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A Polypharmacy Model and the Association of Polypharmacy with All-Cause Mortality and Incident Cognitive Impairment in the REGARDS Cohort

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By

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B.A., Amherst College, 2005

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An abstract of

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Dissertation Abstract:
A Polypharmacy Model and the Association of Polypharmacy with All-Cause Mortality and Incident Cognitive Impairment in the REGARDS Cohort

By
Winn T. Cashion

Importance: Medications are a cornerstone of medicine. Americans frequently use many medications simultaneously. While medications are tested individually for safety and efficacy, such complex drug regimens may have many unintended effects, including direct drug toxicity, drug-drug interactions, and adverse drug reactions. The phenomenon of taking many drugs simultaneously is known as "polypharmacy." While polypharmacy can be appropriate and the standard of care, it often occurs unnecessarily and exposes the patient to pharmacologic risk.

Objective: This dissertation sought to fill some of the pharmacoepidemiologic knowledge gaps by exploring factors related to polypharmacy and assessing the associations between polypharmacy and 1) all-cause mortality and 2) cognitive impairment using data from the large REGARDS cohort.

Methods: We first transformed the very large REGARDS medication database by assigning generic names, drug classes, and prescription/OTC/supplement status to each manually recorded medication name. We documented the generic name assignments for over 99% of entries using internet queries of **Drugs.com** and **Google**.

The REGARDS Cohort data (total n= 30,183, comprised of blacks and whites ages ≥45 in the continental U.S.) were used. During an in-home study visit, pill-bottle inspections were conducted of all the medications used in the last two weeks. The cohort member's polypharmacy status was subsequently determined by summing the total number of generic (prescription or OTC) ingredients.

Study 1: A logistic model assessed whether polypharmacy status was associated with demographics, socioeconomic status, lifestyle, comorbidities, and biomarkers.

Study 2: Polypharmacy status (major [≥8 ingredients], minor [6-7 ingredients], none [0-5 ingredients]) was determined by counting the total number of generic (prescription or over-the-counter) ingredients. Cox Proportional Hazards models (using both time-on-study and age-time-scale methods to model time to event) were used to assess the relation of polypharmacy to mortality. Several alternative models were constructed to assess confounding by indication and to consider effect modification by CKD.

Study 3: Multiple logistic regression models (using both first follow-up and last follow-up Six Item Screener score to define incident impairment) were constructed to assess the association of polypharmacy and incident cognitive impairment.

Results: Overall, 171,573 in-home visits drug names were transcribed.

Study 1: The mean number of total generic ingredients was 4.12 (SE= 0.039), with 15.7% of the cohort using ≥8 total generic ingredients. White race and stroke belt/buckle or Southern residence were associated with a higher polypharmacy prevalence.

Study 2: Major polypharmacy was associated with increased mortality in all models, with hazard ratios and 95% confidence intervals ranging from 1.22 (1.07-1.40) to 2.35 (2.15-2.56). Minor polypharmacy was associated with mortality in some, but not all, models. The polypharmacy-mortality association did not differ in those with and without CKD.

Study 3: For all models constructed, the major polypharmacy-cognitive impairment odds ratios (ORs) were all greater than 1, but never with a point estimate exceeding 1.30, and most not statistically significant. Conversely, for minor polypharmacy-cognitive impairment, the associations were all near 1, with none of them statistically significant. The two-way polypharmacy-CKD status interactions assessed were not significant.

Conclusions: American adults are using a substantial number of medications. This may expose them to potential risks of drug toxicity, drug interactions, and adverse drug events. While residual confounding by indication cannot be ruled out, in this large US cohort, major polypharmacy was associated with mortality in all models. These findings suggest that a simple ingredient count sum is not strongly associated with incident cognitive impairment.

The racial and regional variation in polypharmacy merit further study. Moreover, the polypharmacy-mortality association should be replicated. However, if these associations are causal, then they could have major public health impacts.

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CHAPTER 1: INTRODUCTION AND AIMS AND HYPOTHESES:

1.0: Introduction:

Many Americans are taking high levels of prescription, over-the-counter (OTC), and supplemental medications.[1] The reasons for this intensity of medication use are multifactorial.[2,3,4,5] However, the extent and ramifications of this high medication burden (termed "polypharmacy") are largely unknown. In particular, the potential magnitude of the effects of polypharmacy-related drug toxicity and drug-drug interactions on mortality and cognition within the general American population and among Chronic Kidney Disease (CKD, individuals with reduced renal function as estimated by the ability to filter blood—the glomerular filtration rate) patients is not fully understood. This dissertation seeks to contribute to the field of pharmacoepidemiology by exploring correlates of and two potential effects of polypharmacy.

1.1: Dissertation Aims and Hypotheses:

1.1.1:

Study 1: Polypharmacy model as a function of individual variables, paying special attention to race and region.

- **Aim**: The purpose is to construct a polypharmacy model using individual-level characteristics.
- **Hypothesis:**
  - **H1:** Individual (age, race, gender, income, education, geography etc.) characteristics will not be associated with polypharmacy.

1.1.2:

Study 2: The association between polypharmacy and mortality.

- **Aim**: The purpose is to measure association of polypharmacy and mortality, while adjusting for a wide range of covariates, and test for effect modification according to CKD status.
- **Hypothesis:**
  - **H1**: After adjusting for covariates and assessing interaction, polypharmacy will not increase the mortality hazard.
  - **H2**: After adjusting for covariates and assessing interaction, polypharmacy will not increase the mortality hazard, *and there will be no*

heterogeneity of effect across CKD (i.e., there will be no effect modification by this variable).

1.1.3:

Study 3: **Description of drug use with potential cognitive effects and association of polypharmacy with cognitive impairment.**

Descriptive component:

- Histogram of number of drugs taken with potential cognitive effects

Inferential component:

- **Aim**: After adjusting for covariates and assessing interaction according to CKD status, the purpose is to test for an association between polypharmacy and incident cognitive impairment.
- **Hypothesis**:
  - **H1:** Polypharmacy will not be associated with cognitive impairment over time.
  - **H2**: Polypharmacy will not be associated with cognitive impairment over time, *and there will be no heterogeneity of effect according to CKD status (i.e., no effect modification by CKD status)*

CHAPTER 2: LITERATURE REVIEW:

2.1: Terminology:

Pharmacoepidemiology has been defined as "the application of epidemiologic reasoning, methods, and knowledge to the study of the uses and effects (beneficial and adverse) of drugs in human populations." [6] That is to say, pharmacoepidemiology encapsulates the "branch of medical science dealing with the effects of drugs in populations."[7] Relative to the two roots words, pharmacology and epidemiology, pharmacoepidemiology is remarkably understudied. **Pharmacology**, "the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes,"[8] and **epidemiology**, "the study of the causes, distribution, and control of disease in populations" [9], have both enjoyed centuries of innovative inquiry, whose research has each individually altered human civilization. One has only to think of the salubrious effects of improved sanitation and penicillin to appreciate this. However, while each discipline has thrived and done its share to contribute to an over 50% increase in the life expectancy in the first 90 years of the last century, the new, hybrid study of pharmacoepidemiology has only relatively recently blossomed.[10,11] Nevertheless, hopefully, increasingly, both practitioners and researchers are grasping the great health and economic significance of this emerging field.

As a descriptive pharmacoepidemiologic picture has developed, one obvious feature of Americans' use of medications is the phenomenon of **polypharmacy**, a term coined in 1959 whose etymology vividly illustrates its simultaneous potential utility and liability in modern medicine.[12] "*Poly,* from the Greek word polus (many, much) and *pharmacy,* from the Greek word pharmakon (drug, poison) literally means many drugs or, alternatively, much poison."[12] No consensus modern-day definition of polypharmacy exists.[13] Medication use can

be traced back thousands of years, and one must wonder if it is as old as humanity itself.[14] No less than Sir William Osler in 1891 observed, "A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals." For example, as early as 63 B.C., polypharmacy can be documented, as Mithridates sought a "universal antidote for poisoning by combining many substances in a single formulation."[14] Indeed, medicine is still the "cornerstone of modern therapeutics."[15] With time, however, polypharmacy, thought of as a crude therapeutic attempt, lost its cachet, and the concept of a "magic bullet" (the belief that a single compound should ameliorate all of a disease) came into vogue. While pharmacology continues aspiring to find each disease's magic bullet, it has (at least temporarily) resigned itself to accepting the inherent therapeutic limitations and toxicities of any particular drug.

Currently, polypharmacy is often defined two distinct ways: using more drugs than is clinically warranted or simultaneously using more than a certain threshold drug number, often five.[16] Critically, medications or drugs encompass anything (other than food) that is ingested, injected, or applied topically or ophthalmologically. Thus, medicine describes both what might be classically referred to as medicines: **1) prescription** drugs, **2) over-the-counter (OTC)** drugs (which are *regulated* by the Food and Drug Administration but available without a prescription), and **3)** "**supplements**," which include **a)** vitamins, **b)** minerals, **c)** "herbals" (herb-based supplements), and **d)** "nutraceuticals" (According to the Oxford English Dictionary website (http://www.oed.com), "a foodstuff, food additive, or dietary supplement that has (or is thought to have) medicinal properties; a functional food").

In the current research polypharmacy status was defined in two ways: dichotomously, indicating whether ≥ 8 total generic ingredients were used by participants, and ordinally, using three categories of total generic ingredient count: **major** (≥ 8 generic ingredients), **minor** (5-6

generics), and **no polypharmacy** (≤ 5 generics). Polypharmacy sometimes has negative connotations, suggesting inappropriate/excessive medication use; however, it can also reflect appropriate care of patients with multiple health conditions and/or conditions requiring multiple medications.

While drugs would ideally always achieve their therapeutic effect without toxicity, this seldom occurs—drug allergies, drug-drug and drug-disease interactions, and direct drug toxicity all pose threats associated with polypharmacy. In fact, William Withering, the botanist physician who first recognized the use of digitalis, described man's search for medical remedies as "subject to the whim, the inaccuracies, and the blunder of mankind".[17] The final set of terms refers to noxious drug effects: **adverse drug reaction (ADR)**, **adverse drug events (ADE)**, **drug-drug interactions**, and **potentially inappropriate medication use**. ADE refers to any unfavorable response associated with a drug, whether of pharmacological etiology or not, while ADR refers to a harmful reaction **caused** by the drug when used at normal doses.[18] Drug-drug interactions occur when one drug affects the pharmacodynamics or pharmacokinetics of another drug. For example, this can occur if one drug upregulates cytochrome p450 liver enzymes, thereby accelerating the clearance of other drugs metabolized in the same pathway and possibly leading to subtherapeutic concentrations of the second drug. Finally, potentially inappropriate medication use denotes cases where the expected therapeutic effect of a drug is exceeded by its expected toxic effect.[19]

The next two sections will briefly put medication use broadly in its economic and cultural context, followed by a discussion of specific aspects related to polypharmacy.

2.2 Medication Economics:

Medication use and the occurrence of polypharmacy are closely tied to strong economic forces. Pharmaceutical companies are a major economic force. In 2007, the global pharmaceutical market was valued at over $700 billion and a single drug (Lipitor) grossed $12 billion worldwide.[8] Thus, not surprisingly, it is estimated that 10-12% of American health care spending goes for prescription drugs.[8] In America alone, an estimated 3.2 billion prescriptions were ordered in 2003.[20] In addition to vast revenues, pharmaceutical companies also report blockbuster earnings, because "profit margins for big pharma have historically exceeded all other industries by a significant factor."[8]

Pharmaceutical companies aggressively advertise their products[21], by marketing their "medicines as indispensable commodities."[5] For example, medicines can be portrayed as means of coping with the inevitable aches and occasional bodily dysfunction associated with stressful lives lived in chaotic environments.[5]

The scale of the pharmaceutical marketplace is vast. "For example, there are over 100 different systemic analgesic products, almost all of which contain aspirin, acetaminophen, NSAIDs, or a combination of these agents as primary ingredients."[8] In fact, more than 500,000 medicine variants saturate the market, with 300,000 variants available OTC.[5]

While medications' costs are immense, they may actually be exceeded by the cost of ADR. "For every $1.00 spent on drug therapy, as much as $1.30 may be spent managing drug-related problems."[22] In 2000, the estimated numbers were $133 billion for medications and $177 billion to treat drug-related problems.[22] Hanlon et al. estimated that the annual expense of drug-related problems is $180 billion.[23] Moreover, the FDA reckons the annual hospitalization expense of inappropriate drugs to be $20 billion.[24]

Self-medication through OTC is also of great economic importance, with Americans spending over $16 billion on these drugs in 2007.[8] In spite of the billions spent in OTC aisles, self-diagnosis and self-treatment is often the far more frugal alternative to seeing the physician—"when the cost of doctor visits and prescription medicines becomes prohibitive, self-medication provides a more affordable, though often less desirable, response to illness."[5]

2.3 Medication Use Culture:

Sociologically, medication use (both prescription and nonprescription) has great significance in America.[5] In fact, there may even be something to self-medicating that is uniquely American. Within a culture that prizes freedom and the supremacy of the individual, diagnosing one's own malady and treating it himself is "empowering."[5,25] Additionally, loose legal constraints for self-medication, increased wealth, and previously unimaginable access to medical knowledge via the internet embolden Americans to blaze their own health/medication path.[15] Not surprisingly, then, an estimated 70-90% of illnesses involve some variety of self-treatment, and for some conditions, such as arthritis, patients "continuously self-medicate."[25] In aggregate, Americans purchase approximately 5 billion OTC products each year, distributed among 800 active ingredients grouped into 100 drug classes.[26] In fact, 50% of all medication doses taken in America are for OTC products.[8]

Patients often show poor adherence to prescription medication, which itself poses risk to the patient, both for incomplete therapeutic effect as well as toxicity associated with widely fluctuating serum drug levels.[27] For example, "of the billions of prescriptions filled each year, it is estimated that approximately half are taken improperly."[20] In one American survey 21% of individuals "rarely or never read the label on nonprescription products".[25] The less than optimal adherence potentially magnifies any potential harmful polypharmacy effects.

Medication use also resonates within America's consumerism "more is better" culture.[5,15] Instead of merely being used to treat an acute disease or prevent the progression of a chronic disease, to some extent, medicine can sometimes be used as a "life accessory," something that makes life a little easier or better and perceived as improving overall health without the demands of exercise or diet.[28] As such, medicine can be integrated so much into the individual's "daily routine" that she no longer recognizes her habits as including medication use—"pharmacists note that some patients only report routine use of medicines after careful prompting because they have ceased to consider that taking these products is out of the ordinary."[5] Taking medicine has become ubiquitous (and quotidian).[29]

Consistent with Americans' fondness for OTC and supplements, Americans often expect to leave an office visit with a prescription[3] and view its receipt as a validation of the legitimacy of their condition.[30] In fact, it has been estimated that "60% of all physician visits include a prescription for medication."[31] Moreover, physicians, as participants in the service industry, recognize this expectation and often prescribe liberally to satisfy their patient "consumers."[3]

Amidst this strong direct-to-consumer marketing, hard sell tactics by pharmaceutical sales representatives, patient expectations, physician pressure to satisfy patients, and an ever-expanding set of potential drugs, rational prescribing may become very difficult. Moreover, beyond being overwhelmed, physicians may be ill-equipped to deal with practical prescribing problems systematically, instead swayed by "peers, pharmaceutical company marketing, health care systems, and patient demands and expectations."[16] In stark contrast to this complex interplay of prescribing forces, the WHO recommends each physician establish her own "personal formulary" to treat common conditions.[16] Such a formulary would likely reduce the

alarming frequency of the "prescribing cascade," whereby one drug's side effect, perceived as a symptom of a new disease, is treated with yet another medication[32], whereby a pharmacologic palimpsest is created from the "accumulating layers and layers of drug therapy."[17] This cascade occurs with alarming frequency, estimated to take place 80% of the time according to Rollason et al.[30] For example, Carnahan et al. documented that 35% of individuals given a cholinesterase inhibitor (which increases acetylcholine levels) were simultaneously receiving an anticholinergic (which decreases acetylcholine levels).[33]

Moreover, the reality that many patients see multiple doctors for medications only increases the risk of excess drug prescription and its harmful effects.[30] In such a way, "prescribers should recognize that patients often come to them with a legacy of drugs acquired during previous medical experiences."[15]

Academic medicine, whose research is frequently funded by pharmaceutical companies[21], often promotes multiple medication use as the standard of care[34] through clinical practice recommendations that can sometimes function as "medicine generators."[35] Furthermore, new research frequently expands the realm of pharmacologic intervention through new agents, new indications or off-label uses, and more aggressive preventative use.[36]

2.4: Rationale for Exclusion of Supplements/Complimentary and Alternative (CAM) Medicines from Polypharmacy Definition:

Natural medicines unequivocally have played an integral role in the development of modern therapeutics; in fact, nature is teeming with botanical chemical diversity, the source of limitless compounds to screen in antineoplastic, angiogenic, immunosuppressive, or anti-inflammatory assays during the drug discovery process. As such, nature is the "backbone of our pharmacopoeia, because more than 50% of drugs used in Western pharmacopoeia are isolated

from herbs or derived from modification of chemicals first found in plants."[37] While nature may provide the crude starting material, extensive scientific testing and drug development is required to ensure that the finished pharmaceutical product is safe and effective.

Despite efforts of CAM marketing to reassure the public, it should not be forgotten that ultimately "there is no alternative medicine. There is only scientifically proven, evidence-based medicine supported by solid data or unproven medicine, for which scientific evidence is lacking." [38] That is to say, CAM does not transcend the biomedical paradigm that has transformed medicine in the last century--both formal pharmaceuticals and herbals can have strong biological effects, but only one group of products is formally evaluated for safety and efficacy.

A piece of landmark legislation regarding drugs occurred in 1994, with passage of the Dietary Supplement Health Education Act (DSHEA), with strong backing from the CAM industry and swayed by "strong manufacturer lobbying efforts."[38,8] "DSHEA broadened the traditional definition of dietary supplements, which had previously encompassed only essential dietary nutrients."[39] Furthermore, not only did DSHEA create many new potentially lucrative categories of "dietary supplements," it also effectively renounced the government's authority to regulate these products, by not requiring documentation of safety or efficacy.[15,40] Furthermore, supplement "Good Manufacturing Practice (GMP) standards" were not created for well over a decade after DSHEA, which "allowed supplement manufacturers to self-regulate the manufacturing process and resulted in many instances of adulteration, misbranding, and contamination."[8] In contrast, prescription drugs considered by the FDA often undergo 2-6 years of toxicological evaluation before a drug candidate is ever studied for human toxicity, and

exacting GMP criteria are in place.[8] For these reasons, we excluded supplements/CAMs for our polypharmacy research definition.

2.5 Physiology, Pharmacology and Polypharmacy:

While medicine use is at the core of the medical profession, no compound affects only one receptor or triggers only one pathway within a single organ system. Hence, side effects and the potential for toxicity are inherent in therapeutic medicine use. Nevertheless, the aggregate benefit of the well-defined use of individual medications is unquestioned: "Medications are probably the single most important technology in preventing injury, disability, and death in the geriatric population".[41] Conversely, when used inappropriately or in excess, medications can be very dangerous—"Any symptom in an elderly patient should be considered a drug side effect until proved otherwise".[41]

Physiologic changes that accompany aging can make optimal medication management and use difficult. In particular, aging affects both **1) pharmacokinetics** and **2) pharmacodynamics**. With aging, the body's adipose content tends to rise while plasma volume falls. Thus, hydrophilic drugs will be more concentrated in the plasma and hydrophobic drugs will accumulate more in adipose tissue.[42] Moreover, the body's ability to metabolize and excrete drugs and their metabolites is often diminished, as the function of the two organs critical for drug clearance (liver and kidney) declines over time.[43] This fact makes CKD patients especially intriguing pharmacoepidemiologically, as they may be exposed to toxic levels of drugs due to impaired renal clearance. Secondly, pharmacodynamic changes also occur during aging. The density of neurons, neurotransmitters, and plasma membrane receptors can change over time, resulting in decreased or increased sensitivity of particular neuropathways.[44] For instance,

geriatrics may exhibit reduced response to beta blockers but react more strongly to opiodes than younger patients.

Since a physician is obligated to "do no harm," prudent prescribing is essential, especially in geriatric situations.[45] Therefore, it is critical that she select individual medications likely to provide the greatest health benefit while minimizing the risk for harm, i.e., the medicine with the widest **therapeutic window,** the range of drug concentrations for which the therapeutic benefit outweighs potential toxicity, is sought.[15] However, when different drugs are used in combination with one another, as is often the case and especially in polypharmacy, finding a therapeutic window that simultaneously satisfies each individual drug and the diseases being treated can be very difficult. Because of the geriatric pharmacodynamic/pharmacokinetic changes and pharmacologic burden, in order to minimize the risk of harm, it has been advised that the "number of medications, and doses per day, should be kept as low as possible".[15]

Unfortunately, the sheer scale of medication use is paralleled by an immense degree of medication management complexity, because there are not distinct medication phenotypes for which well-established *a priori* prescribing guidelines can be employed; there are countless polypharmacy drug combinations. Indeed, the majority of patients have distinct amalgamations of medications.[46,47] For example, in the study by Moen et al., "100% of those aged 65-75 years were taking a unique combination of drugs."[46] This medication diversity dooms meticulous drug oversight—"the uniqueness of…drug regimens suggests no single prescriber could have extensive clinical experience with even a small fraction of the drug regimens patients receive."[47]

2.6 Geriatric Pharmacoepidemiology and Polypharmacy:

Geriatric medication use merits special attention not only for the aforementioned physiologic and pharmacologic changes of aging, but also because of the dramatic demographic

shifts occurring that have resulted in enormous growth of the geriatric population.[48] As a striking example of geriatric's demographic force, "half of all those who ever lived to 65 years or more are alive at present."[49] With the accumulation of drug-treated comorbidities with time, polypharmacy is especially germane to geriatrics.

Despite the great need for detailed understanding of geriatric pharmacoepidemiology, unfortunately there exists a great knowledge gap in this domain. In fact, due to "systemic exclusion" in medication research, there persists a geriatric "pharmaco-epistemiological" void.[34,50] For example, one author noted that over 30% of research published in important journals excluded geriatrics without apparent reason.[34] Because geriatrics remain so under-researched, "available scientific evidence often does not provide a definitive answer concerning the benefits or risks of many drug therapies in our oldest patients."[34] Therefore, geriatric drug management is often guided by habit and opinion, instead of well-established research.[50] Bereft of rigorous research to guide them, geriatric prescribers must maneuver "uncharted physiologic territory" and "must expect the unexpected and think of the unthinkable in the geriatric patient."[51]

Beyond the evidence vacuum, additional factors make geriatric medication management uniquely difficult: multiple chronic conditions, frailty, pharmacodynamic and pharmacokinetic changes, and the ability of drug toxicity to frequently resemble geriatric syndromes.[41] In fact, one geriatrics reference text advises that "any symptom in an elderly patient may be a drug side effect until proved otherwise."[17]

2.7: Polypharmacy Prevalence:

The prevalence of polypharmacy is high. Kaufman et al's. large randomized survey of American adults ($\geq$ 18 years) found that 81% had used at least 1 medicine in the last 7 days;

25% had taken at least 5 medications, and polypharmacy was much more prevalent among geriatrics.[1] Many studies, in many different healthcare settings and from around the world, have documented the scale of polypharmacy[52,53,54,55,56]. In one case, polypharmacy can be achieved with only 1 pill—polypill is a prescription cardiovascular disease medication that contains 4 active compounds—simvastatin, losartan, amlodipine, and bendroflumethiazide.[14,57] For example, in 2004, based on a study of over 13,000 nursing home residents, it was estimated that 40% of American nursing home patients received at least 9 medications.[58] The prevalence of polypharmacy is also high among American outpatients, with Loya et al. finding that 38% of their sample was taking 5 or more medications simultaneously.[59] The situation is no different among other industrialized countries. Studies in various types of samples from Singapore, Taiwan, Sweden, Denmark, and Holland have found the prevalence of polypharmacy (using at least 5 medications) to be 59%, 81%, 50%, 34%, and 61% respectively.[52,53,54,55,56]

2.8 Trends in Medication Use:

The trend is for still greater drug consumption in the future, as demonstrated by multiple studies. "Polypharmacy for the participants increased by 61% from 9.05 filled prescriptions per subject in 1983-1984 to 10.6 in 1993-1994 and 14.5 in 2003-2004."[60] Haider et al's. work during roughly the same period recorded a 130% increase in polypharmacy prevalence.[61] Finally, not only does the population as a whole seem to be moving towards heavier medication use, but the aging of the population may only accelerate the pace of this shift, with an "estimated increase of 0.4 drugs per 10 years of age."[30]

2.9 Suboptimal Medication Use:

Due to the complexities of medication use described previously, it should not be surprising that suboptimal medication use is nearly ubiquitous. However, suboptimal use is not always synonymous with medication overuse—frequently medication underuse exists side-by-

side with overuse. For example, Denneboom et al. documented the potential for drug regimen improvement for 98% of the geriatric sample.[62] There are three broad varieties of suboptimal medication utilization: "1) underuse, 2) overuse, and 3) inappropriate use."[16] Each of these puts the patient's health at unnecessary risk: the omission of beneficial treatment in underuse, accumulation of toxicity in overuse, and the potential harm of adverse drug events with inappropriate use. Different dimensions of suboptimal medication use often coexist. For example, "a perverse mix of overtreatment and undertreatment" is often present.[50] Suboptimal use is very common—"approximately one third of all drugs prescribed in the US are considered unnecessary."[63] Many studies in many different patient populations have documented alarmingly high rates (sometimes over 50% of patients) of potentially inappropriate prescribing.[64,65,66,67,68,69,70,71,72] Multiple studies have reported high risks (sometimes over 25%) of new potentially inappropriate prescribing that commences during hospitalization.[69,73,74] "Unnecessary" drug use is also very prevalent, sometimes occurring in over half of patients sampled.[16,68,75] Finally, "therapeutic nutrients/minerals" are one of the "most commonly prescribed unnecessary drug classes."[68]

A multitude of studies have chronicled the risk for pharmacologic interactions among patients.[76,59,77,78,79,80] For example, in Ibrahim et al's. study of diabetic patients receiving in-house treatments, "93% were at risk for moderate drug-drug interactions, and 71% could have mild drug-drug interactions, and 39% could potentially be subject to at least one severe drug-drug interaction."[79] In Yoon et al's. study of older women using at least one herbal and one traditional medicine, a moderate- or high-risk drug-drug interaction was discovered in 74% of women, and over half of the drug-drug interactions involved a prescription interacting with OTC

or herbal drugs.[76] In Loya et al's. research, over 30% of the sample were at risk for one or more drug-herbal interactions.[59]

2.10: Risk Factors for Polypharmacy, Drug-Drug Interactions, and Potentially Inappropriate Medication:

2.10.1: Risk Factors for Polypharmacy:

Factors associated with polypharmacy have been studied in a number of settings. Greater comorbidity[12,58,54,81,82,83,84,85] and more need for help with activities of daily living[58] is positively associated with polypharmacy. Also, a greater number of appointments or having multiple prescribers is associated with polypharmacy[45,54,81,86]. A number of demographic factors have been linked to polypharmacy. These include female sex[12,30,58,84], older age[12,30,47,81, 83,84,87], and white race.[58,81] A number of SES variables have also been associated with polypharmacy, such as low educational attainment[12,30,88], lower social status/low SES[12,87], and being unemployed.[12,87] Finally, a community-level variable, place of residence (urban or rural), has also been correlated with polypharmacy.[54,88,89]

2.10.2: Risk Factors for ADR/ADE:

Risk factors for receiving a medication whose risk may reasonably be expected to exceed its benefit include: female sex, age, poverty, less education, depression, level of clinical care, level of cognition, communication capacity, and polypharmacy.[53,70,90,91,92,93,94,95]

Risk factors linked with ADR/ADE are similar, such as female gender, older age, comorbidity, extent of medication use, more prescribers, and the use of potentially inappropriate prescriptions.[65, 71, 73,96, 97,98,99,100] Moreover, as would be anticipated from impaired drug clearance, both unknown and clear renal failure have been linked with ADR.[101] Consistent with the physiologic and pharmacologic changes of aging, older age is a strong risk factor for ADR, with "adverse reactions from medications are up to 7 times more common in persons aged 70 to 79 years as those in 20 to 29 years."[19] A dose response relationship between drug burden and

ADE risk has been documented: 13% for 2, 58% for 5, and 82% for 7+ drugs.[45] Curiously, Field et al. reported supplement users experiencing fewer ADEs.[73] This could potentially be explained by CAM users tendency to have greater health consciousness.

