3-level hierarchy permitting classification at the therapeutic level, pharmacological level and drug category level.[120] For example, for simvastatin: the broadest category is metabolic agents [level 1=358]; the more detailed category is antihyperlipidemic agents [level 2=019]; and the most detailed category is HMG-CoA reductase inhibitors [level 3=713]). Not all drugs have three classification levels; some may only have two [e.g. for digoxin: cardiovascular agents [level 1]; inotropic agents [level 2]), others only have one.[124] Beginning with 2006, multiple-ingredient drugs are assigned a single generic drug code encompassing all of a drug's ingredients, rather than being assigned generic drug codes for each ingredient.[124]

The First DataBank Enhanced Therapeutic Classification System is an advanced drug classification system with virtually unlimited levels of specificity, for easy formulary maintenance and drug selection. It allows drugs to reside in multiple therapeutic classes, with links to drug concepts at any level of the hierarchy.[115] The First DataBank Enhanced Therapeutic Classification identifier (ETC_ID) is an eight-character numeric column that identifies a unique therapeutic classification. This number is a stable identifier permanently associated with the ETC description. For example, simvastatin has three levels of ETC_ID: ETC_ID level 1: cardiovascular therapy: 00002553 (or 2553), ETC_ID level 2:

antihyperlipidemic agents: 00000263 (or 263), and ETC_ID level 3: HMG-CoA reductase inhibitors: 00002747 (or 2747).[115] In addition, multi-ingredient formulations are represented with a single class description (for example, ACE inhibitor and calcium channel blocker combination).

1.4.4 US National Drug File Reference Terminology (NDF-RT) and Veterans Health Administration (VA) Drug Class Index

The VA NDF-RT is a non-proprietary drug reference terminology that includes drug knowledge and classifies drugs, most notably by mechanism of action, physiologic effect and therapeutic category.[126] The VA drug classes (approximately 400) are similar to the categories and classes in the other classification systems. NDF-RT along with RxNorm (see the section 1.4.5) has been accepted by a federal standards-setting body, as recommended standards. The VA drug classification system uses five-character alpha-numeric code specifies a broad classification and a specific type of product. The first two characters are letters and form the mnemonic for the major classification. Character 3 through 5 are numbers and form the basis for sub-classificaiton. For example, simvastatin is assigned to CV350 (CV: cardiovascular agents, CV350: Antilipemic drugs). NDF-RT supports multiple indications and can identify specific characteristics of each drug, which is a crucial capability of a classification system. The NDF-RT contains a novel reference hierarchy to describe physiologic effects of drugs.[126] The physiologic effects reference hierarchy contains 1699 concepts arranged into two broad categories organ specific and generalized systemic effects.[126]

1.4.5 RxNorm by US National Library of Medicine (NLM)

The lack of interoperability of among the terminologies used in the commercial coding schemes was the primary motivation for the US National Library of Medician (NLM) to develop a public-use coding scheme, RxNorm.[116] RxNorm contains the names of prescription and many OTC formulations that exist in the United States. A drug is assigned to a concept unique identifier (CUI). Drugs whose names map to the same CUI are taken to be the same drug (i.e., identical as to active ingredient, strength and dosage form). For example, the CUI for Simvastatin 20 mg oral tablet [Zocor®] is 104491. RxNorm also provides normalized names for clinical drugs and links drug names to other drug coding schemes including National Drug Data File Plus, Micromedex, Medi-Span®, Gold Standard, and Multum. RxNorm also includes the NDF-RT from the VA. The goal of the RxNorm is to allow various systems using different drug nomenclatures to share data efficiently at the appropriate level of abstraction. The RxNorm Navigator (RxNav) allows you to query the RxNorm database by any of its components.[138]

1.4.6 Summary

The coding system to be utilized depends on the objective of the study. Analyses of focusing on beneficial or adverse effects of medications must consider drug ingredient. Therefore, the coding system must allow for easy identification of the ingredients or combinations of ingredients contained in the drug products.[112] Drug coding schemes with hierarchical codes for drug ingredients also make analysis easier and save time on programming. In other potential studies involving the costs of drugs, it is essential to identify with a unique code the

manufacturer and the dosage form of each single drug product. However, various drug coding schemes, while working well on their own, present a barrier when medical information systems containing these varying names and codes need to be cross-linked or reconciled.[139] An international standardized nomenclature of drug names, codes and classification system will be an ultimate solution to conducting global pharmacoepidemiologic studies and exchanging and comparing health information and research outcome in public health.

1.5 BIAS AND CONFOUNDING IN PHARMACOEPIDEMIOLOGY

In order to obtain accurate and valid results derived from observational studies in pharmacoepidemiology, several factors that must be considered including appropriate study designs, inclusion/exclusion criteria, drug exposure and outcome measurements, the changing phenomenon of drug exposure, potential biases, confounding factors (e.g., indications for prescribing), medical adherence, and the natural course of the disease.[140,141] In this section, the importance of biases, sources of confounding and available solutions specifically for pharmacoepidemiologic studies will be discussed and summarized in **Table 5**.

1.5.1 Bias and Available Solutions

In general, common threats to internal validity in pharmacoepidmeiology include selection bias and information or misclassification bias. Bias must be prevented through attention to the proper design and conduct of a study and cannot be routinely addressed at the analysis stage.[142] Conceptually, bias can be introduced by factors related to who is included in the study (selection bias), and errors of assessment and measurement (differential misclassification bias).

Table 5. Common Biases and Potential Solutions in Pharmacoepidemiology

Bias	Definition/Characteristics	Example	Potential Solutions
Selection Bias (the selection into the study groups of subjects who differ in characteristics from those in the target population)			
Referral	• Occurs when drug exposure is associated with the likelihood of referral into the institution where the study takes place (e.g., hospitals) • Typically in hospital-based case-control studies • Frequently when a known/suspected association of the drug with the outcome • Usually occurs when an outcome presents in a manner such that an accurate diagnosis is not always obtained immediately • From a perspective of medical surveillance, referral bias can be regarded as a type of detection bias	• Patients taking NSAIDs and presenting with mild abdominal pain may be more likely to be suspected as having a gastric ulcer and sent for further tests than patients with similar pain but without taking (results would be biased upward) • Women exposed to oral contraceptives may be more likely to be subjected to diagnostic tests for deep venous thrombosis compared to women not exposed	• Restrict the participants to more serious cases of the disease • Identify cases and controls from the same screening program
Self-selection	• When study participants themselves decide to participate or leave a study based on drug exposure or change in health status • Those who did not join the study might belong to a special disease-exposure category • Particularly in case-control and retrospective cohort studies	• Mothers of children with birth defects who also have something to report (e.g., medications) may be more likely to participate (biased towards an increased risk)	• Systematically identify and recruit all eligible cases (e.g., select from population-based registries and prescription drug databases)
Prevalence	• When prevalent cases rather than new (incident) cases are selected, usually in case-control studies • Patients who stay on treatment for a longer time may be less susceptible to the event of interest • Reflect an association with a prognostic factor rather than with incidence	• Observational studies "failed" to show initial harmful effect of hormone replacement therapy (biased towards null) due to combination of prevalent users who tolerate therapy (survivor cohort effect)	• Limit study recruitment incident cases with a clearly documented calendar time of diagnosis
Protopathic	• Occur when the initiation, discontinuation, or modification of a drug occurs in response to a symptom of the outcome (at this point undiagnosed) • Reflect a reversal association between outcome and drug exposure • Usually in retrospective studies	• Estrogen was prescribed for uterine bleeding (before the diagnosis of endometrial cancer). This biased the result to increased risk of endometrial cancer with estrogen use.	• Have a full-understanding of the pathophysiologic mechanism of disease development • Using "lag-time" (or an index date) to define drug exposure periods

Table 5 (Continued)

Bias	Definition/Characteristics	Example	Potential Solutions
Misclassification Bias (An error occurs when each time participants in a study are classified with regard to their drug exposure and disease status)			
Recall	• A differential misclassification bias • Systematic differences in how exposure groups or disease groups remember certain information • More likely happen in retrospective studies, particularly case-control studies	• Mothers with children having birth defects may give more valid and complete report of their drug exposures during the pregnancy	• Select controls who are likely to have the same cognitive processes affecting memory of past drug exposures (e.g., alternative birth defects)
Detection	• A differential misclassification bias • Can affect either cohort or case-control studies • Occurs when a presumably drug exposure leads to a closer surveillance that may result in a higher probability of detection of subclinical outcomes in exposed individuals • In case-control studies, if cases are more likely to be identified (or selected into the study) due to the exposure to a drug, detection bias can be regarded as a type of selection bias (i.e., referral bias)	• In a cohort study, women taking postmenopausal hormonal supplements are more likely to see their doctors and be detected cancer at early stages than other women. This differential follow-up may lead to an excess number of diagnosed diseases in the treated group and falsely elevated risk, or to more complete preventive care leading to decreased risk. • In case-control studies, it occurs when the procedures for obtaining drug exposures are not similar in cases and controls (e.g., drug assessment is more thorough among cases)	• Blinding of relevant study personnel • Standardization of the measurement process (e.g., specific training of interviewers) • For the analytic purpose to detect the possibility of detection bias, information should be obtained on the frequency of access to medical care and health awareness by participants. Stratification by disease severity helps too.
Immortal-time	• A differential misclassification bias • The exposed subjects will have a major survival advantage over their exposed counterparts because they are guaranteed to survive or to be event-free at least until their drug was dispensed. • Results of improper exposure definitions and analyses that cause serious misclassification • More likely to occur in cohort studies	• Definition of exposed to inhaled corticosteroid: subjects who received their first prescription for an inhaled corticosteroid 90 days after cohort entry (90 days immortal time period)	• Time-dependent methods for analyzing risks may be used to account for complex changes in drug exposure and confounders over time (e.g., Cox proportional hazard models with time-dependent exposures) • Nested case-control design • Active comparative groups

Abbreviations: **NSAIDs**: non-steroidal anti-inflammatory drugs

1.5.1.1 Selection Bias

Selection bias is a distortion of an estimated effect due to the selection into the study groups of subjects who differ in characteristics from those in the target population.[141] In pharmacoepidemiology, four types of selection bias seem particularly important: referral bias, self-selection bias, prevalence study bias and protopathic bias.[140]

Referral bias (**or referral filter bias or Berkson's bias or admission rate bias**) can occur when drug exposure is associated with the likelihood of referral into the institution where the study takes place (often a hospital).[143] Referral bias typically occurs in hospital-based case-control studies and leads to a higher exposure rate among the hospital cases than the hospital controls.[144,145] This is frequently in the case when there is already a known or suspected association of the drug with the outcome of interest, so referral to an institution where the diagnosis is made is more likely for patients taking this drug.[143] In addition, it usually occurs when an illness or outcome presents in a manner such that an accurate diagnosis is not always obtained immediately.[140] From a perspective of medical surveillance, referral bias can be regarded as a type of detection bias.[144] An example of referral bias is a study of gastric ulcer in which cases and controls are identified in the same referral hospital. Because a patient taking a non-steroidal anti-inflammatory drug (NSAID) and presenting with mild abdominal pain may be more likely to be suspected as having a gastric ulcer and sent for further tests than a patient with similar pain but who is not taking a NSAID. This may bias the results towards increased risk between NSAIDs use and mild non-bleeding gastric ulcer. Another example, knowledge of a well-established association between deep venous thrombosis (DVT) and oral contraceptives may make women exposed to oral contraceptives more likely to be subjected to diagnostic tests

for DVT compared to women not exposed. A general solution for addressing referral bias is to restrict the study participants to more serious cases of the disease. The reason for this is that it can be expected that for most diseases, regardless of previous drug exposure, all serious cases will eventually be diagnosed correctly.[140] Identifying cases and controls from the same screening program can be another solution.[144]

Self-selection bias may occur when study participants themselves decide to participate or leave a study based on both drug exposure and change in health status.[140] Self-selection bias may particularly occur in case-control or retrospective cohort studies because both outcome and exposure are already manifested when study subjects are recruited. For example, mothers of children with birth defects who also have something to report (e.g., medications) may be more (or less) likely to participate. Also, those who are lost to follow-up in cohort studies might belong to a special disease-exposure category. This can be controlled for by systematically identifying and recruiting all eligible cases. Relying on population-based registries for case and prescription drug ascertainment is an excellent way to minimize the occurrence of selection bias.[140]

Prevalence bias may occur when prevalent cases rather than new (incident) cases are selected for a study, which may occur in case-control studies. An association between drug use and prevalent cases could thus reflect an association with a prognostic factor rather than with incidence. In addition, patients who stay on treatment for a longer time (i.e., prevalent to drug exposure) may be less susceptible to the event of interest. Limiting study recruitment to newly diagnosed or incident cases with a clearly documented calendar time of diagnosis favors the ascertainment of drug exposures that are relevant to disease incidence.[140]

Protopathic bias (or reverse causality bias) occurs when the initiation, discontinuation, or modification of a drug occurs in response to a symptom of the outcome (at this point undiagnosed).[143] Protopathic bias reflects a reversal association between outcome and drug exposure. It may particularly occur in case-control studies. For example, analgesics were used in response to the pain caused by an undiagnosed tumor.[146] Another example is that patients could stop taking aspirin because of the presence of bloody stools. If the presence of blood was the first expression of colon cancer, we would subsequently find a negative association between current aspirin use and colon cancer. This scenario may particularly occur in pharmacoepidemiology because diseases are often identified after their first clinical expression and because exposure to drugs may change from day to day, frequently with changes in actual or perceived health status. Therefore, it is critically important to have a full-understanding of the pathophysiologic mechanism of disease development when designing pharmacoepidemiology studies.[140] A general solution to prevent protopathic bias is the use of "lag-time" (or an index date) to define drug exposure periods. Using this approach, a specific time period before the date of diagnosis with the disease under study would be excluded from the exposure assessment. Tamim et al showed that the ORs stabilized at lag-time around 6 months using two methods.[147]

The goal to prevent selection bias is to recruit a study population that accurately represents the target population concerning the drug exposure and outcome association. Remedial strategies include random sampling from the source population, systematically recruiting a series of consecutive subjects, implementing a tracking procedure for those who drop out (e.g., document the reason and their health status), restricting to incident cases, and minimizing the number of lost to follow-up (e.g., select adherent patients).

1.5.1.2 Misclassification Bias

Misclassification bias refers to the possibility of error when participants are classified with regard to their drug exposure and disease status. There are two types of misclassification bias: **non-differential (or random) misclassification** and **differential misclassification (also called information bias).** Non-differential misclassification occurs when the degree of misclassification is random or similar for all patients and independent of both drug exposure and outcome status. It usually biases the results toward the null value, but may reverse the measure of effect in some extreme circumstances. Differential or systematic misclassification can occur when misclassification is related to drug exposure-outcome association. Differential misclassification can bias results toward or away from the null hypothesis based on the situations.[141] In pharmacoepidemiology, common differential misclassification biases include **recall bias, detection bias, and immortal time bias.**

Recall bias occurs if individual's memories of exposure or outcome systematically differ based on exposure or outcome status.[142] It is more likely to happen in retrospective studies, particularly case-control studies. For example, mothers with children having birth defects may give more valid and complete report of their drug exposures during the pregnancy compared to mothers with children without birth defects. In order to minimize this type bias, it is important to select controls who are likely to have the same cognitive processes affecting memory of past drug exposures (e.g., alternative birth defects). [140]

Detection bias (or medical surveillance bias) can occur in cohort studies or case-control studies. It occurs when a presumably drug exposure leads to a closer surveillance that may result in a higher probability of detection of subclinical outcomes in exposed individuals (i.e., when identification of the outcome is not independent of the knowledge of exposure).[144,148] In cohort

studies, it is particularly likely when an exposure of a drug or therapy leads to frequent and thorough checkups, and the outcome is a disease that characterized by a high proportion of subclinical cases.[141] For example, women taking postmenopausal hormonal supplements are more likely to see their doctors and be detected cancer at early stages than other women. This differential follow-up may lead to an excess number of diagnosed diseases in the treated group and falsely elevated risk, or to more complete preventive care leading to decreased risk.[140] In case-control studies, it occurs when the procedures for obtaining drug exposures are not similar in cases and controls (e.g., drug assessment is more thorough among cases). If cases are more likely to be identified (or selected into the study) due to the exposure to a drug, detection bias can be regarded as a type of selection bias (i.e., referral bias, see more details in the previous discussion of referral bias).[144] The potential solutions include blinding of relevant study personnel and systematic standardization of the measurement process (e.g., specific training of interviewers).[140] If these strategies are not feasible (especially in case-control studies), to examine the occurrence of this bias in the analysis stage, information should be obtained on the frequency and quality of medical care received by the study participants, and variables that indicate awareness of health problems.[144] Finally, when detection bias occurs, the proportion of less advanced disease in a cohort study is higher in the exposed group. In a case-control study, the association is found to be stronger or present for less advanced cases. Therefore, stratification by disease severity at diagnosis is an additional strategy to examine and take into consideration the possibility of detection bias.[144]

In addition, **immortal time bias (or immortal person-time)** is increasingly common in cohort studies of drug effects because drug exposure often changes over time (i.e., time-varying). Immortal time usually arises when the determination of an individual's treatment status involves

a delay or wait period during which follow-up time is accrued. This wait period is considered immortal because individuals who end up in the treated group have to survive until treatment definition is fulfilled.[149] It is particularly problematic because it necessarily biases the results in favor of the treatment under study by defining an artificial survival advantage to the treatment group. Several criteria can be used to identify immortal time bias: (1) Was treatment status determined after the start of follow up or defined using follow-up time? (2) Was the start of follow-up different for the treated and untreated group relative to the date of diagnosis? (3) Were the treatment groups identified hierarchically (one before the other)? (4) Were subjects excluded on the basis of treatment identified during follow-up? (5) Was a time fixed analysis used?[149] For example, Sin et al. suggested inhaled corticosteroids given after hospital discharge were associated with a 29% reduction in the rate of all-cause mortality among elderly patients hospitalized for chronic obstructive pulmonary disease.[150] The results may be biased due to the immortal time bias. The exposed subjects who received their first prescription for an inhaled corticosteroid 80 days after cohort entry had to be alive on day 90. Thus, the drug exposed subjects will have a major survival advantage over their exposed counterparts because they are guaranteed to survive or to be event-free (e.g., immortal time period: 90 days) at least until their drug was dispensed. Time-dependent methods (e.g., Cox proportional hazard models with time-dependent exposures) or nested case-control designs are recommended to use to account for complex changes in drug exposure and confounders over time.[51,151]

1.5.2 Confounding

The biggest challenge in pharmacoepidemiology is to identify the appropriate designs, measures, and analytic techniques to avoid or control confounding. Confounding occurs when the estimates of a measure of association between drug exposure and the outcome(s) of interest is masked by the effect of one or several extraneous variables that are also associated with drug exposure and the outcome of interest (but not part of the causal pathway).[140,152] Failing to control for confounders can lead to spurious results.

Confounding by indication is probably the most important and challenging confounder in pharmacoepidemiology. It is also widely referred to as **indication bias, channeling, confounding by severity, or contraindication bias**.[60,140,153] In general, confounding by indication occurs when an observed association between a drug and an outcome is due to the underlying diagnosis or other clinical features and not to any effect of the drug. Confounding by indication describes the various factors related to an individual's condition that determine the initiation and choice of a specific drug (e.g., statins for patients with high cholesterol), and thus comparisons of drug users to nonusers usually have to be made for patients sharing similar indications or conditions, as the condition itself is commonly one of the most important risk factors for the outcome of interest.[143,154] The term broadly covers the more subtle considerations affecting the choice of a specific drug among patients with similar indications (sometimes referred to as channeling), relating to disease severity (confounding by severity), comorbid conditions, contraindications, patient demographics, the drug's adverse-effect profile, and subjective impressions of the prescribing physician.[143] For example, Laporte et al. reported that

upper gastrointestinal (GI) bleeding was associated with the use of selective COX-2 inhibitors.[155] These results were confounded by the fact that the patients who were treated with COX-2 inhibitors were at higher risk of developing a GI hemorrhage independent of the COX-2 inhibitor use. A possible solution in this scenario would be to select patients without any history of GI bleeding and new users of NSAIDs.

However, Salas et al. suggested applying the term "confounding by severity" specifically to the situation in which the severity of disease acts a confounder.[156] Confounding by severity should be considered a special form of confounding by indication, in which not only the disease that forms the indication but also its severity (and complications) is a potential confounder. If one controls for the disease (or indication) but not for its severity, the possibility of residual confounding remains. Moreover, in the product information of registered medicines, the indications for treatment pertain to diagnoses itself rather than to the severity of the manifestation of their clinical patterns. Thus, when drug treatments are compared, controlling for these indications does not preclude confounding by severity.[156] In patients with type 2 diabetes, for instance, oral hypoglycemic agents are used early in the course of the disease, and insulin is reserved for patients who have more severe disease or who have not responded to oral agents. Because treatment type is correlated with disease severity and duration, it is difficult to design a convincing observational study that compares oral agents with insulin for outcomes that are related to disease duration or severity. Confounding by severity in observational studies usually makes the therapy appears to be less effective it appeared in the experimental studies (RCT can balance the severity distribution of the compared group).[157] However, confounding by severity can be useful for other purposes. For example, although a positive association between

β-agonists and asthma death was suspected to be confounded by disease severity, it can be informative because the amount of β-agonist used can be a proxy of prognosis.[158]

Confounding by indication usually is not a problem or concern when a study is focusing on unexpected drug effects or side effects (because the indication is usually not related to the outcome), or the decision about whether to treat is not based on a formal indication (usually in primary prevention such as routine measles vaccination in healthy infants).[154] Ideally, under the assumption of the choice between alternative treatments is effectively random, confounding by indication may seem less of a problem when doing comparisons among multiple alternative treatments. In practice, it is challenging to control for confounding by indication because "indication" is a complex and multi-factorial phenomenon involving the physician's knowledge, the longitudinal nature of disease and other factors which may not be entirely evident and which may act in different directions.[140] If confounding by indication cannot be ruled out, RCTs are preferred over non-experimental studies. If RCTs cannot be used, non-experimental study designs can be used to qualitatively demonstrate some degree of beneficial effect. Specifically, if confounding by indication is such that treated patients would have a worse clinical outcome than untreated patients, yet the outcome observed in treated patients is better than that observed in untreated patients, some degree of confidence that the drug has a beneficial effect can be built.[154] Moreover, some potential solutions to prevent or control confounding by indication should be considered (see section 1.5.3 for potential solutions) in non-experimental studies.

Moreover, when **effect modification (or interaction)** exists, the stratum-specific effect provides more information than the overall adjusted results. Effect modification indicates a variation in the drug effect, according to different levels of a third variable. Consequences of this may lead to changes in prescribing practice or a better understanding of mechanisms.[140] For

example, different dosage and potency are likely to have different effects that should be presented in the analysis. Reducing the information related to drug exposure into an exposed versus non-exposed group increases the possibility of misclassification, biasing the results towards the null. It is important in pharmacoepidemiology to consider differences in drug dose and potency in studying drug effects.

1.5.3 Available Solutions to the Confounding

The solutions available to minimize confounding in pharmacoepidemiologic can be broadly categorized into: (1) approaches that collect more information on potential confounders and apply efficient sampling designs to reduce the time and resources it takes to complete the study, and (2) analytic approaches that try to make better use of the existing data with the goal of improved control of confounding.[49] Strategies to adjust confounding (at the design and/or analysis levels) in non-experimental studies vary depending on several aspects, especially on whether the potential confounders can be measured in a given study.[158] At the design stage, matching and restriction can be used to control for measured confounders, and crossover design and active comparative group can be used to control for unmeasured confounders. Several "analytic" methods can be used to overcome the confounding including standardization, stratification, multivariate analysis, propensity scores, marginal structural models, two-stage sampling, external adjustment, sensitivity analysis, and instrumental variable approach.[159] Each of them will be described briefly and subsequently.

1.5.3.1 Control for Measured Confounders at the Design Stage

Restriction and matching have in common that they can only adjust factors that are measured and are then used either to restrict the study population or to identify strata of patients that are homogeneous with regard to the risk of study outcome. Briefly, restriction allows the investigators to examine one stratum of the confounding variable, which effectively removes the effect of the confounder on the outcome. For example, if age is a confounder, then investigators can restrict the study population to older adults. Similarly, matching removes the effects of the confounder by forcing its distribution to be identical between groups of comparison.[160] Matching is commonly used in case-control studies. Common matching factors are age, race, sex, socioeconomic status and occupation. Matching may be of two types: (1) group match (or frequency matching) and (2) individual matching. Group matching consists of selecting the controls in a manner that the proportion of controls with a certain characteristics is identical to the proportion of cases with the same characteristic (e.g., 25% married). This type of matching generally requires that all of the cases be selected first. For individual matching, for each case selected, a control is selected who is similar to the case in terms of specific variable(s).[44] It limits the generalizability to other populations if one chooses many variables to restrict study participants. Similarly, the more variables that one chooses to match, the more difficult it will be to find a suitable control. Once restriction or matching is used, one cannot study that characteristic.[44]

1.5.3.2 Control for Measured Confounders at the Analysis Stage

Under the assumptions of no unmeasured confounding, usual strategies for controlling confounding can be applied at the analysis stage including **standardization, stratification, multivariate modeling** and **marginal structural models**.

Standardization is often used for comparing vital statistics from populations that have different age or sex distribution. A standardized rate is a weighted average of stratum-specific rates. There are two methods of standardization: direct and indirect. The factors that can be managed by standardization are limited (two to three at most). Use of standardization in pharmacoepidemiology is limited since pharmacoepidemiologic research usually requires the manipulation more than three factors.[140]

Stratification uses confounding factors to identify strata of patients that are homogenous with regard to the risk for the outcome. The limitation of stratification is that each time a new factor is added, stratum-specific cell sizes become smaller, and the probability of having people not exposed or not sick in each stratum becomes larger. The stratum specific estimate of the measure of association cannot then be computed or provide any statistical information due to a lack of power.[140]

Multivariate modeling allows many factors to be adjusted at the same time in a mathematical model and is the most common technique used to adjust for confounding. The estimate represents the individual contribution of each factor for the risk of the outcome, adjusted for all other factors. In order to maintain reasonably stable estimates of parameters, there are general rules of thumb for ensuring an optimal sample size: approximately 10 observations are required per factor in a multiple regression model where the outcome is continuous, and approximately 10 events per factor for logistic regression models where the

outcome is binary.[161] In addition, the most frequently applied empirical assessment of confounding includes comparing changes in the estimate of the drug-outcome association as a function of increasing adjustment until the incremental change in estimate becomes small (i.e., a change of less than 10% was suggested as a cut-off point).[162] Hence, while multivariate analysis provides a more efficient tool of controlling for several confounders simultaneously, the adequacy of the data in meeting these requirement and assumptions required for each model must be examined.

The above methods, however, are constrained to a limited number of covariates (or limited number of covariates per outcome). In an effort to overcome this limitation, the **exposure propensity score (or propensity score, PS)** analyses, developed by Rosenbaum and Rubin, have become a widespread tool to combine information from various confounding factors into a single variable in many research fields.[107,108] This approach is useful when many confounders or rare outcomes exist in pharmacoepidemiologic studies (especially in automated databases). A PS is the probability (or propensity) that an individual would be treated given their individual measured covariates. It can be estimated by using multivariate logistic regression model where the dependent variable is drug exposure, and the independent variables are covariates related to drug exposure.

Each participant is assigned an estimated probability of drug exposure ranging from 0 to 1 that reflects the probability of being prescribed a given drug, given all measured confounders. The probability of being prescribed a drug or assigned a treatment is dependent only on the PS covariates otherwise treatment assignment is random. The 3 techniques most commonly used to control for confounding based on the PS are: (1) as a matching factor prior to analysis (e.g., Greedy matching technique),[163] (2) stratification on the PS during analysis (e.g., use quintiles of

the PS of the entire study population),[164] or (3) as a covariate in multivariate analyses.[165] The use of propensity score-based weighting (e.g., inverse-probability-of-treatment weighted estimator or standardized mortality/morbidity ratio weight) has also been proposed.[166,167] **Figure 2** summarizes the methodological approach to building the propensity score. All methods have advantages and disadvantages and also involve different underlying assumptions that have to be considered. The PS method has extended uses in estimating treatment effects conditional on pretreatment variables in a way that treatment can be continuous, ordinal or discrete, and in case-cohort studies as well.[168] The PS method's advantages including the ability to deal with many covariates, frequent exposures, or rare outcomes (to avoid the risk of over-fitting in the model) in the automated databases, and offer increased feasibility compared to RCTs in situations where ethical or cost concerns are relevant.[169] By using the PS method, the effects of all of the prognostic covariates used in estimating the treatment effect are removed from the estimation of treatment effect, thus reducing the bias. However, the analysis of drug exposure-outcome association may lack transparency because a number of covariates are bundled into one propensity score. It also has been postulated that, if a variable is more of a risk factor for an outcome than it is a predictor of treatment, confounding might be better controlled by inclusion of the variable as an individual confounder of the outcome rather than in the PS model.[170] Further, PS methods only have advantages when there are seven or fewer outcome events per confounder. When there are eight or more outcome events per confounder, logistic regression represents a preferable approach.[171] Another limitation of using a PS approach is that residual confounding cannot be excluded when unmeasured or imperfectly measured confounders exist in the databases.

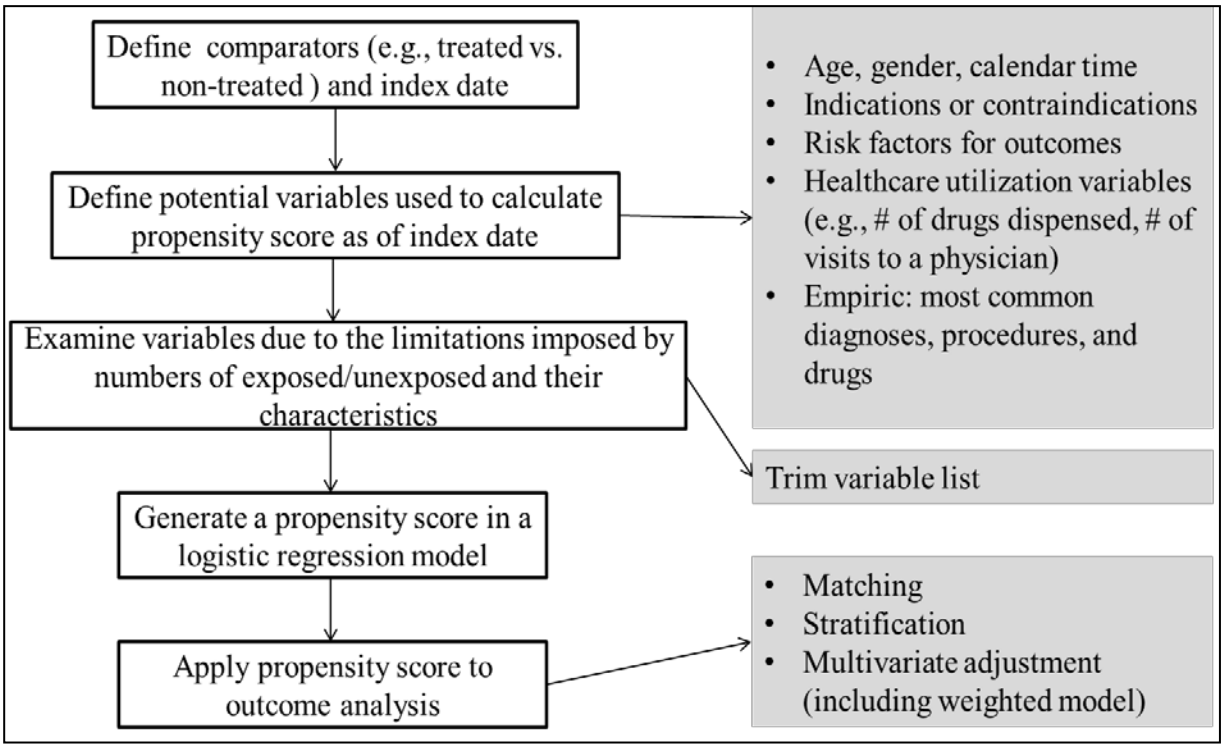

Figure 2. Approach to Build the Propensity Score

The techniques discussed above may be inadequate in longitudinal observational studies when more complex biases are present, such as when exposure is time-dependent and time-varying confounders are present. A time-varying confounder is a variable affected by prior exposure that predicts both subsequent outcome and subsequent exposure. One solution to this problem is to employ a more complex analytical approach that incorporates prediction of treatment as well as censoring in specific time intervals. Robins et al. developed a new model called **marginal structural models**.[166] Marginal structural models use inverse-probability of exposure weights to create an artificial population in which covariate imbalances are removed and causal effects can be accurately estimated.[172] With respect to the PS approach, the marginal structural model is an extension of the inverse-probability of treatment weighted estimator. Stabilized inverse-probability weights and the mean of the stabilized inverse-probability close to

one can be used to evaluate whether the marginal structural model performs appropriately.[172] Stabilized inverse-probability weights with a mean far from one may indicate a violation of some of the hypotheses of the model (e.g., a misspecification of the weight model or a violation of the positivity assumption).[172,173] Compared with the standard errors in the conventional models, marginal structural models increase the median standard error of the estimates nearly 20% while controlling for time-varying confounding.[172] This increase in standard error is a trade-off between bias and precision. [173] Marginal structural models can be used in observational studies with time-varying confounding, as well as in RCTs if the study is randomized at baseline but post-baseline changes in treatment are not randomized.[172]

1.5.3.3 Unmeasured Confounders that Can be Measured in A Validation Study

If confounders that are unmeasurable in the main study but measurable in validation sub-studies, two-stage sampling or external adjustment may be considered. **Two-stage sampling** designs rely on an internal validation study to collect information on covariates that were not measured in the main study.[140] In stage one, information is collected on drug exposure and disease outcomes for the entire cohort (main study) such as a large automated database. To use the resource optimally, in stage two, a subgroup of the main study will be sampled and contacted, and detailed information will then be obtained. Regression coefficients and standard errors will then be weighted for multivariate analysis according to the specific sampling fraction.[174] The balanced design, wherein an equal number of individuals in each cell of the second stage's 2×2 table, is usually the most efficient strategy compared to random and disease- or drug-exposure-based sampling.[175] This strategy decreases the occurrence of small cells (which are responsible for large variance) by forcing an over-representation of individuals who belong to small groups

in the drug-disease cross classification.[140] Interaction can also be evaluated in the two-stage sampling. Two-stage sampling designs can be valuable tools to adjust for unmeasured confounders if access to individual patients is possible in the automated databases in pharmacoepidemiology.[158] However, two-stage sampling can be time-consuming to identify a subgroup and can lead to additional data collection.

If internal validation studies are not feasible or too costly, **external adjustment** (i.e., using external data sources) can be used under certain assumptions (e.g., similar characteristics of participants in the main and external datasets). For example, the Medicare Current Beneficiary Survey studies a representative sample of Medicare beneficiaries to measure a wide variety of characteristics (e.g., limitations of daily living activities, cognitive impairment) that are not captured in Medicare claims data. Traditionally, these external variables can be further added as additional confounders in the model. A new technique of **propensity score calibration** was developed to apply in external adjustments. The error component of the PS in the validation study is then quantified and can be used to correct the PS in the main study, using established regression calibration techniques.[176] The advantage of PS calibration is that it implicitly takes into account the joint effect of unmeasured confounders, as well as the relation between measured and unmeasured confounders.[158]

1.5.3.4 Control for Unmeasured Confounders at the Design Stage

If residual confounding by unmeasured factors is suspected and unmeasured confounders are truly unmeasured because of technical difficulties or factors were unknown to the investigators, strategies to adjust unmeasured confounding including application of an **active comparison group** and/or **crossover study designs** (see section 1.2.7 for details) at the design stage.

Active (or competing) comparator design can be seen as a special type of restriction because the choice of a comparator group is restricted to patients with similar indications. When comparing the effects of two active therapies that are prescribed under the assumption of similar effectiveness and safety, it is less likely that predictors of the outcome are imbalanced and will cause confounding.[158] For example, two similar selective COX-2 inhibitors, rofecoxib and celecoxib, were likely to be equally prescribed to patients at risk for cardiovascular events, so that an increased risk of myocardial infarction associated with one compared with the other is unlikely to be attributable to confounding by indication.[177] The measurement of association while using active comparative group design is "relative excess risk" as a comparative relative risk adjusted for the baseline risk, or "absolute excess risks".[158,178]

1.5.3.5 Control for Unmeasured Confounders at the Analysis Stage

Proxy adjustment, instrumental variable and/or **sensitivity analysis** can be used to control for unmeasured confounders at the analysis stage. **Proxy adjustment** refers to adjusting for a surrogate of an unmeasured factor is equivalent to adjusting for the factor itself. For example, older age serves as a proxy for many factors, including co-morbidity, frailty, and cognitive decline. Further, having regular annual check-ups is indicative of a health-seeking lifestyle and is likely to be a proxy for increased overall treatment adherence.[49] The number of prescription drugs dispensed, the number of physician visits, and hospitalizations before the index drug exposure are frequently used proxies in pharmacoepidemiology. If many proxies are identified, they can then be adjusted for in a large PS model. Collinearity may likely occur but is irrelevant, as the individual parameters estimated in the large PS regression will not be interpreted but only

used for predicting treatment.[179] However, it is challenging empirically to know with enough certainty whether a variable is a proxy confounder or an instrument.

By adjusting for an **instrument variable**, the indication for treatment may be controlled for under the following assumptions that an instrumental variable is: (1) causally related to the treatment, (2) weakly associated or not associated with any potential confounder, and (3) not associated with the outcome other than through the treatment.[154] Thus, an instrument is an external factor that influences an outcome only through its effect on treatment. However, it is extremely challenging to find good instruments for studying the effectiveness and safety of drugs. In addition, instruments used in healthcare services research are often only weakly associated with the actual treatment, which leads to imprecise estimates and requires large sample sizes. Adjusting for an instrumental variable is useful when the choice of medication used is influenced more by prescriber preference than patient risk factors (i.e., there is exposure variation between providers). This can be further adjusted for measured patient or physician characteristics.[158] Some instruments used in pharmacoepidemiology include regulatory or coverage interventions and provider treatment preference (e.g., distance to specialist provider, physician prescribing preference, regional treatment preference, hospital formulary, surgeon treatment preference, medication co-payment level, and dialysis preference level).[49] For example, strong prescriber preference was observed among patients starting NSAID therapy either with non-selective NSAIDs or COX-2 inhibitors. An instrumental variable can be used such as grouping physicians into those who always initially prescribed non-selective NSAIDs (instrumental variable=0) and those who always started with prescribing COX-2 –selective NSAIDs (instrumental variable=1).[180]

Sensitivity analysis, defined as a quantitative analysis of the potential for systematic error, is a more formal approach used to communicate this uncertainty with respect to the validity of findings (i.e., how robust study findings are to implicit and explicit assumptions).[140] In other words, sensitivity analyses make informed assumptions about potential residual confounding and calculate its effect on the risk estimate of the drug-outcome association. Existing approaches include an array approach which is helpful to explore the effect of residual confounding over a wide range of parameter constellations,[181] and a rule-out approach to assess how much confounding would have to be present to fully explain the observed findings (i.e., observed point estimate would move to the null).[182] The details and calculations of these two approaches are beyond the scope of this review, however, we can easily perform these sensitivity analyses using a spreadsheet program available at http://www.drugepi.org/dope-downloads/.[181] Sensitivity analysis not only brings to the forefront the important issues related to the validity of results but it is also provides a means for presenting objective evidence that may be used by readers to evaluate the magnitude of the threat to validity and give them a sense of confidence in the study results. In addition, it can provide direction for future research by serving in a hypothesis-generating manner. Sensitivity analysis is limited to one binary confounder, which may not be helpful if several confounders are unmeasured and the joint effect of such confounders is unknown.

1.5.4 Healthy-User Effect and Related Confounding and Biases in Observational Studies of Preventive Interventions

Because numerous high-profile observational studies of the effect of prevention on health outcomes reported exaggerated relationships that were later contradicted by RCTs recently, a growing body of research identifies sources of bias and confounding in observational studies that are related to patient behaviors or underlying patient characteristics, known as **the healthy user effect, the healthy adherer effect, confounding by functional status or cognitive impairment, and confounding by selective prescribing**.[183] These special confounding and biases resulting from patient-level tendencies to engage in healthy behaviors or physician's perceptions of the health of patients, and potential solutions will be described specifically and briefly in this section.

The healthy user effect is described as patients who receive preventive therapies or tests are more likely to seek other preventive service or partake in other healthy behavior (e.g., healthy diet, exercise, or avoid tobacco).[184] An observational study evaluating the effect of a preventive therapy (e.g., hormone replacement therapy) on a related outcome (e.g., cardiovascular disease) without adjusting for other related preventive behaviors will tend to overstate the effect of the preventive therapy under study. Similarly, **the healthy adherer effect** arises when patients who adhere to preventive tests or therapies are more likely to pursue health-seeking behaviors than their non-adherent counterparts.[183] For example, in a study of elderly patients initiating statins, patients who filled ≥ 2 statin prescriptions during a 1-year ascertainment period were more likely than patients who filled only one prescription to receive prostate-specific antigen tests, fecal occult blood tests, screening mammograms, influenza vaccinations, and pneumococcal vaccinations during follow-up.[185] In addition, **confounding by functional status or cognitive**

impairment refers to poor functional or cognitive status limits some patients' interest in, or ability to visit, their physician.[183] Studies do not account for functional status or cognitive impairment will overstate the effect of a preventive therapy. For example, Jackson LA et al. found that elderly women with higher levels of functional impairment had significantly lower rates of breast and cervical cancer screening.[186] **Confounding by selective prescribing** refers to physicians are less likely to prescribe preventive treatments patients who are frail, have terminal, or acute illness (both in the inpatient and outpatient settings).[187] For example, patients with terminal cancer or end-stage renal disease, may be less likely to receive or more likely to discontinue a preventive therapy. Failing to account for selective prescribing that correlate with the health of patients will lead to overestimation of the benefits of a preventive therapy.

Several approaches can be used to minimize these bias and confounders, and affirm the validity of the results in pharmacoepidemiology. The approaches include: (1) using new user designs; (2) restricting the study population to subjects who are similar in having similar patterns of the use of preventive tests or therapies; (3) using an intention-to-treat analysis; (4) using an active comparator (i.e., another preventive therapy); (5) adjusting for functional status, cognitive impairment, frailty, or disease severity; (6) identifying proxies for further adjustment (e.g., vaccines, mammography, colonoscopy, or medications for dementia); (7) adjusting for unmeasured confounders using propensity score or instrumental variables; and (8) conducting sensitivity or secondary analyses (e.g., evaluating negative control outcomes events that should not be affected by the treatment under study, but may confound or bias the results).[183]

1.5.5 Summary

A thorough understanding of the potential sources of bias and confounding in non-experimental studies is important to designing studies that minimize their influence on results. Several strategies can be used to avoid major bias in pharmacoepidemiology including: (1) restricting the design to new (or incident) users, those without contraindications, and those who are adherent to prevent prevalent bias; (2) systematically identify and recruit all eligible cases to prevent self-selection bias ; (3) applying "lag-time" (or an index date) to define drug exposure periods to prevent protopathic bias; (4) restricting the outcome of interest to more serious cases (instead of mild or subclinical diagnosis) to prevent referral bias; (5) selecting controls who are likely to have the same cognitive processes affecting memory of past drug exposures to prevent recall bias; (6) to prevent detection bias, blinding relevant study personnel, standardizing the measurement process, and/or obtaining information on the frequency of access to medical care and health awareness by participants; (7) to prevent immortal-time bias, using nested case-control or active comparative design, and time-dependent statistical methods to account for complex changes in drug exposure and time-varying confounders.

Strategies used to control confounding in non-experimental studies in pharmacoepidemiology vary from whether confounders can be measured or not. For measurable confounders, one can use restriction and/or matching (including matching by PS) at the design stage, or apply standardization, stratification, multivariate analysis (including PS adjustment), or marginal structural model at the analysis stage. For confounders cannot be measured in the main study, but can be measured in a validation study, two –stage sampling or external adjustment can be used to control these confounders. For confounders that are truly unmeasured, crossover

design or active comparative group can be used at the design stage. Crossover design is usually used to evaluate the association between a transient exposure and acute event (e.g., vaccine safety). In addition, proxy adjustment, instrumental variables, and/or sensitivity analysis may be potential approaches to control for unmeasured confounders at the analysis stage. Beyond the above strategies and under a distinctive set of challenges and unique set of resources, pharmacoepidemiologists are developing and implementing innovative study designs and new analytic approaches in order to maximize the validity of results from non-experimental studies.

2.0 OBJECTIVES AND SPECIFIC AIMS

The burdens of chronic diseases and functional disability increase with age. Chronic diseases are costly health conditions which negatively affect quality of life, contributing to declines in functioning and the inability to remain in the community.[188] Hypertension, cardiovascular disease (CVD), stroke, chronic lower respiratory disease, cancer, diabetes, arthritis, dementia, depression, and some infectious diseases are common health threats in the US population.[188] The prevalence of multi-morbidity, referring to co-occurrence of several medical conditions within an individual, also increases with age. CVD and cancer are the top two leading causes of death among all people age ≥ 65 years, irrespective of sex, race, or Hispanic origin.[188] Prevention and control of hypertension, dyslipidemia, diabetes, cancer, and disability, are key strategies to promote health and well-being at all ages.