2.10.3: Risk Factors for Drug-Drug Interaction:

The number of drugs being used by the patient is the critical variable in determining risk for drug-drug interaction. Moreover, "it has even been suggested that when the number of drugs prescribed to a patient reaches eight, the risk of a drug-drug interaction approaches 100%."[30] Therefore, it is critical to treat conditions as effectively as possible, while simultaneously minimizing drug burden.[102] Risk for interactions can be reduced by consulting pharmacists who are cognizant of common interactions and the mechanisms of interactions. However, given the extreme complexity of some patients' regimens, even very knowledgeable pharmacists can overlook interactions. For example, "no pharmacist (even the most experienced) studied…correctly recognized all the potential drug-drug interactions when presented with scenarios involving eight or more medicines."[103]

2.10.4: Risk Factors for Potentially Inappropriate Drug Use:

Risk factors for receiving a medication whose risk may reasonably be expected to exceed its benefit include: female sex, age, poverty, less education, depression, level of clinical care, level of cognition, communication capacity, and polypharmacy.[53,70,90,91,92,93,94,95] For polypharmacy, the relationship is very intuitive—as the number of medications increases, the likelihood that at least one is potentially inappropriate also climbs. In fact, according to Onder et al., "the most important determinant of risk of receiving an inappropriate medication was the number of drugs being taken."[94] It should be noted that there are multiple metrics of "potentially inappropriate prescribing," and the construct itself may lack some validity, as two commonly

used metrics (Beers criteria and Medication Appropriateness Index) can display very poor consistency, with $\kappa = 0.14$--an agreement little better than through chance.[104]

2.11: Risks of Medication Use:

While medications are often instrumental in preventing disease, eradicating infection, or preserving function, the medication user and drug prescriber (the patient in the case of OTC drugs and supplements) must remain vigilant to the many medication perils that can shift medication from a net therapeutic influence to a net toxic influence. Ignoring for a moment the immense economic cost of medication to focus only on the health hazards, drug toxicity can take many forms: drug-drug interactions, drug-disease interactions, drug-food interactions, and direct parenchymal toxicity capable of affecting any organ system. All of these varieties of drug-induced pathology can be encapsulated into the broad category of adverse drug reactions.

2.11.1: Risks of Polypharmacy:

Polypharmacy has been established as a risk factor for many severe health events, including mortality[83,105], cognitive decline[106,107], loss of independence[81], falling[108,109], injuries[110], and ADRs.[111] Interestingly, polypharmacy has also been reported as a risk factor for underprescribing (not prescribing a medication when it is clinically indicated)[56]. Although there would be no direct toxicity in this case, there could be a great loss of potential therapeutic benefit from the overlooked medication opportunity. While certainly not always caused by polypharmacy, drug underuse occurs with distressing regularity. Danneboom et al. state that over 60% of their patients lacked at least one drug that would be beneficial, and in a quarter of these medication oversights "were considered to be of direct clinical relevance".[62] Consistent with this number, Hajjar et al. documented that 64% of the sample were medication underusers, and an amazing 42% of the sample had concurrent "underuse and unnecessary use of medications".[81] Finally, polypharmacy adversely affects medication adherence.[112]

2.11.2: Risks of Drug Interactions and Potentially Inappropriate Drugs:

Theoretically, drug interactions take a variety of forms: drug-drug, drug-disease, drug-CAM, drug-food, drug-alcohol, and drug-nutritional state.[2] In fact, "at least one half of the most commonly prescribed medications for the elderly have the potential to interact with alcohol".[113] The pleiotropic interaction potential of drugs reflects the fact their physiologic/toxicologic versatility must be appreciated whenever a prescription is written or OTC product selected. The presence of drug-drug or drug-disease interactions has been associated with accelerated loss of ADLs.[45] Multiple studies have failed to report a relationship between potentially inappropriate drugs (PID) and mortality[74,105,114,115,116], change in functional status[114], Health-Related Quality of Life[117], or ADE/ADR.[74,116] However, one study tied PIDs to a greater risk of hospitalization[115], another to nursing home admission[118], a third to greater healthcare expenses and utilization[67], and a fourth to "adverse health outcomes".[95]

2.11.3: Risks of ADRs/ADEs:

ADRs have been recorded as a major cause of hospitalization among geriatrics.[45,81] Furthermore, one author estimated that 3-5% of all hospitalizations and 5-10% of all hospital expenses are attributable to ADRs.[74] Remarkably, if categorized as a disease, ADRs are estimated to be the fourth most common cause of death.[8] Even for inpatients, ADRs remain a major hazard, being the "most common cause of adverse events in hospitalized patients".[119] While many ADEs are preventable[120], many are not, such is the inherent risk of drugs designed to have strong biological effects. For example, one author estimated that over 100,000 Americans die each year from drugs "that haven properly prescribed and correctly taken".[45] Moreover, although often regarded as benign, OTC drugs are thought to be the cause of almost 20% of all drug-related hospitalizations.[30]

2.12: Cognitive Impairment:

Cognition has a very heterogeneous phenotype, spanning from normal to demented, with many variations in between. For clinical assessment, cognitive function is assessed using five dimensions: "**attention, language, visuospatial function, memory**, and **executive function.**"[121] Note, however, that these dimensions often overlap and seldom can be assessed in isolation. For example, item recall requires speech as well as memory.[121] A brief definition of each of these dimensions is provided below. For a description of how each dimension is assessed clinically, please refer to the following reference.[121]

Attention is the capacity to focus on a specific stimulus even in the presence of distractions. **Orientation** is related to attention and concerns the ability to respond to stimuli and a temporal and spatial awareness. **Language** is the substrate for communication and necessary for many cognitive processes. **Visuospatial function** permits spatial self-orientation and facilitates the processing and understanding of visual stimuli. **Memory** refers to the "registration, acquisition, storage, and subsequent retrieval of new information." As defined above, memory requires the successful orchestration of multiple cognitive steps. **Executive function** refers to the complex process by which other cognitive dimensions are controlled and managed.[121]

A cognitively normal individual has all these cognitive dimensions intact, although normal aging may induce slight changes in neurological function[43,122]. Conversely, dementia is defined as "an acquired syndrome characterized by persistent global or multifocal impairments in many cognitive functions, occurring in a background of a relatively preserved state of alertness."[123] DSM-IV criteria for dementia include memory impairment, at least one of the following: aphasia, apraxia, agnosia, executive function deficit, and that this dysfunction

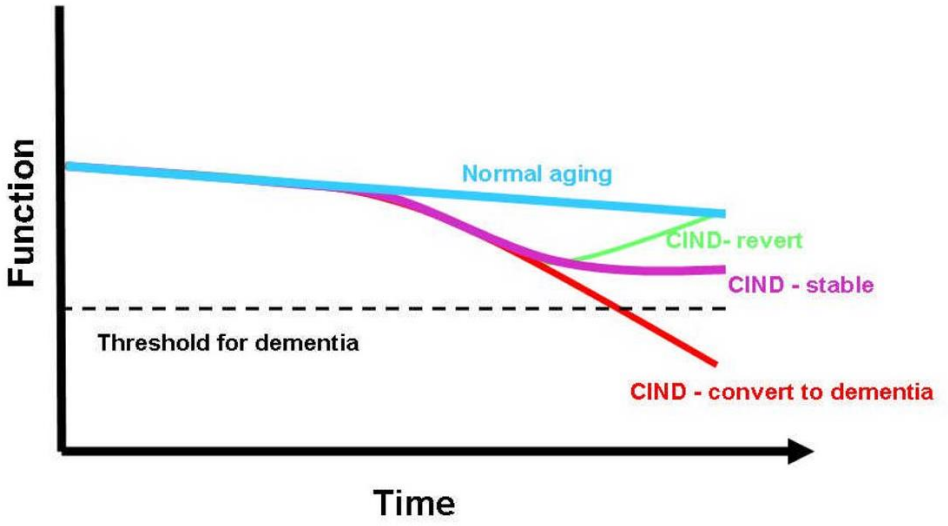
significantly affects daily life.[123] Dementia is primarily a disease of the elderly, with its prevalence exponentially increasing beyond age 65 years.[123] Conversely, dementia is not an inevitable aging comorbidity.[122] Many conditions can produce dementia. However, its most common phenotype's—progressive cognitive impairment among a geriatric, most common causes include Alzheimer disease and vascular dementia.[122]

Phenotypically, the vast space left between normal age-specific cognition and dementia is occupied by a wide range of cognitive function levels that have various names. Two such terms are: **mild cognitive impairment (MCI)**[124] and **cognitive impairment, no dementia (CIND)**[125]. Although an intermediate phenotype, mild cognitive impairment is a risk factor for progression to dementia.[122] Moreover, recognition of pre-dementia cognitive impairment may offer the opportunity to take steps to prevent or slow down the cognitive-decline progression.[126]

In 1995, the term **mild cognitive impairment** was introduced "to describe older adults with relatively isolated memory loss that is normatively rare among matched peers...., preserved general cognition (Mini Mental Status Exam > 24/30), intact activities of daily living, and no dementia on examination."[126] Note the special mention of memory with respect to MCI.[127]

CIND refers to those with "clinically significant impairment on cognitive tests who did not meet criteria for dementia and who were also not normal."[126] Some of the possible clinical courses for CIND are shown below, in **Figure 2.2**[126]:

Figure 2.2: Cognitive function over time: normal aging and the disparate paths CIND can take. Figure taken from reference 126.



Note the normal slow decline in cognitive function over time with normal aging. In the case of CIND, three possible eventual outcomes are shown: subsequent cognitive decline that progresses to dementia with time, stable CIND whereby cognitive function remains temporally stable, and reversion to normal cognitive function, whereby a "cognitive recovery" occurs.[126]

The manner and comprehensiveness of the cognitive exam when assessing for cognitive impairment depend on the clinical or research setting.[126] For an individual clinical assessment, each of the five cognitive dimensions defined above may be tested, as well as mood.[126] However, there is no single standard test for MCI or CIND.[126,128] In the case of large epidemiologic studies (e.g., REGARDS), the assessment duration needs to be much shorter, and "single tests of a domain may be utilized"[126]

"In five large-scale epidemiological studies the prevalence of CIND has ranged from 11–23%"[126] As shown in the figure, many of these CIND cases will progress to dementia relatively quickly, although some may regain normal age-specific cognitive function.[126] MCI is up to three times more prevalent than full-scale dementia.[126] Risk factors for cognitive impairment have been sought. Some of the reported risk factors include high BMI, hypertension, diabetes, and high LDL cholesterol.[126] Of note, certain anticholinergic medications may contribute to cognitive impairment.[126,129]

2.12.1: Neurological Risks of Medications:

Many medications affect the central nervous system, and these side effects can strongly adversely affect quality of life. Unfortunately, many very common drug classes, including beta blockers; NSAIDs; some antibiotics; corticosteroids; and histamine H2 receptor antagonists, can precipitate acute, or even persistent, confusion.[130] One especially vulnerable neurologic target is the cholinergic synapse, which is critical for "regulation of attention, memory, and sleep," but is susceptible to metabolic or pharmacologic perturbations.[130] For example, Cao et al. documented that "anticholinergic drug burden" was a statistically significant predictor of "poor performance on the Mini-Mental State exam, difficulty in activities of daily living, balance difficulty, mobility difficulty, slow gait, and upper extremity limitations."[131] Starr et al. found that "polypharmacy had a detrimental effect on life long cognition."[107] Another group published that taking anticholinergic and sedative drugs was linked with diminished physical and cognitive function.[132] These findings have been replicated in a longitudinal study: "increasing exposure to medication with anticholinergic and sedative effects…is associated with lower objective physical function over 5 years in community dwelling older people."[133] Finally, Weiner et al. linked users of multiple "CNS-active" drugs with greater risk of falls.[134] Unfortunately, medication

precipitated changes in mental acuity often present idiosyncratically, which can make physician recognition of drug toxicity difficult.[130]

Many individuals take drugs that have potential cognitive side effects. For example, two separate studies reported the prevalence of use of medications with anticholinergic effects at 27% and 10%.[135,136] In a study of older African Americans, Campbell et al. reported that over half used a possible anticholinergic.[137] An Italian study by Cancelli et al. found that over 20% of older adults used anticholinergic drugs.[138] In two studies of older French adults, Carriere et al. reported that 7.5% used anticholinergics and Lechevallier-Michel et al. reported 14% using anticholinergic drugs.[139,140] While the cholinergic synapse may be a key and major mechanism for cognitive impairment, it is possible that other important pathways of cognitive impairment have been effectively overlooked. Additionally, Elliott et al. reported that benzodiazepines were ordered (often inappropriately) for approximately 33% of geriatric inpatients.[141] Slowly metabolized benzodiazepines are the type of drug that most commonly brings on or aggravates dementia.[130]

2.13 Chronic Kidney Disease:

2.13.1 Chronic Kidney Disease Overview:

Chronic Kidney Disease (CKD) is defined as "functional or structural abnormalities of the kidneys for three or more months, irrespective of cause."[142] The severity of CKD is categorized using a 5-stage rubric, with stage 1 being the least advanced and stage 5 being the most advanced stage of disease. With stage 5, also known as end stage renal disease (ESRD), the patient requires dialysis or transplantation in order to survive. Kidney function is calculated using the glomerular filtration rate, the amount of plasma the kidney is able to filter per second per unit of surface area. In turn, the glomerular filtration rate is computed using creatinine as a

biomarker. Creatinine is a muscle protein that naturally reaches the plasma at a rate that is dependent on muscle mass and diet.[142] A steady state plasma creatinine concentration is reached when the rate of renal clearance equals the rate of generation. Therefore, by estimating the rate of creatinine production using age, gender, and race and measuring the steady-state creatinine concentration, the rate of renal creatinine clearance (i.e., the GFR) can be estimated using two empirical techniques: the Modification of Diet in Renal Disease equation or the Cockcroft-Gault equation.[142] It is critical that the GFR (which adjusts for variability in creatinine production), instead of simply creatinine levels, be used to assess kidney function, because "the use of unadjusted serum creatinine measurements as a screening tool for early CKD is insensitive and results in the widespread misclassification."[142] In addition to creatinine, albuminuria (protein leaking into the urine) is a very useful marker of incipient kidney injury.[142]

CKD is emerging as a major public health challenge, as epidemics in diabetes and hypertension ripple downstream and cause kidney damage. In the only ten years between 1988-1994 and 1999-2004, the prevalence of CKD increased by 30%, to an estimated 13.1%.[143] The startling prevalence trend is mirrored by disconcerting incidence secular patterns—from 1991 to 2001 the demographic-adjusted ESRD incidence rose by 43%.[144]

Although many conditions (e.g., polycystic kidney disease) and syndromes (e.g., lupus) can cause progressive renal damage, the vast majority of CKD is caused by one of two highly prevalent chronic diseases: hypertension and diabetes. Diabetes alone "accounts for almost half of all incident cases of kidney failure."[142] Beyond poor blood pressure and glycemic control, there are many other risk factors for CKD including: male sex, older age (on average, GFR naturally decreases over time), African American race, hyperlipidemia, and obesity.[142] Fortunately, the pace of GFR decline can be attenuated through good blood pressure and

glycemic management, maintaining a careful diet, losing weight, and lessening renin-angiotensin activity.[142] Unfortunately, however, because the early phases of CKD are often asymptomatic, many individuals are oblivious to their CKD and therefore unable to take action to mitigate its development.[15]

CKD is a strong risk factor for many severe health outcomes. A dose-response relationship between the degree of renal impairment and the mortality rate has been observed.[145] Moreover, CKD is firmly established as a strong risk factor or implicated causally in a number of chronic and potentially lethal conditions, including hypertension, acidosis, anemia, and systemic inflammation.[142] In fact, for all stages of pre-ESRD CKD, death (especially from cardiovascular disease) is more probable than development of ESRD.[142] Remarkably, cardiovascular disease mortality is estimated to be 10-20 fold greater among ESRD dialysis patients relative to the general population.[146] CKD is also a risk factor for cognitive impairment.[147,148]

2.13.2 Chronic Kidney Disease and Medication Use:

Medication use is fraught with potential complications among CKD patients, as their reduced renal clearance leads to concentrating of drugs and toxic metabolites. CKD patients often need dose adjustment for drugs with renal clearance, as a smaller dose will achieve the same serum concentration. However, if the reduced renal function is unknown to patients and clinicians, then supratherapeutic prescription doses often will be given. Nevertheless, many comorbid conditions that can be treated with drugs often accompany CKD.[149] As such polypharmacy may often be medically indicated in CKD patients. For example, one international study found that the mean number of medications to patients hospitalized with CKD exceeded 9.[150]

2.14: Literature Gaps in Knowledge:

2.14.1: Study 1 Knowledge Gaps:

To our knowledge, no studies have reported racial polypharmacy disparities for the general black and white American adult (≥ 45 years) population. In an older study, Gupta *et al*. found race to be associated with prescription drug count among Louisiana elderly on Medicaid.[151] Dwyer et al.[58] reported a black-white disparity among nursing home residents, but Qato et al.[152] failed to detect a black race-medication use relationship. Similarly, when considering antipsychotic prescribing in hospitalized UK patients, Connolly *et al*. found no black-white differences.[153] Similarly, among Veterans Affairs nursing home residents, Hanlon *et al.* reported no black-white polypharmacy difference.[154] Conversely, among the hospitalized elderly with heart failure, Masoudi *et al.* reported higher mean prescription counts among whites than blacks.[155] Moreover, Brown *et al.* reported lower rates of antidepressant use among blacks compared to whites.[156]

Although several studies evaluating geographic polypharmacy distributions have been conducted in Scandinavia,[55,88,89,157] we are not aware of any studies that have looked at regional variation in polypharmacy in the United States. Nevertheless, regional and within-state variation in the use of specific medications and medication classes has been investigated in the United States.[158-161]

2.14.2: Study 2 Knowledge Gaps:

Studies looking at the relationship between polypharmacy and mortality in the general, biracial American population are limited. Several previous studies investigated the association between polypharmacy and mortality in a variety of populations. Jyrkka et al. reported mixed results in a Finnish study,[162] and Espino et al. found a positive association in a study of Mexican Americans.[105] Iwata et al. reported higher one-year mortality among Japanese elderly

polypharmacy users following hospital discharge.[163] Incalzi et al. reported higher in-hospital mortality among Italian polypharmacy patients.[164] Richardson et al. reported higher two-year mortality among older United Kingdom polypharmacy users.[165]

Conversely, Pozzi et al. reported no Italian polypharmacy-mortality association.[166] Similarly, among hospitalized elderly Italians, no association between polypharmacy and in-hospital mortality was observed by Nobili et al.[167]

2.14.3: Study 3 Knowledge Gaps:

Many studies have documented anticholinergic use prevalences. However, by comparison, fewer seem to have considered the broader set of drugs which may affect cognition, regardless of mechanism (e.g., through non-cholinergic effects). In a study of older African Americans, Campbell et al. reported that over half used a possible anticholinergic.[137] Cancelli et al. found that over 20% of older Italians used anticholinergic drugs.[138] In two studies of older French adults, Carriere et al. reported that 7.5% used anticholinergics and Lechevallier-Michel et al. reported 14% using anticholinergic drugs.[139,140] While the cholinergic synapse may be a key and major mechanism for cognitive impairment, it is possible that other important pathways of cognitive impairment have been effectively overlooked. We hope that our broad search for drugs with possible cognitive effects has incorporated some "non-cholinergic" drugs that still may affect cognition.

In a study of older Finns, Jyrkka et al. reported that polypharmacy could not predict cognition changes over a three-year interval.[168] In a Swedish study, Monastero et al. reported that polypharmacy was a risk factor for cognitive impairment.[169] Starr et al. found that polypharmacy adversely affected cognition in a relatively small Scottish study.[107] In another European study, del Ser et al. reported that the number of prescribed drugs was a predictor for

cognitive impairment among stroke survivors.[106] However, to our knowledge, polypharmacy has not been explored for its associations with cognitive impairment among American adults.

As mentioned above, CKD is established as a risk factor for cognitive impairment. However, to our knowledge, nothing is known as to whether CKD may function as an effect modifier in a potential polypharmacy-cognitive impairment association.

CHAPTER 3: METHODS:

3.1: Description of REGARDS Study:

The **R**easons for **G**eographic **a**nd **R**acial **D**ifferences in **Stroke** (REGARDS) Study's overarching goal is to "determine the causes for the excess stroke mortality in the Southeastern US and among African-Americans."[170] The University of Alabama at Birmingham (UAB) serves as the REGARDS coordinating center, with support from the University of Vermont (central lab), Wake Forest University (ECG Reading site), EMSI (home visits), and the University of Cincinnati (stroke adjudication).[170] A brief overview of the nature of the REGARDS data that will be utilized in this dissertation follows in the next few paragraphs.