While clinical risks associated with chronic disease are well-known, the use of medication and therapeutic risk-benefit balance are often under recognized. Improved methodology in pharmacoepidemiologic research may extend new understanding of the medication use and enable one to evaluate the influence of the policy and evidence-based studies (e.g., guidelines), and the effectiveness or therapeutic risk-benefit balance of the treatments in "real-world" practices. There is also growing interest in potential agents or medications to prevent or slow cancer development or progression. The overall aim of this dissertation is to

apply pharmacoepidemiologic methodology to examine medication utilization, therapeutic risk-benefit balance in older adults and evaluate potential chemopreventive agents for ovarian cancer prevention.

Specific Aims:

Aim 1: The aim of the first study is to examine whether utilization patterns of cholesterol-lowering medications in community-dwelling older adults changed following the release of the National Cholesterol Education Program Adult Treatment Panel III guidelines and results from the Prospective Study of Pravastatin in the Elderly at Risk in 2002, using the data from Health, Aging and Body Composition (Health ABC) study.

Aim 2: The aim of the second study is to examine whether the use of statins is associated with a decreased risk of gait speed declines of 0.05 m/s or more and 0.1 m/s or more per year in community-dwelling older adults in the Health ABC study.

Aim 3: The aim of the third study is to evaluate the associations of aspirin, NA-NSAIDs, or acetaminophen use with the risk of incident ovarian cancer, using the data from Hormones and Ovarian Cancer Prediction (HOPE) study, the second-largest population-based case-control study on ovarian cancer in the US.

3.0 MANUSCRIPT 1: CHANGES IN CHOLESTEROL-LOWERING MEDICATIONS USE OVER A DECADE IN COMMUNITY-DWELLING OLDER ADULTS

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3.1 ABSTRACT

Background: The impact of evidence-based guidelines and controlled trial data on use of cholesterol-lowering medications in older adults is unclear.

Objective: To examine whether utilization patterns of cholesterol-lowering medications in community-dwelling older adults changed following the release of the National Cholesterol Education Program Adult Treatment Panel III guidelines and results from the Prospective Study of Pravastatin in the Elderly at Risk in 2002.

Methods: Community dwelling older adults who were enrolled in the Health, Aging and Body Composition Study in 1997-1998 were followed for up to 11 years. An interrupted time-series analysis with multivariable generalized estimating equations (GEE) was used to examine *level* and *trend* changes in cholesterol-lowering medication use before and after 2002, adjusting for sociodemographics, health-related behaviors and health status.

Results: Cholesterol-lowering medication use increased nearly 3-fold from 14.9% in 1997-1998 to 42.6% in 2007-2008, with statins representing the most common class used (87%-94%). Multivariable GEE results revealed no difference in the *level* of cholesterol-lowering medication use after 2002 (adjusted odds ratio: 0.95, 95% confidence interval [CI] 0.89-1.02). Multivariable GEE results revealed *trends* changes in the rate of increase in cholesterol-lowering medication declined after 2002 (adjusted ratio of odds ratios 0.92, 95% CI 0.89-0.95).

Conclusions: The use of cholesterol-lowering medication increased substantially over a decade in community dwelling elders, but was not related to a change in level or trend following the release of the guidelines and evidence-based data.

3.2 INTRODUCTION

3.2.1 Epidemiology of Cardiovascular Disease and Dyslipidemia in the Elderly

Cardiovascular disease remains the leading cause of death and disability among the elderly in the US, with the average age of first myocardial infarction being 65 years for men and 70 years for women.[1] Approximately 60% of hospital admissions for acute myocardial infarction and 81% of coronary heart disease (CHD) mortality are in people aged ≥ 65 years.[1, 2] Although cardiovascular disease remains the leading cause of death and disability among the elderly in the US, the incidence of coronary heart disease (CHD) and associated mortality actually declined by approximately 25% from 1997 to 2007.[1-3] This decline may be due to improved medical care and use of evidence-based preventive medications, including cholesterol-lowering therapy.[3, 4]

With regard to further reducing the burden of CHD morbidity and mortality, the emphasis is on the treatment of acute events and secondary or primary prevention through treatment and control of risk factors. A meta-analysis of individual data from 61 prospective studies reaffirmed that higher total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C) and lower high-density lipoprotein cholesterol (HDL-C) are associated with higher risk of CHD mortality in both men and women in different age groups.[5] Although the relative risk for CHD mortality

associated with high total cholesterol or low HDL-C decreases with advancing age, this lower relative risk is offset by the greater absolute and attributable risk for CHD in the elderly.[6]

From the National Health and Nutrition Examination Survey (NHANES) years 1999 – 2004 (n=3,810 aged ≥ 65 years),[7] women had a higher prevalence of hypertension than men (77% vs. 63%, $p \leq 0.001$), a similar rate (76%) of awareness of hypertension, and a lower rate of control on treatment (43% vs. 58%, $p \leq 0.001$). Diabetes affected approximately 22% of older males and females. Women had a higher rate of awareness of diabetes than men (79% vs. 64%, $p \leq 0.01$). About 50% prevalent diabetic older males and females were treated pharmacologically and goal attainment among those treated with diabetes was 50%. Overall, dyslipidemia prevalence was 60% (men: 62% vs. women: 59%). Men were less likely to be aware of their dyslipidemia than women (59% vs. 71%, $p \leq 0.001$), although both genders were equally likely to be treated (41% vs. 45%). Compared to those aged of 65-74 years, those aged ≥ 85 years had a lower prevalence of dyslipidemia (64% vs. 46%, $p \leq 0.001$), a lower rate of awareness of dyslipidemia (68% vs. 39%, $p \leq 0.001$), had a lower treatment rate (45% vs. 24%, $p \leq 0.001$). Sixty-five percent of the older male and female medically treated for dyslipidemia reached their LDL cholesterol goal. Age of 85 years and above was negatively associated with awareness and treatment of dyslipidemia. Low annual household income (< $15,000 in 2002 dollars) was negatively associated with awareness and controlled on treatment of dyslipidemia. Female, higher education, and more doctor visits in the past year were positively and strongly associated with awareness, treatment of dyslipidemia.

3.2.2 Drugs for Lipid Lowering Therapy

The treatment of dyslipidemia may require two approaches, therapeutic lifestyle changes and medications. In the cases that cholesterol levels cannot reduced effectively by dietary modification and increased physical activity, or for persons with other risk factors of CHD, the use of cholesterol-lowering medications is recommended.[8] There are several classes of cholesterol-lowering drugs, but statins (or HMG-CoA reductase inhibitors) are the drug class of choice because of their demonstrated safety and efficacy in lowering LDL-C and reduction in cardiovascular mortality. Other available cholesterol-lowering medications including bile acid sequestrants (colesevelam, colestipol, cholestyramine), cholesterol absorption inhibitor (ezetimibe), fibrates (gemfibrozil, fenofibrate, fenofibric acid), niacin, and fish oil capsules, may be required in patients who are statin-intolerant, have mixed dyslipidemia, or in whom standard doses of statins may not be sufficient to achieve LDL-C goals.[9]

3.2.3 Statin Therapy for Secondary Prevention of Cardiovascular Disease in the Elderly

Recommendations for the detection and control of hypercholesterolemia for adults have been offered since 1988 (**Table 6**), by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP).[8, 10-12] Results from several meta-analyses[13-15] and subgroup analyses of randomized clinical trials (RCTs)[16-26] show that statins have benefits of lowering the risk of all-cause mortality and CHD mortality, reduce cardiovascular events, stroke, and the need for revascularization among patients (aged 60-82) with established CHD. In a meta-analysis of data from 90,056 patients in 14 RCTs (47% of patients had pre-existing CHD), statins reduced the

risk of major coronary events similarly among those aged < 65 years and ≥ 65 years (22% vs. 19%).[13] In another meta-analysis of 18 RCTs (n=51,351) conducted by Robert et al,[14] 62% of the participants were aged ≥ 60 and 12% were aged ≥ 70 years. Statins reduced risk of all-cause mortality and CHD mortality by 15% for those aged ≥ 60 and 23% for those aged ≥ 70 years, respectively. Afilalo et al. conducted a meta-analysis from the individual data of nine RCTs (four were unpublished data), in which 19,569 participants were aged 65 to 82.[15] Statins reduced risks of all-cause mortality by 22%, CHD mortality by 30%, nonfatal MI by 26%, need for revascularization by 30% and stroke by 25%.

Table 6. NCEP ATP Guidelines Recommended Drug Therapy According to LDL-C Levels

NCEP Guidelines (first published year)	Risk groups	LDL-C levels (mg/dL) to initiate drug therapy	Minimal Goals of LDL-C levels (mg/dL) if under drug treatment
ATP I (1988)[11]	With CHD or ≥ 2 risk factor[a]	≥ 160	< 130
	Without CHD and with < 2 risk factors[a]	≥ 190	< 160
ATP II (1993)[12]	With CHD	≥ 130	< 100
	Without CHD and ≥ 2 risk factors[b]	≥ 160	< 130
	Without CHD and with < 2 risk factors[b]	≥ 190	< 160
ATP III (2002)[9]	High risk: with CHD or CHD risk equivalent[c] (10-year risk > 20%)	≥ 100	< 100 (optimal <70)
	Moderate-high risk: ≥ 2 risk factors[d] (10-year risk of 10-20%)	≥ 130	< 130
	Moderate risk: < 2 risk factors[d] (10-year risk < 10%)	≥ 160	<130
	Low risk: 0-1 risk factor [d]	≥ 190	< 160

Abbreviations: CHD: coronary heart disease; HDL-C: high-density lipoprotein cholesterol ; LDL-C: low-density lipoprotein cholesterol; NCEP ATP: National Cholesterol Education Panel Adult Treatment Panel

[a]: Risk factors include male sex, family history of premature CHD, cigarette smoking, hypertension, low levels of HDL cholesterol (<35 mg/dL), diabetes, definite cerebrovascular or peripheral vascular disease, or severe obesity;

[b]: Positive Risk factors include age (men ≥ 45 years and women ≥ 55 years), family history of premature CHD, current cigarette smoking, hypertension, low levels of HDL-C (<35 mg/dL), diabetes. Negative risk factors include high HDL-C (≥ 60 mg/dL).

[c]: CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease, transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery), diabetes, and 2+risk factors with 10-year risk for hard CHD 20%.

[d]: Risk factors include cigarette smoking, hypertension, low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥ 45 years; women ≥ 55 years).

3.2.4 Statin Therapy for Primary Prevention of Cardiovascular Disease in the Elderly

Limited data are available for elderly patients without CHD.[27] Other subgroup analysis from the RCTs suggested that statins reduced the incidence of major cardiovascular events in both those aged < 65 and ≥ 65 years, without known CHD, regardless their baseline cholesterol levels.[20, 28-33] This shifted primary prevention toward an emphasis on the consideration of the patient's global risk for CHD rather than focusing only on lipid levels when determining those who would benefit from primary prevention.

3.2.5 Lipid-Lowering with Non-Statin Drugs in the Elderly

Except fibrates, little evidence shows that other lipid-lowering medications have benefits to reduce CHD risk in older adults. Only three RCTs of non-statin drugs were for primary prevention of CHD,[34-36] but none of them enrolled participants aged > 75 years. The studies of other lipid-lowering medications mainly focused on the efficacy and safety in lowering cholesterols in older adults. No differences in safety and efficacy of colesevelam, ezetimibe, and niacin were observed between those aged < 65 years and ≥ 65 years.[37-39]

The results from the RCTs of fibrates in older adults are mixed in reducing the risk of cardiovascular disease. Of 2,531 men with CHD, HDL-C ≤ 40 mg/dL and LDL-C ≤ 140 mg/dL in Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT),[40] the mean age of participants was 64 years (50% were aged ≥ 66 years). After one-year treatment, Gemfibrozil significantly reduced the risk of the composite outcomes (CHD death, nonfatal myocardial infarction, or stroke) by 24%, compared to placebos. Risk reductions were similar between

those aged < 66 years (26%) and those aged ≥ 66 years (22%). The Fenofibrates Intervention and Event Lowering in Diabetes (FIELD) study did not show an overall decrease in CHD events with fenofibrate in diabetic patients aged 50–75 years (with or without CHD), but did reduce total cardiovascular events (the composite of CVD death, myocardial infarction, stroke and coronary and carotid revascularization).[35] However, a subgroup analysis by age showed a significant decrease in total cardiovascular events in those aged < 65 years, but not in patients aged ≥ 65 years.

3.2.6 Significance of Current Study

In 2002, NCEP ATP III guidelines were published and for the first time strongly recommended the use of statins for older persons with established CHD or at high risk for developing CHD (e.g., diabetes mellitus).[8] These recommendations were based in part upon the results from the subgroup analysis of several previous trials with statins,[15-18, 20] and the 2002 Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).[19] Conclusively extrapolating the results from subgroup analysis to all older adults was controversial, in part because most of these trials had defined an upper age limit (70-75 years of age) that favored the inclusion of only "younger" older adults.[16-18] The 2002 Medical Research Council/British Heart Foundation Heart Protection Study (HPS) included an appropriate proportion (28%) of participants aged ≥ 70 years.[20] Among 1,263 individuals aged 75 to 80 years at baseline, the rate of major coronary events was significantly lower in the statin group than placebo group.[20] The PROSPER is the only trial focused on an exclusively elderly cohort involving 5804 older men and women (aged 70 to 82 years).[19] They found that that the risk of CHD death, or non-fatal myocardial infarction was

significantly reduced in those with established CHD, but not in those receiving the drug for primary prevention (e.g., diabetes mellitus).[19]

There is limited information about the use of cholesterol-lowering medications before and after 2002 in older adults aged ≥ 75 years. From the National Health and Nutrition Examination Survey 1999-2002 to 2003-2006, cholesterol-lowering medication use significantly increased in older adults aged ≥ 60 years (46% vs. 57%), but no information was reported in those aged ≥ 60 years with CHD and/or with diabetes.[41] Physician prescribing inertia despite clinical practice guidelines or evidence-based data may be due to lack of familiarity of the benefits of specific pharmacotherapy, or difficulty in balancing the impact on quality of life with patient's comorbidities, functional status, life expectancy and preferences.[42] In addition, these publications are somewhat inconsistent regarding the need for cholesterol-lowering medications in the elderly (e.g., those with diabetes but without CHD).[8, 19, 43-46] To date, no formal assessment of the impact of these publications on use of cholesterol-lowering medications in the elderly has been undertaken. Therefore this study compares the utilization patterns of cholesterol-lowering medications in community-dwelling older adults before and after the release of the NCEP ATP III guidelines and results from the PROSPER in 2002. The Health, Aging and Body Composition Study, a cohort study enrolled the well-functioning elders aged ≥ 70 years, provided a great opportunity to examine our research question.

3.3 METHODS

3.3.1 Study Design, Sample, and Source of Data

An interrupted time-series analysis was used to examine yearly *level* and *slope* (*trend)* changes in the utilization of cholesterol-lowering medications.[47] A random sample of 3075 black and white men and women, aged 70-79, were recruited from Medicare beneficiaries residing in Pittsburgh, PA and Memphis, TN.[48, 49] The baseline visit of the Health Aging and Body Composition Study occurred in 1997/1998 at which time participants were aged 70 to 79 and reported no difficulty walking one-quarter of a mile (400 m), climbing 10 steps without resting, performing basic activities of daily living; no use of a cane, walker, crutches or other special equipment to ambulate. [48, 49] Twenty baseline participants were excluded because of missing medication information. The study was approved by the Institutional Review Boards of the Universities of Pittsburgh and Tennessee, and written informed consent was obtained from each participant.

3.3.2 Data Collection and Data Management

The information collected annually during in-person visits by trained interviewers included blood samples, a battery of detailed physiological measurements and questionnaire material regarding sociodemographic characteristics, multiple aspects of health status, and medication use.[48, 49] From the collected fasting blood samples obtained in 1997-1998, 2002-2003, 2004-2005, 2007-2008, serum cholesterol, HDL-C and triglyceride values were determined by a colorimetric technique on a Vitros 950 analyzer (Johnson & Johnson, New Brunswick, NJ).

LDL-C was calculated using the Friedewald equation.[50, 51] Both health and behavior factor and medication use data were used to define specific conditions of interest in this study (i.e., diabetes mellitus and hypertension). Hypertension was defined by self-reported diagnosis of hypertension and use of anti-hypertensive medications.[52] Diabetes was defined by self-reported diagnosis of diabetes or use of anti-diabetic medications.[53] Several comorbidities examined in the current study (i.e., CHD, stroke, or peripheral artery disease [PAD]) were centrally adjudicated by a post hoc committee based on conclusive evidence from hospitalization or death records.[48, 49]

For medications, at baseline (1997-1998), and annually for 10 years (except years 2000-2001, 2003-2004, and 2005-2006), participants were asked to bring all prescription medications taken in the previous month. Trained interviewers transcribed information from the medication containers on medication name, dosage form, and whether the medication was taken as needed. The medication data were coded using the Iowa Drug Information System and then entered into a computerized database.[54] These methods of medication data collection are considered highly accurate and concordant with information contained in pharmacy claims data.[55]

3.3.3 Outcome Variable: Cholesterol-Lowering Medication Use

The dichotomous outcome variable was use of any cholesterol-lowering medication from any of two discrete classes: 1) statins, and 2) others (i.e., fibrates, bile acid binding resin agents, probucol, niacin, and cholesterol absorption inhibitors (i.e., ezetimibe)). These two classes correspond to IDIS codes 24060009-24060404 and 88080004.[54]

3.3.4 Primary Independent Variable

The independent variable for these analyses was time (i.e., baseline [1997-1998] and each follow-up year). The year 2002 was the year in which the NCEP ATP III guidelines and the results of the PROSPER were released. Therefore, two non-overlapping time segments were defined for the time series: 1997-2002 and 2003-2008.

3.3.5 Covariates

Several characteristics that could potentially confound or modify cholesterol-lowering medication use were adjusted for in the analysis, and were grouped into three domains: 1) sociodemographic, and 2) health-related behaviors and 3) health status.[56-59] Sociodemographic factors that were characterized as categorical variables included race (black, white), sex, study site, education (postsecondary education, high school graduate, and less than high school graduate), and living status (alone, not alone). Age was considered as a continuous variable. A dichotomous time-varying variable for prescription drug coverage was also included to account for patients on and off insurance over the study period.

Health-related behaviors were characterized as categorical variables for smoking status and alcohol use (current, past, or never). Health status factors were characterized as dichotomous measures (present vs. absent) for self-reported health conditions, including congestive heart failure, kidney disease, pulmonary disease, and cancer. A time-varying dichotomous variable was created for self-rated health (excellent/good vs. not excellent/good). A categorical variable for body mass index (BMI- underweight or normal [<25.0 kg/m^2],

overweight [25.0–29.9 kg/m^2], or obese [≥30.0 kg/m^2] was created.[60] The number of overall prescription medications (excluding cholesterol-lowering drugs) was included as a time-varying continuous variable as a proxy for comorbidity.[61] Dichotomous variables were created for cognitive impairment (3MS < 80) and high depressive symptoms (Center for Epidemiologic Studies Depression Scale score >15).[62, 63] Interviewers were trained with the standard manual of operation and certificated for all the clinical assessments (e.g., 3MS test).[64]

3.3.6 Main Statistical Analyses

All analyses were performed using SAS® version 9.3 (SAS Institute Inc. Cary, NC). Appropriate descriptive statistics (mean, standard deviation, frequency and percentage) were employed to summarize participant characteristics and main analytic variables. For descriptive purposes, we also reported the prevalence of fibrate and ezetimibe use separately from other non-statin agents because fibrates were the second commonly used cholesterol lowering medications and ezetimibe was introduced to the market in 2002.[41] We conducted a multivariable interrupted time-series analysis (using generalized estimating equations [GEE]) to estimate changes in the *level* and the *slope (trend)* of the outcome rates after 2002.[47, 65] This analysis used the SAS® GENMOD procedure with an autoregressive working correlation structure to account for potential multiple years of data from the same participants and the resulting stochastic non-independence of observations.[47, 65] Specifically, level changes were calculated by comparing the predicted prevalence use in the year 2002-2003, which was extrapolated from the slope of the time series 1997-2002, with the observed prevalence use in the year 2002-2003. The *level* changes were calculated as an adjusted odds ratio (OR) and 95 percent confidence interval (95%

CI). An odds ratio greater than one for *level* changes would indicate that the 2002 publications did have an immediate impact on cholesterol-lowering medication use. *Slope or trend* changes were calculated as the ratio of adjusted odds ratios and 95% CI. This approach estimates the change in cholesterol-lowering medication use following 2002 publications controlling historical year-to-year changes prior to 2002 as well sociodemographic, health-related behaviors and health status factors.[66] A ratio of adjusted odds ratios for *slope or trend* changes greater than one would indicate that the guidelines had an impact on yearly rate of increase in cholesterol-lowering medication use. Both sociodemographic, health-related behaviors and health status factors were controlled for in these multivariable analyses.

3.3.7 Sensitivity Analysis and Stratified Analysis

A series of sensitivity analyses were conducted to better understand and assure the robustness of the main findings. First, changes in utilization patterns of cholesterol-lowering medications were evaluated among four mutually exclusive subgroups using the definitions of risk factors based on the 2002 NCEP ATP III guidelines.[8] The four subgroups were: 1) any CHD (including myocardial infarction, angina pectoris, surgical or percutaneous revascularization); 2) no CHD, diabetes only (CHD risk equivalent); 3) no CHD or diabetes, but either with PAD, stroke, or ≥ 2 CHD risk factors (hypertension, current smoking, or low-levels of HDL-C [i.e., < 35 mg/dL]), and 4) no CHD or diabetes or PAD or stroke, and < 2 CHD risk factors. Those with PAD (n=83) or stroke only (n=86) were considered into group 3 because of insufficient sample sizes for examining the impact of these conditions separately, and many of these elders had multiple comorbidities/risk factors. The composition of each risk group changed over time as it gained

(or lost) participants who developed or acquired some risk factors (or died). However, once participants were considered to have the comorbidities including CHD, diabetes, hypertension, PAD, and stroke, these conditions were considered permanently. For the second sensitivity analyses, we replaced missing covariate values with those generated using the multiple imputation.[67] Most demographic and health behavior/status covariates had complete information, and none had more than 5% with missing information. The third sensitivity analysis was performed by restricting the analysis to only those with data for the entire 10 year time period. The final sensitivity analyses used 2004-2005 as the index year to separate the pre- and post-guideline periods and allow for a potential lag effect from dissemination and physician awareness of the guidelines. A year lag effect was selected because it may take at least 1 to 1.5 years for physicians being informed about these publications through different sources.[68, 69] Finally, stratification analyses by sex, age and race were conducted to examine any differences in utilization patterns.

3.4 RESULTS

The baseline characteristics are shown in **Table 7** according to all participants. Among 3055 participants, mean age was 74 years, 52% were female, 41% were black, 30% lived alone, 62% had prescription medications coverage, 5% had severe depressive symptoms, and 10% had cognitive impairment. **Table 8** shows the prevalence of cholesterol-lowering medication use in the elderly from 1997-2008. Overall, 14.9% of the elders took cholesterol-lowering drugs at baseline (1997-1998) with statins accounting for 87% of the overall rate. The overall rate of cholesterol-lowering drugs use increased to 26.7% in 2001-2002 and to 42.6% by 2007/2008. In particular, statin use increased to 24.9% in 2001-2002 and to 39.1% in 2007-2008. The use of fibrates slightly increased from 1% in 1997-1998 to 2% in 2007-2008, and the use of bile acid sequestrants, probucol, and niacin remained the same over that 10 year time period (about 1.5%). The use of ezetimibe increased from 0.1% in 2002 when introduced to the market to 5% in 2007-2008.

Table 9 shows the results of the multivariable interrupted time-series analysis estimating changes in the *level and the slope (trend)* of cholesterol lower drug use rates after 2002. There was no *level* change of any cholesterol-lowering medication use the year before compared with the year after 2002 (adjusted OR 0.95, 95% CI 0.89 to 1.02). The multivariable results also revealed a decline in *trend* changes for the rate of increase in cholesterol-lowering medication after 2002 (adjusted ratio of odds ratios 0.92, 95% CI 0.89 to 0.95). Similar results for lack of

change in level but changes in trend were seen for statin and other cholesterol lowering medications **(Table 9).**

Sensitivity and Stratification Analyses

At baseline, 18% had any history of CHD, 11% had diabetes only, 27% were in the group that had PAD, stroke or 2 or more risk factors, and 43% were in the group of less than 2 risk factors **(Table 7).** The prevalence of cholesterol-lowering medication use in 1997-1998 was 30.6% among those with any history of CHD; 11.8% among those with diabetes only; 14.0% for those who had PAD, stroke, or 2 or more risk factors; and 9.7% for those with no CHD, DM, PAD or stroke and less than 2 risk factors (**Figure 3**). For these same groups, the percentage of elderly patients who took cholesterol-lowering medications in 2001-2002 was 49.9%, 30.1%, 24.0% and 14.6%, respectively, and 68.8%, 46.1%, 35.4%, and 26.6%, respectively took cholesterol-lowering medications in 2007-2008. A similar pattern was seen with statins for each of the four groups. Similar findings were also seen for *level* and *trend* changes as noted for the overall sample (data not shown). None of the additional sensitivity analyses appreciably changed our main findings (data not shown). Females were less likely than males to take any cholesterol-lowering medications (females vs. males: 15.1% vs. 14.8% in 1997-1998; 24.5% vs. 29.2% in 2001-2002; and 37.4% vs. 48.9% in 2007-2008, respectively). Older adults aged ≥ 75 years were less likely than those aged < 75 years to take any cholesterol-lowering medications (aged ≥ 75 vs. age < 75 years: 13.7% vs. 15.8% in 1997-1998; 24.6% vs. 27.9% in 2001-2002; and 41.2% vs. 43.3% in 2007-2008, respectively). Blacks were less likely than whites to take any cholesterol-lowering medications (whites vs. blacks: 17.2% vs. 11.8% in 1997-1998; 30.2% vs. 21.2% in 2001-2002; and 45.7% vs. 36.8% in 2007-2008, respectively). Similar findings were also seen by sex, age, and race for level and trend changes (data not shown).

3.5 DISCUSSION

Our study found that the use of cholesterol-lowering medications in the elderly nearly tripled during the period of 1997-2008 (14.9% to 42.6%). Moreover, as one might expect given their greater ability to reduce LDL-C, statins were the most common drug class used. These findings are consistent with that reported by other studies.[41, 59, 70-72] It was interesting to find that only half of those with known CHD and/or diabetes received any cholesterol lowering agent. It is difficult to determine if this represents under use of an important medication for secondary prevention as shown in other studies,[73-75] or rational omission since published data is only valid for those up to 82 years of age,[19, 76] and the mean age of Health ABC study participants in 2007-2008 was 82.4 ± 2.8 years. It is also notable that use of cholesterol lowering agents for primary prevention (i.e., those without CHD equivalent risk factors) occurred in up to 26.6% participants despite the lack of convincing efficacy evidence and the potential for greater adverse drug effects in older adults.[27] Similar to the reports by other studies,[41, 59, 70] despite the observed increase in cholesterol-lowering medication use in both racial groups, blacks remained less likely than whites to take cholesterol-lowering medications. A possible explanation is that long-term persistence in statin use has been shown to be worse in older blacks than whites.[77]

We hypothesized that after the release of the NCEP ATP III guidelines and the results from the PROSPER Study in 2002, that the use of cholesterol-lowering medication would increase immediately (i.e., change in *level)*. However, our study showed this new data in 2002 had no immediate impact on cholesterol-lowering medication use. One possible explanation for this finding is that the dissemination and implementation of clinical guidelines and evidence-based results are complex and take years to overcome barriers in clinical practice.[78,79] Additional

unique factors in the elderly that may further contribute to the lag in dissemination of evidenced-based guidelines in to clinical practice for the elderly include difficulty in translating the results from highly selective trial populations to a heterogeneous community population, competing causes of morbidity and mortality (e.g., cancer), polypharmacy and drug interactions, short remaining life expectancy, reported poor adherence of statins, and patient economic concerns.[77, 80-82]

We also hypothesized that after 2002 that there would be an increase in yearly rate of cholesterol-lowering medication use *(i.e., change in slope).* Instead, we saw that there was a decrease in the yearly rate of increase of cholesterol-lowering medication use. Although the use of cholesterol-lowering medication in the elderly has increased substantially over time, the *change in slope* declined with advancing age is consistent with the findings from other studies.[73-75]

So what are the clinical implications of these study findings for clinical pharmacy practice? The potential underuse of cholesterol lowering therapy in those elders aged ≥ 80 with CHD or risk equivalent that was observed in this study may be appropriate as summarized by a recent review.[44] The authors concluded that there is insufficient evidence to support the initiation or continuation of cholesterol-lowering treatment in this patient group.[44] Moreover, it may also be appropriate to not utilize cholesterol-lowering medications in those elders with CHD or risk equivalent that also have a limited life expectancy given that it takes 2 to 5 years of statin treatment to reduce the risk of cardiovascular events.[15] Lack of secondary prevention with cholesterol-lowering medications in older adults may also be justified given that they are at higher risk to experience adverse effects (e.g., myalgia with statins). This increase in the risk of cholesterol-lowering medication adverse effects may be due to a number of factors including: 1)

age-related decline in systemic clearance, 2) multiple comorbidities and medications, 3) drug interactions (e.g. macrolides inhibiting CYP3A4 hepatic enzyme metabolism of atorvastatin, lovastatin or simvastatin), and 4) medication adherence difficulties that can be seen especially in those with cognitive impairment.[83, 84] Having said this, the use of these agents should not be considered as contraindicated for elders aged ≥ 80 years in good health since the potential benefit may be most pronounced in this patient group due to the known increased risk of coronary heart disease with increasing age. It is important for health care professionals to discuss these potential benefits and risks with older patients with CHD or risk equivalent and take into account their informed preferences.[82]

Some limitations should be taken into account when interpreting the results of this study. Inherent to most longitudinal studies examining a broad range of older adults, the potential for survivor bias should be considered. However, the results from a sensitivity analysis, restricted to participants in the study from 1997-2008, yielded similar results. It is also possible that any use of cholesterol-lowering medications may be underestimated as medication use was measured at multiple fixed annual time points. We also cannot rule out potential confounding by such factors as family history of premature CHD, dietary therapy, and adherence to medications as information about these were not collected in the Health ABC study. Lastly, the study sample was drawn from two US cities and may not be generalizable to all other populations.

3.6 CONCLUSION

This study found that the use of cholesterol-lowering medication increased substantially over a decade in community dwelling elders, but was not related to a change in level or trend following the release of the guidelines and evidence-based data. Further studies are warranted to better guide cholesterol-lowering therapy and investigate the potential benefits and barriers of treatment among the oldest old elders (≥85 years) with CHD or at high risk.

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3.8 TABLES AND FIGURES

Table 7. Baseline Characteristics of the Health ABC Cohort and Four Subgroups (N=3,055)[a]

Sociodemographic Factors	All (n=3,055)	Any CHD (n=556)	Diabetes only (n=349)	PAD, or Stroke or 2+ risk factors (n=836)	<2 risk factors (n=1314)
Age, mean (SD)	73.6 (2.9)	74.0 (2.9)	73.5 (2.9)	73.4 (2.9)	73.6 (2.9)
Female sex	1574 (51.5)	202 (36.3)	169 (48.4)	404 (48.3)	799 (60.8)
Black race	1266 (41.4)	220 (39.6)	211 (60.5)	372 (44.5)	463 (35.2)
Pittsburgh site	1516 (49.6)	305 (54.9)	164 (47.0)	401 (48.0)	646 (49.2)
Education					
Postsecondary	1285 (42.2)	227 (40.8)	117 (33.7)	355 (42.7)	586 (44.6)
High school	996 (32.7)	182 (32.7)	105 (30.3)	283 (34.1)	426 (32.4)
Less than high school graduate	766 (25.1)	147 (26.4)	125 (36.0)	193 (23.2)	301 (22.9)
Living alone	920 (30.2)	146 (26.3)	111 (31.8)	257 (30.7)	406 (30.9)
Prescription drug coverage	1883 (61.7)	383 (68.9)	213 (61.2)	499 (59.9)	788 (60.0)

Table 7 (Continued)

Health-related behaviors	All (n=3,055)	Any CHD (n=556)	Diabetes only (n=349)	PAD, Stroke, or 2+ risk factors (n=836)	< 2 risk factors (n=1314)
Smoking status					
Current	316 (10.4)	53 (9.6)	30 (8.7)	187 (22.4)	46 (3.5)
Past	1397 (45.8)	311 (56.0)	165 (47.6)	324 (38.8)	597 (45.5)
Never	1337 (43.8)	191 (34.4)	151 (43.80)	324 (38.8)	670 (51.0)
Alcohol use					
Current	1505 (49.5)	276 (49.8)	100 (28.7)	422 (50.8)	707 (54.0)
Past	677 (22.3)	141 (25.5)	134 (38.5)	192 (23.1)	210 (16.0)
Never	859 (28.3)	137 (24.7)	114 (32.8)	216 (26.0)	392 (30.0)

Table 7 (Continued)

Health Status Factors	All (n=3,055)	Any CHD (n=556)	Diabetes only (n=349)	PAD, Stroke, or 2+ risk factors (n=836)	< 2 risk factors (n=1314)
Congestive heart failure	40 (1.3)	22 (4.2)	6 (1.7)	10 (1.2)	2 (0.2)
Chronic kidney disease	45 (1.5)	11 (2.0)	5 (1.4)	12 (1.4)	17 (1.3)
Pulmonary disease	127 (4.2)	26 (4.7)	20 (5.8)	26 (3.1)	55 (4.2)
Cancer	577 (18.9)	112 (20.2)	57 (16.3)	164 (19.6)	244 (18.6)
Excellent/good self-rated health	2558 (83.8)	418 (75.2)	261 (74.8)	691 (82.8)	1188 (90.4)
Body mass index					
Under/Normal	982 (32.1)	173 (31.1)	71 (20.3)	233 (27.9)	505 (38.4)
Overweight	1293 (42.3)	237 (42.6)	146 (41.8)	364 (43.5)	546 (41.6)
Obese	780 (25.5)	146 (26.3)	132 (37.8)	239 (28.6)	263 (20.0)
Number of prescription drugs, mean (SD)	2.9 (2.6)	4.4 (2.9)	4.0 (2.7)	2.9 (2.4)	2.1 (2.3)
Severe depressive symptoms (CES-D > 15)	144 (4.8)	31 (5.6)	15 (4.4)	41 (4.9)	57 (4.4)
Cognitive impairment (3MS< 80)	304 (10.0)	59 (10.7)	44 (12.7)	89 (10.7)	112 (8.6)

Table 7 (Continued)

Lipid profiles	All (n=3,055)	Any CHD (n=556)	Diabetes only (n=349)	PAD, Stroke, or 2+ risk factors (n=836)	< 2 Risk factors (n=1314)
Total cholesterol (mg/dL), mean (SD)	202.8 (38.7)	193.7 (39.5)	201.1 (39.4)	199.7 (40.0)	209.0 (36.3)
LDL-C (mg/dL), mean (SD)	121.7 (34.8)	115.5 (35.5)	122.3 (35.4)	122.7 (35.7)	123.4 (33.4)
HDL-C (mg/dL), mean (SD)	53.9 (17.0)	49.3 (16.4)	50.6 (15.6)	46.8 (12.4)	61.2 (17.2)
Triglyceride (mg/dL), mean (SD)	138.7 (82.9)	148.3 (87.1)	144.1 (91.7)	156.2 (102.6)	122.3 (58.3)

a Data represented as N (%), unless otherwise stated;
Abbreviations: CES-D: Center for Epidemiologic Studies-Depression scale; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol, PAD: peripheral artery disease

Table 8. Prevalence of Cholesterol-Lowering Medication Use from 1997-2008

	1997-1998 (n=3055) n (%)	1998-1999 (n=2908) n (%)	1999-2000 (n=2820) n (%)	2001-2002 (n=2631) n (%)	2002-2003 (n=2515) n (%)	2004-2005 (n=1780) n (%)	2006-2007 (n=1592) n (%)	2007-2008 (n=1344) n (%)
Any cholesterol lowering medications	456 (14.9)	509 (17.5)	586 (20.8)	702 (26.7)	737 (29.3)	656 (36.9)	676 (42.5)	573 (42.6)
Any statins	395 (12.9)	461 (15.9)	542 (19.2)	654 (24.9)	695 (27.6)	615 (34.6)	620 (38.9)	525 (39.1)
Any fibrates	35 (1.2)	30 (1.0)	32 (1.1)	33 (1.3)	29 (1.2)	29 (1.6)	33 (2.0)	28 (2.1)
Any bile acid sequestrants, probucol, niacins	43 (1.4)	33 (1.1)	33 (1.2)	35 (1.3)	40 (1.6)	21 (1.2)	21 (1.3)	21 (1.6)
Any ezetimibe	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)	38 (2.1)	77 (4.8)	69 (5.1)

Table 9. Effect of the Release of the NCEP ATP III Guidelines and Results from PROSPER Study in 2002 on Cholesterol-Lowering Medications Use[a]

Drug Class	Level Changes		Slope (Trend) Changes			
	Observed vs. Predicted (using pre-guideline trend) Difference in Use in year 2003 (Adjusted OR, 95% CI) [a]	P-value	Pre-Guideline Trend per year (Adjusted OR and 95% CI) [a]	Post-Guideline Trend per year (Adjusted OR and 95% CI) [a]	Post- vs. Pre-Guideline Difference in Trends Over Time per year (Adjusted ROR, 95% CI) [a]	p-value
Any Cholesterol Lowering Medication Use	0.95 (0.89, 1.02)	0.18	1.18 (1.15, 1.20)	1.09 (1.02, 1.15)	0.92 (0.89, 0.95)	<0.0001
Any Statin Use	0.95 (0.88, 1.01)	0.12	1.19 (1.16, 1.22)	1.07 (1.01, 1.13)	0.90 (0.87, 0.93)	<0.0001
Any Fibrate/Other Use	1.04 (0.83, 1.30)	0.74	1.02 (0.93, 1.08)	1.24 (1.01, 1.46)	1.22 (1.10, 1.35)	0.0003

a Multivariate generalized estimating equations models adjusted for sociodemographics (race, age, sex, site, education, living status), health behavior (alcohol use), and health status (pulmonary disease, body mass index, polypharmacy, and prescription medications coverage). Polypharmacy and prescription coverage are time-varying variables.
Abbreviations: CI: confidence interval; OR: odds ratio; ROR: ratio of odds ratio

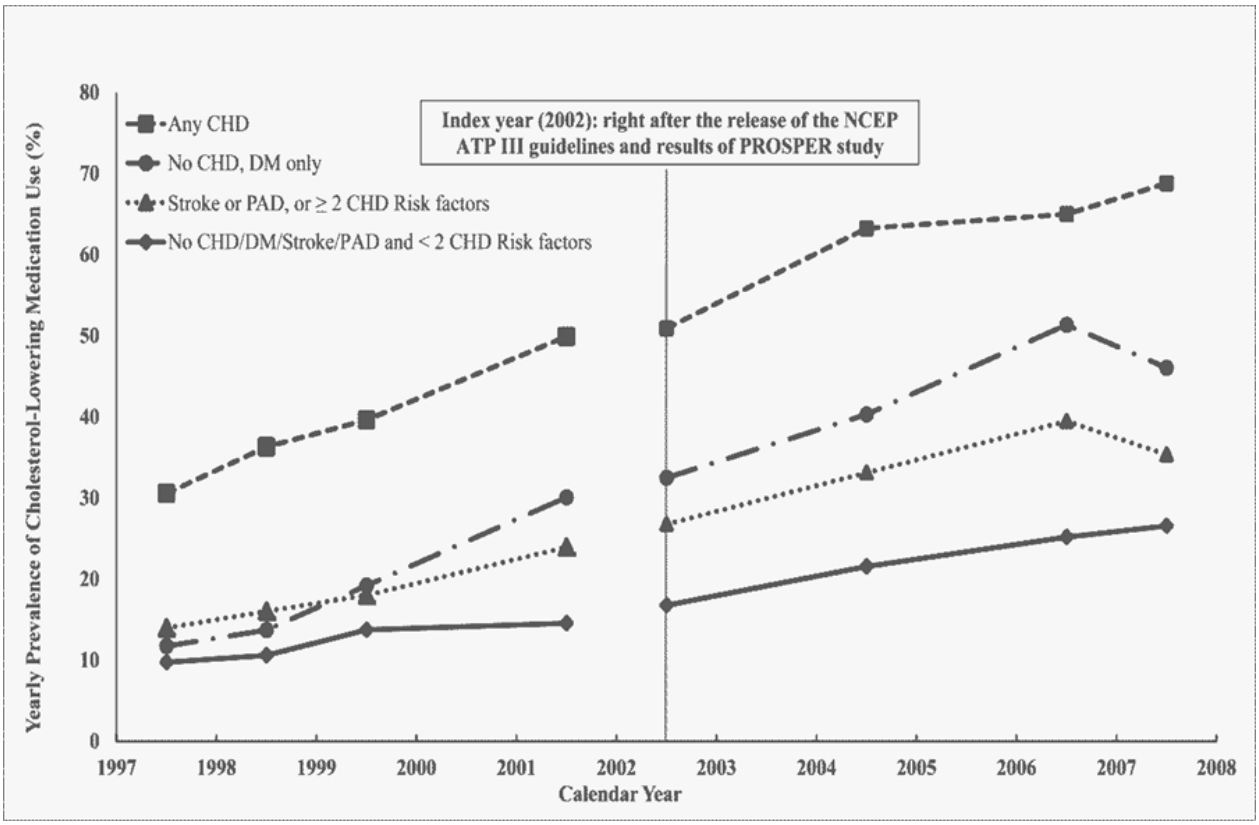

Figure 3. Yearly Prevalence of Cholesterol-Lowering Medication Use by Four Groups from 1997-2008

4.0 MANUSCRIPT 2: ASSOCIATIONS BETWEEN STATIN USE AND GAIT-SPEED DECLINE IN COMMUNITY-DWELLING OLDER ADULTS

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4.1 ABSTRACT

Background: The evidence that statin use may impact physical function decline in older adults is mixed.

Objective: To examine whether the use of statins is associated with a lower risk of gait speed decline of 0.05 m/s or more and 0.1 m/s or more per year in community-dwelling older adults.

Design: Longitudinal cohort study.

Setting: Health, Aging and Body Composition study.

Participants: 2405 participants with medication and gait speed data 1998-1999 and 1999-2000 were included.

Measurements: Any use, summated standardized daily doses (low, moderate, high) and duration (<2 years, ≥ 2 years) of statin use were computed. The effect of lipophilic/hydrophilic statins on gait speed decline was also evaluated. The primary outcomes were small, meaningful decline in usual gait speed (≥ 0.05 m/s), and substantial usual gait speed decline (≥ 0.1 m/s per year) during a 20-m walk annually over a four-year time period. Multivariable generalized estimating equations (GEEs) were used, adjusting for demographic, health-related behaviors and health status factors.

Results: The use of statins increased from 16.2% in 1998-1999 to 25.6% in 2002-2003. Approximately 34% to 38% of participants had gait speed decline ≥ 0.05 m/s per year, and 23% of participants had decline ≥ 0.1 m/s per year. Compared to non-users, any statin use was associated with a 16% risk reduction of gait speed decline ≥ 0.05 m/s per year (aOR = 0.84, 95%

CI = 0.74-0.96). A similar finding was seen in low-dose, long-term, and hydrophilic statin users. However, only low-dose statin users had a 22% decrease in the risk of gait speed decline ≥ 0.1 m/s per year (aOR = 0.78, 95% CI = 0.61-0.99).

Conclusion: Statin use may decrease the risk of gait speed decline, suggesting low-dose statin may be a treatment option for older adults.

4.2 INTRODUCTION

4.2.1 Epidemiology of Impaired Physical Function and Disability in the Elderly

The public health challenge of age-related disability and loss in physical function emerges an important topic in our rapidly aging population (1, 2). Maintenance of physical function is important in the elderly because of its relationship to the ability to live independently and to overall quality of life (3). The prevalence of physical limitations varies by age, sex, race, and education (2). National Health Interview Survey 2001-2007 showed that the prevalence of one or more physical limitations increases with advancing age (age of 50-59: 16.5%; age of 60-69: 22.9%; age of 70-79: 31.4%; age of 80 and over: 42.9%), as does the prevalence of having three or more physical limitations (age of 50-59: 8.1%; age of 60-69: 11.5%; age of 70-79: 16.2%; age of 80 and over: 26.7%) (2). Non-Hispanic black adults aged ≥ 50 years have higher prevalence of physical limitations compared to non-Hispanic white (age of 50-59: 24.1% vs. 17.2%; age of 60-69: 33.9% vs. 24.4%; age of 70-79: 43.9% vs. 35.2%; age of 80 and over: 58.4% vs. 52.1%) (2). For both non-Hispanic white and black older adults aged ≥ 50 years, women are more likely than men of the same age to have one or more physical limitations (**white**: age of 50-59: 20.5% vs. 13.8%; age of 60-69: 28.2% vs. 20.3%; age of 70-79: 39.5% vs. 29.6%; age of 80 and over: 55.4% vs. 46.3%; **black**: age of 50-59: 27.8% vs. 19.5%; age of 60-69: 39.8% vs. 26.7%; age of 70-79: 50.4% vs. 33.8%; age of 80 and over: 63.5% vs. 48.2%) (2). For both non-Hispanic

white and black older adults aged ≥ 50 years with less than a high school education have higher a prevalence of physical limitations than those with at least a high school diploma (2).