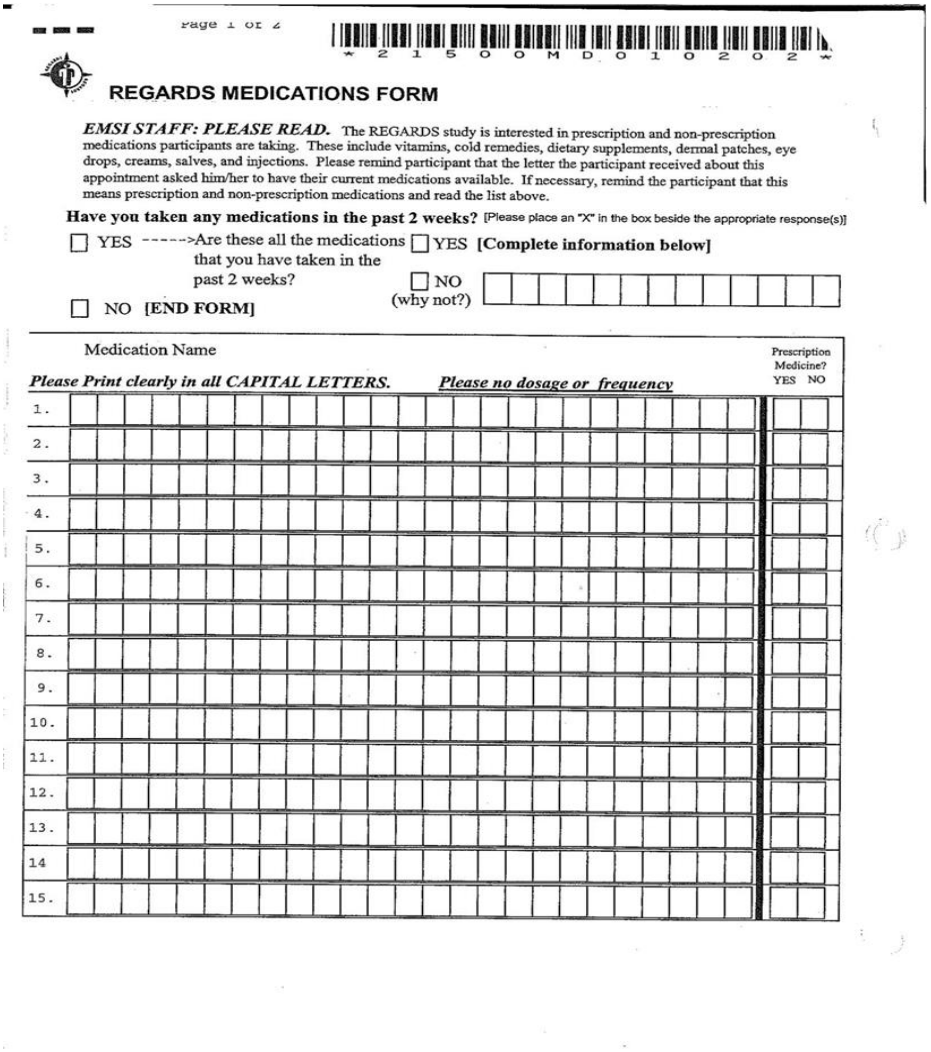
REGARDS is a nation-wide cohort study that is designed to oversample the Southeastern states and African Americans.[170] Overall the study sought to enroll 30,000 cohort members from 2003-2007, 30% from the "Stroke Belt", 20% from the "Stroke Buckle", and the rest from among other states (excluding Alaska and Hawaii). Moreover, within each regional group, sampling tried to achieve 50% African-American and 50% white. Finally, among each region-race subgroup, sampling tried to obtain equal numbers of men and women[170]. Stratified random sampling was conducted using a commercial nationwide database from Genesys Inc.[170] Individuals were excluded from REGARDS based on non-black/non-white race, ongoing cancer treatment, lack of English proficiency, or if they were expected to be difficult to follow.[170]

A letter and study pamphlet was mailed to each potential cohort member randomly selected from the Genesys database. Approximately two weeks later, one of the roughly 100 trained telephone interviewers called to inquire about study participation.[170] If meeting the inclusion criteria, the interviewer then obtained verbal informed consent from the potential cohort member and began the computer-assisted telephone interview (CATI), which lasted

approximately 30-45 minutes and where a wide range of demographic, SES, medical, lifestyle, cognitive, and social information was collected.[170]

The next step for cohort members was the in-home visit. After the CATI, the cohort member's contact information was forwarded to Examination Management Services, Inc (EMSI), whose trained technicians were contracted to administer the in-home exam.[170] EMSI has "extensive experience in scheduling and executing protocols of this complexity (or greater)."[171] EMSI then scheduled the hour-long in-home visit and reminded the participant to fast for 10-12 hours prior to the specimen collection and to collect all the medicines they have used within the previous two weeks for documentation during the visit.[170] During the in-home exam, height, weight, waist circumference, blood pressure, and pulse were measured.[170] Additionally, an ECG was administered, blood was drawn, and urine sample taken.[170] Finally, the EMSI personnel examined each medicine presented and cataloged its use on a standardized form, shown in **Figure 3.1**.[170]

Figure 3.1: 1st page of REGARDS Medication form filled out by EMSI personnel during in-home exam



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* 2 1 5 0 0 M D 0 1 0 2 0 2 *

REGARDS MEDICATIONS FORM

EMSI STAFF: PLEASE READ. The REGARDS study is interested in prescription and non-prescription medications participants are taking. These include vitamins, cold remedies, dietary supplements, dermal patches, eye drops, creams, salves, and injections. Please remind participant that the letter the participant received about this appointment asked him/her to have their current medications available. If necessary, remind the participant that this means prescription and non-prescription medications and read the list above.

Have you taken any medications in the past 2 weeks? [Please place an "X" in the box beside the appropriate response(s)]

☐ YES ----->Are these all the medications that you have taken in the past 2 weeks? ☐ YES **[Complete information below]**

☐ NO (why not?)

☐ NO **[END FORM]**

	Medication Name *Please Print clearly in all CAPITAL LETTERS.* *Please no dosage or frequency*	Prescription Medicine? YES NO
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		
13.		
14		
15.		

Following the in-home visit, biological samples were dispatched overnight to a central lab for analysis and the hand written medication form was scanned using a process similar to the Teleform system.[170] As compensation for cohort members' time, participants were sent a thank you note and $30 check after the in-home visit.[170] Following the biochemical assays, study members were sent a report summarizing their blood tests and ECG.[170]

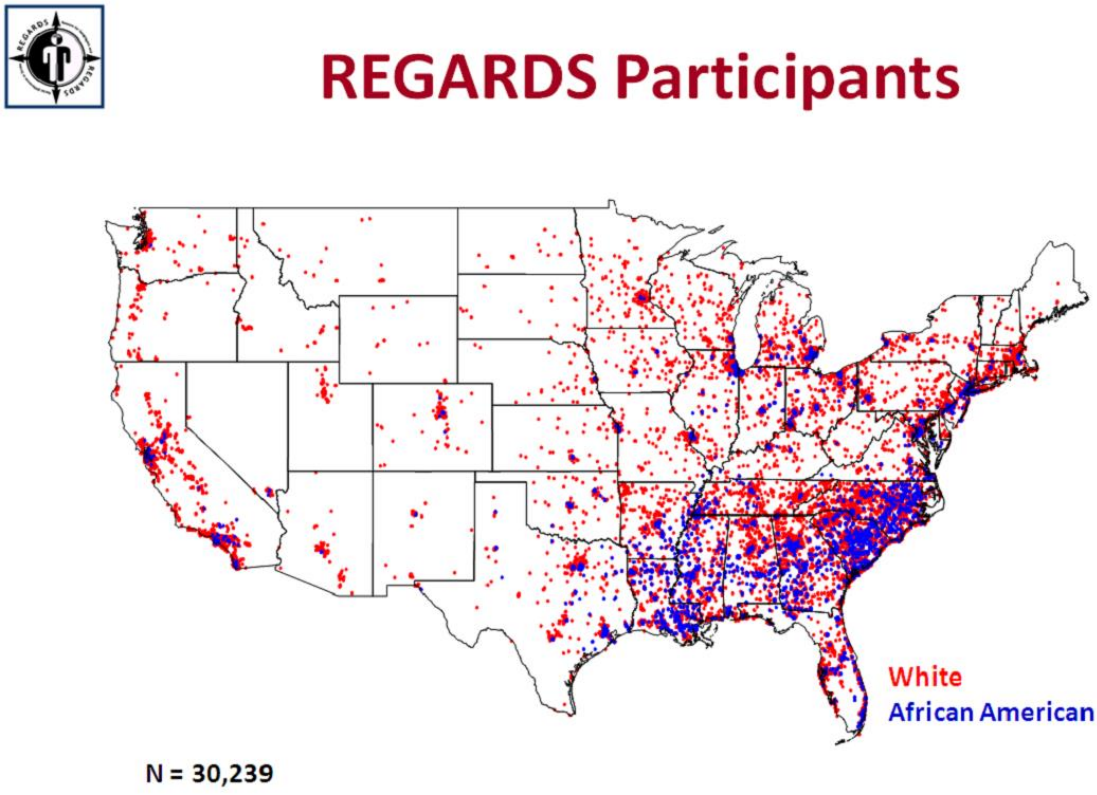
REGARDS follows study participants through a number of mechanisms. First, cohort members are called each six months. To decrease loss-to-follow-up, proxy information of two

relatives or friends was requested.[170] Finally, REGARDS obtained access to the cohort member's medical records "by having the participant sign a permission form for release of records."[170] The access extends to "death certificates, admission notes, discharge summaries, procedure reports, laboratory reports, and clinic notes."[171]

3.2: REGARDS Sample

The geographic distribution of the REGARDS sample is shown below. Over half the counties in the continental United States have at least one REGARDS participant. The oversampling of blacks and stroke belt residents is apparent in **Figure 3.2**.

Figure 3.2: Geographic and Racial Distribution of REGARDS Cohort



3.2.1: Sample Sizes and Medication-Use Assumptions for 0.29% of cohort:

The total cohort size is 30,183. However, 30,157 cohort members were present in the medication file (26 (0.09%) "apparently" had missing medication forms). However, for 25 of those, other in-home variables were collected and it was assumed that the medication form was left blank simply because no medications were taken. These 25 were classified as non-medication users. The one individual for whom no other in-home variables were recorded was assumed to have a missing medication form and excluded from analysis. Amongst the 30,157 cohort members present in the medication form file, 63 (0.21%) were missing all medication form variables. However, for 62 of these individuals, other in-home variables were collected, and the reason for the missing medication form data was assumed to be that it was left blank because no medications were being taken. As such, these 62 were also classified as non-medication users. Finally, 1 cohort member was present in the medication file but was missing all medication form and in-home variables. As such, she was excluded from analyses. Thus, the total analytic N = 30,181 (two cohort members excluded for missing data).

For the mortality analysis, 554 of these 30,181 lacked any outcome follow-up vital status or follow-up time and were thus excluded from analyses. Thus, the final analytical mortality N = 29,627.

3.3: Covariate Data

Information on many broad categories of covariates was collected, including demographics (age, race, gender, region of residence, relationship status), Socioeconomic Status (education, income, insurance status), lifestyle (alcohol use, smoking, BMI category, exercise frequency), comorbidities (diabetes, dyslipidemia, atrial fibrillation, myocardial infarction (MI) history, coronary artery disease (CAD) history, CKD status, and stroke history), and self-

reported health and stress. The covariate definitions and their possible values are shown in **Table 3.1** below:

Table 3.1: REGARDS Covariates and Possible Covariate Values

Covariate Class	Variable	Possible Variable Values
DEMOGRAPHICS	Age	45-54, 55-64, 65-74, 75-84, 85+
	Race	Black, White
	Gender	Male, Female
	Geog. Region	Buckle, Belt, Nonbelt
	Relationship Status	Divorced, Married, Other, Single, Widowed
SES	Education	College Grad, Some College, HS Grad, <HS
	Income	<20k, 20-34k, 35-74k, >75k, Refused
	Insurance Status	Yes, No
	Medical Care	Yes, No
LIFESTYLE	Alcohol Use	Heavy, Moderate, None
	Smoking	Current, Past, Never
	BMI Category	Underweight, Normal, Overweight, Obese
	Exercise Frequency	None, 1-3 times/wk, 4+ times/wk
COMORBIDITIES	Diabetes	Yes, No
	Hypertension	Yes, No
	Dyslipidemia	Yes, No
	Atrial Fibrillation	Yes, No
	CAD History	Yes, No
	CKD Status	Yes, No
	Stroke Sympt./Hist.	Yes, No
SELF-ASSESSMENT	SR Health	Excellent, Very Good, Good, Fair, Poor
	Stress Level	Perceived Stress Scale: scores from 0-16

The incomes are annual incomes in thousands. Heavy alcohol use is defined as 8 or more drinks per week for women and 15 or more drinks per week for men. Moderate alcohol use is defined as any alcohol use less than heavy use. The comorbidities are defined in the following ways: hypertension [yes/no: Systolic Blood Pressure ≥ 140 mmHg, Diastolic Blood Pressure ≥ 90 mmHg, or SR antihypertensive use; diabetes as fasting glucose ≥126 mg/dL or non-fasting

glucose ≥ 200 mg/dL or taking diabetes medications; dyslipidemia as total cholesterol > 240 mg/dL or LDL ≥ 160 mg/dL or HDL ≤ 40 or taking a lipid-lowering medication; atrial fibrillation as self-reported or EKG evidence; coronary artery disease (CAD) [yes/no: SR MI (myocardial infarction), bypass, angioplasty, stenting or ECG MI evidence]; and CKD as self-reported dialysis or glomerular filtration rate ≤ 60 mL/min/1.73m^2. Stroke-symptom is a self-reported history of any of the following: sudden unilateral weakness/numbness, loss of vision, loss of speech comprehension, or aphasia.

3.4: Database Construction

The medication database was constructed from the handwritten medication lists collected during the REGARDS in-home visit, where study participants were asked to provide pill bottles for all the medicines (including creams, eye drops, injections, herbal/multivitamin/nutraceuticals) they had used in the previous two weeks. These lists of raw medication names were hand-written on a standardized form. Next, the form was optically scanned to create an electronic list of medications. A total of 171,574 medication names were manually recorded and scanned. Of these, there were 34,776 distinct spellings/names of different recorded medication names that required further classification.

A team of pharmacy students and a research pharmacist at Samford University made the initial generic name assignments of these 34,776 medication names, one-by-one. An effort was then made by the author to confirm the generic name identity of these preliminary recorded medication name assignments. In cases where the recorded medication name corresponded exactly or differed by only one letter from the assigned generic name, no additional effort was made to confirm the generic name classification, and these generic name assignments were considered definitive.

In cases where the REGARDS medname and the assigned generic name differed by two or more characters, because of a multiple-character misspelling or because a brand name was transcribed as the REGARDS medname, additional work was needed.

Using the preliminary Samford University generic name assignments, an effort was made to confirm the assignment and provide an internet link that showed the rationale behind the particular assignment. In total, over 99% of the medications recorded during the in-home visit were confirmed manually as part of the data component element of the dissertation. During this process, the recorded medication name was copied into the search field in the **Drugs.com** website. The search results were then scanned in an effort to find a "medication match." If no satisfactory matches were found when searching the **Drugs.com** database, a similar query was conducted using the **Google** search engine. Analogously, the **Google** output was scanned in an effort to find a medication match. If no match could be found for the particular recorded medication name of interest, then the recorded medication name was assigned a generic name of "unknown." However, in most cases, a match was found. In these cases, the generic name was definitively assigned, and the link detailing the match was copied and pasted in the master medication file. In total, over 14,700 internet links precisely documenting the basis for the generic name assignment were compiled. In total, there were over 1275 distinct generic names that were assigned. A SAS Macro was then written that allows for the calculation of the prevalence of drug use of any of the distinct singleton generics. It should be noted that this Macro is easily modified to allow for the assessment of generic prevalence according to covariate value (e.g., aspirin use in women compared to men). A screenshot of the generic name assignment process is shown in **Figure 3.4**. Note the mis-spellings of medication names and the use of medication brand names.

Figure 3.3: Example of the process of generic name assignment of in-home visit recorded "regards_medname" and assignment documentation.

	A	B	C
1	**regards_medname**	**generic_name**	**Citation**
2	ZEN	supplement	http://www.drugnatural.com/p/655681?utm_source=GoogleBase&utm_medium=GoogleBase&utm_te
3	NEXUS	supplement	http://www.amazon.com/NEXUS-Mens-Fitness-Formula-night/dp/B004W97G4S
4	ZIAGEN	Abacavir	http://www.drugs.com/mtm/ziagen.html
5	ZIAGEN ABC	abacavir	abc abbreviation for abacavir
6	ZIAGER	abacavir	http://www.drugs.com/mtm/ziagen.html
7	EPZICOM	abacavir;lamivudine	http://www.drugs.com/epzicom.html
8	TRIZIVAR	abacavir;lamivudine;zidovudine	http://www.drugs.com/trizivir.html
9	TRIZIVIR	Abacavir;Lamivudine;Zidovudine	http://www.drugs.com/trizivir.html
10	ACARBOSE	Acarbose	
11	PRECASE	Acarbose	http://www.drugs.com/pro/precose.html
12	PRECOL	unknown	drugs.com precose or japanese drug "precol"
13	PRECOSE	Acarbose	http://www.drugs.com/pro/precose.html
14	ACEBUTLOL	acebutolol	
15	ACEBUTOLOL HCL	acebutolol	
16	ACEBUTRLOL	acebutolol	
17	ACEBUTULOL CPS 200 MG	acebutolol	
18	ACEHATOLOL HCL	acebutolol	google and drugs.com
19	SECETERAL	Acebutolol	google and drugs.com = sectral
20	SECTRAL	Acebutolol	http://www.drugs.com/mtm/sectral.html
21	SECTROL EQ	acebutolol	http://www.drugs.com/mtm/sectral.html

The generic classification of supplements proved particularly challenging. Since supplements are not regulated by the FDA, there are no universally applicable generic names associated with each supplement. Moreover, many supplements contain dozens of ingredients, making their concise classification impossible. Initially, one of the goals of the medication database construction conducted as part of this dissertation was to systematically classify all supplements according to their chemical composition. After some initial efforts to achieve this, it became clear that the wide range of supplement recorded medication names and their associated complexity were not readily tractable. As such, for subsequent supplement recorded medication names, simple summary generic names like "supplement" or "multivitamin" were assigned. However, internet searches using **Google** and/or **Google Shopping** were conducted in an effort to find the product label to confirm that the particular recorded medication name was a supplement. In these cases, the link detailing the supplement was copied into the master

medication dataset. An example of the challenges implicit in ascertaining the composition of supplements is shown in **Figure 3.4**.

Figure 3.4: The recorded medication name and the generic name are the first two columns, respectively. Note the extreme heterogeneity of recorded supplement names.

VITACAL MAGO	multimineral;multivitamin;boron;silica	http://www.trivita.com/us-en/content/labels/337_lbl.pdf
PROTEGRA CARDIN MULTIVIT	multimineral;multivitamin;fatty acid	http://www.amazon.com/Protegra-Cardio-Formula-Softgels-60/dp/B00006L7
FORWARD PLUS DAILY REGIME	multimineral;multivitamin;fatty acid;nutraceutical	https://www.goodnnaturalonline.com/store/product_info.php?manufacturers_
FORWARD PLUS REGIMENT	multimineral;multivitamin;fatty acid;nutraceutical	https://www.goodnnaturalonline.com/store/product_info.php?manufacturers_
MVT/MINERAL/HERB	multimineral;multivitamin;herbal	
ATHURZ SELECT PLUS LUTEN	multimineral;multivitamin;nutraceutical	http://www.walgreens.com/store/catalog/Vitamins/A-thru-Z-Select-Tablets/ID
BAREFOOT CORAL CALCIUM PL	multimineral;multivitamin;nutraceutical	http://www.maxvite.com/234/2827/Natures_Benefit_Barefoot_Coral_Calcium
BAREFOOT CORAL CALLIUM PL	multimineral;multivitamin;nutraceutical	http://www.maxvite.com/234/2827/Natures_Benefit_Barefoot_Coral_Calcium
COMPLETE 50 PLUS	multimineral;multivitamin;nutraceutical	http://www.americarx.com/Products/18035.html
DAILY ONE CAPS	multimineral;multivitamin;nutraceutical	http://www.vitaminshoppe.com/store/en/browse/sku_detail.jsp?id=TL-1
DAILY ONE CAPS W/IRON	multimineral;multivitamin;nutraceutical	http://www.vitaminshoppe.com/store/en/browse/sku_detail.jsp?id=TL-1
FOCUS FACTOR	multimineral;multivitamin;nutraceutical	http://www.drugstore.com/products/prod.asp?pid=221030&catid=50461&aic
FOCUS FACTOR-MEMORY AID	multimineral;multivitamin;nutraceutical	http://www.drugstore.com/products/prod.asp?pid=221030&catid=50461&aic
FORMULAVVM-75	multimineral;multivitamin;nutraceutical	http://www.vitaminshoppe.com/store/en/browse/sku_detail.jsp?id=SL-1
GNC MEGA MEN	multimineral;multivitamin;nutraceutical	http://www.gnc.com/product/index.jsp?productId=3597819&CAWELAID=359
GNC MULTIGEL	multimineral;multivitamin;nutraceutical	http://www.gnc.com/product/index.jsp?productId=2133391&CAWELAID=293
GNC ULTRA MEGA VITAMIN	multimineral;multivitamin;nutraceutical	http://www.gnc.com/search/index.jsp?kwCatId=&kw=gnc%20ultra%20mega
ICAPS LUTFEIN &ZEAXANTHIN	multimineral;multivitamin;nutraceutical	http://www.walgreens.com/store/catalog/Vitamins/Lutein-and-Zeaxanthin/ID=
ICAPS W LUTEIN AND ZEAXAN	multimineral;multivitamin;nutraceutical	http://www.walgreens.com/store/catalog/Vitamins/Lutein-and-Zeaxanthin/ID=
MEGA MAN MULTIVIT	multimineral;multivitamin;nutraceutical	http://www.gnc.com/product/index.jsp?productId=4033434
MEGA MEN MULTIVITAMINS	multimineral;multivitamin;nutraceutical	http://www.gnc.com/product/index.jsp?productId=4033434
MEGAMEN MULTIVITAMIN	multimineral;multivitamin;nutraceutical	http://www.gnc.com/product/index.jsp?productId=4033434
MILLTRIUM SENIOR	multimineral;multivitamin;nutraceutical	http://www.walgreens.com/store/catalog/Vitamins/Milltrium-Senior-with-Lutei
MOTHER NATURES MIRACLE	multimineral;multivitamin;nutraceutical	http://mothernaturesmiracle.com/

With the generic name assigned, prescription and OTC medications were next classified according to pharmacologic class(es), using the class designations provided by the website drugs.com (http://www.drugs.com/drug-classes.html). In total, over 350 distinct classes were assigned. Supplements, because of their heterogeneity (there were over 250 distinct supplement "generic names" in the dataset) and lack of FDA oversight, were not assigned a drug class beyond simply "supplement." The ability to assess the prevalence of use of any therapeutic drug class in the entire cohort was achieved using SAS Macros. It should be noted that simple modifications to this Macro would also allow for the comparison of drug class prevalences

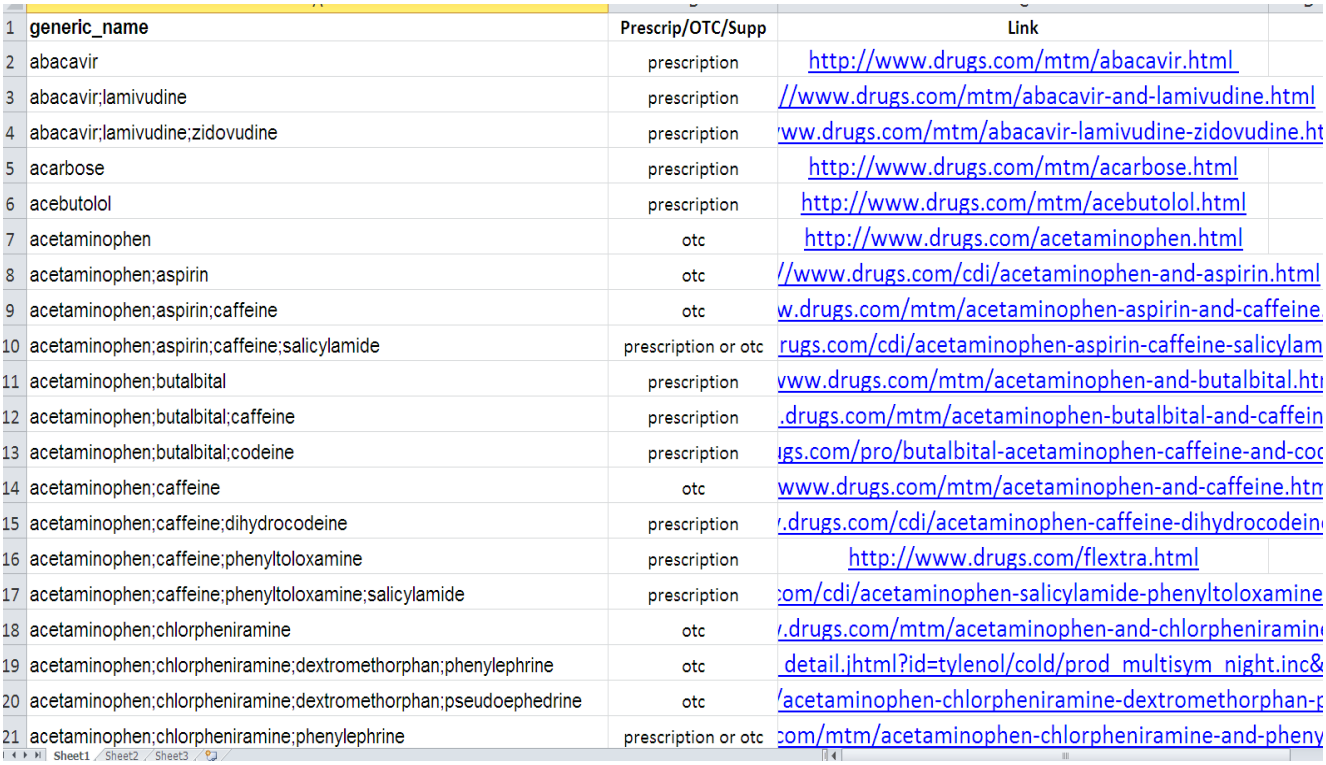
according to covariate values (e.g., among CKD positive versus negative cohort members). An example of drug class assignments of the generic names is shown in **Figure 3.5**.

Figure 3.5: Drug generic names and their corresponding pharmacological classes. Note that a single generic can belong to multiple classes. Also note the many multi-ingredient generics.