4.2.2 Gait Speed and Potential Factors that Influence Gait Speed

The ability to walk underlies many basic and community functions necessary for independence (4). The appearance of difficulties in walking marks a critical point such that assessment of gait speed has been described as the "sixth vital sign"(5), with the potential to serve as a core indicator of health and function in aging and disease (4).

Judgment about how an individual's gait speed compares with those of the population to which they belong requires the availability of reference values (6, 7). Gait speed is determined by physical features such as age, sex, height, presence or absence of disease and physical fitness (8, 9). Numerous large scale epidemiological studies have documented gait speed in healthy, community-dwelling older adults (10, 11), and normative values have been established specific to this group (6, 12). The usual gait speed for healthy women aged between 70-79 years is 1.13 m/s and for men 1.26 m/s (12). For women and men aged 80-99, the values are 0.94 m/s and 0.97 m/s, respectively (12). For well-functioning older adults, the gait speed < 0.80 m/s is an indicator of prevalent mobility limitations, <1.0 m/s is associated with adverse health outcomes and mortality in well-functioning older adults, and <1.2 m/s is associated with difficulty in crossing streets in the community (11, 13-15). A recent meta-analysis showed that the gait speed estimate for usual pace was 0.58 m/s (95% CI: 0.75-1.02) in older adults aged ≥ 70 years across the hospital settings, and 0.46 m/s (95% CI: 0.65-0.83) in acute care settings (16). Abellan et al. proposed a gait speed of 0.8 m/s as a predictor of poor clinical outcomes and 0.6

m/s as a threshold to predict further functional decline in those older adults already impaired (10).

Slowing of movement with aging appears to be a universal biological phenomenon and is likely to reflect the integrated performance of numerous organ systems. Factors that influence walking ability can be classified into six main physiological subsystems: central nervous system, perceptual system, peripheral nervous system, muscles, bone, and/or joints, and energy production and/or delivery (17). Impaired physical function and subsequent disability can occur as a result of age-related losses of muscle mass and strength or an acute event (e.g., stroke or hip fracture), or as a consequence of chronic disease (e.g., osteoarthritis or congestive heart failure) (18). Neurologic and musculoskeletal deficits linked with reductions in motor discharge rate, lower activation of muscle fibers, poor balance performance, physical fitness are other contributing factors (6, 9). In addition, area with growing body of evidence suggests a relationship between chronic inflammation and age-related muscle and strength loss, risk of disability, frailty, and physical function decline (18-28). Inflammatory cytokines have a catabolic effect on muscle (22, 29-31), and have been implicated in the pathogenesis of musculoskeletal disorders such as osteoarthritis (32). Higher IL-6 levels were significantly associated with lower muscle mass (30), weaker grip strength (30) and lower gait speed (33). A recent study showed that each doubling in CRP and IL-6 change over 9 years was associated with higher risk of physical or cognitive impairment (odds ratio for CRP: 1.29 [95% CI 1.15-1.45] and odds ratio for IL-6: 1.45 [95% CI 1.20-1.76]) among 1051 participants in the Cardiovascular Health Study All Starts Study (34).

4.2.3 Potential Mechanisms that How Statins Affect Physical Function

Multiple factors appear to be involved in frailty and age-related physical function decline (25, 26, 35). The Muscial effect of statins on physical performance may be explained by three mechanisms. Firstly, statins might affect physical function by retarding the deleterious effects of atherosclerosis on blood vessels in skeletal muscle, ensuring better perfusion and therefore, preventing muscle wasting and reducing muscle weakness and/or fatigue (36, 37). Indeed, statins increase the production of nitric oxide in the endothelium which has local vasodilator properties, in addition to antithrombogenic, antiproliferative and leukocyte adhesion inhibiting effects (36, 37). Secondly, statins may elicit their effect by reducing the risk of incident of cardiovascular events, which are major determinants of physical performance in older adults (38). The literatures suggest that statins may exert a beneficial effect on stroke (39) and dementia (40-42) prevention. Recent studies show that statins improve endothelial function in peripheral arteries (43). Finally, the most intriguing hypothesis is that statins may reduce chronic inflammation, which, in turn, is an important determinant of disability and impaired function (20). Anti-inflammatory effects of statins may affect type II (fast-twitch) muscle fibers to a greater degree than type I (slow-twitch) muscle fibers. Indeed, in older adults, higher levels of inflammatory markers are strong independent predictors of incident disability probably through an accelerated muscle catabolism leading to muscle wasting (23). Several studies have demonstrated that statins reduce levels of CRP and other inflammatory markers independent of their effects on cholesterol (44-47). Therefore, the evidence appears to provide a rationale for a direct effect of statins on physical function impairment or disability.

It is possible that the potential beneficial effect of statins may be counteracted by the muscle-related adverse events (e.g., myalgia, muscle weakness, cramps) (48-54). The incidence of myopathy among statin users was as high as 5%-10% (55, 56). A variety of different hypotheses have been suggested to account for the myotoxic effects of statins (57). These included statin-induced interruption of glycoprotein synthesis in the muscle membrane (58), deficiency in chloride channel activation in the muscle membrane (59), and increased intracellular calcium concentrations leading to impaired membrane function (60), all of which may result in myocyte injury. Decreased intracellular cholesterol which is associated with low plasma cholesterol from statin therapy may result in reduced membrane lipid content, which in turn may cause physical modification of membrane fluidity and a decrease in cell proliferation (61). In addition, HMG-CoA reductase catalyses the formation of mevalonate from HMG-CoA. Mevalonate is an important precursor not only of cholesterol but also of ubiquinone (co-enzyme Q), dolichols and isopentenyl adenine. All these products are involved in cell replication and dolichols is required for glycoprotein synthesis (62). Deficits in these products may adversely affect myocyte duplication and cause disruption of the cell membrane, predisposing to myotoxic consequences. Ubiquinone is utilized by mitochondria for electron transport, reduced synthesis of ubiquinone may result in defective mitochondrial myopathies (63) and defective ATP synthesis predisposing myocyte instability (64). However, the precise mechanisms remain unclear and there is no clear consensus of opinion regarding which is more likely to be responsible.

4.2.4 Significance of the Current Study

The preservation of physical function is critically important for prolonged, independent living and overall quality of life for older adults (3). Hence, identifying modifiable factors to delay physical function decline in older adults is a significant priority of public health interest.

Gait speed is a simple, but important indicator of functional status in older adults (10, 11, 65). Declines in gait speed consistently predict future physical disability, mortality, and major health-related outcomes (e.g., hospitalizations, nursing home admissions, falls, cognitive decline/dementia and poor quality of life) in older adults (10, 11, 13, 66-68). In older adults, every 0.1 m/s slower gait speed is associated with a 12% higher mortality (11). Despite the importance of gait speed decline, a paucity of literature has identified risk or protective factors, other than physical exercise, for age-related gait speed decline, or the magnitude of important gait decline in gait speed associated with these factors (69).

Evidence suggests that statins have anti-inflammatory effects, which is beyond their cholesterol-lowering and anti-atherosclerosis effect, and therefore may be candidates for preventing physical disability and related outcomes (10, 44-47, 70-76). The evidence that exists shows mixed results. Previous studies showed that statin use was associated with improved walking speed, walking distance, better physical performance, and improved physical activity in individuals with peripheral arterial disease (PAD) (77-81). However, Gray SL et al. did not find that statin use, regardless of any use, dose- and duration-response, lower risk of mobility limitation or physical function decline in community-dwelling older adults aged 65-79 years at baseline (82, 83) over 6 years of follow-up.

To our knowledge, the association between statin use and gait-speed decline over a 20-m walk in community-dwelling older adults has not been previously explored. The objective of this study was to examine whether the use of statins is associated with a decreased risk of clinically meaningful gait speed decline (i.e., 0.05 m/s or more and 0.1 m/s or more per year) in community-dwelling older adults. We hypothesized that statin users when compared to non-users had a decreased risk of gait speed decline. Dose-response, duration-response, and lipophilicity/hydrophilicity of statin use were also examined. We hypothesized that high-dose, long-term and hydrophilic statin use was associated with a decreased risk of gait speed decline compared to non-users.

4.3 METHODS

4.3.1 Study Design, Sample, and Source of Data

Participants were from the Health, Aging and Body Composition (Health ABC) Study, which is a prospective cohort study of 3,075 initially well-functioning white and black adults aged 70-79 years (84, 85). Participants were recruited in 1997 and 1998 from a random sample of Medicare beneficiaries residing in Pittsburgh, Pennsylvania and Memphis, Tennessee. Eligibility criteria included no self-reported difficulty in walking one-quarter of a mile (400 m), climbing 10 steps without resting, and performing basic activities of daily living. In addition, eligible participants could not use a cane, walker, crutches or other special equipment to ambulate (84, 85). The

study was approved by the Institutional Review Boards of the Universities of Pittsburgh and Tennessee, and written informed consent was obtained from each participant.

4.3.2 Study Subsample

The Year 2 (1998-1999) Health ABC visit was used as baseline since serial testing of 20-m gait speed began at this visit. A total of 2,045 participants who had both medication information and gait speed data from the 1998-1999 and 1999-2000 clinic visits were included in the current analysis.

4.3.3 Data Collection and Data Management

The data collected during annual in-person visits included results from blood tests (e.g., serum creatinine), a battery of detailed physiological measurements using standardized methods and responses to questionnaires regarding sociodemographic characteristics, multiple aspects of health behavior and status, and medication use (84, 85). Health behavior and health status factors, as well as medication use, were used to define a numbers of conditions of interest for this study (e.g., diabetes mellitus and hypertension) (86, 87). Several comorbidities examined in the current study (i.e., coronary heart disease [CHD), congestive heart failure [CHF], stroke, or peripheral artery disease [PAD]) were centrally adjudicated by a post hoc committee based on conclusive evidence from hospitalization or death records (84, 85).

At baseline (1998-1999) and annually for four years (except year 2000-2001), participants were asked to bring all prescription medications taken in the previous month. Trained interviewers

transcribed information from the medication containers on medication name, dosage form, dose, and whether the medication was taken as needed. The medication data were coded using the Iowa Drug Information Service (IDIS) and then entered into a computerized database (88). These methods of medication data collection are considered highly accurate and concordant with information contained in pharmacy claims data (89).

Gait speed was measured over a 20-m course in an unobstructed corridor at baseline (1998-1999) and continued annually for the next four years (90, 91). A 20-m gait speed was summarized in meters per second (m/s). Participants were instructed to walk at their usual pace from a starting point and walk past an orange cone indicating the end of the course. Timing started with the first step after the starting line and ended after the first step over the finishing line. Participants were allowed to use walking aids during the test, such as cane. Gait speed has high test-retest reliability in older adults with intraclass correlation coefficients greater than 0.9 (8).

4.3.4 Independent Variables

Statin use was determined from the coded prescription medication data, corresponding to IDIS codes 24060202-24060208. The primary independent variable was use versus no use of statins at baseline and annually (as a dichotomous time-varying variable). Statin exposure had to precede the ascertainment of gait speed measures in the subsequent year. For example, statin use in 1998-1999 was a potential risk/protective factor for gait speed measure assessed in 1999-2000. Statin nonusers were always the reference group for all of the analyses.

Several operational definitions of statin use (i.e., dose, duration, and lipophilicity/ hydrophilicity) were used to examine the robustness of the findings. A *priori* standardized daily dose (SDD) was used to test dose-response relationships between time-varying exposure of statin doses and gait speed measures (92). For current users of each individual statin medication at baseline, 1999-2000, and 2001-2002, we calculated the daily dose by multiplying the number of dosage forms taken the previous day by medication strength. Little information is available regarding the comparative effect of statins on inflammatory markers. Some studies suggest that effects on C-reactive protein (CRP), may be independent of degree of lipid lowering, but comparative metrics are not available for anti-inflammatory effects (75, 93). To compare across statins, we converted the daily dose to units of equivalent dose reported to decrease LDL-C by 37% (94, 95). The following daily doses were considered to equal one unit of equivalent dose (atorvastatin 10mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, simvastatin 20 mg, rosuvastatin 5 mg) (94, 95). The SDD were operationally defined based on the distribution of the data and clinical relevance into three categories: low-dose (<1.0 SDD), moderate-dose (1.0 SDD), and high-dose (> 1.0 SDD) use.

To examine the relationship between the duration of statin use and outcome measures, we operationally defined a time-varying independent categorical variable (i.e., short-term: use < 2 years vs. long-term: use ≥ 2 years) for the duration of each statin use based on the data distribution. For example, at baseline, duration of use of statin was operationally defined as either "long-term" (e.g., continuous use for previous 2 years) or "short-term" (use only at the baseline in-person medication review). At follow-up, duration of use among current users was operationally defined as either long-term (use of any statin medications at most recent and

previous in-person medication reviews) or short-term (use at most recent in-person medication review only).

In addition to this, some *in vitro* and *in vivo* experiments suggest that lipophilic statins (i.e., lovastatin, simvastatin, atorvastatin, fluvastatin) might be more likely to produce muscular adverse effects than relatively hydrophilic statins (i.e., pravastatin, rosuvastatin) (96). Therefore, analyses were stratified by lipophilic versus hydrophilic of statins.

4.3.5 Primary Outcome Measure: Gait Speed Decline per year

Previous studies show that gait speed alone is strongly associated with morbidity and mortality in older adults (11, 13, 97). The best initial estimates of small meaningful change for gait speed are near 0.05 m/s. The best estimates of substantial change for clinical and research use are near 0.10 m/s for gait speed (98). The *primary* outcome variables were gait speed decline 1) by 0.05 m/s or more, and 2) gait speed decline by 0.1 m/s or more per year (98).

4.3.6 Covariates

Several characteristics that could confound or modify the association between statin use and gait speed were adjusted for in the analysis, and were grouped into three domains: (1) sociodemographic factors, (2) health-related behaviors and (3) health status (99-102). Age was considered as a continuous variable. Other sociodemographic factors that were characterized as categorical variables included race (black or white), sex, study site, education (postsecondary education, high school graduate, or less than high school graduate), and living status (alone or

not alone). A dichotomous time-varying variable for prescription drug coverage was also included to account for patients who were on and off insurance over the study period.

Health-related behaviors were characterized as categorical variables for smoking status, alcohol use (current, past, or never), and exercise level (yes vs. no) which was based on self-report of having high to moderate intensity exercise in the previous week. Health status factors were characterized as time-varying dichotomous measures (present vs. absent) for comorbidities including hypertension, diabetes, CHD, CHF, stroke and PAD to control the confounding by indications. Hypertension was defined by self-reported diagnosis of hypertension and use of anti-hypertensive medications (86). Diabetes was defined by self-reported diagnosis of diabetes or use of anti-diabetic medications (87). Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) less than 60 ml/min, which was calculated using the four-variable version of the Modification of Diet in Renal Disease equation (103, 104). Dichotomous measures (present vs. absent) were used for self-reported pulmonary disease, osteoarthritis, and Parkinson disease at initial baseline for the Health ABC. A time-varying dichotomous variable was created for self-rated health (excellent/good vs. not excellent/good). A categorical variable for body mass index (BMI: underweight or normal [<25.0 kg/m^2], overweight [25.0–29.9 kg/m^2], or obese [≥30.0 kg/m^2]) was created (105). Dichotomous variables were created for cognitive impairment (Modified Mini-Mental State [3MS] < 80) (106) and high depressive symptoms (Center for Epidemiologic Studies Depression Scale score >15) (107). Two continuous variables were considered, leg muscle strength (i.e., average maximum torque [Nm]) and body composition (i.e., average total body lean mass [kg]) (52). Time-varying variables (yes vs. no) of medications related to falls and mobility problems including

benzodiazepines, and anticholinergic medications were also controlled (92, 108-110). In addition, three dichotomous time-varying variables (yes/no) for other medications with anti-inflammatory effects were created including (1) angiotensin converting enzyme inhibitors (ACEIs), (2) non-steroidal anti-inflammatory drugs (NSAIDs), and (3) other medications (i.e., systematic glucocorticoids, immunosuppressive medications, and some medications for rheumatoid arthritis, asthma, inflammatory bowel diseases, systemic lupus erythematosus and other systemic inflammatory diseases [**Appendix**]) (111-116). The number of overall prescription medications (excluding statins, benzodiazepine, ACEIs, and anti-inflammatory drugs) was included as a time-varying continuous variable as a proxy for comorbidity (117).

4.3.7 Main Statistical Analysis

All analyses were performed using SAS® version 9.3 (SAS Institute Inc. Cary, NC).

Appropriate descriptive statistics (mean, standard deviation, frequency and percentage) were used to summarize participant characteristics and main analytic variables. For descriptive purposes, the prevalence of statin use and gait speed decline over time were reported. For primary outcome (gait speed decline $\geq$ 0.1 m/s per year), multivariable generalized estimating equations [GEEs] models was conducted to examine the association between statin use and gait speed decline. This analysis used the SAS® GENMOD procedure with an autoregressive working correlation structure to account for potential multiple years of data from the same participants and the resulting stochastic non-independence of observations (118). A forward selection procedure was performed to determine the impact of each variable on the association of statin use and gait speed decline. In the final multivariate models, odds ratios (ORs) and 95%

confidence intervals (CI) for statin use were computed adjusted for demographics, baseline gait speed measures and covariates with a p-value less than 0.15 from the forward selection procedure. A similar approach adjusted for same covariates was conducted using other operational definitions of statin use as main predictors to test dose-response, duration-response, and lipophilicity or hydrophilicity of statin use.

4.3.8 Sensitivity and Stratification Analyses

A series of sensitivity analyses were conducted to better understand and assure the robustness of the main findings. First, we assessed change in gait speed (m/s) per year as a continuous outcome variable, and examined the associations between statin use using a series of conditional linear mixed model implemented in SAS® MIXED procedure (119, 120). The subject-specific random effect was used to accommodate the likely correlation between repeated measurements for the same participants. The change in gait speed was the successive difference in the particular functional performance measure of interest (i.e., from baseline to 1999-2000, from 1999-2000 to 2000-2001, from 2001-2002 to 2002-2003). Similar to the main analyses, other operational definitions of statin use were evaluated based on dose-response, duration, and lipophilicity of statins, separately. The second sensitivity analysis was performed by restricting the analysis to only those with data for the entire five year time period. The last sensitivity analysis was to determine if the cut point for meaningful change in gait speed for a 20-m walk is the same as the one derived from 10 feet to 10-m walk in Perera S's study (98). Finally, a stratification analyses were conducted by race, sex, and baseline gait speed (<1.0 m/s, 1.0-1.22 m/s and >1.22 m/s) due to the flooring and ceiling effects of gait speed decline. Walking 1.22

m/s is a minimum speed needed to cross a street at a timed crosswalk (15), and walking less than 1.0 m/s is a risk factor for mortality (13).

4.4 RESULTS

The baseline characteristics of the overall participants and according to statin use are shown in **Table 10.** Of the 2,405 participants, the mean age was 74.6 years, 51% were female, 37% were black, and 63% had prescription medication coverage. Among 2,405 participants, 390 (16.2%) participants used statins. Compared with non-users, statin users were more likely than non-users to be younger, white, from Pittsburgh site, have prescription drug coverage, smoke previously, drink alcohol currently, have high- or moderate-intensity exercise, have more chronic comorbidities (i.e., hypertension, diabetes, CHD, CHF, stroke, PAD, and CKD). Statin users were also more likely to be benzodiazepine and ACEI users and took more prescription drugs.

Table 11 provides the information on statin use over the study period. At baseline, 390 (16.2%) older adults used a statin, with 48% using low doses, 71% had been taking a statin for 2 years or longer, and 86% used lipophilic statins. Statin use increased steadily over the course of the study, to 20.1% in 1999-2000 and 25.6% in 2001-2002.

Table 12 describes the prevalence of gait speed decline for the overall participants and according to statin use over time. Statin users had a faster gait speed at baseline (1.17 m/s vs. 1.14 m/s, p=0.02), and this trend was seen during the follow-up years. The overall gait speed decline of 0.1 m/s or more per year changed slightly from 22.2% in 1999-2000 to 23.9% in 2002-2003. Compared to non-users, statin users had less gait speed decline of 0.05 m/s or more per

year (34.5% vs. 28.7% p =0.03) , and decline of 0.1 m/s or more per year (23.3% vs. 18%, p =0.03) in 1999-2000. However, statin users had similar proportions of gait speed decline of 0.05 m/s or more and 0.1 m/s or more per year as non-users in 2000-2002 and 2002-2003.

Table 13 shows the univariate and multivariate associations between statin use and gait speed decline of 0.05 m/s or more per year. There was a 16% risk reduction in gait speed decline of 0.05 m/s or more per year among any statin users compared to non-users (adjusted OR 0.84; 95% CI 0.74-0.96). A similar protective effect was seen in low- and high-dose, long-term and hydrophilic statin use.

Table 14 shows the univariate and multivariate associations between statin use and gait speed decline of 0.1 m/s or more per year. Compared with non-users, any statin use was likely to decrease the risk of gait speed decline of 0.1 m/s or more per year (adjusted OR 0.89; 95% CI 0.76-1.05), but was not statistically significant. A similar finding was seen in high-dose, long-term and hydrophilic of statin use when individually compared to nonusers. However, there was a 22% risk reduction in gait speed decline of 0.1 m/s or more per year among low-dose users compared to non-users of statins (adjusted OR 0.78; 95% CI 0.61-0.99).

Sensitivity and Stratification Analyses

None of the additional sensitivity analyses appreciably changed our main findings. First, the results from the mixed models revealed that any statin users (0.011 m/s, 95% CI 0.002-0.020), low-dose (0.021 m/s, 95% CI 0.008-0.034) and long-term (0.012 m/s, 95% CI 0.002-0.022) statin use had a less mean gait speed decline per year compared to non-users. Secondly, the restriction of the analysis to only those with data for the entire time period had similar findings (data not shown). Thirdly, the results from testing different cut points showed that statins use had a decreased risk of gait speed decline between 0.04-0.06 m/s per year (data not

shown). Lastly, the analysis stratified by sex yielded similar results. However, any statin use reduced the risk of gait speed was more predominant in blacks (OR: 0.76, 95% CI: 0.58-1.01) than in whites (OR: 0.94, 95% CI: 0.78-1.08). The stratification analysis only supported that any statin use reduced the risk of gait speed decline among those with baseline gait speed between 1.0 to 1.22 m/s (OR: 0.73, 95% CI: 0.55-0.98) compared to non-users, but not among those with baseline gait speed less than 1.0 m/s (OR: 0.92, 95% CI: 0.63-1.36) or 1.22 m/s or greater (OR: 1.05, 95% CI: 0.83-1.32).

4.5 DISCUSSION

Our study showed that statin use, compared to non-users, had a decreased risk of decline in gait speed of 0.05 m/s or more per year in community-dwelling older adults (98). In addition, low-dose statin use had a decreased risk of gait speed decline of 0.1 m/s or more per year (98), which has been related to outcomes of self-reported motility and other health-related adverse events. These findings are consistent with the protective effects of statins in physical function decline from two small randomized trials (81, 121), and two longitudinal studies (77, 78) in individuals with PAD. The overall protective association between any statin use and risk of small meaningful decline in gait speed is reassuring in the context of concerns of statin-related muscular adverse events in older adults. Furthermore, the muscle-related adverse events of statin use are associated with dose and blood level (122, 123). The statin-related muscular adverse events may occur in up to 10% of the adults receiving high-dose statins (56), however, the precise estimate is unknown for older frail adults. Low-dose statin use may minimize muscle-

related adverse effects in older adults, and therefore may be less likely to counteract beneficial effects on slower gait speed decline due to anti-inflammatory effect. The beneficial effects of statins in gait speed decline may be due to better endothelial function resulting in enhanced lower extremity blood flow (77), besides a reduction in inflammation-mediated sarcopenia. Regression of arterial plaque may be responsible for these associations. However, our study findings were in contrast of previous studies conducted in other community-dwelling populations, which were not restricted to a specific disease (i.e., PAD) (50, 82, 83, 124). Possible explanations of these discrepancies of the association with physical function decline include different populations (e.g., women only, younger baseline age), without testing for dose- and duration-response, and less precise outcome measure (e.g., self-reported outcomes vs. objectively assessed physical function measures).

It is also notable that hydrophilic statins may have better beneficial effect in gait speed decline than lipophilic statins. Hydrophilic statins are less capable of entering nonhepatic cells. This is one possible reason why statin-related muscular adverse events appear to be reported less frequently with the use of hydrophilic statins. However, due to limited sample size of hydrophilic statin users, further studies will be required to elucidate how different statins with different lipophilic properties and safety profiles are associated with the risk of myotoxicity (125, 126).

Strengths of this study include the prospective design in a large sample of community-dwelling older adults, well-collected medication information, the availability of serially obtained, standardized gait speed measures, and the ability to adjust for numerous potential confounders. However, some limitations should be considered when interpreting the results of this study. Inherent to most longitudinal studies examining older adults, the potential for survivor bias

should be considered. This may lead to an underestimation of the association because individuals who missed follow-up assessments (e.g., due to health problems or death) were more likely to have gait speed decline than included participants. However, the results from a sensitivity analysis, restricted to participants in the study from 1998-2003, yielded similar results (data not shown). It is also possible that any use of statins may be underestimated as medication use was measured at multiple fixed annual time points. We also cannot rule out potential confounding by such factors as adherence to medications and use of health care services because information about these was not collected in the Health ABC study. Given the high rates of non-adherence in statin users, it is possible that the protective effects of statins from gait speed decline were underestimated. Despite employing several strategies, unmeasured confounding by indications cannot be ruled out completely (127). Lastly, the study sample was drawn from two US cities and may not be generalizable to all other populations.

4.6 CONCLUSION

In conclusion, findings from this study suggest that statin use may benefit in a decreased risk of age-related gait speed decline. Although our results do not suggest any negative effects on gait speed decline at higher dose, given that older adults are at higher risk to experience other adverse effects of statin use, low-dose statins are suggested for older adults to start with, and hydrophilic statins may be used for those with multiple comorbidities and medications. Further studies and randomized clinical trials are needed to confirm the observed associations between statin use and declines in gait speed in other older adults populations.

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4.8 TABLES

Table 10. Baseline Characteristics of the Health ABC Cohort and According to Statin Use[a]

	All cohort (N= 2405)	Statin Users (N= 390)	Statin Non-Users (N= 2015)
Sociodemographics			
Age, mean (SD) ǂ	74.6 (2.8)	74.3 (2.7)*	74.7 (2.9)
Female sex	1235 (51.4)	195 (50.0)	1040 (51.6)
Black race	894 (37.2)	114 (29.2)***	780 (38.7)
Pittsburgh site	1257 (52.3)	239 (61.3)****	1018 (50.5)
Education			
Postsecondary	1084 (45.2)	192 (49.4)	892 (44.4)
High school	793 (33.1)	129 (33.1)	664 (33.0)
Less than high school graduate	522 (21.8)	68 (17.5)	454 (22.6)
Living alone	697 (29.0)	105 (26.9)	592 (29.4)
Prescription drug coverage	1521 (63.3)	282 (72.3)***	1239 (61.6)

Table 10 (Continued)

	All cohort (N= 2405)	Statin Users (N= 390)	Statin Non-Users (N= 2015)
Health-related behaviors			
Smoking status			
Current	206 (8.6)	22 (5.6)***	184 (9.2)
Past	1119 (46.6)	219 (56.2)	900 (44.7)
Never	1077 (44.8)	149 (38.2)	928 (46.1)
Alcohol use			
Current	1226 (51.2)	223 (57.2)*	1003 (50.0)
Past	507 (21.2)	79 (20.3)	428 (21.3)
Never	663 (27.7)	88 (22.5)	575 (28.7)
Having high or moderate-intensity exercise in the past 7 days	690 (28.7)	141 (36.2)***	549 (27.3)
Health Status Factors			
Hypertension‡	1104 (45.9)	220 (56.4)****	884 (43.9)
Diabetes mellitus‡	363 (15.1)	75 (19.2)*	288 (14.3)
Coronary artery disease‡	450 (18.7)	165 (42.3)****	285 (14.1)
Congestive heart failure‡	103 (4.3)	28 (7.2)**	75 (3.7)
Stroke‡	133 (5.5)	33 (8.5)**	100 (5.0)
Peripheral artery disease‡	151 (6.3)	48 (12.3)****	103 (5.1)

Table 10 (Continued)

	All cohort (N= 2405)	Statin Users (N= 390)	Statin Non-Users (N= 2015)
Health Status Factors			
Chronic kidney disease	484 (20.3)	108 (27.8)****	376 (18.8)
Pulmonary disease	99 (4.1)	10 (2.6)	89 (4.4)
Osteoarthritis	1345 (55.9)	219 (56.2)	1126 (55.9)
Parkinson disease	15 (0.6)	0 (0)	15 (0.7)
Excellent/good self-rated health	2057 (85.5)	327 (83.9)	1730 (85.9)
Body mass index			
Under/Normal	798 (33.2)	110 (28.2)*	688 (34.1)
Overweight	1030 (42.8)	187 (48.0)	843 (41.8)
Obese	577 (24.0)	93 (23.8)	484 (24.0)
Severe depression symptoms (CES-D >15)	102 (4.3)	16 (4.1)	86 (4.3)
Cognitive impairment (3MS < 80)	187 (7.8)	22 (5.6)	165 (8.2)

Table 10 (Continued)

	All cohort (N= 2405)	Statin Users (N= 390)	Statin Non-Users (N= 2015)
Leg muscle strength: Average maximum torque (Nm), Mean (SD)	104.6 (37.3)	106.1 (38.5)	104.4 (37.1)
Body composition: Total body lean mass (Kg), Mean (SD)	48.8 (10.3)	48.6 (9.7)	48.8 (10.4)
Anticholinergic use‡	345 (14.4)	52 (13.3)	293 (14.5)
Benzodiazepines‡	146 (6.1)	33 (8.5)*	113 (5.6)
ACEI‡	402 (16.7)	90 (23.1)***	312 (15.5)
NSAID use[b]‡	513 (21.3)	71 (18.2)	442 (21.9)
Other drugs with anti-inflammatory effect use [c]‡	96 (4.0)	17 (4.4)	79 (3.9)
Number of prescription drugs, mean (SD)[d]‡	2.7 (2.4)	3.4 (2.5)****	2.6 (2.3)

Abbreviations: ACEI: angiotensin converting enzyme inhibitors; CES-D: Center for Epidemiologic Studies-Depression scale; CNS: central nervous system; 3MS: Mini-Mental Status examination; NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation

[a] Data represented as N (%), unless otherwise stated; Numbers of missing information: education (n=6), prescription drug coverage (n=4), smoking (n=4), alcohol drinking (n= 11), history of congestive heart failure (n=36), kidney disease (n=19), pulmonary disease (n=8), severe depression (n=19), and cognitive impairment (n=2).

[b] Including non-aspirin NSAIDs aspirin use ≥ 1200 mg/day, and prescription salicylates medications.

[c] Other drugs with anti-inflammtory effect include systemic glucocorticoids, immunosuppressive agents, Alefacept , Anakinra, Antithymocyte globulin, Olsalazine, Efalizumab, Etanercept, Hydroxycholoroquine, Infliximab, Muromonab-CD3 (OKT3), Montelukast, Natalizumab, Omalizumab, Rituximab, Sulfasalazine, Thalidomide, Zafirlukast, Zileuton

[d] numbers of total prescription drugs – numbers of prescription statin, anticholinergic, benzodiazepines ACEI, NSAID, and other drugs with anti-inflammatory effect

*: P <0.05, **: P < 0.01, ***: P<0.001, ****: P<0.0001 from chi-square or t-test between statin users and non-users.

‡: time-varying variables

Table 11. Prevalence of Statin Use Over Time[a]

	1998-1999 (Year 2) (N= 2405), N%	1999-2000 (Year 3) (N= 2206), N%	2001-2002 (Year 5) (N= 1968), N%
Statin Use: Any users	**390 (16.2)**	**444 (20.1)**	**504 (25.6)**
High-dose (>1 SDD)	59 (2.5)	76 (3.5)	137 (7.0)
Moderate-dose (1 SDD)	143 (6.0)	195 (8.8)	235 (11.9)
Low-dose (< 1 SDD)	188 (7.8)	173 (7.8)	132 (7.0)
Long-term (≥ 2 years)	278 (11.6)	321 (14.6)	338 (17.2)
Short-term (< 2 years)	112 (4.7)	123 (5.6)	166 (8.4)
Lipophilic statin use[b]	334 (13.9)	398 (18.0)	461 (23.4)
Hydrophilic statin use[b]	56 (2.3)	46 (2.1)	43 (2.2)

Abbreviations: SDD: standardized daily dose;
[a] Detail medication information were only collected from Years 1, 2, 3, 5 and 6.
[b]: Lipophilic statins include atorvastatin, lovastatin, fluvastatin and simvastatin, and hydrophilic statins include pravastatin and rosuvastatin

Table 12. Gait Speed and Change in Gait Speed According to Statin Use Over time

Variables	1998-1999 (Year 2)[a] (N=2405)	1999-2000 (Year 3) (N=2405)	2000-2001 (Year 4) (N=2206)	2002-2003 (Year 6) (N=1968)
Gait speed in m/s (mean [SD])	1.14 (0.23)	1.15 (0.22)	1.15 (0.22)	1.10 (0.22)
Statin users	1.17 (0.22)*	1.19 (0.20)****	1.17 (0.22)	1.11 (0.20)
Statin non-users	1.14 (0.23)	1.14 (0.22)	1.15 (0.22)	1.10 (0.22)
Gait speed decline ≥ 0.05 m/s per year, N (%)				
Overall	--	807 (33.6)	805 (36.5)	754 (38.3)
Statin users	--	112 (28.7)*	166 (37.4)	185 (36.7)
Statin non-users	--	695 (34.5)	639 (36.3)	569 (38.9)
Gait speed decline ≥ 0.1 m/s per year, N (%)				
Overall	--	534 (22.2)	501 (22.7)	470 (23.9)
Statin users	--	70 (18.0)*	114 (25.7)	119 (23.6)
Statin non-users	--	464 (23.3)	387 (22.0)	351 (24.0)

a: Year 1 (1997-1998) did not measure a 20-m gait speed; Year 4 (2000-2001) did not collect medication data.
P values (statin users versus nonusers): * P <0.05, **: P < 0.01, ***: P<0.001, ****: P<0.0001

Table 13. Univariate and Multivariate Associations between Statin Use and Gait Speed Decline of 0.05 m/s or More Per Year

	Gait speed decline ≥ 0.05 m/s per year (yes/no), Crude OR (95% CI)	**P value**	**Gait speed decline ≥ 0.05 m/s per year (yes/no), Adjusted OR (95% CI)[a]**	**P value**
Non-users	Reference	--	Reference	--
Any users	0.93 (0.83, 1.05)	0.27	**0.84 (0.74, 0.96)**	**0.01**
High-dose (>1 SDD)	0.87 (0.68, 1.13)	0.31	**0.76 (0.58, 0.99)**	**0.05**
Moderate-dose (1 SDD)	1.01 (0.85, 1.20)	0.91	0.96 (0.79, 1.16)	0.67
Low-dose (< 1 SDD)	0.88 (0.73, 1.07)	0.20	**0.76 (0.62, 0.94)**	**0.009**
Long-term (≥ 2 years)	0.93 (0.82, 1.07)	0.34	**0.83 (0.71, 0.96)**	**0.02**
Short-term (< 2 years)	0.93 (0.76, 1.15)	0.52	0.88 (0.70, 1.10)	0.25
Lipophilic statin use[b]	0.97 (0.85, 1.10)	0.60	0.88 (0.76, 1.01)	0.06
Hydrophilic statin use[b]	0.69 (0.47, 1.02)	0.06	**0.60 (0.41, 0.87)**	**0.007**

Abbreviations: OR: odds ratio; SDD: standardized daily dose;

[a] Separate multivariable Generalized Estimating Equation analysis were used to adjust for baseline demographics (race, sex, site). Models included time-varying statin use, age, coronary heart disease, diabetes, stroke, peripheral artery disease, self-rated health, gait speed at previous year, anticholinergics, benzodiazepines, angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, other anti-inflammatory drugs, and number of prescription drugs.

[b] Lipophilic statins include atorvastatin, lovastatin, fluvastatin and simvastatin, and hydrophilic statins include pravastatin, and rosuvastatin.

Table 14. Univariate and Multivariate Associations between Statin Use and Gait Speed Decline of 0.1 m/s or More Per Year

	Gait speed decline ≥ 0.1 m/s per year (yes/no), Crude OR (95% CI)	P value	Gait speed decline ≥ 0.1 m/s per year (yes/no), Adjusted OR (95% CI)[a]	P value
Non-users	Reference	--	Reference	--
Any users	0.99 (0.86, 1.14)	0.87	0.89 (0.76, 1.05)	0.17
High-dose (>1 SDD)	1.00 (0.75, 1.34)	0.98	0.89 (0.66, 1.20)	0.45
Moderate-dose (1 SDD)	1.06 (0.86, 1.30)	0.59	1.01 (0.81, 1.26)	0.91
Low-dose (< 1 SDD)	0.91 (0.73, 1.13)	0.40	**0.78 (0.61, 0.99)**	**0.04**
Long-term (≥ 2 years)	0.96 (0.82, 1.13)	0.65	0.85 (0.71, 1.01)	0.07
Short-term (< 2 years)	1.06 (0.84, 1.35)	0.61	1.02 (0.79, 1.31)	0.89
Lipophilic statin use[b]	1.01 (0.87, 1.17)	0.88	0.92 (0.78, 1.08)	0.31
Hydrophilic statin use[b]	0.83 (0.54, 1.27)	0.39	0.72 (0.47, 1.12)	0.15

Abbreviations: OR: odds ratio; SDD: standardized daily dose;

[a] Separate multivariable Generalized Estimating Equation analysis were used to adjust for baseline demographics (race, sex, site). Models included time-varying statin use, age, coronary heart disease, diabetes, stroke, peripheral artery disease, self-rated health, gait speed at previous year, anticholinergics, benzodiazepines, angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, other anti-inflammatory drugs, and number of prescription drugs.

[b] Lipophilic statins include atorvastatin, lovastatin, fluvastatin and simvastatin, and hydrophilic statins include pravastatin, and rosuvastatin.

5.0 MANUSCRIPT 3: ASPIRIN, NON-ASPIRIN NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, OR ACETAMINOPHEN AND RISK OF OVARIAN CANCER

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5.1 ABSTRACT

Background: Aspirin, non-aspirin nonsteroidal anti-inflammatory drugs (NA-NSAIDs) and acetaminophen all have biological effects that might reduce the risk of ovarian cancer. However, epidemiologic data on this question are mixed.

Methods: A population-based, case-control study in western Pennsylvania, eastern Ohio, and western New York State included 902 women with incident epithelial ovarian cancer who were diagnosed between February 2003 to November 2008 and 1,802 matched controls. Regular use (at least 2 tablets per week for 6 months or more) of aspirin, NA-NSAIDs, and acetaminophen before the reference date (9 months before interview date) was assessed by in-person interview. We used logistic regression to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The OR for aspirin use was 0.81 (95% CI= 0.63–1.03). Decreased risks were found among women who used aspirin continuously (0.71 [0.54–0.94]) or at a low-standardized daily dose (0.72 [0.53–0.97]), who used aspirin for the prevention of cardiovascular disease (0.72 [0.57–0.97]), who used aspirin more recently, or who used selective COX-2 inhibitors (0.60 [0.39–0.94]). No associations were observed among women using non-selective NA-NSAIDs or acetaminophen.

Conclusions: Risk reductions of ovarian cancer were observed with use of aspirin or selective COX-2 inhibitors. However, the results should be interpreted with caution due to the inherent study limitations and biases.

5.2 INTRODUCTION

Ovarian cancer is the second leading gynecologic cancer, following cancer of the uterine corpus, and causes more deaths per year than any other cancer of the female reproductive system.[1] It afflicts about 1 in 70 women, and is the fifth leading cause of cancer death among women in the United States.[1,2] Approximately 21,550 new cases of ovarian cancer are diagnosed annually, resulting in 14,600 deaths.[1,2] Thus, strategies that focus on prevention may provide the most rational approach for meaningful reductions in incidence and deaths attributable to ovarian cancer.

Ovarian cancer has a poorly understood etiology and natural history. Two dominant hypotheses explain the genesis of the disease.[3] The ovulation hypothesis relates ovarian cancer risk to incessant ovulation, while the pituitary gonadotropin hypothesis implicates elevations in gonadotropin/estrogen levels. Epidemiologic and biologic observations do not entirely support either hypothesis. Previous work has suggested that ovarian cancer may be related to chronic pelvic inflammation that acts in concert with ovulation.[4] This theory could be an important consideration for prevention of ovarian cancer and is supported by the mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs, including aspirin and non-aspirin NSAIDs (NA-NSAIDs), act through non-competitive and irreversible inhibition of cycloxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes in the synthesis of prostaglandins to produce anti-inflammatory and anti-neoplastic effects.[5] In addition, NSAIDs may suppress ovulation and affect cell proliferation, angiogenesis, and apoptosis of the epithelium in ovarian cancer cell lines.[6] Acetaminophen, another commonly used analgesic and antipyretic drug, has weak anti-inflammatory activity and may have an anti-gonadotropic effect.[7]

Acetaminophen may also inhibit ovarian carcinogenesis through the depletion of glutathione leading to necrosis.[8] Therefore, aspirin, NA-NSAIDs, or acetaminophen may be potential agents for the chemoprevention of ovarian cancer. NSAIDs and acetaminophen are two of the most frequently used classes of medication in the United States.[9,10] NSAIDs generated about $14 billion in sales world-wide in 2008.[11] Because of the widespread use of aspirin, NA-NSAIDs and acetaminophen, any association with an increased or decreased cancer risk may have important public health implications.

Several studies have described associations between aspirin or NA-NSAIDs use and the risk of ovarian cancer, but the findings are contradictory and inconclusive. Previous studies were relatively small and lacked information or statistical power to assess the effects of dose, duration, drug classes, or indications. The purpose of this study was to describe the associations of aspirin, NA-NSAIDs, or acetaminophen use with ovarian cancer risk, using the data from Hormones and Ovarian Cancer Prediction (HOPE) study, the second-largest population-based case-control study on ovarian cancer.

5.3 METHODS

5.3.1 The HOPE study

Study population and recruitment details have been published previously.[12] Briefly, this is a case-control study involving 902 women with incident ovarian cancer (cases) from a contiguous region comprising western Pennsylvania, eastern Ohio, and western New York State. Cases were residents of this region with histologically confirmed, primary, epithelial ovarian, fallopian tube, or peritoneal cancer diagnosed between February 2003 and November 2008. Both borderline/low-malignant potential and invasive tumors were included. For brevity, the term "ovarian cancer" is used here to describe all cases. Women were referred from comprehensive hospital tumor registries, clinical practices, or pathology databases and contacted with the permission of their gynecologists. Age-adjusted incidence rates for 2003-2007 for the catchment counties in our study were similar to the rates based on the Surveillance and Epidemiology End Results (SEER) data (overall incidence rate in SEER was 14 vs. HOPE, 13 cases per 100,000). The ascertained cases were representative of the population from this region and considered as population-based. Eligible women had to be at least 25 years of age and recruited within 9 months of initial diagnosis. We excluded a total of 1,608 women (ineligible on the basis of age and time since diagnosis, residence outside of the counties in which referral hospitals were located, prior diagnosis of ovarian cancer, being non-English-speaking, or dead). Of 1,270 eligible cases, 902 completed the interview.

Controls were identified through random-digit-dialed phone numbers. Controls consisted of women at least age 25 who lived in the same telephone exchanges as cases. These women were further screened to ensure that they had no previous oophorectomy or diagnosis of ovarian cancer. Controls were frequency matched to cases by 5-year age groups and telephone exchange in approximately a 2:1 ratio. Overall, 1,802 eligible controls completed interviews (Figure).

A standardized 2-hour interview (see eAppendix [http://links.lww.com] for questionnaire) was conducted by trained interviewers in the homes of participating women. The questionnaire included a reproductive and gynecologic history, a contraceptive history, a medical history, a family history, and information on lifestyle practices. A life-events calendar, which marked milestones such as marriages and births, was used to aid recall of reproductive history, infertility treatment, hormone use, and use of aspirin, over-the-counter (OTC) and prescription pain relievers until the reference date. The reference date was calculated as 9 months before the interview (for both cases and controls) to ensure that exposures occurred before the ovarian cancer diagnosis in cases and within a similar time frame for cases and controls. The study protocol was approved by the University of Pittsburgh Institutional Review Board and by the human subject committees at each hospital where cases were identified. All study subjects gave informed consent.