	A	B	C	D	E
1	**generic_name**	**class_1**	**class_2**	**class_3**	**class_4**
2	abacavir	nucleoside reverse transcriptase inhibitor			
3	abacavir;lamivudine	nucleoside reverse transcriptase inhibitor			
4	abacavir;lamivudine;zidovudine	nucleoside reverse transcriptase inhibitor			
5	acarbose	alpha-glucosidase inhibitor			
6	acebutolol	cardioselective beta blocker	antiarrhythmic agent		
7	acetaminophen	miscellaneous analgesic			
8	acetaminophen;aspirin	miscellaneous analgesic	salicylate	platelet aggregation inhibitor	
9	acetaminophen;aspirin;caffeine	miscellaneous analgesic	salicylate	cns stimulant	platelet
10	acetaminophen;aspirin;caffeine;salicylamide	miscellaneous analgesic	salicylate	cns stimulant	platelet
11	acetaminophen;butalbital	miscellaneous analgesic	barbiturate		
12	acetaminophen;butalbital;caffeine	barbiturate	miscellaneous analgesic	cns stimulant	
13	acetaminophen;butalbital;codeine	miscellaneous analgesic	barbiturate	narcotic analgesic	
14	acetaminophen;caffeine	miscellaneous analgesic	cns stimulant		
15	acetaminophen;caffeine;dihydrocodeine	miscellaneous analgesic	cns stimulant	narcotic analgesic	
16	acetaminophen;caffeine;phenyltoloxamine	miscellaneous analgesic	cns stimulant	antihistamine	
17	acetaminophen;caffeine;phenyltoloxamine;salicylamide	miscellaneous analgesic	cns stimulant	antihistamine	antimig
18	acetaminophen;chlorpheniramine	miscellaneous analgesic	antihistamine		
19	acetaminophen;chlorpheniramine;dextromethorphan;phenylephrine	miscellaneous analgesic	antihistamine	antitussive	mouth
20	acetaminophen;chlorpheniramine;dextromethorphan;pseudoephedrine	miscellaneous analgesic	antihistamine	antitussive	mouth
21	acetaminophen;chlorpheniramine;phenylephrine	miscellaneous analgesic	antihistamine	vasopressor	decong
22	acetaminophen;chlorpheniramine;phenylpropanolamine	miscellaneous analgesic	antihistamine	decongestant	anorexi
23	acetaminophen;chlorpheniramine;pseudoephedrine	miscellaneous analgesic	antihistamine	decongestant	
24	acetaminophen;codeine	miscellaneous analgesic	narcotic analgesic		
25	acetaminophen;dextromethorphan	miscellaneous analgesic	antitussive	mouth and throat product component	
26	acetaminophen;dextromethorphan;doxylamine;phenylephrine	miscellaneous analgesic	antitussive	mouth and throat product component	misc an
27	acetaminophen;dextromethorphan;doxylamine;pseudoephedrine	miscellaneous analgesic	antitussive	mouth and throat product component	misc an

Additionally, for each unique generic name a medication type (prescription, OTC, supplement) was assigned using the **Drugs.com** database. These medication types were essential to calculating total ingredient sums in defining polypharmacy, as supplements were excluded from consideration when computing these sums. An example of this process is shown in **Figure 3.6**. Again, a link was copied into the adjacent cell to document the basis for classification. The entire database construction process, encompassing generic name assignment/confirmation, drug class assignments, and medication type coding took over two years.

Figure 3.6: Example of prescription/OTC/Supplement classification for assigned generic names.



	generic_name	Prescrip/OTC/Supp	Link
2	abacavir	prescription	http://www.drugs.com/mtm/abacavir.html
3	abacavir;lamivudine	prescription	//www.drugs.com/mtm/abacavir-and-lamivudine.html
4	abacavir;lamivudine;zidovudine	prescription	ww.drugs.com/mtm/abacavir-lamivudine-zidovudine.ht
5	acarbose	prescription	http://www.drugs.com/mtm/acarbose.html
6	acebutolol	prescription	http://www.drugs.com/mtm/acebutolol.html
7	acetaminophen	otc	http://www.drugs.com/acetaminophen.html
8	acetaminophen;aspirin	otc	//www.drugs.com/cdi/acetaminophen-and-aspirin.html
9	acetaminophen;aspirin;caffeine	otc	w.drugs.com/mtm/acetaminophen-aspirin-and-caffeine
10	acetaminophen;aspirin;caffeine;salicylamide	prescription or otc	rugs.com/cdi/acetaminophen-aspirin-caffeine-salicylam
11	acetaminophen;butalbital	prescription	www.drugs.com/mtm/acetaminophen-and-butalbital.ht
12	acetaminophen;butalbital;caffeine	prescription	.drugs.com/mtm/acetaminophen-butalbital-and-caffein
13	acetaminophen;butalbital;codeine	prescription	gs.com/pro/butalbital-acetaminophen-caffeine-and-co
14	acetaminophen;caffeine	otc	www.drugs.com/mtm/acetaminophen-and-caffeine.htm
15	acetaminophen;caffeine;dihydrocodeine	prescription	.drugs.com/cdi/acetaminophen-caffeine-dihydrocodein
16	acetaminophen;caffeine;phenyltoloxamine	prescription	http://www.drugs.com/flextra.html
17	acetaminophen;caffeine;phenyltoloxamine;salicylamide	prescription	om/cdi/acetaminophen-salicylamide-phenyltoloxamine
18	acetaminophen;chlorpheniramine	otc	.drugs.com/mtm/acetaminophen-and-chlorpheniramin
19	acetaminophen;chlorpheniramine;dextromethorphan;phenylephrine	otc	detail.jhtml?id=tylenol/cold/prod_multisym_night.inc&
20	acetaminophen;chlorpheniramine;dextromethorphan;pseudoephedrine	otc	/acetaminophen-chlorpheniramine-dextromethorphan-p
21	acetaminophen;chlorpheniramine;phenylephrine	prescription or otc	com/mtm/acetaminophen-chlorpheniramine-and-pheny

Sheet1 Sheet2 Sheet3

With these raw data "basis set" files documenting the recorded medication name, generic names, drug classes, and drug types, SAS merges were used to create the complete REGARDS medication database. In particular, SAS was used to define a polypharmacy exposure variable using total generic ingredient counts. The particular sequence of merges necessary to integrate all the desired pharmacologic information into a single database is briefly described in the following sentences. Merging by generic name allowed for the creation of a file with each distinct recorded medication name, assigned generic name, and drug class. Next a merge on generic name with the file containing generic name/medication type classification integrated medication type into the database. Next, we incorporated study ID numbers into the previously un-identified recorded medication name, generic name, drug class, and drug type file by merging

on the recorded medication name on the raw file that contained the list of all recorded medications and the associated ID numbers. Finally, the covariate information was incorporated into the medication file by merging (on ID number) this file with the covariates file. Thus, a file that had one line for each transcribed and scanned medication (171,574 lines total), with the associated ID number, assigned generic name, assigned drug classes, assigned drug type, and associated covariates was generated.

Next, a "vector" file was constructed that summarized medication use with each cohort member represented by one line of data. This was done using SAS "retain" and "output" statements in an array command and using the internal SAS variables first.id_num and last.id_num, so that a single line of data summarized medication use for each cohort member.

The SAS code and "raw data", whether SAS datasets or Excel spreadsheets with assigned generic names or drug classes, is available on the request to the REGARDS Executive Committee. Conditional upon the approval of the REGARDS executive committee, we hope many other researchers will be able to utilize this data.

3.4.1: Comprehensiveness of Medication Inventory:

Of the 20,586 cohort members whose medication form checked the box for whether or not the medication inventory was comprehensive of all medications taken in the previous two weeks, over 98.3% answered in the affirmative that the inventory was all-inclusive.

3.5: Analysis:

3.5.1 The Challenge of Confounding by Indication:

The phenomenon of **confounding by indication** presents serious methodological challenges to the validity of the inferences drawn from pharmacoepidemiologic research.

Confounding by indication, the fact that those taking and not taking medications are systematically different (beyond drug use), and residual confounding present threats to validity.

Formally, confounding by indication can be defined as "occurring when the risk of an adverse event is related to the indication for medication use but not the use of the medication itself."[172] That is to say drugs are not taken randomly—medications are always taken for a very specific reason or indication. If not careful, the medication indication can easily obscure the true medication effect. For example, if one were to study the effects of an anti-hypertensive on cardiovascular disease mortality comparing those that used the anti-hypertensive to those that didn't, due to their presumed greater baseline comorbidity, the anti-hypertensive users would be expected to experience greater mortality even if the anti-hypertensive were highly effective in controlling blood pressure and preventing cardiovascular disease mortality. Thus, in order to obtain a better assessment of a drug's effect, one must account for the baseline health differences between drug users (generally sicker) and non-drug users (generally healthier).

Confounding by indication can be at least partially (if not necessarily entirely) addressed during analysis. By measuring a number of presumed potential confounders and controlling for them in a multivariate model or propensity score, confounding by indication's magnitude can be diminished. However, we would be naïve to think that confounding by indication could totally be eliminated: "Although…theoretically possible [to control for confounding by indication], it is in practice often impossible to obtain a sufficiently accurate estimate of the effect of this confounder, even when the reason for prescribing seems very straightforward. This is because 'indication' is a very complex and multifactorial phenomenon involving the physician's knowledge and many factors, sometimes not rational, which act in different directions."[173] The "art of medicine" as it pertains to selecting an appropriate pharmacological treatment further

complicates any attempt to control for confounding by indication.[174] Moreover, if the indication for a single drug can be so complex, the possibilities for polypharmacy's indications are orders of magnitude more complicated.

The term "confounding by indication" implicitly assumes that an exposure-outcome's confounders could be readily specified. The assumption is seriously impugned by the study of polypharmacy, as polypharmacy is such a composite pharmacoepidemiologic endpoint (polypharmacy could result from any of billions of possible drug regimens). Therefore, *a priori* specifying a comprehensive list of confounding factors is very challenging, if not impossible.

3.5.2: Use of Propensity Scores to Account for Confounding by Indication:

Propensity scores have been proposed as one means to attempt to control for confounding by indication.[175,176] Conceptually, propensity scores are fairly straightforward. Propensity scores predict the likelihood (propensity) of a certain treatment of interest (i.e., polypharmacy) given a set of covariates. Thus, the propensity model predicts the probability an individual will have polypharmacy as a function of his/her age, race, gender, comorbidities, etc.

If polypharmacy is defined dichotomously, then propensity scores can be estimated using a logistic model where the outcome of interest is polypharmacy yes/no and the model's independent variables are the potential confounders that contribute a propensity towards polypharmacy. A unique propensity score is generated for each permutation of potentially confounding covariates. Note that the potential confounders on which the propensity score is based are aggregated into the propensity score. Assuming all such potential confounders are included in the propensity score, then the propensity-adjusted model would only include exposure status (i.e., polypharmacy) and outcome, with the single propensity score perhaps included as the single covariate.

With the estimated propensity score, there are multiple ways to attempt to control for confounding by indication with the propensity score, including propensity-based matching or stratification and using the propensity score as a model covariate.[177]

For study 2, we used propensity-quintile or –decile based stratification (the stratification approach). For study 3, we used dummy variables representing propensity quintile or decile as a model covariate (the covariate approach). For neither study did we use propensity-based matching.

3.6: Statistical Methodologies:

3.6.1: Use of Sampling Weights to Estimate National/Regional Medication Use Patterns:

REGARDS intentionally oversampled blacks and stroke belt residents, sampling a total of 108 region/race/sex/age strata.[170] However, to allow for national/regional extrapolation of REGARDS findings, sampling weights were calculated for each cohort member. Utilization of the SAS survey suite of procedures (e.g., PROC SURVEYFREQ, PROC SURVEYMEANS, PROC SURVEYLOGISTIC) with strata and weight statements, allowed for national and regional estimates of medication use to be obtained.

3.6.2: Age as the Time-Scale Models:

The traditional time scale for cohort follow-up time-to-event data is time-on-study. Some have suggested that while time-on-study might be appropriate for randomized controlled trials, for cohort data, the attained age as the time-scale (conditioning on age at study entry) might be more appropriate.[178,179]. For our second study, models using both time-scales were constructed.

3.6.3: Proportional Hazards (PH) Assumption Testing for Study 2:

No strongly nonparallel univariable log-log survival vs. log(follow-up time) plots were observed for any variable (the plots did sometimes cross, but for limited data portions). Many of the log-log survival plots were linear, suggesting a possible univariable Weibull survival distribution[180]. However, for multivariable models, Cox PH models (without the Weibull survival assumption) were utilized.

For the univariable time-on-study Schoenfeld residual correlations, all variables had a correlation $p > 0.05$ or a correlation coefficient absolute value < 0.07. Because of the small (albeit sometimes statistically significant) absolute correlations, the PH assumption was considered reasonable for all variables. Bivariable (including one time-dependent term) extended-Cox models were constructed; some had statistically significant time-dependent terms.

For the time-on-study models, the PH assumption was deemed reasonable for all variables considered one-at-a-time. For the univariable age-time-scale models, the PH assumption was deemed reasonable (Schoenfeld Residual correlation $p > 0.05$ or correlation coefficient absolute value < 0.15) for all variables considered one-at-a-time.

Chapter 4: RESULTS

4.0: Results Introduction:

In this section, a brief re-statement of the specific study aims and hypotheses is provided.

Next, each study is presented in full.

4.0.1: Study Aims and Hypotheses

Study 1: Polypharmacy model as a function of individual variables, paying special attention to race and region.

- **Aim**: The purpose is to construct a polypharmacy model using individual-level characteristics.
- **Hypothesis:**
  - **H1:** Individual (age, race, gender, income, education, geography etc.) characteristics will not be associated with polypharmacy.

Study 2: The association between polypharmacy and mortality.

- **Aim**: The purpose is to measure association of polypharmacy and mortality, while adjusting for a wide range of covariates, and test for effect modification according to CKD status.
- **Hypothesis:**
  - **H1**: After adjusting for covariates and assessing interaction, polypharmacy will not increase the mortality hazard.
  - **H2**: After adjusting for covariates and assessing interaction, polypharmacy will not increase the mortality hazard, *and there will be no heterogeneity of effect across CKD (i.e., there will be no effect modification by this variable*).

Study 3: Description of drug use with potential cognitive effects and association of polypharmacy with cognitive impairment.

Descriptive component:

- Histogram of number of drugs taken with potential cognitive effects

Inferential component:

- **Aim**: After adjusting for covariates and assessing interaction according to CKD status, the purpose is to test for an association between polypharmacy and incident cognitive impairment.
- **Hypothesis**:
  - **H1:** Polypharmacy will not be associated with cognitive impairment over time.
  - **H2**: Polypharmacy will not be associated with cognitive impairment over time, *and there will be no heterogeneity of effect according to CKD status (i.e., no effect modification by CKD status)*

4.1: STUDY 1: In press, **Annals of Epidemiology**

Geographic Region and Racial Variations in Polypharmacy in the United States*:* *The **RE**asons for **G**eographic **A**nd **R**acial **D**ifferences in **S**troke Study*

4.1.1: ABSTRACT

Purpose: Medications can have unintended effects. High medication use populations may benefit from increased regimen oversight. Limited knowledge exists concerning racial and regional polypharmacy variation. We estimated total medication distributions (excluding supplements) of American black and white adults and assessed racial and regional polypharmacy variation.

Methods: REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort data (N=30,239 U.S. blacks/whites ages ≥45 years) were analyzed. Home pill-bottle inspections assessed the last two weeks' medications. Polypharmacy (≥ 8 medications) was determined by summing prescription and/or OTC ingredients. Population-weighted logistic regression assessed polypharmacy's association with census region, race, and gender.

Results: The mean ingredient number was 4.12 (SE = 0.039), with 15.7% of REGARDS using ≥8 ingredients. In crude comparisons, women used more medications than men, and blacks and whites reported similar mean ingredients. A cross-sectional, logistic model adjusting for demographics, socioeconomics, and comorbidities showed increased polypharmacy prevalence in whites vs. blacks (OR, [95% CI]: 0.63, [0.55-0.72]), women (1.94, [1.68-2.23]), and Southerners {broadly Southeasterners and Texans} (1.48, [1.17-1.87]) vs. Northeasterners {broadly New England and upper Mid-Atlantic}. Possible limitations include polypharmacy misclassification and model mis-specification.

Conclusion: Polypharmacy is common. Race and geography are associated with polypharmacy variation. Further study of underlying factors explaining these differences is warranted.

Abbreviations/Acronyms:
ADR: adverse drug reaction
CATI: computer-assisted telephone interview
CI: confidence interval
HS: high school
MI: myocardial infarction
OTC: over-the-counter
REGARDS: REasons for Geographic And Racial Differences in Stroke
SAS: statistical analysis software
SE: standard error
SES: socioeconomic status

4.1.2: INTRODUCTION

Adult Americans take many prescription and over-the-counter (OTC) medications[1], each year purchasing approximately four billion prescriptions.[2] There are over 300,000 distinct OTC products.[3] Over $300 billion is spent annually in the United States on prescriptions.[4]

In addition to pharmaceuticals' well-established benefits, medication errors also occur, the most frequent class of medical error.[5] Based on a meta-analysis, if categorized as a disease, adverse drug reactions (ADRs) are estimated to be up to the fourth leading cause of death.[6]

Polypharmacy, broadly conceptualized as high medication use, encapsulates the dual potential for poly-therapeutic effects and/or poly-toxicities.[7] Unfortunately, polypharmacy has no universally accepted definition.[8] Polypharmacy sometimes has negative connotations, suggesting inappropriate/excessive medication use; however, it can also reflect appropriate care for patients with multiple health conditions and/or conditions requiring multiple medications. Nevertheless, polypharmacy has been associated with adverse health events, including cognitive decline,[9,supp ref] falls,[10,supp ref] ADRs,[11] and drug-drug interactions.[12]

Although some data on America's medication use have begun emerging,[13] population-based medication variation according to geography and race merit further elucidation. Large-scale, national studies assessing multivariable-adjusted racial and/or geographic polypharmacy variations in the general black and white adult population are, to our knowledge, largely unavailable. Here we use data from a large, population-based cohort to characterize cross-sectional racial and geographic polypharmacy patterns in the United States.

4.1.3: METHODS

Study Design and Population:

We used the **RE**asons for **G**eographic **A**nd **R**acial **D**ifferences in **S**troke (REGARDS) cohort study data.[14] REGARDS utilized a two-stage survey design, with simple random sampling within strata defined by three geographic areas [stroke buckle (coastal plains of the Carolinas and Georgia) / stroke belt (eight Southern states: North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, Louisiana) / stroke nonbelt (the rest of the continental United States)], two race categories (black/white), age groups, and sex (male/female).[14] After excluding 58 participants with data anomalies or missing medication information, the analytic cohort included 30,181 community-dwelling black and white Americans ages ≥45 years residing in the contiguous United States. The population-based cohort was sampled from Genesys'[15] commercial database, with oversampling of blacks and "stroke belt"[16,17] residents.

Detailed REGARDS methodology is presented elsewhere.[14] Briefly, a study pamphlet was mailed to potential participants; a telephone interviewer then called to inquire about participation. Individuals were excluded for non-black/non-white race, ongoing cancer treatment, poor English proficiency, cognitive impairment judged by the telephone interviewer, having a medical condition preventing long-term follow-up, or current nursing home residence or presence on a nursing home waiting list. The cooperation rate (number of study participants enrolled divided by the number who were contacted and met inclusion criteria) was 49%.[18,19] For those agreeing to participate, the interviewer obtained verbal informed consent and began a computer-assisted telephone interview (CATI).

CATI-derived data included information about demographics, socioeconomic status (SES) including education (nine levels ranging from never attended/kindergarten only to graduate/professional school) and annual income (nine levels ranging from < $5,000 to > $150,000), and comorbidities (cardiovascular disease history, hypertension, diabetes, dyslipidemia, and chronic kidney disease). Each participant's race was self-reported as black or white. Following the CATI, an in-home exam was conducted. Participants were asked to collect all medicines used in the previous two weeks prior to the exam. Blood pressure was measured during the in-home exam. Blood samples were analyzed at a central laboratory, and the results were used to estimate glomerular filtration rate to define chronic kidney disease. Institutional Review Boards reviewed the research at all participating institutions, and signed informed consent was obtained.

Drug Classification and Polypharmacy Definition:

Cohort members were called prior to in-home exam and reminded to assemble their medications. Health professionals trained in the study protocol examined each medication provided (i.e. "pill bottle inspection") and recorded the name (generic/brand) on a standardized form with space for up to 20 medication names. All rendered medications taken in the past two weeks (including medications administered ophthalmically, dermally, via injection, etc.) were recorded. Neither dosage nor use frequency/history was recorded. These records were processed into an electronic database of 34,776 distinct recorded medication names.

All medications were assigned a generic name (e.g., acetaminophen instead of Tylenol) by a research pharmacist and graduate students using primarily data from *Drugs.com.*[20] For combination formulations (e.g., 3 ingredient-component antihypertensive), the drug count was the total number of ingredients. For 1.62% of recorded medications, a generic name could not be

assigned, and these were marked as "unknown." Each "unknown" medication was assumed to correspond to one drug ingredient.

Polypharmacy status was expressed as a binary variable, indicating whether or not ≥ 8 total ingredients (excluding supplements) were documented. This cut-point was chosen *a priori*, because it is an approximate midpoint between possible thresholds of 5 or 10 medications[21,supp ref] and because it corresponds to the highest quintile of medication-use (21.1%) in the REGARDS cohort. To study whether the associations examined were sensitive to the polypharmacy definition, an alternative analysis was conducted in which the polypharmacy threshold was set at ≥ 5 instead of ≥ 8. Some participants had the same ingredient listed multiple times, whether due to different medication formulations (e.g., long-, medium-, and short-acting insulin) or using the same medicine twice (e.g., two acetaminophen-containing, multi-component analgesics); in such cases the total ingredient sum counted the medication as many times as it was recorded.

Because of their heterogeneity and limited regulatory oversight (the Food and Drug Administration's purview is very different for prescription/OTCs than with supplements),[22] supplements (vitamins/minerals, herbal preparations, and nutraceuticals) were not considered. Some vitamins and minerals are available both as supplements and prescriptions; we tried to distinguish the prescription forms which counted towards polypharmacy (e.g., isotretinoin) from the OTC-available forms (e.g., vitamin A) that were considered supplements.

On the standardized medication form, there was a box to check if the medication inventory were complete of all medications used within the previous two weeks. Of the 20,586 participants who reported medication use and checked the box, 98.3% indicated that their medication inventories were complete.

Statistical Analysis:

Sampling fractions from region-age-race-sex strata were used to provide weighted, nation-level estimates. Analyses for this report incorporated sampling weights using Statistical Analysis Software (SAS) 9.3 survey procedures.

Medication counts and their distributions were determined from participants' two-week total medication (prescriptions/OTCs) ingredient sums. Logistic regression was used to assess the multivariable-adjusted association between the independent variables listed in **Table 1** and polypharmacy. The three exposures of interest were: race [black, white], census-defined regions [South, West, Midwest, Northeast], and gender [female, male]. The covariates were as follows:

Demographics: age [45-54, 55-64, 65-74, 75-84, 85+ years]

SES: education [< High School (HS), ≥ HS]; income [<$20k, $20-34k, $35k-74k, ≥$75k, "refused"])

C**omorbidities:** chronic kidney disease [yes/no: self-reported dialysis or estimated glomerular filtration rate ≤ 60 mL/min/1.73m^2]; cardiovascular disease history [yes/no: self-reported MI (myocardial infarction), bypass, angioplasty, stenting or electrocardio-gram MI evidence or self-reported stroke]; diabetes [yes/no: fasting glucose ≥ 126 mg/dL, non-fasting ≥ 200 mg/dL, or self-reported use of anti-hyperglycemic medication or insulin]; hypertension [yes/no: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported antihypertensive use]; and dyslipidemia [yes/no: total cholesterol ≥ 240 mg/dL, low-density lipoprotein ≥ 160 mg/dL, high-density lipoprotein ≤ 40 mg/dL, or self-reported use of lipid-lowering medication].

Sampling weights allowed geographic estimates following the census regions[23] boundaries (**Figure 1**) of South, Midwest, West, and Northeast.

Three distinct logistic regression models were constructed. The level of statistical significance was $\alpha = 0.05$. For all models, census region, race, and gender were the exposures of interest and polypharmacy was the outcome. Model 1 adjusted for age categories. Model 2 also adjusted for education and income. Model 3 included all variables used in Model 2 and added comorbidities (chronic kidney disease, hypertension, dyslipidemia, diabetes, and cardiovascular disease history). Model collinearity was checked using the SAS macro's condition indices/variance decomposition proportions.[supp ref] All models were *a priori* no-interaction models.

4.1.4: RESULTS

Characteristics of the Cohort and Their Medications:

A total of 171,573 drug names were obtained and transcribed from the medication inventories conducted during in-home visits. Among sampling-weighted, non-supplemental medications, 91.8% were single-ingredient drugs and 16.0% of transcribed medications were available OTC. The mean age of participants was 65 years; 42% were black; 45% were male; 68% resided in the South (**Table 1**). The prevalences of dyslipidemia and hypertension were both nearly 60%, and the prevalence of diabetes was 22%.

The Midwest had the highest proportion of black cohort members. The West had the highest proportion of cohort members with at least a HS education and with an annual income ≥ $75,000. There was relatively little regional variability with regards to comorbidities.

Among black cohort members, a greater proportion was female and fewer had completed HS relative to whites. Black cohort members reported lower incomes and had higher rates of diabetes and hypertension relative to whites.

Males reported higher incomes than females. Males also had higher prevalences of dyslipidemia and cardiovascular disease history.

Prevalence of Medication Use and Mean Ingredient Counts:

Overall, 27,060 participants (89.7%) used ≥ 1 medication ingredient(s) in the two weeks preceding the in-home visit. **Figure 2** shows sampling-weighted ingredient sum prevalence distribution in the entire analytic cohort (national estimate) and according to gender, race, and census region. As these are sampling-weighted calculations, they represent national estimates for black and white adults age ≥ 45 years.

For the overall national estimate, less than 15% of participants reported taking no medications in the preceding two weeks. The prevalence of polypharmacy (≥8 drug ingredients) was 15.7%. The mean (standard error [SE]) ingredient count was 4.12 (0.039).

Females had higher mean ingredient counts [4.53 (0.057)] than males [3.66 (0.054)]. Females also had a higher rate of polypharmacy (18.4%) than males (12.7%).

Mean ingredient counts (blacks = 4.08, whites = 4.13) and polypharmacy proportions (blacks = 16.3%, whites = 15.7%) were similar regardless of race (**Figure 2**).

The South's mean number of total ingredients was 4.53 (SE = 0.057), substantially higher than that of the West (3.90, [0.099]), the Midwest (3.87, [0.082]), and the Northeast (3.83, [0.12]). Similarly, the polypharmacy prevalence in the South (19.3%) was higher than in the West (13.9%), the Midwest (13.5%), and the Northeast (13.0%).

Multivariable Race- / Census Region- / Gender-Polypharmacy Associations:

The multivariable-adjusted odds ratios (ORs) for the three exposures of interest (race, census region, and gender) in the three models constructed are shown in **Table 2**. Analogous sensitivity analyses using the alternate polypharmacy definition did not yield substantially

different ORs. Crude, sampling-weighted odds ratios (ORs) and 95% confidence intervals (CI) are also shown.