5.3.2 Assessment of aspirin, NA-NSAIDs and acetaminophen use

Since most analgesic use is sporadic, regular use was defined as at least 2 tablets/week for 6 months or more. This definition created an exposure group that was homogeneous in its consistency of usage, and thus maximized the likelihood of detecting an association with ovarian

cancer. Women who used less than this minimal level were defined as non-users. Participants were first asked if they took any aspirin, OTC pain relievers or NA-NSAIDs, or prescription medications for pain or inflammation on a regular basis before the reference date. Women who responded affirmatively were then asked the drug name, dose and frequency (numbers of pills taken per day, week, or month), the age at which they started, and duration (months or years) of use. For each episode, the primary reason for using the drug was recorded. The conditions were grouped as arthritis/burstitis/rheumatism, gout, menstrual cramps, injury, surgical/dental pain, back pain, headache, muscle ache, heart disease prevention (only listed for aspirin), others, or unknown. Aspirin products were defined as any product containing generic aspirin. NA-NSAIDs included celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumatone, naproxen/naproxen sodium, rofecoxib, sulindac, valdecoxib, or other NA-NSAIDs. Acetaminophen products were defined as any product containing acetaminophen.

5.3.3 Statistical Methods

Student's t test was used for continuous variables, and the Chi-square test for categorical variables to compare differences between cases and controls. Unconditional logistic regression was used to calculate multivariable-adjusted odds ratios (ORs) as estimates of the relative risk and related 95% confidence intervals (95% CIs) for analgesics use. Potential confounders fell into 2 groups: those variables that (1) a priori were thought to be related to the exposure and also were risk factors for ovarian cancer and (2) those variables that previously published studies considered confounders. Confounders included the following: age (at reference year); interview

year; region of residence (western Pennsylvania, eastern Ohio, and western New York); education; race; religion; parity; breastfeeding; history of infertility; contraceptive use and duration; menstrual status (age at menarche, menopausal status and age at menopause); use of postmenopausal hormone and duration; indications for aspirin, NA-NSAIDs, or acetaminophen use; prior hysterectomy or tubal ligation; history of endometriosis; history of pelvic inflammatory disease; family history of breast cancer or ovarian cancer in first-degree relative; body mass index; cigarette smoking; alcohol consumption; comorbidities; and yearly household income.

Data were analyzed initially by constructing frequency counts of cases and controls by exposure variables and calculating ORs adjusted for age, region of residence, and interview year (Table 1). Second, confounders were forced into the models but were kept in the final regression model only if they changed the parameter estimates by at least 15%. The final multivariate model included age, region of residence, interview year, race, education, breastfeeding, numbers of full-term births, duration of oral contraceptive use, body mass index, postmenopausal hormone use, prior tubal ligation, arthritis, and diabetes (Tables 2-4). For the primary analyses of NSAIDs, women who had never used aspirin or NA-NSAIDs on a regular basis were the referent group. Risk was assessed separately among the subgroups of women who had used aspirin only, NA-NSAIDs only, and any NSAIDs (aspirin plus NA-NSAIDs). For the acetaminophen analyses, nonusers were considered as never having used acetaminophen regularly (but did not exclude aspirin or NA-NSAIDs use) before the reference date.

Duration of use was defined by three indicators as follows: (1) continuous (had used for at least 1 year and until or beyond the reference date); (2) current (used only less than a year and used on the reference date); and (3) past (discontinued use at least 1 year before the reference

date). To examine dose-response effects, the average daily dose was calculated by multiplying the number of dosage forms per day with the strength of the medication taken during the most recent period before the reference date. For aspirin, the average daily dose was converted to a standardized daily dose by dividing it by 325 mg, assuming it was used as antithrombotic therapy for cardiovascular disease based on the dosage suggested by American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.[13] For NA-NSAIDs and acetaminophen, the average daily dose was then converted to a standardized daily dose by dividing it into minimal effective analgesic doses per day.[14] The minimal effective analgesic doses per day for individual agents were as follows: acetaminophen (1500 mg), celecoxib (200 mg), diclofenac (100 mg), etodolac (400 mg), fenoprofen (800 mg), flurbiprofen (150 mg), ibuprofen (1200 mg), indomethacin (75 mg), ketorolac (40 mg), ketoprofen (75 mg), mecolfenamate (150 mg), meloxicam (7.5 mg), nabumetone (1000 mg), naproxen (500 mg), piroxicam (20 mg), rofecoxib (25 mg), tolmetin (600 mg), sulindac (300 mg), and valdecoxib (10 mg).[15-17] Dosages were categorized into three clinically relevant categories: low-dose ($\leq$ 0.5 standardized daily dose), moderate-dose (0.5-1 standardized dose) and high-dose ($>$ 1 standardized dose).[14] Morever, the subgroup analyses were conducted by recency of use (e.g., age at first/last time use), self-reported indication and two types of NA-NSAIDs (i.e., non-selective NA-NSAIDs and selective COX-2 inhibitors). For the analysis on indications for analgesics, women who used different analgesics or the same analgesics but for different indications were considered separately. Analyses were also conducted separately among women with borderline and invasive epithelial ovarian tumors, and various histologic subgroups (i.e., serous, mucinous, endometrioid, clear cell, mixed cell and other epithelial cells); age less than 55 and 55 or more years; with and without arthritis; and with and without diabetes. All analyses

were carried out using STATA, version 11.0, statistical package (StataCorp LP, College Station, Texas, USA).

5.4 RESULTS

Population characteristics are described in **Table 15**. Ninety-seven percent of the women were white; 61% of cases and 57% of controls were older than age 55. Cases were more likely to be older, black, and nulliparous, and to have a body mass index of 30 kg/m^2 or more. Controls were more likely to be educated beyond high school, to have breastfed, have used oral contraceptives or postmenopausal hormones, have a history of tubal ligation, and have cormobidities including arthritis and diabetes. Overall, 489 cases and 1,015 controls reported having used aspirin, NA-NSAIDs, or acetaminophen on a regular basis.

Table 16 describes the regular use of aspirin or NA-NSAIDs and risks of ovarian cancer. The adjusted OR for regular use (versus never-use) of aspirin was 0.81 (95% CI= 0.63–1.03). ORs were reduced among continuous users (0.71 [0.54–0.94]), women who had used aspirin at low-standardized daily dose (0.72 [0.53–0.97]), women who began using aspirin only after age 45 (0.66 [0.50–0.88]), and women who stopped using after age 55 (0.70 [0.53–0.93]). Of those in the low-standardized daily dose group, the OR for using aspirin at daily doses of ≤81 mg was 0.66 (0.48–0.90). There were no associations between NA-NSAIDs or acetaminophen and ovarian cancer (**Table 19**).

In **Table 17**, the adjusted OR for regular use of aspirin for prevention of cardiovascular disease was 0.72 (0.57–0.97). Seventy-one percent of women had used aspirin 81 mg daily for

this purpose. A decreased OR was more evident among women who used aspirin for cardiovascular prevention for at least 5 years (0.66 [0.48–0.92]). Risk patterns remained essentially unchanged when stratified by indications for NA-NSAIDs use (**Table 20**).

ORs were reduced among women who used selective COX-2 inhibitors (0.60 [0.39–0.94]), but not in users of non-selective NA-NSAIDs (**Table 18**). The protective effects of selective COX-2 inhibitors were found only in women who used celecoxib (0.46 [0.25–0.84]), with no evidence of association in women who used rofecoxib or valdecoxib.

Cases included 677 women with invasive epithelial ovarian tumors, 97 with borderline or low-malignant potential epithelial ovarian tumors, 75 with peritoneal tumors, 32 with fallopian tumors, and 21 with "other/missing" type. Among the various histologic types of ovarian cancer, 516 cases were diagnosed with serous, 66 with mucinous, 100 with endometrioid, 54 with clear cell, 77 with mixed cells and 89 with other epithelial tumors. The results were similar for borderline or low-malignant potential and invasive tumors, and across categories of histologic types (**Table 21)**. Stratification by age (less than 55 and 55 or more), arthritis status, and diabetes status, did not reveal any important differences in the associations between aspirin, NA-NSAIDs, or acetaminophen use and ovarian cancer.

5.5 DISCUSSION

Aspirin or selective COX-2 inhibitors were associated with reduced risk of ovarian cancer, especially among middle aged and older women who took aspirin at low doses (or for prevention of cardiovascular disease) continuously over a long period of time. The results do not support

the regular use of non-selective NA-NSAIDs and acetaminophen in the chemoprevention of ovarian cancer. We were able to evaluate dose-effects comprehensively among NSAIDs by using a standardized daily dose, and we had sufficient sample size to perform stratified analyses by indications of analgesic use and types of NA-NSAIDs.

Our results provide an additional direction for future study on the relationship between aspirin use and risk of ovarian cancer. Low-dose and continuous aspirin use had modest protective association with about 20 to 30% risk reduction, but without a dose-response relationship. A protective effect was not found in moderate to high-dose groups, which could have been due to smaller sample sizes with insufficient power. Our results agree with a study conducted by Hannibal et al.,[18] in which there were similar findings with aspirin use. However, findings were null in a randomized controlled trial[19] and 5[21-25] of 8 cohort studies,[20-27] and inconsistent in 12 previous case-control studies.[7,18,28-37] Ten[7,20,22-24,28,30,31,34,35] studies found no association with aspirin use regardless of the duration or frequency of use, 4 studies found protective effects,[25,32,33,36] and 2 studies found harmful effects on ovarian cancer.[18,37] Our results of null associations with NA-NSAIDs use support findings in 5[7,23,24,26,,30] of 9 previous studies.[7,20,23, 24,26,,27,30,32,37] Two studies[7,31] showed protective results of acetaminophen, not found in our study or 10 others.[18,20,21,23,24,25,29,32,33,37] These inconsistent findings may reflect inhibition of the progression, rather than the induction, of ovarian cancer; differences in the definition of regular analgesics use; incomplete or lack of information of dose, frequency, indication, and the list of medications queried; and different exposure assessments. Most analgesic use is sporadic, and recall of sporadic use may be less accurate. Furthermore, cumulative exposure could be assessed only approximately, due to incomplete information on dose and duration. Some studies evaluated dose in numbers of pills or tablets per week. However, different brands may not

contain standardized amounts of the active ingredient. The list of NA-NSAIDs queried is heterogeneous and not comprehensive. This could lead to a misclassification of users and non-users, which would bias the results towards the null and attenuate the protective effect. The methodologic differences in assessing exposure remains an issue until validated operational definitions can be developed.

Given that most analgesic use may be episodic, it is conceivable that low-dose and continuous aspirin use for antithrombotic therapy may be more effective than sporadic use in reducing the synthesis of prostaglandins, further inhibiting chronic inflammation, cell proliferation, DNA synthesis, and suppressing immune response to neoplastic cells.[38] The biologic explanations for the protective association between aspirin or selective COX-2 inhibitors and ovarian cancer could be due to anti-carcinogenic effects via inhibition of COX-2 and COX-independent mechanisms. Aspirin and selective COX-2 inhibitors could also suppress carcinogenesis through pathways independent of prostaglandins. Increased COX-2 expression appears to be involved in the development of cancer by promoting cell division, inhibiting apoptosis, altering cell adhesion and stimulating angiogenesis. Some tumors expressing COX-2 are reported to exhibit more aggressive phenotype and poor clinical prognosis.[39] Recent preclinical data demonstrated that prostaglandin E2 is strongly associated with surrounding stroma in the tumor microenvironment in ovarian cancer and tumor progression.[40] COX-2 is expressed in epithelial ovarian cancer; the rate of expression ranges from 31% to 89%.[39] Furthermore, aspirin and selective COX-2 inhibitors could act indirectly by inhibiting ovulation.[41] In our study, the protective effect of selective COX-2 inhibitors was only found in using celecoxib. Rofecoxib is a more potent COX-2 inhibitor than celecoxib, although Gorsch et al[42] found that celecoxib had unique and stronger anti-carcinogenic activity.

Our study is the second largest case-control study in ovarian cancer research, with a population-based design that contributes to generalizability of the results. The population had relatively high use of OTC and prescription analgesics, and provided detailed information on types, frequency, dose, duration and indications. The study collected data on a large number of potential confounders, which allowed for robust multivariate analyses. Complete dosage information allowed us to evaluate the risk by standardized daily doses and to conduct stratified analysis of selective COX-2 inhibitors.

Our study has certain limitations and biases that may have contributed to the observed results. First, we had no data on the characteristics of excluded and non-responding cases. Based on additional sensitivity analyses, the protective results for aspirin at low-standardized daily dose, continuously and recently, would be nullified if the responding controls had at least twice the exposure of non-responding controls, or if non-responding cases had at least 1.7 times the exposure of the responding cases. Although responders and non-responders might not have the same analgesic exposure, it is unlikely that non-responders in either the case or control groups would have double or half of the exposure of the responders. Therefore, we believe the results are robust even with the non-responders. Second, cases may be more motivated to remember their analgesic use than controls. However, any tendency for the cases to better recall exposures would result in ORs greater than 1.0 rather than the protective effects observed here. Alternatively, controls might exaggerate their exposure relative to cases, if controls believed analgesics have a chemoprotective effect. This bias could over-estimate the protective effect. To reduce the impact of recall bias, a defined reference date was used for assessing exposures. The protective effects of recent aspirin use might be due to recall limitation since patients were more likely to recall the medications used recently. Third, measurement and misclassification

errors are presumably present when relying on self-reported and single measurement of analgesics use without verification.[43] Regular use was defined to improve recall; however, this means that sporadic analgesic use could not be assessed. Including sporadic use in the non-user group, or evaluating aspirin/NA-NSAID use without excluding acetaminophen users, might attenuate the association and bias results toward the null. The results from additional analyses were similar when comparing non-regular users of any analgesics with 7 mutually exclusive groups (aspirin only, NA-NSAID only, aspirin plus NA-NSAID, acetaminophen only, aspirin plus acetaminophen, NA-NSAID plus acetaminophen, aspirin plus NA-NSAID plus acetaminophen) (**Table 22**). However, duration and dose-response effects could not be evaluated due to small sample sizes in the last 4 of these subgroups.

Fourth, we did not collect comprehensive information on medical co-morbidities related to cardiovascular disease, health-conscious behaviors, or factors related to adverse histories of aspirin use. Although the observed effect might be biased by the residual or unmeasured confounding, little change was found when two health-related behavior factors (i.e., how often having a routine gynecologic check-up or engaging in physical activities) were included in a separate analysis (for aspirin use, OR= 0.79 [95% CI= 0.62–0.99]; for NA-NSAIDs, 1.04 [0.82–1.32]). Fifth, while different NA-NSAIDs may have different effects on ovarian cancer, all were grouped into a single category. This limits our ability to evaluate the effect of individual NA-NSAIDs. Sixth, survival bias is possible. Since aspirin is used in the primary and secondary prevention of coronary heart disease, especially among high-risk women, it is possible that earlier mortality among aspirin users (e.g., from heart disease) precludes diagnosis of ovarian cancer and therefore produces a false impression of beneficial effect. Finally, the majority of women were white, limiting generalizability of the results to other ethnicities.

Our data suggest a lower risk of ovarian cancer among women who used aspirin at a low-standardized daily dose continuously, or who used selective COX-2 inhibitors. These results should be interpreted with caution due to inherent study limitations and biases. Future research on these associations should better characterize accompanying medical conditions, health and lifestyle behaviors, the dose, frequency, and duration of analgesic use, age of therapy initiation, genetic susceptibility, and the overall risk-benefit balance.

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5.7 TABLES

Table 15. Characteristics of Ovarian Cancer Cases and Controls in the HOPE Study

	Case (n = 902) No. (%)[a]	Control (n = 1,802) No. (%)[a]	OR[b] (95% CI)
Age (years); mean (SD)	58.29 (12.8)	57.02 (12.4)	-
Race			
White[c]	856 (95)	1758 (97)	1.00
Black	35 (4)	29 (2)	2.23 (1.35–3.68)
Other	11 (1)	15 (1)	1.43 (0.65–3.14)
Education			
Not high school graduate[c]	83 (9)	82 (4)	1.00
High school graduate	303 (34)	535 (30)	0.56 (0.40–0.78)
Post-high school	251 (28)	553 (31)	0.45 (0.32–0.64)
College graduate or post-college	265 (29)	632 (35)	0.43 (0.30–0.60)
Contraceptive use[d]			
Never use[c]	120 (13)	121 (7)	1.00
Any hormonal	481 (53)	1168 (65)	0.41 (0.31–0.55)
Non-hormonal	297 (33)	508 (28)	0.58 (0.43–0.77)
Oral contraception use[d], years			
Never use[c]	367 (41)	531 (30)	1.00
<1-4	321 (35)	667 (37)	0.69 (0.56–0.85)
<5-9	142 (16)	331 (18)	0.61 (0.47–0.78)
>9	71 (8)	273 (15)	0.37 (0.27–0.51)
No. of full-term births[e](%)			
Never pregnant[c]	167 (19)	167 (9)	1.00
0	46 (5)	63 (4)	0.75 (0.49–1.17)
1	120 (13)	231 (13)	0.52 (0.38–0.71)
2	264 (29)	601 (33)	0.43 (0.33–0.56)
≥ 3	305 (34)	740 (41)	0.37 (0.29–0.48)
Ever breastfeeding			
Never pregnant[c]	167 (18)	167 (9)	1.00
Ever pregnant but never breastfeeding	432 (48)	747 (42)	0.56 (0.44–0.72)
Any breastfeeding	303 (34)	888 (49)	0.33 (0.26–0.43)
Postmenopausal hormone use[d]			
Never use[c]	603 (67)	1137 (63)	1.00
Estrogen only	155 (17)	304 (17)	0.87 (0.69–1.09)
Estrogen + Progesterone	118 (13)	307 (17)	0.67 (0.53–0.85)

Table 15 (Continued)

	Case (n = 902) No. (%)[a]	Control (n = 1,802) No. (%)[a]	OR[b] (95% CI)
History of tubal ligation[d]			
No[c]	666 (74)	1162 (65)	1.00
Yes	201 (22)	616 (34)	0.57 (0.47–0.68)
BMI (kg/m^2)[d]			
< 25[c]	300 (33)	670 (37)	1.00
25-29	267 (30)	528 (29)	1.12 (0.91–1.37)
≥ 30	334 (37)	603 (34)	1.25 (1.03–1.51)
Self-reported comorbidities[f]			
Arthritis	335 (37)	825 (46)	0.63 (0.51–0.73)
Hypertension	329 (37)	662 (37)	0.90 (0.76–1.09)
Diabetes	86 (10)	217 (12)	0.74 (0.57–0.96)
Family history of breast and ovarian cancers in first-degree relatives[d,g]			
No known family history[c]	715 (79)	1491 (83)	1.00
Breast cancer only	147 (16)	255 (14)	1.16 (0.93–1.45)
Ovarian cancer only	32 (4)	44 (2)	1.49 (0.93–2.37)
Breast and ovarian cancer	6 (1)	10 (1)	1.24 (0.45–3.46)
Annual household income[d]			
< $20,000[c]	137 (15)	245 (14)	1.00
$20,000 – $34,999	166 (19)	307 (17)	0.99 (0.74–1.31)
$35,000 – $69,999	304 (34)	615 (35)	0.96 (0.74–1.24)
≥ $70,000	201 (23)	436 (25)	0.87 (0.66–1.16)
Refused	75 (9)	151 (9)	0.96 (0.68–1.37)
NSAIDs[h] regular use[i]			
Non-users[c, j]	456 (51)	850 (47)	1.00
Aspirin only	169 (19)	360 (20)	0.79 (0.63–0.98)
NA-NSAIDs only	167 (18)	336 (19)	0.91 (0.73–1.13)
Aspirin plus NA-NSAIDs	110 (12)	256 (14)	0.74 (0.57–0.95)
Acetaminophen regular use[i]			
Non-users[c, k]	738 (82)	1447 (80)	1.00
Acetaminophen	164 (18)	355 (20)	0.90 (0.73–1.11)

[a] Except for age

[b]:Except for age, all the ORs were adjusted by age (continuous), region of residence, interview calendar year in the logistic regression.

[c] Reference category.

[d] Data were not summed to total due to the missing or unknown values.

[e] Number of full-term births, including both live and stillbirths; full-term is >6 months; twins and other multiples count as 1.

[f] Reference category is no arthritis, no hypertension, and no diabetes; respectively

[g] first-degree relatives including natural father and mother and blood-related brothers, sisters, sons and daughters.

[h] NSAID: includes aspirin or all other reported NA-NSAIDS.

[i] Regular use defined as ≥ 2 tablets/week for ≥ 6 months.

[i] Non-user: women who indicated that they didn't use aspirin or NA-NSAID (but might or might not have used acetaminophen) ≥ 2 tablets/week for ≥ 6 months ("minimal level").

[k] Non-user: women who indicated that they didn't used acetaminophen (but might or might not have used aspirin or NA-NSAID)≥ 2 tablets/ week for ≥ 6 months ("minimal level").

Table 16. Regular Use of Aspirin or NA-NSAIDs and Risk of Ovarian Cancer in the HOPE study

	Aspirin only			NA-NSAID only			Aspirin plus NA-NSAID		
	No. Cases	No. Controls	OR (95% CI)[a]	No. Cases	No. Controls	OR (95% CI)[a]	No. Cases	No. Controls	OR (95% CI)[a]
Nonusers [b]	456	850	1.00	456	850	1.00	456	850	1.00
Regular users [c]	169	360	0.81 (0.63–1.03)	167	336	1.06 (0.83–1.36)	110	256	0.95 (0.70–1.27)
Types of users [d]									
Continuous	121	283	0.71 (0.54–0.94)	96	199	1.10 (0.78–1.55)	93	211	0.99 (0.72–1.36)
Current	6	17	0.50 (0.19–1.32)	11	31	0.93 (0.64–1.37)	4	12	0.76 (0.23–2.57)
Past	42	60	1.34 (0.86–2.10)	60	106	1.19 (0.77–1.84)	13	33	0.76 (0.37–1.55)
Standardized-daily dose[e]									
Low	92	227	0.72 (0.53–0.97)	102	189	1.12 (0.83–1.51)	69	163	0.88 (0.62–1.24)
Moderate	46	81	0.84 (0.55–1.28)	42	97	0.96 (0.62–1.47)	26	57	1.21 (0.72–2.05)
High	31	52	1.08 (0.66–1.79)	23	50	1.01 (0.58–1.78)	15	36	0.90 (0.46–1.75)

Table 16 (Continued)

	Aspirin only			NA-NSAID only			Aspirin plus NA-NSAID		
	No. Cases	No. Controls	OR (95% CI)[a]	No. Cases	No. Controls	OR (95% CI)[a]	No. Cases	No. Controls	OR (95% CI)[a]
Age at first use (years)									
< 45	50	75	1.32 (0.73–1.61)	77	162	1.04 (0.74–1.46)	62	79	1.10 (0.77–1.59)
≥ 45	119	285	0.66 (0.50–0.88)	90	174	1.08 (0.78–1.49)	48	177	0.79 (0.53–1.17)
Age at last use (years)									
< 55	48	90	1.08 (0.73–1.61)	91	200	1.04 (0.76–1.42)	40	79	1.12 (0.73–1.75)
≥ 55	121	270	0.70 (0.53–0.93)	76	136	1.10 (0.77–1.56)	70	177	0.85 (0.59–1.21)

[a]: The ORs were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births , duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.
[b]: Non-user: Women who indicated that they did not use aspirin or NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months ("minimal level"). Reference category.
[c]: Regular user: women who indicated that they had used aspirin/NA-NSAIDs/aspirin plus NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months
[d]: Duration of use was defined by three indicators: (1) continuous (had used for at least 1 year and until or beyond the reference date); (2) current (used only less than a year and used on the reference date); (3) past users (discontinued use at least 1 year before the reference date).
[e]: To examine dose-response effects, the average daily dose was converted to a standardized daily dose by dividing by 325 mg for aspirin and minimal effective analgesic doses per day for other agents. Dosages were categorized into three clinically relevant categories: low-dose (≤ 0.5 standardized daily dose), moderate-dose (0.5-1 standardized daily dose) and high-dose (> 1 standardized daily dose).