In the crude analysis and in all multivariable models, polypharmacy was more common in the South than the Northeast, with ORs (95% CIs) ranging from 1.61 (1.32-1.96) in the crude analysis to 1.48 (1.17-1.87) in Model 3. The point estimates for the Midwest and West (relative to the Northeast) were all non-significant.

In crude analysis and in models that did not adjust for comorbidities, there was no statistically significant difference in the prevalence of polypharmacy among blacks compared to whites. However, in Model 3 (which adjusted for demographics, SES factors, *and* comorbidities), blacks were statistically significantly (OR = 0.63; 95% CI: 0.55-0.72) less likely to have polypharmacy.

For gender, in crude analyses and multivariable-adjusted analyses, women were more likely than men to have polypharmacy. The association was strongest in Model 3 (OR = 1.94; 95% CI: 1.68-2.23).

4.1.5: DISCUSSION

Medications are a cornerstone of medical care, and medication regimens are often exceedingly complex, making managing polypharmacy a major challenge across multiple domains (e.g., patients, physicians, pharmacists, insurers, etc.). While not the focus of this research, an obvious implication is that an improved understanding of medication patterns may foster more economical and efficacious drug utilization, while minimizing risks (e.g., embedded electronic medical record software applications to suggest regimen simplification in cases of therapeutic redundancies or pop-up reminders to try to minimize anti-cholinergic burdens in geriatrics).

Consistent with other large studies, the overwhelming majority of REGARDS participants were taking medication(s).[1,13] This widespread medication use highlights the need for nurses, physicians, pharmacists, and allied health providers to remain cognizant to patients' medication regimens, retaining awareness that new signs/symptoms may be medication-induced. Paradoxically, polypharmacy may indicate lost therapeutic opportunities, as polypharmacy is a risk factor for underprescribing,[24] so polypharmacy should not be considered synonymous with overprescribing. Although many REGARDS cohort member's drugs may be appropriately prescribed and properly used, the high mean ingredient count (4.12) and a significant proportion using ≥ 8 ingredients (15.7%) may indicate increased risks for ADRs and drug interactions.[11,12] In this study, however, we could not distinguish "appropriate" from "inappropriate" polypharmacy.

Our most important findings were that, after adjustment for demographics, SES factors, and comorbidities, whites and Southern residents had significantly greater prevalence of polypharmacy. To our knowledge, this is the first time that a multivariate model of the American adult population ages 45 and older has reported findings of racial and geographic medication use differences.

This analysis of REGARDS medication use has several strengths. First, the large sample (N=30,239 for the total cohort, 58 participants were excluded in the presented analyses), allowed for detailed subgroup comparisons. Additionally, medication use was assessed rigorously through pill-bottle verification by trained health professionals. Furthermore, raw drug data coding by trained staff using a systematic strategy for ascertaining misspelled medications' identities ensured accurate classification. Finally, despite considerable effort, 1.62% of collected

medications could not be assigned a generic name ("unknowns"). These unknowns were not excluded but instead were assumed to represent a single non-supplemental ingredient.

This study also has a number of limitations. Data were not collected on medication dose or use frequency/history, which would help distinguish sporadic from persistent polypharmacy. However, defining polypharmacy by ingredient sums (excluding supplements) may be the most biologically plausible approach, since supplements do not undergo the same regulation and often contain many "active" ingredients (e.g., multivitamin). Polypharmacy misclassification could occur at multiple steps—not all medications were assembled or medications not used in the previous two weeks were included, medication transcription mistakes, electronic medication list scanner errors, and generic assignment misclassification. Some residual selection bias from sampling-weight misspecification could occur. The reasons for medication use are multifactorial and variable; the polypharmacy models may be mis-specified (e.g., important confounders and effect modifiers may have been omitted or the models may have been "overfit" with variables not needed to correct for confounding by indication).

In crude comparisons, blacks and whites had similar mean ingredient counts and polypharmacy prevalences. However, upon multivariable adjustment that included comorbidities, blacks had less polypharmacy than whites. The lack of a crude race-polypharmacy association (but a significant adjusted association) may be attributable to blacks' greater comorbidities. To our knowledge, this is the first time a multivariable-adjusted model has reported racial polypharmacy disparities for the general, biracial American adult ($\geq$ 45 years) population.

Our findings are consistent with Dwyer *et al*.[25] who reported that "black/other" nursing home residents were less likely than whites to be exposed to polypharmacy. Among two cohorts of

hospitalized elderly with heart failure from 1998-2001, Masoudi *et al.* also reported higher mean multivariable-adjusted prescription counts at hospital discharge among whites than blacks.[26] By contrast, Hanlon *et al.* found no crude black-white difference in polypharmacy among Veterans Affairs nursing home extended-stay residents.[supp ref] Similarly, in a study of community-dwelling American adults, Qato *et al*. reported no statistically significant racial differences in a multivariable model of "no regular medication use," although this study had a significantly smaller sample than REGARDS.[13]

In geographic analyses, the South had the highest prevalence of polypharmacy compared to all other census regions. To our knowledge, no previous studies have reported significant, multivariable, American regional variation in aggregate medication use. The reasons for higher medication utilization in the South relative to the rest of the country are unclear. Regional variation in healthcare has been reported by others,[27,supp ref] and prescribing quality geographic differences have been documented.[supp ref]

Aparasu *et al*. documented crude, but not multivariable, regional variation in elderly office visit polypharmacy.[28] Similarly, Perry and Turner reported crude mean prescription count regional variation among National Health and Nutrition Examination Survey III 65+ year olds.[29] Additionally, Gupta *et al.* noted intrastate geographic variation with prescription count in Louisiana geriatric Medicaid beneficiaries.[30] Other researchers have investigated different dimensions of medication use geographic variation (e.g., inter- and intra-regional variation abroad and urban/rural variation).[supp ref] Moreover, although not a composite pharmacological assessment like polypharmacy, some United States data on the spatial distributions of use of specific medication classes are available.[supp ref]

4.1.6: CONCLUSIONS:

In summary, this research documents a high frequency of polypharmacy in the United States and shows that polypharmacy is not equally distributed across racial groups and census regions. The geographic variation should be explored at the community level; further investigation into factors that explain the observed polypharmacy racial disparities is merited. Also, future studies should investigate potential consequences of polypharmacy including direct toxicity, drug interactions, and ADRs. Finally, it should be noted that as polypharmacy is appropriate and the standard of care for some patients, higher prevalences of polypharmacy in the South and among whites should not be equated with excessive medication use in these groups.

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4.1.8: TABLES AND FIGURES:

Table 1: REGARDS Cohort's (Sampling-Unweighted) Covariate Distribution According to Census Region, Race, and Gender

Covariate	Cov. Val.	Tot. N	Census Region %*				Race %*		Gender %*	
			NE	MW	W	S	B	W	M	F
Age	85+	590	2.14	2.15	3.15	1.72	1.66	2.16	2.06	1.87
	75-84	4,580	17.2	16.0	18.2	14.3	13.0	16.7	16.3	14.3
	65-74	9,685	30.9	32.2	31.5	32.3	31.2	32.8	33.7	30.8
	55-64	11,539	40.6	38.7	34.2	38.5	40.1	36.9	37.5	38.9
	45-54	3,787	9.20	10.9	12.9	13.2	14.1	11.5	10.5	14.2
Region	South	20,386	-	-	-	100	64.6	69.6	66.4	68.5
	West	2,953	-	-	100	-	9.09	10.3	9.48	10.0
	Midwest	4,689	-	100	-	-	18.5	13.5	16.7	14.6
	Northeast	2,153	100	-	-	-	7.82	6.64	7.50	6.84
Race	Black	12,513	45.5	49.3	38.5	39.7	100	-	35.0	46.7
	White	17,668	54.5	50.7	61.5	60.3	-	100	65.0	53.3
Gender	Female	16,630	52.8	51.8	56.5	55.9	62.1	50.2	-	100
	Male	13,551	47.2	48.2	43.5	44.1	37.9	49.8	100	-
Education	≥ HS	26,364	88.7	86.7	95.6	86.3	80.0	92.7	88.5	86.6
	< HS	3,792	11.3	13.3	4.40	13.7	20.0	7.33	11.5	13.4
Income	< $20k	5,478	17.4	18.8	10.2	19.2	26.9	12.0	12.1	23.1
	$20k - $34k	7,306	22.6	26.6	20.5	24.4	26.4	22.7	23.3	24.9
	$35k - $74k	8,914	29.6	28.7	33.2	29.2	25.2	32.6	34.3	25.7
	≥ $75k	4,754	18.3	13.9	24.4	14.6	8.88	20.6	21.0	11.4
	Refused	3,729	12.0	12.0	11.7	12.6	12.7	12.1	9.30	14.8
Dyslipidemia	Yes	17,228	57.5	58.7	57.1	60.0	55.3	62.1	67.2	52.8
	No	11,817	42.5	41.3	42.9	40.0	44.7	37.9	32.8	47.2
Diabetes	Yes	6,398	21.7	21.1	18.0	22.8	30.9	15.8	22.9	21.3
	No	22,654	78.3	78.9	82.0	77.2	69.1	84.2	77.1	78.7
Hypertension	Yes	17,846	57.6	60.0	52.9	60.2	71.3	50.7	58.3	60.0
	No	12,262	42.4	40.0	47.1	39.8	28.7	49.3	41.7	40.0
CVD Hist.	Yes	6,501	21.2	24.0	18.8	22.1	20.9	22.8	28.2	16.9
	No	23,019	78.8	76.0	81.2	77.9	79.1	77.2	71.8	83.1
CKD	Yes	3,295	10.7	12.0	11.4	11.4	12.1	10.9	11.4	11.4
	No	25,583	89.3	88.0	88.6	88.6	87.9	89.1	88.6	88.6

Tot. N: Cohort N--For example, there were 590 cohort members age 85+. *****: Column percent

B: Black; **CKD**: Chronic Kidney Disease; **CVD**: Cardiovascular Disease; **F**: Female; **HS**: High School; **M**: Male; **MW**: Midwest; **NE**: Northeast; **S**: South; **W**: West; **W**: White; **-**: Not Applic.

Table 2: Results from Sampling-*Weighted, Multivariable-Adjusted* Logistic Regression Models of Polypharmacy Associations

Exposures		Sampling-Weighted Polypharmacy Model ORs (95% CI)			
		Crude (CI)	Model 1* (CI)	Model 2† (CI)	Model 3‡ (CI)
Region	Northeast	**Ref**	**Ref**	**Ref**	**Ref**
	Midwest	1.04 (0.83-1.31)	1.07 (0.86-1.34)	1.03 (0.82-1.29)	1.01 (0.78-1.32)
	West	1.08 (0.86-1.37)	1.08 (0.86-1.37)	1.14 (0.90-1.45)	1.23 (0.93-1.62)
	South	**1.61** (1.32-1.96)	**1.59** (1.30-1.94)	**1.51** (1.23-1.85)	**1.48** (1.17-1.87)
Race	White	**Ref**	**Ref**	**Ref**	**Ref**
	Black	1.05 (0.96-1.15)	1.07 (0.97-1.18)	0.90 (0.81-1.00)	**0.63** (0.55-0.72)
Gender	Male	**Ref**	**Ref**	**Ref**	**Ref**
	Female	**1.55** (1.39-1.73)	**1.50** (1.34-1.68)	**1.35** (1.20-1.51)	**1.94** (1.68-2.23)

Statistically Significant Estimates are Bolded

For model covariate possible values see Table 1

*****: Adjusted for Demographics (Age, Race, Gender, Region)

†: Adjusted for Demographics + SES Factors (Education, Income)

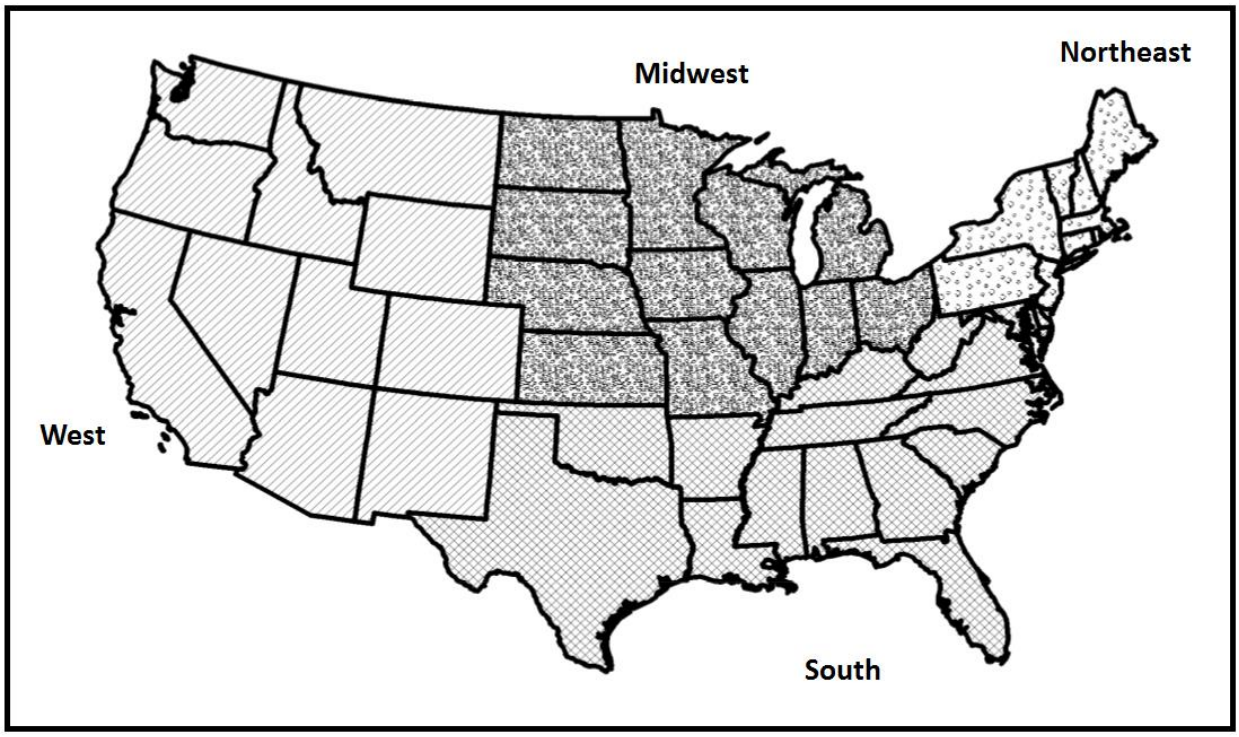
‡: Adjusted for Demographics + SES Factors + Comorbidities (Chronic Kidney Disease, Hypertension, Dyslipidemia, Diabetes, Cardiovascular Disease History)

CI: confidence interval

OR: odds ratio for being polypharmacy (≥ 8 total ingredients) positive

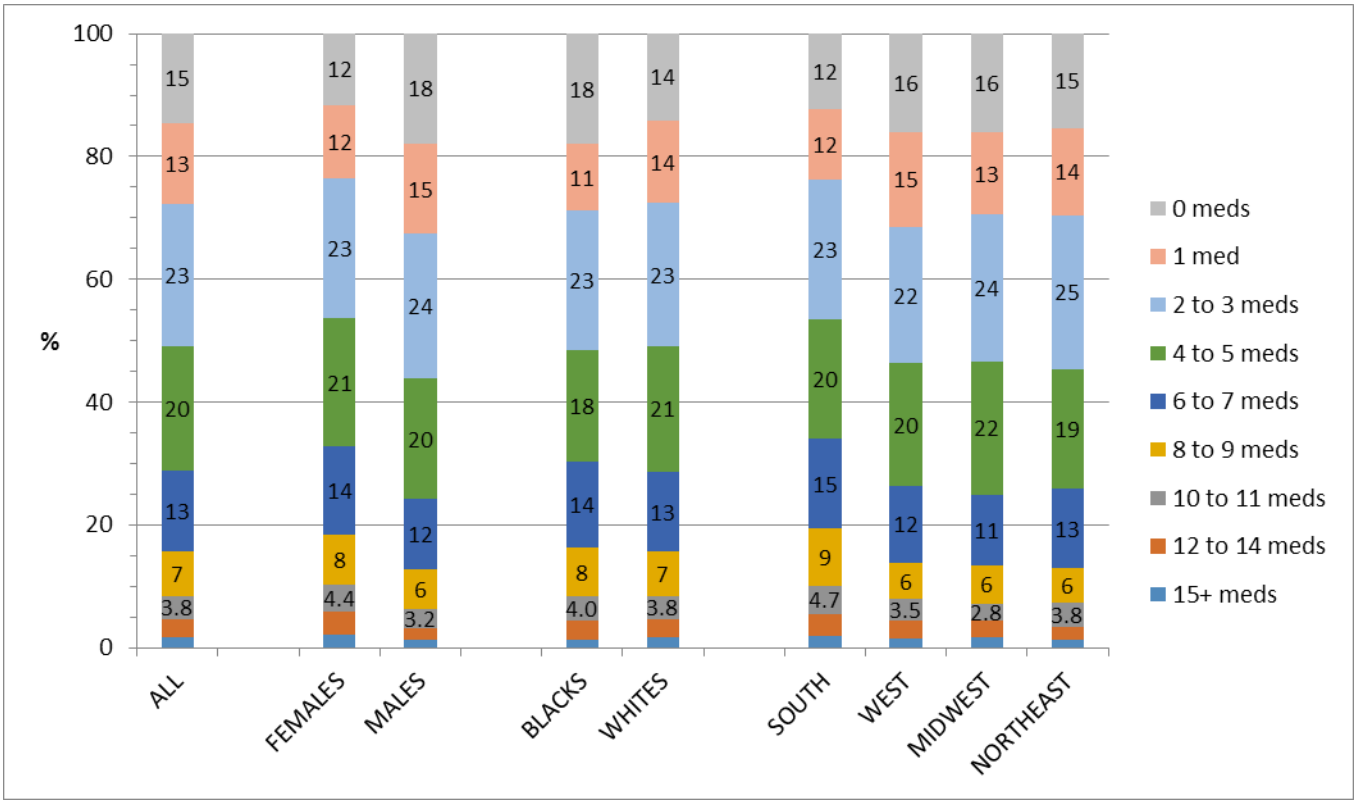
Ref: reference group

<u>Figure 1:</u> Census Regions Used



The four census regions are shown.

<u>Figure 2</u>: Ingredient Sum Prevalence Distribution for Entire Cohort and According to Gender, Race, and Geographic Region, *Adjusted* for Sampling Weights



The percent corresponding to the respective total ingredient sums (excluding supplements) is found within the labeled bars. Because of space constraints, these percentages are not shown for the 12-14 meds and 15+ meds categories.

Meds: total ingredient sum

4.2: STUDY 2:

The Association between Polypharmacy and All-Cause Mortality in the REGARDS Cohort: The *RE*asons for *G*eographic *A*nd *R*acial *D*ifferences in *S*troke Study

4.2.1: ABSTRACT

Context: Many Americans take multiple medications simultaneously; this is known as polypharmacy. The effects of polypharmacy on mortality are uncertain.

Objective: To assess the association between polypharmacy and mortality in a large US cohort and consider potential effect modification by chronic kidney disease (CKD) status.

Design, Setting, and Participants: The REGARDS (***RE***asons for ***G***eographic ***A***nd ***R***acial ***D***ifferences in ***S***troke) cohort data (analytic n= 29,627, comprised of blacks and whites age ≥45 in the continental U.S.) were used. During an in-home visit, pill bottle inspections were conducted to ascertain medications used in the previous two weeks. Polypharmacy status (major [≥8 ingredients], minor [6-7 ingredients], none [0-5 ingredients]) was determined by counting the total number of generic (prescription or over-the-counter) ingredients. Cox Proportional Hazards models (using both time-on-study and age-time-scale methods to model time to event) were used to assess the relation of polypharmacy to mortality. Several alternative models were constructed to assess confounding by indication and to consider effect modification by CKD.

Main Outcome Measure: Vital status, assessed approximately every 6 months.

Results: Over a median follow-up of 4.9 years, 2,538 deaths were observed. Major polypharmacy was associated with increased mortality in all models, with hazard ratios and 95% confidence intervals ranging from 1.22 (1.07-1.40) to 2.35 (2.15-2.56). Minor polypharmacy

was associated with mortality in some, but not all, models. The polypharmacy-mortality association did not differ in those with and without CKD.

Conclusions: While residual confounding by indication cannot be ruled out, in this large US cohort, major polypharmacy was associated with mortality in all models.

4.2.2: INTRODUCTION

Americans consume many prescription and over-the-counter (OTC).[1] With over 300,000 marketed OTC products[192] and approximately 5 billion OTC products purchased annually,[26] 70-90% of illnesses are estimated to involve at least some self-treatment.[25]

While medications' health benefits are beyond dispute, approximately half of all prescriptions may be used improperly.[20] Additionally, drugs' side effects are often treated with more medication, leading to a "prescribing cascade."[32] Drug allergies, drug-drug and drug-disease interactions, and direct toxicity are all hazards. If categorized as a disease, adverse drug reactions (ADRs) are estimated to be the fourth leading cause of death.[8]

Polypharmacy, or high medication use[193], can exert poly-therapeutic effects as well as poly-toxicities.[12] The term "polypharmacy" sometimes has negative connotations, suggesting inappropriate/excessive medication use; however, the simultaneous administration of many drugs can also be the standard of care. Polypharmacy is often defined two ways: using more drugs than clinically warranted or taking more than a threshold drug count, e.g., five.[16]

Polypharmacy is a known risk factor for adverse health events, including cognitive decline[106,107], falls[108,109], and ADR.[111] Based on its associations with drug-drug interactions[102] and ADRs[111], polypharmacy poses plausible mortality risks; however, for mortality, polypharmacy's effects remain unclear.

Individuals with chronic kidney disease (CKD) may be especially vulnerable to any adverse effects of polypharmacy because kidney function is critical for drug excretion; however the role of CKD in the association between polypharmacy and mortality remains uncertain.

To address existing knowledge gaps, we analyzed the large, national REGARDS (**RE**asons for the **G**eographic **A**nd **R**acial **D**ifferences in **S**troke) cohort. The REGARDS data

are well-suited for assessing the association between polypharmacy and all-cause mortality, both overall and by CKD status.

4.2.3: METHODS:

Study Design:

REGARDS is a nationwide, longitudinal cohort study that began in 2003 and was described in detail previously.[170] Briefly, the analytic sample consisted of 29,627 **(supplementary text**) community-dwelling black and white Americans age ≥45 years with at least one follow-up. The cohort recruitment occurred throughout the continental U.S. using the Genesys commercial database[183], with oversampling of blacks and "stroke belt"[184] residents (eight Southeastern states: North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, Louisiana).

Individuals were excluded from REGARDS for non-black/non-white race, ongoing cancer treatment, inability to speak English, nursing home residence, telephone interviewer-assessed cognitive impairment, or if expected to pose follow-up difficulties. The cohort's cooperation rate was 49%[185].

Data:

A computer-assisted telephone interview collected information on demographic, socioeconomic status (SES), medical, and lifestyle variables. Examination Management Services Inc. (EMSI) scheduled a home visit and instructed the participant to collect all medicines used in the previous two weeks. During the home exam, signed informed consent was obtained, and anthropomorphic measurements and blood and urine samples were collected and sent to a central laboratory.

The EMSI personnel examined each medicine present ("pill bottle" inspection including creams/eye drops/injectables) and cataloged its name (generic/brand), but neither dose nor frequency of use, on a standardized form. These records were processed into an electronic database of 34,776 distinct recorded medication names.

For prescriptions/OTCs, the medication was assigned a generic name (e.g., acetaminophen) by a research pharmacist and graduate students using primarily **Drugs.com**. For 1.62% of recorded medications, the generic name could not be identified, and those medications were assigned generic name "unknown". Each unknown drug was assumed to correspond to one generic ingredient.

When assessing polypharmacy, supplements (vitamins/minerals/herbals/nutraceuticals) were not considered, due to their heterogeneity, lack of universal nomenclature, and limited oversight[15,40]. Polypharmacy was characterized using three categories of total generic ingredient count:[54] **no polypharmacy** (≤ 5 total generic ingredients); **minor polypharmacy** (6-7 generic ingredients); and **major polypharmacy** (≥ 8 generic ingredients). Presence of CKD was defined as self-reported dialysis or glomerular filtration rate (GFR) < 60 mL/min/1.73m^2) based on the subject's serum creatinine.[194]

Cohort members were called approximately every six months to ascertain vital status. In addition, deaths were identified through proxy communication and regular checks of the Social Security death index master file and National Death Index queries. During a maximum of over 7 years of follow-up, fewer than 3% of participants were lost to follow-up annually. Of the original cohort (n=30,181), 554 (1.84%) lacked any follow-up vital status or follow-up time and were thus excluded from analyses. A total of 2538 deaths (8.6% of the study cohort) were observed through late September 2010. With respect to follow-up completeness, 50% of

survivors had their vital status ascertained within 115 days of the last recorded follow-up; 75% within 195 days; and 90% of survivors had their vital status ascertained within 2.35 years of the last recorded follow-up.

Covariates:

Known polypharmacy risk factors include comorbidities,[12,58] needing help with activities of daily living,[58] demographics (female sex,[12,30] older age,[12,30] white race[58,81]), and SES (low educational attainment,[12,30] lower social status,[12,87] unemployment[12,87]). We adjusted for potential confounding using the following full-model covariates: demographics (age, race, gender, relationship status, region); SES measures (education, income, insurance status); lifestyle (alcohol, smoking, body mass index [BMI], physical activity); comorbidities (diabetes, atrial fibrillation, hypertension, coronary artery disease (CAD) history, stroke symptoms, dyslipidemia); biomarkers (lipids, heart rate); and self-reported (SR) health and stress. The Institutional Review Board reviewed the research at all participating institutions.

Statistical Analysis:

Chi-square tests were used to assess polypharmacy differences across covariates. Crude covariate-polypharmacy and covariate-mortality odds ratios (ORs) were calculated. Cox Proportional Hazards (PH) models with the time-on-study outcome (or the attained age outcome,[195,196]) until death or censoring examined the polypharmacy-mortality association. CKD status was evaluated *a priori* as a potential effect modifier (the only one considered) of polypharmacy on mortality by including the corresponding two-way interaction terms.