Table 17. Regular use of Aspirin by Self-Reported Indications and Risk of Ovarian Cancer in the HOPE study

	No. Cases	No. Controls	OR (95% CI)[a]
Nonusers [b]	623	1186	1.00
Regular users[c] by indications[d]			
Prevention for CVD	159	392	0.72 (0.57–0.97)
Arthritis/bursitis, rheumatism	44	93	0.80 (0.53–1.21)
Headache	51	94	1.04 (0.71–1.52)
Other pain or injuries	50	75	1.27 (0.85–1.90)

[a]: ORs and p-values were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.
[b]: Non-user: women who indicated that they had not used aspirin ≥ 2 tablets/week for ≥ 6 months ("minimal level"). Reference category.
[c]: Regular user: women who indicated that they had used aspirin ≥ 2 tablets/week for ≥ 6 months
[d]: If patients used aspirin for different major indications before the reference date, each episode was counted separately

Table 18. Regular Use of Non-Selective or Selective NA-NSAID and Risk of Ovarian Cancer among NA-NSAID Only Users in the HOPE Study

	No. Cases	No. Controls	OR (95% CI)[a]
Nonusers [b]	456	850	1.00
Non-selective NA-NSAIDs [c] users	139	261	1.00 (0.78–1.30)
Selective COX-2 NA-NSAIDs[c] users	28	75	0.60 (0.39–0.94)

[a]: ORs and p-values were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.
[b]: Non-user: women who indicated that they had not used aspirin or NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months ("minimal level"). Reference category.
[c]: selective COX-2 NA-NSAIDs users include rofecoxib, celecoxib and valdecoxib, and the rest of NA-NSAIDs were included in non-selective NA-NSAIDs based on the most recent record daily dose of acetaminophen, so we combined moderate- and high-standardized daily dose into one group (moderate-high)

Table 19. Regular use of Acetaminophen and risk of ovarian cancer in the HOPE study

	No of Cases	No. of Controls	OR (95% CI)[a]
Nonuser[b]	738	1,447	1.00
Regular users[c]	164	355	0.98 (0.79, 1.23)
Types of users[d]			
Continuous	98	212	0.98 (0.74, 1.30)
Current	9	24	0.81 (0.36, 1.83)
Past	57	119	1.02 (0.72, 1.45)
Standardized daily dose[e]			
Low	136	291	0.99 (0.77, 1.26)
Moderate-High	28	64	0.98 (0.60, 1.60)
Age at first use (years)			
< 45	86	175	1.02 (0.75, 1.37)
≥ 45	78	180	0.95 (0.70, 1.30)
Age at last use (years)			
< 55	84	183	0.98 (0.72, 1.32)
≥ 55	80	172	0.99 (0.73, 1.35)
Time since first use (years)			
< 10	82	167	1.05 (0.78, 1.43)
≥ 10	81	188	0.91 (0.68, 1.23)
Time since last use (years)			
< 4	114	256	0.94 (0.72, 1.22)
≥ 4	49	99	1.08 (0.74, 1.56)

[a]: ORs and p-values are adjusted by age at reference year, interview year, study center, race, education, breastfeeding, numbers of full-term, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.
[b]: Non-user: Women who indicated that they had not used acetaminophen (but may or may not use aspirin or NA-NSAIDs) ≥ 2 tablets/per week for at least 6 months ("minimal level"). Reference category.
[c]: Regular user: women who indicated that they had used acetaminophen (but may or may not use aspirin or NA-NSAIDs) ≥ 2 tablets/per week for at least 6 months
[d]: Duration of use was defined by three indicators: (1) continuous (had used for at least 1 year and until or beyond the reference date); (2) current (used only less than a year and used on the reference date); (3) past users (discontinued use at least 1 year before the reference date).
[e]: Only 6 cases and 9 controls used high standardized daily dose of acetaminophen, so we combined moderate- and high-standardized daily dose into one group (moderate-high)

Table 20. Regular use of NA-NSAIDs only or Acetaminophen by self-reported indications and risk of ovarian cancer in the HOPE study

	NA-NSAIDs only			Acetaminophen		
	No. Cases	No. Controls	OR (95% CI)[a]	No. Cases	No. Controls	OR (95% CI)[a]
Nonusers [b]	456	850	1.00	738	1447	1.00
Regular users[c] by indications[d]						
Arthritis/bursitis, rheumatism	74	191	0.85 (0.59, 1.21)	62	161	0.88 (0.62, 1.25)
Headache	16	38	0.99 (0.51, 1.91)	50	100	1.05 (0.72, 1.53)
Other pain or injuries	85	127	1.33 (0.96, 1.85)	65	125	1.04 (0.73, 1.46)

[a]: ORs and p-values were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.
[b]: Non-user: for NA-NSAIDs only, women who indicated that they had not used aspirin or NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months ("minimal level"); for acetaminophen, Women who indicated that they had not used acetaminophen (but may or may not use aspirin or NA-NSAIDs) ≥ 2 tablets/per week for at least 6 months. Reference category.
[c]: Regular user: women who indicated that they had used aspirin ≥ 2 tablets/week for ≥ 6 months
[d]: If patients used NA-NSAIDs (or acetaminophen) for different major indications before the reference date, each episode (indication) was counted separately

Table 21. Regular use of Aspirin, NA-NSAID, Acetaminophen and Risk of Ovarian Cancer by Tumor Behaviors and Histologic Types in the HOPE study

	OR (95% CI)[a] among Regular users[b]		
	Aspirin only	NA-NSAID only	Aspirin plus NA-NSAID
Nonusers [c]	1.00	1.00	1.00
Tumor Behaviors			
Borderline or low-malignant potential	0.66 (0.43, 1.02)	1.04 (0.60, 1.60)	0.74 (0.44, 1.24)
Invasive	0.79 (0.62, 1.02)	1.06 (0.82, 1.39)	0.99 (0.73, 1.34)
Histologic Types			
Serous	0.79 (0.59, 1.05)	0.95 (0.70, 1.30)	0.75 (0.52, 1.08)
Non-Serous[e]	0.83 (0.58, 1.19)	1.27 (0.90, 1.78)	1.30 (0.87, 1.93)

[a]: The ORs were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births , duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.
[b]: Regular user: women who indicated that they had used aspirin/NA-NSAIDs/aspirin plus NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months
[c]: Non-user: Women who indicated that they did not use aspirin or NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months ("minimal level"). Reference category
e: Non-serous types include mucinous (n=66), endometrioid (n=100), clear cell (n=54), mixed cells (n=77), and other/unknown epithelial tumors (n=89). Except serous type, other histologic types had small sample sizes, resulting in imprecise estimates.

Table 22. Regular Use of Aspirin, NA-NSAID or Acetaminophen and Risks of Ovarian Cancer in the HOPE Study (Definition of non-users: without use any analgesics regularly)

	No. of Cases	No. of Controls	OR (95% CI)[a]
Nonuser[b]	411	784	1.00
Regular users	491	1018	0.97 (0.81, 1.16)
Aspirin only	136	285	0.79 (0.61, 1.04)
Types of users[c]			
Continuous	**102**	**234**	**0.73 (0.54, 0.98)**
Current	5	15	0.50 (1.18, 1.44)
Past	29	36	1.43 (0.82, 2.51)
SDD[d]			
Low	**77**	**197**	**0.68 (0.49,0.94)**
Moderate	41	61	0.97 (0.62, 1.53)
High	18	27	1.07 (0.54, 2.10)
NA-NSAID only	119	232	1.13 (0.86, 1.49)
Types of users[c]			
Continuous	65	131	1.14 (0.80, 1.62)
Current	8	22	0.85 (0.35, 2.06)
Past	46	79	1.30 (0.85, 2.01)
SDD[d]			
Low	68	120	1.25 (0.88, 1.79)
Moderate	24	58	0.96 (0.56, 1.65)
High	27	54	1.19 (0.70, 2.02)
Aspirin + NA-NSAID	72	146	1.09 (0.76, 1.55)
Types of users[c]			
Continuous	61	125	1.07 (0.74, 1.57)
Current	4	5	2.62 (0.63, 0.80)
Past	7	16	0.82 (0.31, 2.16)
Standardized daily dose[d]			
Low	42	94	0.89 (0.58, 1.38)
Moderate	17	34	1.39 (0.72, 2.67)
High	13	18	1.70 (0.78, 3.70)
Acetaminophen only[e]	45	66	1.26 (0.81, 1.95)
Aspirin plus Acetaminophen[e]	33	75	0.92 (0.58, 1.47)
Acetaminophen plus NA-NSAID[e]	48	104	0.94 (0.62, 1.44)
Aspirin plus Acetaminophen plus NA-NSAID	38	110	0.83 (0.53, 1.30)

[a]: The ORs were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.
[b]: Non-user: Women who indicated that they did not used any aspirin, NA-NSAIDs or acetaminophen ≥ 2 tablets/week for ≥ 6 months ("minimal level"). Reference category.
[c]: Duration of use was defined by three indicators: (1) continuous (had used for at least 1 year and until or beyond the reference date); (2) current (used only less than a year and used on the reference date); (3) past users (discontinued use at least 1 year before the reference date).
[d]: To examine dose-response effects, the average daily dose was converted to a standardized daily dose by dividing it minimal effective analgesic doses per day. Dosages were categorized into two clinically relevant categories: low-dose (≤ 0.5SDD), moderate-to-high dose (>0.5 SDD).
e: Subgroup analyses of dose- and duration-effects were not shown due to relatively small sample size in cases.

6.0 DISCUSSION

6.1 SUMMARY OF STUDY FINDINGS AND CONTRIBUTIONS TO THE LITERATURE

6.1.1 Changes in Cholesterol-Lowering Medication Use Over a Decade in Community-Dwelling Older Adults

The first study of this dissertation found that the use of cholesterol-lowering medications in the elderly nearly tripled during the period of 1997-2008 (14.9% to 42.6%). As expected, statins were the most common drug class used in the cohort studied. It was interesting to find that only half of those with known CHD and/or diabetes received any cholesterol lowering agent. In addition, this study showed that the release of guideline and evidence-based data had no immediate impact (i.e., change in level) on cholesterol-lowering medication use. Instead, there was a decrease in the yearly rate of increase (i.e., decrease in slopes) of cholesterol-lowering medication use.

To the best knowledge of the author, our study was the first one to formally assess the impact that the guideline publications and evidence-based data had on use of cholesterol-lowering medications in the elderly. The recommendation to use statins for older adults with established CHD or at high risk for developing CHD were primarily based on the results from subgroup analyses in clinical trials.[189-193] Conclusively extrapolating the results from the

subgroup analyses to all older adults is controversial, since most of these trials had a defined inclusion upper age limit of 70-75 years.[190,191,193] There is limited information about the use of cholesterol-lowering medications before and after 2002 in older adults aged ≥ 85 years.[194] In addition, these publications are somewhat inconsistent regarding the need for cholesterol-lowering medications in the elderly (e.g., those with diabetes but without CHD).[195-200] The findings from this work are significant and help to fill the gap in the literature by examining the utilization patterns of cholesterol-lowering medications in community-dwelling older adults aged 70 and older before and after the release of the NCEP ATP III guidelines[195] and results from the PROSPER in 2002.[196]

6.1.2 Associations between Statin Use and Gait-Speed Decline in Community-Dwelling Older Adults

The second study of this dissertation showed that statin use, compared to non-users, had a decreased risk decline in gait speed of 0.05 m/s or more per year in community-dwelling older adults.[201] In addition, low-dose statin use had a decreased risk of gait speed decline of 0.1 m/s or more per year.[201]

Gait speed is a simple, but important indicator of functional status in older adults.[202-204] Declines in gait speed consistently predict future physical disability, mortality, and major health-related outcomes in older adults.[4,6-10] Despite its importance, a paucity of literature has identified risk or protective factors (except for physical exercise) for age-related gait speed decline, or the magnitude of important gait decline in gait speed associated with these factors.[205] The evidence that exists shows the mixed results. The beneficial effects of statins in physical function decline were mainly found in smaller studies in individuals that had PAD.[85,206-209] In contrast, two large

longitudinal cohort studies did not find that statins lowered the risk of self-reported mobility limitation in older women, or physical function decline in community-dwelling older adults.[210,211] These later findings may be related to muscle-related adverse events may occur with statin use.[212-218] The contribution of this study to literature is that this is the first study to examine statin use and gait-speed decline over a 20-m walk in community-dwelling older adults. Given the controversial findings previously described, the overall results of this dissertation work provide additional information to a growing body of literature suggesting that low-dose statin may be beneficial for slowing age-related decline in physical function in community-dwelling adults. It is also encouraging that there is no evidence from this study that statin use is associated with deteriorating gait speed decline. Having said this, the muscle-related adverse events should not be a concern of the use of low-dose statins, especially in the older adults with CHD, who received statins for secondary prevention.

6.1.3 Aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer

The third study of this dissertation found that aspirin or selective COX-2 inhibitors were associated with reduced risk of ovarian cancer, especially among middle aged and older women who took aspirin at low doses (or for prevention of cardiovascular disease) continuously over a long period of time. The results do not support the regular use of non-selective NA-NSAIDs and acetaminophen in the chemoprevention of ovarian cancer.

Several studies have examined associations between aspirin or NA-NSAIDs use and the risk of ovarian cancer, but the findings have been contradictory and inconclusive. Previous studies were relatively small and lacked information or statistical power to assess the effects of

dose, duration, drug classes, or indications. This is the first study able to evaluate the risk of ovarian cancer and examine dose-response and duration-response relationships comprehensively. This is also the first study with sufficient sample size to perform stratified analyses by indication for analgesic use and by types of NA-NSAIDs.

6.2 PUBLIC HEALTH SIGNIFICANCE

In general, pharmacoepidemiologic studies have emerged as an important tool for comparative effectiveness research of treatment effects, especially in populations with multiple chronic conditions, or older adults aged ≥ 80 years, which were usually excluded from RCTs. In addition, pharmacoepidemiologic studies are robust tools to screen for adverse drugs effects, understand barriers to drug use and to improve health outcomes and quality. Data derived from pharmacoepidemiologic studies inform clinical medicine, health promotion, health policy and planning in public health.

Cardiovascular disease remains the leading cause of death and disability among the elderly in the US. With regard to further reducing the burden of CHD morbidity and mortality, the emphasis is on the treatment of acute events and secondary or primary prevention through treatment and control of risk factors, such as control of dyslipidemia. However, most of the clinical trials reviewed did not include older adults aged ≥ 80 years or those with multiple comorbidities. Therefore, it is important and relevant to public health to better understand the utilization patterns of cholesterol-lowering medication use and the impact of guidelines and evidence-based data on their use in older adults. The public health significance of the first study is that the results suggest that more efforts are needed to overcome barriers to disseminate and

implement of clinical guidelines of cholesterol-lowering medication use in clinical practice. Different dissemination methods may be needed for clinicians to quickly accept evidence-based data.

The public health challenge of age-related disability and loss in physical function will continue to grow in our rapidly aging population.[219] Loss in physical function seriously threatens the independence and quality of life for older adults and has a significant impact on family and society as well.[220] Maintaining function and preventing or reducing disability are areas of interests to clinicians, policymakers, and older adults themselves.[221,222] Gait speed is a simple, but important indicator of functional status in older adults.[202-204] Declines in gait speed consistently predict future physical disability, mortality, and major health-related outcomes in older adults.[193,195-199] Despite its importance, a paucity of literature has identified risk or protective factors other than physical exercise for age-related gait speed decline, or the magnitude of important gait decline in gait speed associated with these factors.[205] Therefore, identifying modifiable factors to delay age-related gait speed decline in older adults is emerging as a significant priority of public health interest. The results of the second study (i.e., statin use and gait speed decline) in this dissertation provide additional evidence and new insight that statin use may have a decreased risk of clinically important gait speed decline. Low-dose and hydrophilic statin use may reassure in the context of concerns of statin-related muscular adverse events, especially in older adults.

Ovarian cancer is the second most common gynecologic cancer, following uterine cancer, and causes more deaths per year than any other cancer of the female reproductive system.[223] It afflicts approximately 1 in 70 women, and is the fifth leading cause of cancer death among females in the United States.[5,223] However, ovarian cancer has a poorly understood etiology

and natural history. Thus, strategies that focus on prevention may provide the most rational approach for meaningful reductions in the incidence and deaths attributable to ovarian cancer. Moreover, aspirin, NA-NSAIDs and acetaminophen are three of the most frequently used medication classes in the United States,[224,225] Because of the widespread use of aspirin, NA-NSAIDs and acetaminophen, any association with an increased or decreased cancer risk may influence many users. The results of the third study (i.e., analgesics use and risk of ovarian cancer) in this dissertation suggest that aspirin or selective COX-2 inhibitors were associated with a decreased risk of ovarian cancer, especially among middle aged and older women who took aspirin at low doses continuously over a long period of time. The regular use of non-selective NA-NSAIDs and acetaminophen were not associated with the risk of ovarian cancer. The risk-benefit balance need to be evaluated in the use of aspirin or COX-2 inhibitors in older adults because of potential gastric side effects (e.g., peptic ulcer disease) from aspirin use and cardiovascular side effects from COX-2 inhibitor use.

6.3 STUDY LIMITATIONS

The results in this dissertation work should be interpreted with caution due to inherent study design, limitations and potential biases. In general, despite employing several strategies to address confounding by indication, including adjustment, sensitivity and subgroup analyses, all observational studies of pharmacological exposures are subject to this problem.[182] This could obscure or mask protective association of medication use because of initial poorer health status of users compared to non-users.

Some limitations should be considered when interpreting the results of the "Changes in Cholesterol-Lowering Medications Use over a Decade" and "Statin Use and Gait Speed Decline" Studies using the data from the Health ABC study. Inherent to most longitudinal studies examining older adults, the potential for survivor bias should be considered. This may bias the results towards null. However, the results from sensitivity analyses, restricted to participants in the study for the entire period of follow-up, yielded similar results. It is also possible that use of medications may be underestimated as medication use was measured at multiple fixed annual time points. Unmeasured confounders such as family history of CHD, adherence to medications which were not collected in the Health ABC study, cannot be ruled out. Given the high rates of non-adherence in statin users, it is possible that the protective effects of statins from gait speed decline were underestimated.

The third study of examining analgesics and the risk of ovarian cancer in a case-control study has several limitations and biases. First, we had no data on the characteristics of excluded and non-responding cases. The protective results for aspirin use would be nullified if non-responders in either the case or control groups would have had double or half of the exposure of the responders. Second, cases may be more motivated to remember their analgesic use than controls. However, any tendency for the cases to better recall exposures would result in ORs greater than 1.0 rather than the protective effects observed here. To reduce the impact of recall bias, a defined reference date was used for assessing exposures. The protective effects of recent aspirin use might be due to recall limitation since patients were more likely to recall the medications used recently. Third, measurement and misclassification errors are presumably present when relying on self-reported and single measurement of analgesics use without verification.[43] Fourth, we did not collect comprehensive information on medical co-morbidities

related to cardiovascular disease, health-conscious behaviors, or factors related to adverse histories of aspirin use. The observed effect might be biased by the residual or unmeasured confounding.

Finally, limiting generalizability of the results to other populations (e.g., different ethnicities) should be considered in all of the three studies.

6.4 FUTURE RESEARCH

The findings from the study that examined the changes in cholesterol-lowering medication use from 1997-2008 implicate the need for future studies to better guide cholesterol-lowering therapy and investigate the potential barriers of treatment among the oldest old elders (≥ 80 years) with CHD or at high risk. The results from the study that evaluated the association between statin use and gait speed decline was the first study to show that statin user may benefit in a decreased risk of clinically important age-related gait speed decline over a 20-m walk. Taken together with mixed results of statin use and physical function decline, further studies and RCTs are needed to confirm the observed associations between statin use and declines in gait speed in diverse populations (e.g., aged 85 years and older). The results from the study regarding analgesic use and risk of ovarian cancer call for future research with better characterized accompanying medical conditions, health and lifestyle behaviors, genetic susceptibility, and the overall risk-benefit balance of low-dose aspirin use. Ultimately and ideally, randomized, controlled trials are warranted to confirm the beneficial effects of low-dose statin in preventing or delaying functional decline, and the effects of low-dose aspirin use in preventing ovarian cancer.

APPENDIX

OTHER MEDICATIONS WITH ANTI-INFLAMMATORY EFFECTS

Type	Non-steroidal anti-inflammatory Drugs (NSAIDs)	Other drugs with anti-inflammatory effect		
		Systematic glucocorticosteroids (Oral only)	Immunosuppressive drugs	Other Miscellaneous Drugs
Medication (by alphabetical order)	Aspirin(> 1200mg/day), Celecoxib, Choline salicylate, magnesium salicylate, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flubiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Meclofenamate Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Phenyl salicylate, Piroxicam, Rofecoxib, Salicylamide, Salsalate, Sulindac, Tolmetin, Trolamine salicylate Valdecoxib	Budesonide, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone acetonide Dexamethasone	Azathioprine, Chlorambucil Cyclophosphamide, Cyclosporine, Leflunomide, Methotrexate, Mercaptopurine, Mycophenolate mofetil, Sirolimus, Tacrolimus	Alefacept Anakinra, Anti-thymocyte globulin, Olsalazine, Efalizumab, Etanercept, Hydroxychloroquine, Infliximab, Muromonab-CD3 (OKT3), Montelukast, Natalizumab, Omalizumab, Rituximab, Sulfasalazine, Thalidomide, Zafirlukast, Zileuton

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