The age-time-scale models included the same covariates, except attained age was instead the outcome of interest (conditioning on study-entry age, with birth-cohort stratification). Models 1-7 are sequential subsets of the "full" model 8. Model 1 adjusted for demographics

(age, region, race, gender, relationship status). Model 2 adjusted for demographics + SES factors (education, income, insurance, medical care). Model 3 adjusted for demographics + lifestyle variables (smoking, alcohol use, BMI, physical activity). Model 4 adjusted for demographics and SES and lifestyle variables. Model 5 adjusted for all of model 4's covariates plus comorbidities (CKD, diabetes, CAD history, hypertension, dyslipidemia, atrial fibrillation, and stroke symptoms). Model 6 added self-reported health to the model 5 covariates. Model 7 added perceived stress to the model 6 covariates. Model 8 added the polypharmacy*CKD interaction terms to model 7.

Multiple models were utilized because the causal pathway for polypharmacy-all-cause mortality is not established, particularly for a heterogeneous sample like REGARDS. Aside from models 1-7, no other "reduced" models were considered.

Two propensity-adjusted models were utilized to address confounding by indication.[197] In these models, all candidate confounders were included in a multiple logistic regression (propensity) analyses that used binary polypharmacy status (defined as ≥ 8 total ingredients) as the dependent variable. Each participant's polypharmacy propensity was estimated, and participants' propensities (irrespective of actual polypharmacy status) were divided into quintiles or deciles. After stratifying on estimated propensity quintiles or deciles, a stratified, no-interaction (HR assumed constant for all propensity quintiles/deciles) Cox PH regression used only major/minor polypharmacy as mortality predictors.

Collinearity was assessed for the time-on-study models using the Statistical Analysis Software (SAS) macro.[188] No problematic collinearity was detected. SAS 9.2 was used. The PH assumption for the time-on-study models was checked by constructing univariable log-log survival plots and by examining univariable-model Schoenfeld residuals[198] failure-time

correlations.[180] For the age-time-scale models, the PH assumption was assessed using Schoenfeld residuals. The PH assumption was deemed reasonable for all models constructed.

4.2.4: RESULTS

Overall, 171,573 in-home visit drug names were transcribed. Among all 30,181 participants, 21.1%, 15.8%, and 63.2% were categorized as receiving major, minor, and no polypharmacy, respectively. The REGARDS cohort characteristics comparing the major polypharmacy group (**PP+**) to all other participants (**PP-**) are presented in **Table 4.2.1**. In the analytic sample, the mean age was 64.9 years, 45% were male, 41% black, 56% stroke- belt residents, 35% college graduates, 24% with normal BMI, 11% with CKD, and 16% and 31% were in "excellent" and "very good" self-reported health, respectively. Relative to the **PP-** group, those with major polypharmacy (**PP+**) included a greater proportion of females, stroke-belt residents, and those with less education, lower income, higher BMI, more comorbidities (CKD, hypertension, dyslipidemia, diabetes, CAD, atrial fibrillation), and lower self-reported health (**Table 4.2.1**). In crude analyses, older adults, blacks, males, individuals with less education or income, smokers, those with poorer SR health, and those with comorbid conditions showed higher mortality.

Median cohort follow-up was 4.9 years; 2538 deaths were observed. As seen in the Kaplan-Meier plot (**Figure 4.2.1a**), major polypharmacy had the lowest survival, followed by minor polypharmacy, and the no-polypharmacy group (log-rank $p < 0.0001$). In all time-on-study (**Table 4.2.2**) and age-time-scale PH models, major polypharmacy was significantly associated with mortality. The hazard ratio (HR) estimates ranged from 1.26 (95% CI: 1.11-1.42) to 2.35 (2.15-2.56), depending on the model. The minor polypharmacy HR estimates were smaller, ranging from 1.12 (0.98-1.27) to 1.50 (1.35-1.67).

The interaction of polypharmacy*CKD status on mortality is shown in **Figure 4.2.1b**. CKD strongly predicted survival, and within each CKD level, there was a progressive decrease in survival going from no polypharmacy to minor to major polypharmacy. The model 8 CKD*polypharmacy interaction terms were all non-significant (all interaction p >0.30).

The two methods of modeling time-to-event (age-time-scale [**Table 4.2.3]** and time-on-study) gave similar results with less than 3% difference across model-specific HR estimates. The models that controlled for propensity scores using stratification (**Table 4.2.4**) gave results consistent in magnitude with "traditional" models that included covariates as separate terms.

4.2.5: DISCUSSION

While the potential benefits of medications are unquestioned, adverse health effects of polypharmacy are also well documented.[106,107] In this longitudinal study conducted using a racially diverse, nationwide sample of the general U.S. adult population, we found that 1) major polypharmacy was associated with mortality in all models; 2) the association was consistently less pronounced for minor polypharmacy; 3) there was no evidence that the effect of polypharmacy on mortality is modified by CKD; 4) propensity-based and traditional covariate-based analyses produced similar results.

Several previous studies investigated the association between polypharmacy and mortality in a variety of populations. Jyrkka et al. reported mixed results in a Finnish study,[162] and Espino et al. found a positive association in a study of Mexican Americans.[105] Iwata et al. reported higher one-year mortality among Japanese elderly polypharmacy users following hospital discharge.[163] Incalzi et al. reported higher in-hospital mortality among Italian polypharmacy patients.[164] Richardson et al. reported higher two-year mortality among older United Kingdom polypharmacy users.[165]

Conversely, Pozzi et al. reported no Italian polypharmacy-mortality association.[166] Similarly, among hospitalized elderly Italians, no association between polypharmacy and in-hospital mortality was observed by Nobili et al.[167]

The finding of significant HRs for major polypharmacy after adjusting for potential confounders in all models constructed and the graded polypharmacy-mortality relationship ([major polypharmacy HR] > [minor polypharmacy HR]) is biologically plausible. On the other hand, we found little support for our *a priori* hypothesis that polypharmacy would be more harmful among those with CKD. It is important to point out that the inter-relation between CKD and polypharmacy may be complex and not sufficiently described by a simple dichotomized CKD*polypharmacy interaction terms. For example, polypharmacy may decrease mortality in individuals with more severe kidney disease for whom a regimen of multiple drugs may be beneficial. Alternatively, polypharmacy may increase mortality in individuals with mild renal impairment who, perhaps unaware of their diminished renal drug clearance, may suffer greater drug toxicity.

Our analysis has important strengths. Rigorous exposure and outcome assessments minimized misclassification. Many potential confounders were measured. The large sample size and long follow-up provided ample statistical power. Moreover, the sample was generated from the general, biracial population of community-dwelling American adults (≥ 45 years), with minimal exclusion criteria, suggesting that the results may be considered reasonably generalizable.

Confounding by indication, the fact that those taking and not taking medications are systematically different (beyond drug use), and residual confounding presented additional methodological challenges. Data on many potential confounders were collected (and the number

of events sufficient to make large models feasible), so residual confounding may be limited by these efforts, as well as by the propensity score-based analyses.

Absent an established biological mechanism linking polypharmacy and all-cause mortality, it is possible that a model's supposed "confounders" may function as polypharmacy-based mediators acting in either a causal or preventative outcome pathway. Because of the complex exposure patterns (billions of drug combinations) and numerous biological processes converging in death, it appears difficult to *a priori* distinguish confounders from mediating factors. We addressed this problem by conducting analyses that compared the "full" model (with many possible confounders) to a series of reduced models (models 1-7) that removed particular variable sets.

This investigation had important limitations. No information on medication indication, dose, or use frequency/duration of use was collected. A more comprehensive polypharmacy metric could consider these parameters. Also, it is implicitly assumed that one baseline medication measurement accurately represents pharmacological burden throughout follow-up. Our polypharmacy metric did not distinguish eye drops/skin creams from pills/injectables when aggregating total generic ingredients.. Additionally, there is the possibility of medication (exposure) misclassification at multiple stages—incompletely assembled medications, medication transcription mistakes, electronic database scanning errors, and during the generic name assignment. Finally, given the heterogeneous biological nature of both exposure and outcome, selecting an "optimal" modeling strategy that accounts for the underlying pharmacology is difficult; the results are conditional on the models utilized. However, the qualitative consistency of results across models was reassuring.

Drugs play vital and irreplaceable roles in medicine. However, some patients are possibly "getting too much of a good thing" via polypharmacy. While polypharmacy may be the standard of care , polypharmacy can occur unnecessarily and inappropriately, exposing the patient to potentially serious risks. Amidst strong pharmaceutical marketing, patient's belief that prescriptions validate his condition, physician pressure to satisfy patients, and an ever-expanding set of potential drugs, optimal (or even rational) prescribing becomes challenging.

In conclusion, we found an association between polypharmacy and increased all-cause-mortality. As hypothesized, mortality was related to the degree of polypharmacy; however, contrary to expectation, no CKD effect modification was observed. Further study is warranted to understand the impact of drug dosages and the relative contributions of different drug classes to the observed relation of polypharmacy to mortality. The specificity of the biological pathway(s) (e.g., refined pharmacological exposure, considering parameters beyond medication count) and exploration of potential CKD-based polypharmacy vulnerability (or therapeutic opportunity) merit further study.

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We thank Drs. Mitchel Klein and Beau Bruce for their statistical guidance.

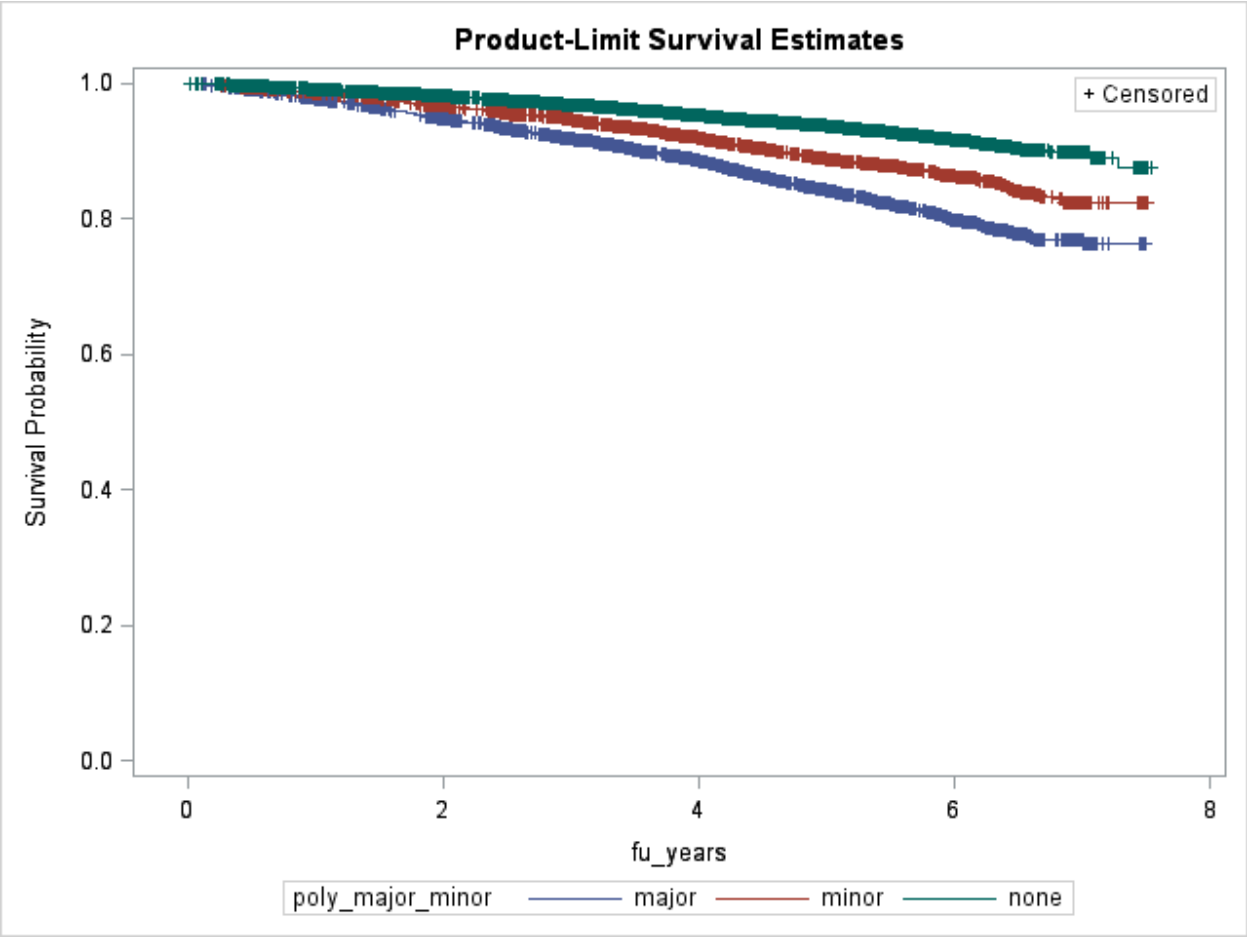
4.2.6: TABLES AND FIGURES:

Table 4.2.1: Polypharmacy Exposure Status (defined as ≥ 8 total generic ingredients = major polypharmacy [PP+] vs. no/minor polypharmacy [PP-], 0-7 total generic ingredients) according to Covariate Value and Association between Covariates and Mortality among the entire cohort with exposure assessed and at least one-follow up outcome assessment (n=29,627).

Covariate	Cov. Values	N	%	PP+ (n)	crude PP OR** (95% CI)	crude mort. OR (95% CI)
Age	85+	582	1.96	138	**2.31** (1.86-2.86)	**19.3** (14.4-25.8)
	75-84	4,518	15.2	1,185	**2.64** (2.34-2.98)	**11.8** (9.31-15.1)
	65-74	9,568	32.3	2,291	**2.34** (2.09-2.61)	**4.86** (3.83-6.17)
	55-64	11,295	38.1	2,209	**1.80** (1.62-2.02)	**2.30** (1.80-2.94)
	45-54	3,664	12.4	435	**Ref**	**Ref**
Region	Buckle	6,200	20.9	1,526	**1.42** (1.32-1.53)	**0.76** (0.68-0.85)
	Belt	10,267	34.7	2,273	**1.24** (1.16-1.32)	0.94 (0.86-1.03)
	Nonbelt	13,160	44.4	2,459	**Ref**	**Ref**
Race	White	17,449	58.9	3,653	0.97 (0.92-1.03)	**0.86** (0.79-0.94)
	Black	12,178	41.1	2,605	**Ref**	**Ref**
Gender	Male	13,304	44.9	2,455	**0.75** (0.70-0.79)	**2.11** (1.94-2.29)
	Female	16,323	55.1	3,803	**Ref**	**Ref**
Education	College Grad	10,325	34.9	1,681	**0.47** (0.43-0.51)	**0.38** (0.33-0.42)
	Some College	7,928	26.8	1,691	**0.65** (0.59-0.71)	**0.53** (0.47-0.60)
	HS	7,654	25.9	1,786	**0.73** (0.67-0.80)	**0.58** (0.51-0.65)
	< HS	3,697	12.5	1,090	**Ref**	**Ref**
Income	>/= $75k	4,684	18.0	613	**0.36** (0.33-0.40)	**0.25** (0.21-0.29)
	$35k - $74k	8,795	33.9	1,555	**0.52** (0.48-0.56)	**0.41** (0.37-0.46)
	$20k - $34k	7,155	27.6	1,647	**0.72** (0.67-0.78)	**0.74** (0.66-0.83)
	< $20k	5,331	20.5	1,559	**Ref**	**Ref**
Relationship Status	Widowed	5,608	19.4	1,485	**1.50** (1.31-1.73)	**1.61** (1.32-1.96)
	Divorced	4,299	14.9	918	1.13 (0.98-1.31)	0.92 (0.75-1.14)
	Married	17,470	60.4	3,390	1.01 (0.88-1.15)	0.94 (0.78-1.14)
	Single	1,558	5.38	301	**Ref**	**Ref**
Medical Care	Yes	21,839	79.5	4,852	**1.43** (1.32-1.54)	**0.66** (0.60-0.73)
	No	5,631	20.5	938	**Ref**	**Ref**
Insurance	Yes	27,670	93.5	5,976	**1.65** (1.45-1.88)	**1.45** (1.20-1.76)
	No	1,931	6.52	276	**Ref**	**Ref**
Smoking	Current	4,270	14.5	872	1.08 (0.99-1.17)	**2.27** (2.02-2.55)
	Past	11,888	40.3	2,794	**1.29** (1.21-1.37)	**1.75** (1.60-1.92)
	Never	13,355	45.3	2,569	**Ref**	**Ref**
BMI	Underweight	312	1.06	47	1.07 (0.78-1.47)	**2.39** (1.81-3.16)
	Norm Weight	6,971	23.7	990	**Ref**	**Ref**
	Overweight	10,860	36.9	1,926	**1.30** (1.20-1.42)	**0.76** (0.69-0.84)
	Obese	11,284	38.3	3,220	**2.41** (2.23-2.61)	**0.67** (0.61-0.75)
Alcohol Use	Heavy	1,175	4.04	160	**0.49** (0.42-0.58)	**0.79** (0.64-0.99)
	Moderate	9,673	33.3	1,561	**0.60** (0.56-0.64)	**0.72** (0.66-0.79)
	None	18,201	62.7	4,416	**Ref**	**Ref**
Self-Reported Health	Poor	1,036	3.50	621	**23.2** (19.5-27.6)	**6.76** (5.55-8.24)
	Fair	4,410	14.9	1,809	**10.8** (9.44-12.3)	**3.48** (2.97-4.09)
	Good	10,357	35.0	2,419	**4.73** (4.16-5.37)	**2.09** (1.79-2.44)
	Very Good	9,027	30.5	1,102	**2.16** (1.88-2.47)	**1.26** (1.07-1.49)
	Excellent	4,738	16.0	287	**Ref**	**Ref**
Exercise Habits	None	10,041	34.4	2,825	**2.09** (1.94-2.24)	**1.90** (1.72-2.11)
	1-3 times/wk	10,511	36.0	1,975	**1.23** (1.14-1.33)	0.91 (0.81-1.02)
	>3 times/wk	8,635	29.6	1,365	**Ref**	**Ref**
CKD	Yes	3,248	11.4	1,332	**3.11** (2.88-3.36)	**4.13** (3.75-4.55)
	No	25,123	88.6	4,592	**Ref**	**Ref**
Diabetes	Yes	6,285	22.0	2,752	**4.46** (4.19-4.74)	**2.04** (1.87-2.24)
	No	22,266	78.0	3,312	**Ref**	**Ref**
CAD History	Yes	5,219	18.0	2,110	**3.33** (3.12-3.56)	**2.87** (2.62-3.13)
	No	23,855	82.0	4,035	**Ref**	**Ref**
Hypertension	Yes	17,513	59.2	5,047	**3.68** (3.44-3.94)	**1.79** (1.64-1.96)
	No	12,050	40.8	1,194	**Ref**	**Ref**
Dyslipidemia	Yes	16,932	59.4	4,460	**2.25** (2.11-2.39)	**1.23** (1.13-1.34)
	No	11,594	40.6	1,593	**Ref**	**Ref**
Atrial Fib.	Yes	2,543	8.79	973	**2.60** (2.38-2.83)	**2.30** (2.05-2.57)
	No	26,400	91.2	5,086	**Ref**	**Ref**
Stroke Hist.	Yes	1,889	6.40	789	**2.93** (2.67-3.23)	**3.05** (2.71-3.45)
	No	27,636	93.6	5,429	**Ref**	**Ref**

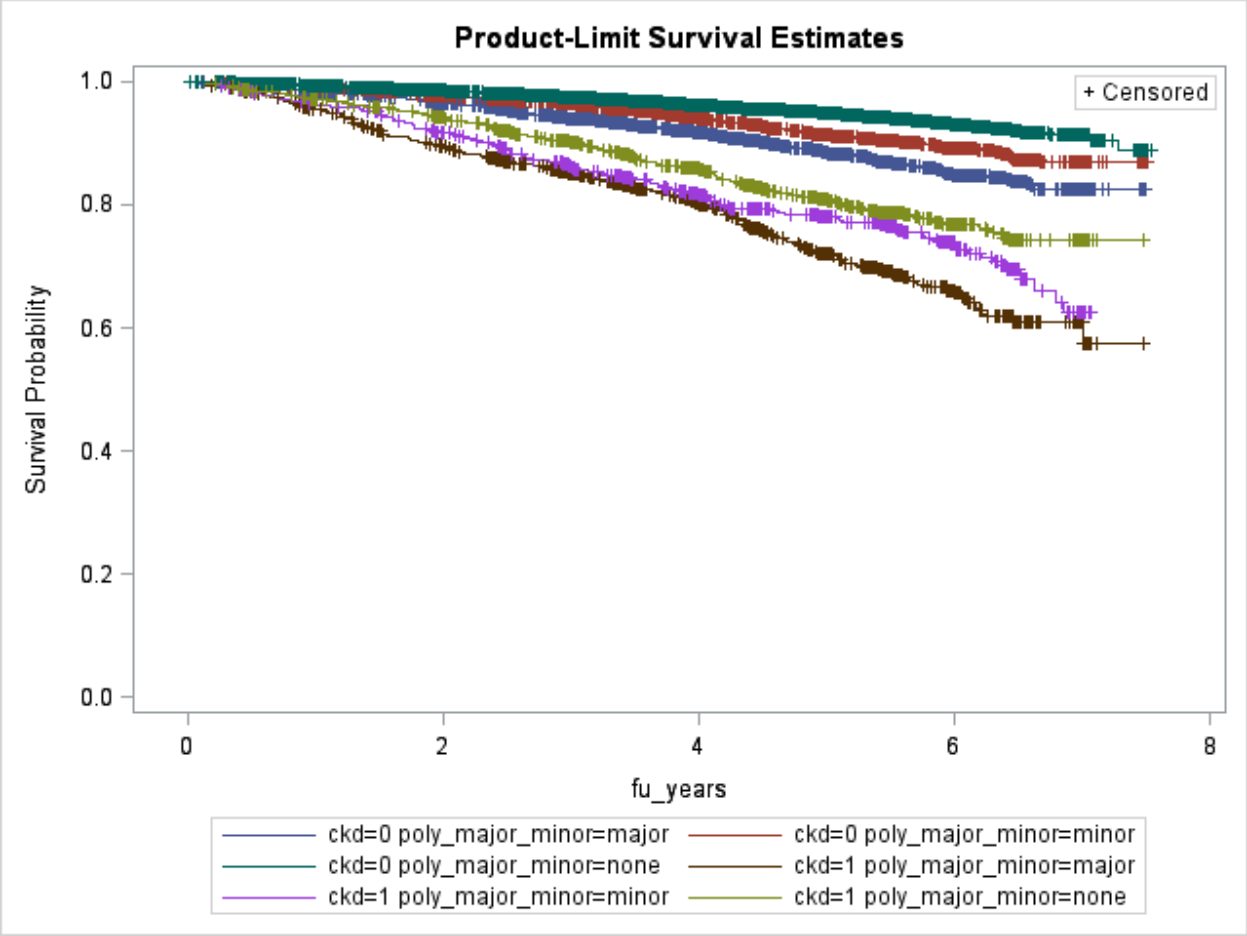
Statistically significant estimates are **bolded**.
*Chi-Square Test
**Mantel-Haenszel
***Stroke Buckle:** Subset (coastal plain of Georgia, North Carolina, and South Carolina) of the stroke belt.
OR= Odds Ratio,
Atrial Fib. = Atrial Fibrillation,
Sympt. = Symptoms

Figure 4.2.1a: Kaplan-Meier All-Cause-Mortality Plot According to Polypharmacy Status (no polypharmacy (green), minor polypharmacy (red), and major polypharmacy (blue)). Log rank p < 0.0001.



fu_years = follow-up years

Figure 4.2.1b: Kaplan-Meier All-Cause-Mortality Plot for Polypharmacy*CKD status (log rank p- value < 0.0001).
Green = ckd -, no PP **Red** = ckd -, minor PP **Blue** = ckd -, major PP
Yellow = ckd +, no PP **Pink** = ckd +, minor PP **Brown** = ckd +, major PP



PP: Polypharmacy
fu_years = follow-up years

Table 4.2.2: Multivariable Analyses of the Association between Major and Minor Polypharmacy (vs. no polypharmacy) and All-Cause Mortality Using Eight Multivariable **Time-On-Study** Models.

	TIME-ON-STUDY MODELS	
	Major PP HR (95% CI)	**Minor PP HR (95% CI)**
Model 1	**2.35** (2.15-2.56)	**1.50** (1.35-1.67)
Model 2	**2.23** (2.03-2.44)	**1.48** (1.32-1.65)
Model 3	**2.17** (1.97-2.38)	**1.47** (1.32-1.65)
Model 4	**2.09** (1.89-2.31)	**1.47** (1.30-1.65)
Model 5	**1.42** (1.26-1.60)	**1.18** (1.04-1.35)
Model 6	**1.26** (1.11-1.42)	1.12 (0.98-1.27)
Model 7	**1.26** (1.11-1.42)	1.12 (0.98-1.27)
Model 8*	**1.30** (1.13-1.50)	1.15 (0.99-1.34)

*HRs for CKD=0 individual, CKD*PP interaction terms both non-significant (p>0.30)

Statistically significant estimates are **bolded**.
PP = polypharmacy

Model 1: Demographics (Age, Region, Race, Gender, Relationship Status)
Model 2: Demographics + SES Factors (Education, Income, Insurance, Medicalcare)
Model 3: Demographics + Lifestyle Factors (Smoking, Alcohol, BMI, Physical Activity)
Model 4: Demographics + SES Factors + Lifestyle Factors
Model 5: Model 4 + Comorbidities (CKD, Diabetes, CAD History, Hypertension, Dyslipidemia, Atrial Fibrillation, Stroke Symptoms)
Model 6: Model 5 + Self-Reported Health
Model 7: Model 6 + Perceived Stress
Model 8: Model 7 + Polypharmacy*CKD interaction terms.

Table 4.2.3: Association between Major and Minor Polypharmacy (vs. no polypharmacy) and All-Cause Mortality Using Eight Distinct **Age-Time-Scale** (Conditioning on Age at Study Entry and Stratifying by Birth Cohort) Models.

	AGE-TIME-SCALE MODELS	
	Major PP HR (95% CI)	**Minor PP HR (95% CI)**
Model 1	**2.31** (2.11-2.52)	**1.48** (1.33-1.65)
Model 2	**2.20** (2.01-2.42)	**1.46** (1.31-1.63)
Model 3	**2.12** (1.93-2.33)	**1.44** (1.29-1.61)
Model 4	**2.06** (1.86-2.27)	**1.44** (1.28-1.62)
Model 5	**1.44** (1.28-1.62)	**1.18** (1.04-1.35)
Model 6	**1.27** (1.13-1.44)	1.11 (0.98-1.27)
Model 7	**1.27** (1.13-1.44)	1.11 (0.98-1.27)
Model 8*	**1.29** (1.12-1.48)	1.14 (0.98-1.32)

*HRs for CKD=0 individual, CKD*PP interaction terms both non-significant (p>0.50)

Statistically significant estimates are **bolded**.
PP = polypharmacy

Model 1: Demographics (Age, Region, Race, Gender, Relationship Status)
Model 2: Demographics + SES Factors (Education, Income, Insurance, Medicalcare)
Model 3: Demographics + Lifestyle Factors (Smoking, Alcohol, BMI, Physical Activity)
Model 4: Demographics + SES Factors + Lifestyle Factors
Model 5: Model 4 + Comorbidities (CKD, Diabetes, CAD History, Hypertension, Dyslipidemia, Atrial Fibrillation, Stroke Symptoms)
Model 6: Model 5 + Self-Reported Health
Model 7: Model 6 + Perceived Stress
Model 8: Model 7 + Polypharmacy*CKD interaction terms.

Table 4.2.4: **Propensity-Stratified** Models (Age-Time-Scale and Time-On-Study) and Their Estimated Major and Minor Polypharmacy-Mortality HRs (vs. no polypharmacy)

	Major PP HR (95% CI)	Minor PP HR (95% CI)
Quintile Stratified, Age-Time-Scale	**1.37** (1.22-1.54)	1.12 (0.98-1.27)
Decile Stratified, Age-Time-Scale	**1.29** (1.14-1.45)	1.10 (0.97-1.25)
Quintile Stratified, Time-on-Study	**1.39** (1.23-1.56)	**1.17** (1.03-1.33)
Decile Stratified, Time-on-Study	**1.30** (1.15-1.47)	**1.15** (1.01-1.31)

PP: Polypharmacy
Statistically significant estimates are **bolded**.

4.3: STUDY 3:

The Association between Polypharmacy and Cognitive Impairment in the REGARDS Cohort: t*he **RE**asons for **G**eographic **A**nd **R**acial **D**ifferences in **S**troke Study*

4.3.1: ABSTRACT

Context: Many Americans take many medications simultaneously, known as polypharmacy. The potential effects of polypharmacy on incident cognitive impairment are incompletely elucidated.

Objective: To assess the association of polypharmacy and incident cognitive impairment after adjusting for covariates and considering potential effect modification according to Chronic Kidney Disease (CKD) status.

Design, Setting, and Participants: The REGARDS (***RE***asons for ***G***eographic ***A***nd ***R***acial ***D***ifferences in ***S***troke) Cohort data (analytic n=21,165, comprised of blacks and whites age ≥45 in the continental U.S.) was used. During an in-home visit, pill-bottle inspections were conducted of medications used in the previous two weeks. The cohort member's polypharmacy status (major, minor, no polypharmacy) was determined by counting the total number of generic (prescription/OTC) ingredients. Multiple logistic regression models (using both first follow-up and last follow-up Six Item Screener (SIS) score to define incident impairment) were constructed to assess the association of polypharmacy and incident cognitive impairment. Multiple logistic models were considered because of the analytic challenge of confounding by indication.

Main Outcome Measure: Cohort member's cognitive impairment status, defined using the SIS.

Results: For all models constructed, the major polypharmacy-cognitive impairment odds ratios (ORs) were all greater than 1, but never with a point estimate exceeding 1.30, and most not

statistically significant. Conversely, for minor polypharmacy-cognitive impairment, the associations were all near 1, with none of them statistically significant. The two-way polypharmacy-CKD status interactions assessed were not significant.

Conclusions: These findings suggest that a simple ingredient count sum is not strongly associated with incident cognitive impairment. However, more sophisticated pharmacologic risk assessment algorithms (models that considered the therapeutic mechanisms (e.g., anticholinergic) of the drug regimen agents) might still robustly predict incident cognitive impairment.

4.3.2: INTRODUCTION

Americans take high levels of prescription and over-the-counter (OTC) medications.[1] Approximately 70-90% of illnesses involve some variety of self-treatment,[25] with Americans buying approximately 5 billion OTC products annually.[26]

Approximately half of all prescriptions may be used improperly,[20] and a "prescribing cascade" may ensue, whereby one drug's side effect is treated with more medication.[32] Drug allergies, drug-drug and drug-disease interactions, and direct drug toxicity are all hazards. If categorized as a disease, Adverse Drug Reactions (ADRs) are estimated to be the fourth leading cause of death.[8]

One feature of Americans' medication consumption is polypharmacy (high medication use). Polypharmacy is a term that encapsulates the simultaneous potential for poly-therapeutic effects and/or poly-toxicities when multiple medications are used simultaneously.[12] "Polypharmacy" can have negative connotations, suggesting inappropriate/excessive medication use. This is not our intent, as polypharmacy can be totally appropriate and the standard of care. Polypharmacy is often defined two ways: using more drugs than clinically warranted or taking more than a threshold drug count, often five.[16]

Many medications affect the central nervous system. Many common drug classes, including beta blockers; NSAIDs; corticosteroids; and histamine H2 antagonists, can precipitate confusion.[130] One vulnerable neurologic target is the cholinergic synapse, which is susceptible to pharmacologic perturbations.[130] For example, Cao et al. documented that "anticholinergic drug burden" was a statistically significant predictor for a number of neurological outcomes.[131] Hilmer et al. reported worse physical functioning among those using anticholinergic or sedative medications.[133]

Chronic kidney disease (CKD) is emerging as public health challenge,[143] and CKD individuals may be especially vulnerable to polypharmacy's adverse effects because the kidney is critical for drug excretion. The relationship between renal function and cognitive impairment has been assessed in REGARDS.[147,199]

Polypharmacy has been investigated for its potential effects on cognitive impairment in multiple European settings. However, to our knowledge, polypharmacy has not been explored for its associations with cognitive impairment among Americans. The REGARDS study, with its large, national sample, extensive follow-up, and detailed covariate data, is well-suited to study the polypharmacy-cognitive impairment association and to explore possible CKD effect modification.

4.3.3: METHODS

Study Design:

The REGARDS data were used. The REGARDS study, a nationwide, longitudinal cohort began in 2003, has been described in detail previously.[170] Briefly, the entire sample consisted of 30,181 community-dwelling black and white Americans age ≥ 45 years. Moreover, 21,165 participants (the statistical models' subsample) were not impaired at baseline and had at least one follow-up cognition measurement. The cohort covered all 48 contiguous states and was generated by sampling Genesys Inc.[183] commercial database, oversampling blacks and "stroke belt"[184] residents (eight Southeastern states: North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, Louisiana).

Individuals were excluded from REGARDS for non-black/non-white race, ongoing cancer treatment, inability to speak English, nursing home residence, cognitive impairment as assessed by telephone interviewer, or if expected to pose follow-up difficulties. The cohort's

cooperation rate was 49%.[185] The annual REGARDS participant drop- out rate was less than 3%. Institutional Review Boards reviewed the work at all participating institutions. Signed informed consent was obtained from all participants.

Data:

A computer-assisted telephone interview was conducted, where a wide range of demographic, socioeconomic status (SES), medical, and lifestyle information was collected. Examination Management Services Inc. (EMSI) scheduled the home visit and instructed the participant to collect all medicines used in the previous two weeks. During the home exam, signed informed consent was obtained, and anthropomorphic measures and blood and urine samples for biomarker assay were collected and sent to a central laboratory for analysis.

The EMSI personnel examined each medicine present ("pill bottle" inspection including creams/eye drops/injectables) and cataloged its name (generic or brand) on a standardized form; neither dose nor frequency of use were obtained. The handwritten forms were optically scanned and read by optimal character recognition software. Overall, 171,573 home visit medicines were transcribed. Of these, 34,776 distinct medication names remained. Misspellings were resolved using the built-in spell-checker of Google and Drugs.com. For 1.62% of recorded medications, misspellings were not resolved and these entries were assigned generic name "unknown". Each unknown medication entry was assumed to correspond to one generic ingredient.

The recorded medication was assigned a generic name by a research pharmacist and graduate students. When assessing polypharmacy exposure, supplements (vitamins/minerals/herbals/nutraceuticals) were not considered, because of their heterogeneity and limited governmental oversight[15,40]. Some vitamins and minerals (e.g., isotretinoin) are

available in prescription forms; we tried to distinguish the prescription-only forms from the OTC-available forms (e.g., vitamin A), which were considered supplements.

Many drugs came in combination formulations, and the drug count for each combination medicine was the total number of active ingredients. Some participants reported taking the same generic ingredient multiple times by listing the same generic multiple times on the medication form, whether due to different medication formulations (e.g., long-, medium-, and short-acting insulin all listed on the medication form) or using the same medicine twice (e.g., taking two multi-component analgesics, both containing acetaminophen); in such cases the total ingredient sum counted the generic name multiple times (e.g., insulin counts 3 towards the total ingredient sum).

Individual drug use was summarized using three polypharmacy levels defined by total generic ingredient count: no polypharmacy (≤ 5 total generic ingredients), minor polypharmacy (6-7 ingredients), and major polypharmacy (≥ 8 ingredients). The potential effect modifier of CKD status (Self-Reported Dialysis or GFR < 60 mL/min/1.73m^2) was determined from the estimated glomerular filtration rate (GFR) using serum creatinine.[194]

Many medications are known to have cognitive effects, intended or otherwise. A list of such singleton drugs was compiled based on drug classes whose therapeutic target was the central nervous system (CNS), a peripheral synapse, or a neuromuscular junction and was used to assess what fraction of the country was exposed to medications with potential cognitive effects, providing a broad assessment of the potential pharmacologically-induced cohort cognitive risk. The non-CNS targeting drugs were included because they **may** "cross-react" with CNS neurons. When these singletons drugs were present in combination formulations, they were still counted. It should be stressed that for some of these medications, the cognitive effects may

be very rare, while for others the cognitive effect is a common-side effect, while for still others the medication's indication is cognitive.

To account for REGARDS' racial/regional oversampling (108 region/race/sex/age strata), sampling-weighted analyses were conducted. Sampling weights were generated for each cohort member. Statistical Analysis Software (SAS) survey procedures (e.g., PROC SURVEYFREQ) with "strata" and "weight" statements were used. The national estimates reflect REGARDS sampling criteria.

Cognitive impairment was assessed using the Six-Item Screener (SIS).[200] The SIS is taken from the Mini-Mental State Exam.[201] The six items include asking the cohort member the day of the week, the month, and year and also a three-item recall, with one point awarded for each correct response. SIS scores range from zero to six points. Cognitive impairment was defined as an SIS score of ≤ 4 after a baseline score of ≥ 5. Two separate cognitive impairment endpoints were considered: the first SIS score following baseline assessment and the last SIS score obtained during follow-up.

Covariates:

Many polypharmacy risk factors are known, including greater comorbidity[12,58], needing help with activities of daily living[58], demographics (female sex[12,30], older age[12,30], and white race[58,81]), and SES variables (low educational attainment[12,30], lower social status[12,87], and being unemployed[12,87]). We adjusted for potential confounding using the following full model covariates: demographics (age, race, gender, relationship status), SES (education, income, insurance status), lifestyle (alcohol, smoking, BMI, exercise habits), perceived health (self-reported health, stress), biomarkers (lipids, heart rate), and comorbidities (CAD history, diabetes, hypertension, atrial fibrillation, dyslipidemia, stroke symptoms).

Statistical Analysis:

Crude odds ratios (ORs) for the association of covariates with major polypharmacy or with cognitive impairment were calculated. As the potential effect modification of polypharmacy by CKD status was an *a priori* hypothesis, two-way interaction terms were included (the only interaction considered). Logistic regression modeled the polypharmacy-cognitive impairment association.[202] Because cohort members had different intervals between SIS assessments, the time-interval between baseline and follow-up SIS assessment(s) was added as a covariate in all models considered.

While it might seem natural to use time-to-event analyses to model the time to first cognitive impairment, the REGARDS cognitive impairment working group has recommended not doing so—hence, the logistic (and not Cox) regression.

Models 1 through 7 are subsets of the full model. Aside from models 1-7, no other subset models were considered. Because of the number of covariates considered (and the innumerable potential reduced models), for simplicity and in order to have a "complete" model, no other reduced models were considered.

Models 1-7 are sequential subsets of the "full" model 8. Model 1 adjusted for demographics (age, region, race, gender, relationship status). Model 2 adjusted for demographics + SES factors (education, income, insurance, medical care). Model 3 adjusted for demographics + lifestyle variables (smoking, alcohol use, BMI, physical activity). Model 4 adjusted for demographics and SES and lifestyle variables. Model 5 adjusted for all of model 4's covariates plus biomarkers (HDL, LDL, heartrate) and comorbidities (CKD, diabetes, CAD history, hypertension, dyslipidemia, atrial fibrillation, and stroke symptoms). Model 6 added

self-reported health to the model 5 covariates. Model 7 added perceived stress to the model 6 covariates. Model 8 added the polypharmacy*CKD interaction terms to model 7.

Multiple models were utilized because the potential causal pathway linking polypharmacy-cognitive impairment is not established. Presumably no single pathway could accurately reflect the polypharmacy-cognitive impairment relationship when applied to the heterogeneous REGARDS sample.

Two propensity-adjusted models were utilized.[197] In these models, model 7's covariates were used in a logistic (propensity) model of polypharmacy status (defined as ≥ 8 total ingredients). Each participant's polypharmacy propensity was estimated. After including propensity quintiles or deciles as model dummy variables, a logistic model assessed the polypharmacy-cognitive impairment while controlling for propensity.

Collinearity was assessed using a SAS macro providing condition indices and variance decomposition proportions.[188] SAS 9.2 was used.

4.3.4: RESULTS

Overall, 171,573 medication names were transcribed during the in-home visit. Key characteristics of the REGARDS cognitive subsample (n=21,165) according to polypharmacy status (dichotomized for simplicity into major polypharmacy vs. no/minor polypharmacy) and cognitive impairment outcome are provided in **Table 4.3.1.** 39% were male, 39% black, 37% college graduates, 24% with normal BMI, 10% with CKD, and 16% and 32% in "excellent" or "very good" self-reported (SR) health, respectively. In crude comparisons (**Table 4.3.1**), those with major polypharmacy were enriched with respect to female gender, older age, less education, lower income, higher BMI, more comorbidities, and lower SR health.

For the univariate associations, greater cognitive impairment was associated with older age, black race, male gender, lower education or income, worse self-reported health, and a variety of comorbidities.

Table 4.3.2 shows the sampling-weighted national black and white adult distribution of drugs with potential cognitive effects estimates. Nearly 70% took ≥ 1 drugs with possible cognitive effects. Over 42% reported taking ≥ 2 such drugs. The mean number of "cognitive drugs" was 1.62.

During follow-up, 2023 and 1741 participants experienced incident cognitive impairment when defining impairment by the first or last follow-up SIS score, respectively. The logistic regression associations between major- and minor-polypharmacy and incident cognitive impairment are shown in **Table 4.3.3** and **Table 4.3.4**.

For all models constructed, the major polypharmacy-cognitive impairment ORs were all greater than 1, but never with a point estimate exceeding 1.30, and most not statistically significant. Conversely, for minor polypharmacy-cognitive impairment, the associations were all near 1, with none statistically significant. The two-way polypharmacy-CKD status interactions assessed in model 8 were not significant for either major ($p > 0.50$ for both models) or minor polypharmacy ($p > 0.75$ for both models).

Logistic model collinearity was not deemed problematic. The single exception was model 4's first follow-up collinearity, where the maximum Condition Index = 32.1 and both age and the intercept's VDPs > 0.5.

4.3.5: DISCUSSION

As the cholinergic synapse is critical for cognition, many studies have documented anticholinergic use prevalences. However, by comparison, fewer seem to have considered the

broader set of drugs which may affect cognition, regardless of mechanism (e.g., through non-cholinergic effects). In a study of older African Americans, Campbell et al. reported that over half used a possible anticholinergic.[137] Cancelli et al. found that over 20% of older Italians used anticholinergic drugs.[138] In two studies of older French adults, Carriere et al. reported that 7.5% used anticholinergics and Lechevallier-Michel et al. reported 14% using anticholinergic drugs.[139,140] While the cholinergic synapse may be a key and major mechanism for cognitive impairment, it is possible that other important pathways of cognitive impairment have been effectively overlooked. We hope that our broad search for drugs with possible cognitive effects has incorporated some "non-cholinergic" drugs that still may affect cognition.

Considering our expanded drugs with cognitive effects basis set, it is not surprising that our cognitive drugs prevalence is substantially higher than that reported by others who restricted their consideration to anticholinergics. This high prevalence of use of medications potentially affecting cognition, while by itself not necessarily a major concern, emphasizes that medications should be taken under the careful supervision of a physician and pharmacist.

In a study of older Finns, Jyrkka et al. reported that polypharmacy could not predict cognition changes over a three-year interval.[168] In a Swedish study, Monastero et al. reported that polypharmacy was a risk factor for cognitive impairment.[169] Starr et al. found that polypharmacy adversely affected cognition in a relatively small Scottish study.[107] In another European study, del Ser et al. reported that the number of prescribed drugs was a predictor for cognitive impairment among stroke survivors.[106]

Our range of polypharmacy-cognitive impairment ORs suggests that polypharmacy is not a strong predictor of incident cognitive impairment. Our conceptualization of polypharmacy may be too simplistic a measure when assessing medications' cognitive risks, as it totally ignores

any specific neurological effects of the medications constituting a polypharmacy regimen. This net null effect could result if some medications (e.g., caffeine) have cognitive-enhancing effects while others (e.g., anticholinergics) may decrease cognitive function.

The non-significance of the CKD*polypharmacy interaction terms refuted our *a priori* hypothesis, in which polypharmacy was expected to exert stronger cognitive impairment among those with CKD. This might have occurred because the polypharmacy metric utilized was pharmacologically too simplistic, without consideration of the particular medications constituting polypharmacy or the dosages.

REGARDS has key strengths that position it to explore polypharmacy-cognitive impairment. Rigorous exposure and outcome assessments minimized misclassification, although there remains possible exposure misclassification—cohort members not presenting all the medications used in the last two weeks, errors in pill bottle transcription, errors in scanner handwriting interpretation, and errors in generic name assignments. Data on many potential confounders were measured. The large sample size provided ample statistical power. Finally, the relatively low annual loss-to-follow-up (<3% for the entire cohort) should have limited any selection bias from selective follow-up for the first follow-up cognition measurement association. Conversely, the median follow-up to last SIS score was 5.07 years. Concerning generalizability, the REGARDS sample was generated from the general population of biracial, community-dwelling American adults, with minimal exclusion criteria, suggesting broad applicability of REGARDS' results.

Confounding by indication, the fact that those taking medications and those not taking medications are systematically different (beyond drug use), and that residual confounding may linger despite adjusting for many expected confounders, is a serious methodological challenge.

Fortunately, information on many potential confounders was collected (and the number of events sufficient to make large models feasible), so residual confounding was presumably lessened by these efforts.

One critical concern is that without a well-established polypharmacy-cognitive impairment biological mechanism to rely on, a model's supposed "confounders" may function as exposure-outcome mediators. Because of the exposure's composite nature (billions of drug combinations) and innumerable neurological processes resulting in cognitive impairment, it is difficult to distinguish potential confounders and causal mediators *a priori* when specifying a model. Therefore, many plausible confounders were incorporated into the full model. However, sensitivity analyses (seven other models) were conducted to determine if the estimated polypharmacy associations were conditional on a particular model.

This investigation had important limitations. No information on medication indication, dose, or frequency/duration of use was collected. A more comprehensive polypharmacy metric could consider these parameters. Also, it is implicitly assumed that one medication baseline measurement accurately represents pharmacological burden throughout follow-up. Additionally, our polypharmacy metric did not distinguish eye drops and skin creams from pills and injectables when aggregating total generics. To the extent that some eye drops and creams may not enter the systemic circulation, they would not be expected to contribute any cognitive risk. Moreover, the possibility of residual confounding by indication cannot be ruled out. Selecting an optimal modeling strategy that accurately accounts for the underlying pharmacology and physiology is difficult; the results are conditional on the models utilized. However, the general consistency of the results (null or nearly null findings) in multiple models provided some confidence about the results.

In conclusion, a high proportion of black and white adults use medications that could potentially affect cognition. However, a simple ingredient count measure (polypharmacy) failed to robustly correlate with incident cognitive impairment. Hopefully, future research will integrate measures of total pharmacologic burden (e.g., polypharmacy) with known neurologic pathways and medications mediating impairment. As such, a pharmacologic algorithm could then incorporate ingredient counts, ingredient constituents, and dosages to estimate medications' potential cognitive hazards.

We document a high prevalence of use of medications potentially affecting cognition. A number of European studies have considered the polypharmacy-cognitive impairment association. However, to our knowledge, no studies have explored this association among American adults. In the multivariable models, polypharmacy was weakly associated with cognitive impairment in some models and not associated with impairment in other models. These findings suggest that, while high pharmacological burden can certainly affect cognition, a simple ingredient count (our polypharmacy definition) may be too crude a pharmacological assessment to accurately predict cognitive impairment risk.

Acknowledgement: We would like to express our great appreciation to Ya Yuan at the University of Alabama, Birmingham, for running the analysis SAS code.

4.3.6: TABLES AND FIGURES

Table 4.3.1: Covariate Distribution and Polypharmacy Exposure and Impairment Status according to Covariate Values

Covariate	Cov. Values	Total N	%	PP+ %	PP OR (95% CI)	Early Impair %	Early Impair OR (95% CI)	Incident Impair %	Incident Impair OR (95% CI)
Age	45-54	3,267	15.4	11.5	**Reference**	4.93	**Reference**	3.61	**Reference**
	55-64	8,037	38.0	20.4	**1.97** (1.75-2.22)	7.04	**1.46** (1.22-1.75)	5.08	**1.43** (1.16-1.76)
	65-74	6,621	31.3	24.2	**2.45** (2.17-2.76)	11.3	**2.46** (2.07-2.94)	9.29	**2.73** (2.23-3.34)
	75-84	2,905	13.7	26.7	**2.80** (2.45-3.21)	16.1	**3.70** (3.07-4.45)	17.1	**5.49** (4.46-6.76)
	85+	335	1.6	23.6	**2.37** (1.80-3.12)	23.6	**5.95** (4.42-8.02)	31.0	**12.0** (8.94-16.1)
Race	White	12,921	61.1	21.0	0.99 (0.92-1.05)	6.86	**0.46** (0.42-0.50)	6.11	**0.50** (0.45-0.55)
	Black	8,244	39.0	21.3	**Reference**	13.79	**Reference**	11.5	**Reference**
Gender	Male	8,345	39.4	18.5	**0.77** (0.72-0.82)	11.4	**1.42** (1.30-1.56)	9.69	**1.37** (1.24-1.51)
	Female	12,820	60.6	22.8	**Reference**	8.33	**Reference**	7.27	**Reference**
Education	< HS	2,164	10.2	29.7	**Reference**	20.1	**Reference**	16.9	**Reference**
	HS	5,431	25.7	23.7	**0.74** (0.66-0.82)	10.7	**0.48** (0.42-0.55)	9.37	**0.51** (0.44-0.59)
	Some College	5,816	27.5	21.6	**0.65** (0.58-0.73)	8.29	**0.36** (0.31-0.41)	7.07	**0.37** (0.32-0.43)
	College Grad	7,741	36.6	16.5	**0.47** (0.42-0.52)	6.78	**0.29** (0.25-0.33)	5.84	**0.30** (0.26-0.35)
Income	< $20k	3,408	16.1	29.8	**Reference**	15.5	**Reference**	13.4	**Reference**
	$20k - $34k	4,903	23.2	23.1	**0.71** (0.64-0.78)	9.65	**0.58** (0.51-0.67)	9.50	**0.68** (0.59-0.78)
	$35k - $74k	6,503	30.7	18.6	**0.54** (0.49-0.59)	8.12	**0.48** (0.42-0.55)	5.94	**0.41** (0.35-0.47)
	> $74k	3,679	17.4	13.6	**0.37** (0.33-0.42)	6.06	**0.35** (0.30-0.42)	4.21	**0.28** (0.24-0.34)
	Refused	2,672	12.6	23.1	**0.71** (0.63-0.79)	10.2	**0.62** (0.53-0.72)	10.4	**0.75** (0.64-0.88)

Relation. Status	Single	1,150	5.43	18.1	**Reference**	8.87	**Reference**	8.52	**Reference**
	Married	12,670	59.9	19.6	1.10 (0.94-1.29)	8.48	0.95 (0.77-1.18)	6.92	**0.80** (0.64-0.99)
	Divorced	3,051	14.4	21.0	**1.20** (1.01-1.43)	9.73	1.11 (0.88-1.40)	7.37	0.86 (0.67-1.09)
	Widowed	3,816	18.0	27.0	**1.68** (1.42-1.98)	12.5	**1.47** (1.17-1.84)	12.87	**1.59** (1.26-1.99)
	Other	478	2.26	22.6	**1.32** (1.02-1.72)	15.3	**1.85** (1.34-2.55)	10.5	1.25 (0.88-1.80)
Medical Care	Yes	16,261	83.2	22.3	**1.56** (1.41-1.73)	9.18	0.91 (0.80-1.03)	7.92	0.97 (0.84-1.11)
	No	3,296	16.9	15.5	**Reference**	9.98	**Reference**	8.16	**Reference**
Insurance	Yes	19,760	93.4	21.6	**1.68** (1.44-1.96)	9.50	0.91 (0.76-1.09)	8.18	0.92 (0.76-1.11)
	No	1,388	6.56	14.1	**Reference**	10.30	**Reference**	8.86	**Reference**
Smoking	Never	9,963	47.3	19.3	**Reference**	9.31	**Reference**	7.74	**Reference**
	Past	8,174	38.8	23.6	**1.30** (1.21-1.39)	9.97	1.08 (0.98-1.19)	9.04	**1.19** (1.07-1.32)
	Current	2,947	14.0	20.4	1.07 (0.97-1.19)	8.96	0.96 (0.83-1.11)	7.53	0.97 (0.83-1.13)
BMI	Underweight	197	0.94	14.2	1.01 (0.67-1.52)	10.2	1.02 (0.64-1.63)	9.14	0.97 (0.59-1.59)
	Norm Weight	5,034	24.0	14.0	**Reference**	9.97	**Reference**	9.40	**Reference**
	Overweight	7,616	36.2	17.6	**1.31** (1.19-1.45)	9.23	0.92 (0.81-1.04)	8.42	0.89 (0.78-1.00)
	Obese	8,168	38.9	28.7	**2.46** (2.24-2.70)	9.57	0.96 (0.85-1.08)	7.30	**0.76** (0.67-0.86)
Alcohol Use	None	12,874	61.9	24.3	**Reference**	10.5	**Reference**	9.23	**Reference**
	Moderate	7,082	34.0	16.2	**0.60** (0.56-0.65)	7.88	**0.73** (0.65-0.80)	6.52	**0.69** (0.61-0.77)
	Heavy	843	4.05	14.0	**0.51** (0.42-0.62)	7.24	**0.66** (0.51-0.86)	5.69	**0.59** (0.44-0.80)
Self-Reported Health	Poor	623	2.95	60.5	**23.2** (18.7-28.6)	12.4	**1.78** (1.36-2.33)	12.4	**2.16** (1.64-2.85)
	Fair	2,966	14.0	42.5	**11.2** (9.54-13.1)	12.6	**1.82** (1.54-2.15)	11.5	**2.00** (1.67-2.39)
	Good	7,410	35.1	23.9	**4.74** (4.08-5.50)	10.3	**1.45** (1.25-1.68)	8.66	**1.45** (1.24-1.71)
	Very Good		31.7	12.5	**2.16**	8.21	1.13	6.96	1.15

		6,698			(1.85-2.52)		(0.97-1.32)		(0.97-1.36)
	Excellent	3,431	16.2	6.21	**Reference**	7.34	**Reference**	6.12	**Reference**
Exercise Habits	None	7,202	34.5	27.8	**2.02** (1.85-2.20)	10.7	**1.17** (1.04-1.31)	9.72	**1.25** (1.11-1.42)
	1-3 times/wk	7,725	37.0	19.0	**1.23** (1.12-1.34)	8.65	0.92 (0.82-1.03)	6.86	**0.86** (0.75-0.98)
	>3 times/wk	5,958	28.5	16.0	**Reference**	9.33	**Reference**	7.91	**Reference**
CKD	Yes	2,050	10.1	42.0	**3.17** (2.89-3.49)	14.9	**1.82** (1.59-2.08)	14.5	**2.11** (1.84-2.41)
	No	18,256	89.9	18.5	**Reference**	8.80	**Reference**	7.47	**Reference**
Diabetes	Yes	4,189	20.5	44.6	**4.49** (4.16-4.83)	11.8	**1.37** (1.23-1.53)	11.5	**1.64** (1.46-1.83)
	No	16,206	79.5	15.2	**Reference**	8.85	**Reference**	7.37	**Reference**
CAD History	Yes	3,400	16.4	40.4	**3.22** (2.98-3.48)	12.3	**1.43** (1.27-1.60)	12.1	**1.72** (1.53-1.93)
	No	17,383	83.6	17.4	**Reference**	8.97	**Reference**	7.40	**Reference**
Stroke Symp.	Yes	3,054	15.2	27.9	**1.70** (1.55-1.85)	11.8	**1.38** (1.22-1.56)	11.4	**1.65** (1.45-1.87)
	No	17,046	84.8	18.6	**Reference**	8.82	**Reference**	7.21	**Reference**

PP+: major polypharmacy (for simplicity, no and minor polypharmacy are aggregated as PP-).
Early Impairment: impairment at first follow-up.
Incident Impairment: impairment at last follow-up.

Table 4.3.2: Sampling-weighted national estimate of distribution of drugs with possible cognitive effects

Cognitive Drug Count	Percentage	CDF (%)
0	64.05	100
1	20.44	35.95
2	8.08	15.50
3	3.69	7.42
4	1.97	3.73
5+	1.76	1.76

Mean = 0.66

CDF: Cumulative Distribution Function, the estimated percentage of blacks and white adults taking that many or more total "cognitive drugs."

Table 4.3.3: Associations between Polypharmacy and Incident Cognitive Impairment (defined using first or last follow-up SIS score) in REGARDS

Model	Major OR (CI)	Minor OR (CI)
1, first follow-up	**1.17** (1.04-1.31)	0.99 (0.87-1.13)
1, last follow-up	**1.28** (1.13-1.44)	1.10 (0.96-1.27)
2, first follow-up	1.09 (0.96-1.23)	0.99 (0.86-1.14)
2, last follow-up	**1.23** (1.08-1.40)	1.11 (0.95-1.28)
3, first follow-up	**1.15** (1.02-1.30)	0.98 (0.85-1.12)
3, last follow-up	**1.30** (1.14-1.48)	1.08 (0.93-1.25)
4, first follow-up	1.09 (0.96-1.24)	0.99 (0.85-1.14)
4, last follow-up	**1.26** (1.10-1.45)	1.09 (0.93-1.27)
5, first follow-up	1.05 (0.90-1.23)	0.99 (0.84-1.17)
5, last follow-up	1.07 (0.90-1.27)	1.00 (0.84-1.20)
6, first follow-up	1.04 (0.88-1.22)	0.98 (0.83-1.16)
6, last follow-up	1.03 (0.86-1.23)	0.99 (0.83-1.18)
7, first follow-up	1.03 (0.87-1.21)	0.98 (0.83-1.15)
7, last follow-up	1.02 (0.85-1.22)	0.99 (0.82-1.18)
8, first follow-up*	1.08 (0.91-1.29)	0.99 (0.83-1.18)
8, last follow-up*	1.04 (0.86-1.27)	0.99 (0.82-1.21)

*OR for CKD negative cohort member

Model 1: Demographics (Age, Region, Race, Gender, Relationship Status)
Model 2: Demographics + SES Factors (Education, Income, Insurance, Medicalcare)
Model 3: Demographics + Lifestyle Factors (Smoking, Alcohol, BMI, Physical Activity)
Model 4: Demographics + SES Factors + Lifestyle Factors
Model 5: Model 4 + Biomarkers (HDL, LDL, Heartrate) + Comorbidities (CKD, Diabetes, CAD History, Hypertension, Dyslipidemia, Atrial Fibrillation, Stroke Symptoms)
Model 6: Model 5 + Self-Reported Health
Model 7: Model 6 + Perceived Stress
Model 8: Model 7 + Polypharmacy*CKD interaction terms.

Table 4.3.4: Propensity-Adjusted Polypharmacy-Cognitive Impairment Model ORs.

Propensity-Based Analyses		
Model	**Major OR (CI)**	**Minor OR (CI)**
Prop. Decile, first follow-up	1.06 (0.90-1.24)	1.01 (0.86-1.19)
Prop. Decile, last follow-up	1.04 (0.88-1.24)	1.02 (0.86-1.22)
Prop. Quintile, first follow-up	1.06 (0.91-1.24)	1.02 (0.87-1.19)
Prop. Quintile, last follow-up	1.07 (0.90-1.26)	1.03 (0.87-1.23)

Adjusted by constructing a model with propensity quintile/decile dummy variables

Table 4.3.5a: List of Drug Classes with Potential Cognitive Effects used for **Table 4.3.2**.

adrenergic bronchodilator	gamma-aminobutyric acid analog
antiadrenergic agents centrally acting	gamma-aminobutyric acid reuptake inhibitor
antiadrenergic agents peripherally acting	general anesthetic
anticholinergic antiemetic	hydantoin anticonvulsant
anticholinergic antiparkinson agent	mao inhibitor
anticholinergic bronchodilator	misc antidepressant
anticholinergic chronotropic agent	misc anxiolytic and sedative and hypnotic
anticholinergic/antispasmodic	miscellaneous anticonvulsant
antimigraine	miscellaneous antipsychotic
atypical antipsychotic	miscellaneous central nervous system agent
barbiturate	narcotic analgesic
barbiturate anticonvulsant	narcotic antitussive
benzodiazepine	phenothiazine antipsychotic
benzodiazepine anticonvulsant	phenylpiperazine antidepressant
carbamate anticonvulsant	potassium channel blocker
carbonic anhydrase inhibitor anticonvulsant	pyrrolidine anticonvulsant
catecholamine	serotoninergic neuroenteric modulator
central stimulant	smoking cessation agent
cholinergic agonist	SNRI antidepressant
cholinergic muscle stimulant	SSRI antidepressant
cholinesterase inhibitor	sympathomimetic agent
CNS stimulant	sympathomimetic amine
dibenzazepine anticonvulsant	tetracyclic antidepressant
dopamine antagonist	thioxanthene
dopaminergic antiparkinsonism agent	triazine anticonvulsant
fatty acid derivative anticonvulsant	tricyclic antidepressant

Table 4.3.5b: List of Singleton Generics with Potential Cognitive Effects Used for **Table 4.3.2**.

acetazolamide	cyclizine	guanabenz	nefazodone	rasagiline
albuterol	desipramine	guanfacine	nicotine	reserpine
alfuzosin	dexmethylphenidate	haloperidol	nortriptyline	risperidone
almotriptan	dextroamphetamine	hydrocodone	olanzapine	rivastigmine
alosetron	diazepam	hydromorphone	opium	rizatriptan
alprazolam	dicyclomine	hydroxyzine	oxazepam	ropinirole
amantadine	diethylpropion	hyoscyamine	oxcarbazepine	rotigotine
amitriptyline	dihydrocodeine	imipramine	oxycodone	salmeterol
amobarbital	dihydroergotamine	ipratropium	oxymorphone	scopolamine
amoxapine	dimenhydrinate	ketamine	paroxetine	selegiline
amphetamine	diphenhydramine	lamotrigine	pemoline	sertraline
aripiprazole	divalproex	levalbuterol	pentazocine	sumatriptan
atomoxetine	domperidone	levetiracetam	pergolide	tamsulosin
atropine	donepezil	levodopa	perphenazine	tegaserod
belladonna	doxazosin	levorphanol	phendimetrazine	temazepam
benztropine	doxepin	lithium	phenelzine	terazosin
biperiden	doxylamine	lorazepam	phenobarbital	terbutaline
bromocriptine	duloxetine	loxapine	phentermine	thioridazine
bupropion	eletriptan	magnesium sulfate	phenytoin	thiothixene
buspirone	entacapone	meclizine	pilocarpine	tiagabine
butabarbital	epinephrine	memantine	pimozide	tiotropium
butalbital	ergoloid mesylate	meperidine	pirbuterol	topiramate
butorphanol	escitalopram	mephobarbital	pramipexole	trazodone
cabergoline	estazolam	meprobamate	prazepam	triazolam
caffeine	eszopiclone	metaproterenol	prazosin	trifluoperazine
carbamazepine	fampridine	methadone	pregabalin	trihexyphenidyl
carbidopa	felbamate	methscopolamine	primidone	trimethobenzamide
cevimeline	fentanyl	methyldopa	prochlorperazine	trimipramine
chloral hydrate	fluoxetine	methylphenidate	procyclidine	valproic acid
chlordiazepoxide	fluphenazine	methysergide	propantheline	varenicline
chlorpromazine	flurazepam	mianserin	propofol	venlafaxine
citalopram	fluvoxamine	midazolam	propoxyphene	vigabatrin
clidinium	formoterol	mirtazapine	protriptyline	zaleplon
clomipramine	frovatriptan	modafinil	pyridostigmine	ziprasidone
clonazepam	gabapentin	molindone	pyritinol	zolmitriptan
clonidine	galantamine	morphine	quetiapine	zolpidem
clorazepate	glycopyrrolate	naratriptan	ramelteon	zonisamide
codeine				

CHAPTER 5: RESEARCH SUMMARY, STRENGTHS, LIMITATIONS, PUBLIC HEALTH IMPACT, CONCLUSIONS, AND FUTURE DIRECTIONS

5.1: Research Summary

Prior to analyses, over two years were spent transforming the REGARDS drug database into an analysis-ready dataset. Although this dataset underlies all the manuscripts presented, it is easy to overlook its scale as no methods manuscript was presented detailing its construction.

Study 1 described the characteristics of medication use in the biracial adult American population. Study 1 documented that medication use is nearly ubiquitous regardless of race, gender, or region and that polypharmacy is highly prevalent, both in the REGARDS study and across the entire nation. We report a number of factors that are associated with having polypharmacy. The factors we are most intrigued by are the racial and regional variations in polypharmacy. We believe these findings are novel. Moreover, we believe our study adds substantially to two seminal general descriptive pharacoepidemiologic papers.[1,152] In particular, the regional and racial polypharmacy disparities may reflect different prescribing and OTC-use cultures in different parts of the country and among different racial groups. If so, then further research into whether the net result is "overprescribing" or "underprescribing" in different regions and races could contribute substantially to more optimal medication use and a great improvement in public health.

Studies 2 and 3 assessed some potential effects of polypharmacy. In study 2, in all the models constructed, we found that major polypharmacy was associated with all-cause mortality. Moreover, for corresponding models, [minor polypharmacy HR] < [major polypharmacy HR], in accordance with our *a priori* expectation that higher drug burdens would be associated with increased mortality. Furthermore, for some, but not all models, the minor polypharmacy-mortality HRs were statistically significant. Confounding by indication, however, represents a

serious threat to the validity of our findings. Despite adjustment for many covariates related to medication use, residual confounding by indication may still linger. The general finding that the magnitude of the HR decreased with increasing numbers of model covariates may reflect progressively diminishing confounding by indication in larger models. Nevertheless, we cannot be certain that confounding by indication has been totally eliminated in the "largest" model. Finally, no effect modification by CKD status of the polypharmacy-mortality association was noted. This refuted our *a priori* hypothesis that polypharmacy would be more harmful among those with CKD. The null finding may be a result of our dichotomizing CKD status, instead of looking at interaction by CKD stages.

Whereas polypharmacy was associated with mortality (study 2) it was not associated with cognitive decline (study 3). This may have occurred because some drugs enhance cognition, whereas others adversely affect cognition, rendering our polypharmacy metric too simplistic a measure to assess the risk one's pharmacological burden poses to her cognitive function. As in study 2, the CKD effect modification assessment gave null results.

The descriptive component (the prevalence of drugs **potentially** affecting cognition) of study 3 was more notable. We document that a majority of black and white American adults use at least one drug which **may** affect their cognition.

5.2: Research Strengths

Many strengths enhance the value of this research. Some of the strengths are dissertation-specific, but many are intrinsic to REGARDS.

The exposure was very rigorously assessed, with the participants reminded to collect all their medications, followed by a pill-bottle inspection by a trained health professional. Following this assessment, over the course of more than two years, the raw handwritten

medication data forms were meticulously transformed into a thoroughly documented, analysis-ready dataset that linked the recorded medname to a corresponding generic, drug class(es), and prescription/OTC/supplement status. Over 99% of the total recorded medications had their generic names documented using internet queries or manually based on slight mis-spellings.

Additionally, multiple statistical techniques were used to try to control for confounding by indication. Furthermore, multiple statistical models were constructed, and the results were generally qualitatively consistent regardless of the model.

REGARDS is a large cohort whose total sample exceeds 30,000 participants. This provides statistical power and allows flexibility in model selection—"large" models are statistically viable. Similarly, over one-hundred rigorously assessed covariates were collected in REGARDS, so we had minimal concern that an important potential confounder went unmeasured.

REGARDS has a relatively low loss to follow-up of less than 3% annually. This limits selection bias from selective follow up. Conversely, the long median follow-up time in studies 2 and 3 means that the total loss-to-follow-up is not trivial.

The REGARDS sample should be considered reasonably generalizable to the general adult black and white American population based on its stratified random sampling methods.[170] Finally, multiple models were considered, and the results were qualitatively consistent across models.

5.3: Research Limitations

Important research limitations should be kept in perspective. First, although vast in its scale and scope, the medication dataset lacked many potentially important parameters (e.g., dose, frequency of use, indication of use, history of use) that could be used to construct a more

comprehensive pharmacological risk metric. This would, for example, help distinguish appropriate from inappropriate polypharmacy. Secondly, although statistical techniques were applied to minimize its impact, the possibility of residual confounding by indication cannot be overlooked. Additionally, we implicitly assume that every medication should count equally towards mortality or cognitive impairment risk in using an unweighted (i.e., some cardiovascular drugs might contribute more towards the outcomes than a nasal decongestant) medication sum to classify polypharmacy. Moreover, only a single medication assessment was made, so we lack longitudinal data on the exposure. Furthermore, considering the extreme biological heterogeneity of the exposure and the outcomes for study 2 and 3, selecting the most appropriate model is very difficult, if not impossible. Finally, as a minor point, the medication form only had space to list up to 20 medications; some cohort members took more than 20 medications, so we have slightly underestimated total drug burden.

5.4: Research Public Health Impact

Considering the high prevalence of the exposure and the severe outcomes considered (mortality and cognitive impairment), the potential public health impact of this research is substantial. One must ask why there is less polypharmacy in blacks and more polypharmacy among Southern residents. If blacks or non-Southerns are being undertreated (or whites or Southerners) are being overtreated pharmacologically, then this research might be the impetus for further research that unravels the reasons for these disparities. If there is a systematic national pharmacologic mismanagement, then the public health implications of this research would be immense. Fortunately, there are proven remedies to improve medication use.

A number of strategies have been proposed as heuristics to optimize prescribing. These include **SAIL**: **simplicity** of drug routine, **adverse effect** possibilities should be anticipated**,**

indication should be clearly established**,** and **list** dose and name of all drugs.[12] Another mnemonic is **TIDE**: take **time** to discuss drugs, **individual** medication nuances should be recognized, **drug-drug interactions** must be appreciated, **educate** patients about various therapeutic options.[12]

Many studies have evaluated the ability of various pharmacological interventions to enhance patient's usage of medications. Some have proven beneficial, while others have demonstrated no net positive effect. For example, one randomized, controlled trial (RCT) found that pharmacist interaction decreased pain and hospitalizations, but had no effects on falls, mobility, ADEs, or cognitive disorientation.[203] A further RCT reported an over 40% decrease in the risk of death for individuals who received pharmacist phone consultations.[204] Garfinkel et al. also reported a dramatic decrease in mortality from their "war against polypharmacy."[205] Schmader et al. found improvements in medication appropriateness and reduced underprescribing, but there was no decrease in the frequency of severe ADRs following medication management.[206] Multiple studies have examined pharmacy management's positive effects on "soft" endpoints (such as "inappropriate prescribing scores"[207], "quality of drug treatment" metrics[208], the reduction in medication burden/polypharmacy[22,209,210], or decreasing drug-drug interactions[211]). Unfortunately, despite some positive findings in the literature, the benefits of careful medication management may be transient.[84]

Another RCT found no effect of in-home pharmacist medication consultation on mortality or hospitalization.[212] Zermansky et al. found no effect of an RCT clinical pharmacy drug assessment on mortality, hospitalizations, or Mini Mental Score.[213] One more RCT, which targeted inappropriate medications among polypharmacy geriatrics, found no effect on health-related quality of life, but did observe fewer ADE for the intervention group.[207]

Poor patient-physician communication may precipitate many occurrences of polypharmacy. An extremely time-constrained general practitioner may find it difficult to stay abreast of the many medications he has prescribed his multi-morbidity patient, let alone the perscriptions specialists have written. This is evinced by the by the fact that there is very frequently discordance between what the physician believes the patient is taking (and the manner of use) and what drugs the individual is using everyday.[45,214, 215] For example, Bikowski et al. found that only 14% of patients and doctors exhibited "complete congruence," denoting "agreement between physician and patient regarding all prescription medications, dosages, and frequency."[214] Similarly, Fulton et al. documented that over half of individuals were consuming drugs that were undocumented, which would pose a particular risk for drug-drug interactions if a new prescription is written.[45] This lack of physician medication awareness even extends to prescription drugs, with Barat et al. noting that a quarter of "prescribed drugs were used without the GP's knowledge."[52]

The communication is also poor for OTC medications, which consumers are more likely to recognize as drugs. One group reported that only half of CKD patients in their sample discussed their use of OTCs.[216]

Perhaps this research, which documented wide variation in medication use, could catalyze a movement toward a structured, standardized medication assessment at each clinical encounter. Such directed patient-physician medication communication would likely provide substantial health benefits to the patient.

The second study finds a consistent association between polypharmacy and mortality. If this association is truly causal (confounding by indication has been overcome and an appropriate

model utilized), then, again, the public health impact is vast, as an intervention as simple as a medication review with a doctor or pharmacist might substantially reduce mortality.

The third study's biggest public health impact is the estimate of the prevalence of "cognitive drug" use. Assuming that all our "cognitive drugs" pose a reasonable (e.g., > 2% risk for cognitive impairment) threat to cognition, then our findings of such high use has significant public health implication, as cognition underlies nearly all aspects of life and cognitive impairment has major economic implications. If too many are unnecessarily taking "cognitive" drugs, then this should be rectified.

5.5: Research Conclusions

We conclude that medication use is highly prevalent in our society. Moreover, a substantial population fraction takes many drugs simultaneously. Unfortunately, we cannot comment on the appropriateness of this medication use. Many factors, including race, region, and gender, are associated with polypharmacy. The race and region findings we believe to be novel and should be investigated further.

We observed a consistent association between major polypharmacy and all-cause mortality in the REGARDS cohort. The finding that degree of polypharmacy was related to mortality risk confirmed our *a priori* hypothesis that major polypharmacy would be more strongly associated with mortality than minor polypharmacy. Refuting another *a priori* hypothesis, no CKD-based effect modification was observed.

We observed universally null findings in our study of the association of polypharmacy with cognitive impairment. Again, no CKD-based effect modification was observed. However, a majority of the nation's black and white adults were exposed to at least one drug with **potential** cognitive effects.

5.6: Research Future Directions

After having embarked on this research endeavor, we feel like the potential journey (using this dataset and for pharmacoepidemiology in general) has only just begun. First, a second REGARDS in-home visit is scheduled to begin in 2013, which will provide longitudinal data on medication use. It would be interesting to see if the polypharmacy phenotype tracks consistently over time, or whether there are substantial temporal changes in medication burden. The second in-home visit will also provide updated data on medication use (e.g., polypharmacy) patterns across the country. It will be interesting to see if the racial and regional variations have persisted in this older cohort.

Considering the years of labor that went into its completion, a descriptive paper detailing the construction of the REGARDS dataset from the raw data should be written. This paper would underlie all research done using the REGARDS medication dataset.

Manuscript 1 could be substantially expanded by ranking the most common generics and drug classes. In fact, this research has already been done, as SAS macros were written to classify prevalence of drug use according to any generic name or drug class.

Another potentially fertile research path would be to refine the exposure so as to make it more physiologically- and pharmacologically-specific, making the medication burden metric much more biologically meaningful. This could be done, for example, by weighting the "polypharmacy contribution" of each medication based on its known risk profile (e.g., digoxin carries greater risks than chlorpheniramine) and the dose.

Thus far, we have ignored medication compliance. REGARDS does assess medication compliance. Future studies could look at whether compliance functions as a polypharmacy effect modifier. Furthermore, the null CKD effect modification findings merit further research.

In particular, one might try using CKD stages, instead of the physiologically simplistic CKD yes/no we utilized.

A great fraction of the time spent on refining the raw data was coding supplements, as they lack universally accepted generic names and are not FDA regulated; thus, they could generally not be readily found using **Drugs.com**. Nevertheless, despite this substantial investment in labor, we excluded them from our polypharmacy definition. Future research must use the supplement data. In particular, we could run an analogous set of analyses for supplements as we did for prescriptions/OTCs in manuscript 1. For example, we could estimate the prevalence of supplement use and "polyherbacy" and generate a model of factors associated with supplement use, paying especially close attention to any regional or racial variations. Similarly, we could use supplement use or "polyherbacy" as our exposure and look at a variety of outcomes, including mortality and cognitive impairment.

We found the geographic patterns in study 1 to be quite intriguing. Further exploration of what census-tract level variables might explain these regional patterns is merited. Similarly, more investigation into what factors may explain the racial polypharmacy disparities is warranted.

We could also look at cause-specific (e.g., cardiovascular) mortality as the outcome of interest. In these cases, the choice of variables to include in the model might be more easily ascertained, as there would be some underlying pathophysiology to guide model selection.

Although REGARDS is an amazing data source, by design, it only includes blacks and whites. It would be interesting to assess medication use patterns in Asians, Latinos, and Native Americans and compare them to our findings among blacks and whites. A resource such as NHANES might provide the data necessary to conduct these comparisons.

Finally, the universally null findings in study 3 were somewhat disappointing. We would want to refine our exposure in future studies. For example, we might try to generate an exposure that mathematically combines a measure of anticholinergic burden with total drug burden.

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