UNIVERSITY OF CALIFORNIA, SAN DIEGO

Hypertension: Correcting Blood Pressure for Antihypertensive Treatments

A Thesis submitted in partial satisfaction of the requirements for the degree

Master of Science

in

Biology

by

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2011

The Thesis of Anish Dhamija is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Co-Chair

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Chair

DEDICATION

To Mama, Papa, Didi, Bhaiya, Bobby Chacha, Raju Bhaiya, Kabir and Miko, for their encouragement, love and support.

EPIGRAPH

Nothing in the world can take the place of persistence. Talent will not; nothing is more common than unsuccessful men with talent. Genius will not; unrewarded genius is almost a proverb. Education will not; the world is full of educated derelicts. Persistence and determination are omnipotent. The slogan press on has solved and always will solve the problems of the human race. No person was ever honored for what he received. Honor has been the reward for what he gave.

Calvin Coolidge

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LIST OF ABBREVIATIONS

- BP = Blood Pressure
- SBP = Systolic Blood Pressure
- DBP = Diastolic Blood Pressure
- BP Drugs = BP lowering medication = BP drug classes = antihypertensive medication
- BMI = Body-Mass Index
- HBP = High Blood Pressure = Hypertension
- mm Hg = millimeters of Mercury; unit of BP measure
- MW = Midwest
- EC = East Coast
- CA = California
- TX = Texas
- FL = Florida

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ABSTRACT OF THE THESIS

Hypertension: Correcting Blood Pressure for Antihypertensive Treatments

by

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Master of Science in Biology

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Professor Brinda K. Rana, Chair
Professor James Nieh, Co-Chair

Hypertension is a chronic disease that is a risk factor for impaired cognition, stroke and heart attacks, among other diseases. Previous studies suggest that not accounting for the use of antihypertensive medication in genetic and population studies may confound results. Thus, identifying a model to correct for Blood Pressure-lowering medications is important.

We assessed BP and antihypertensive medications in 1,237 male twins from the Vietnam Era Twin Study of Aging (VETSA). We used three approaches to correct BP measurements for antihypertensive treatment: (1) the addition of a fixed value of 10 mmHg and 5 mmHg to measured systolic and diastolic BP, respectively, for subjects on antihypertensive medication, (2) an incremented addition of mmHg to BP based on the number of different medications used, and (3) the addition of mmHg according to antihypertensive drug class and ethnicity. We used the classical twin design to estimate heritability of the corrected BPs. We also assessed whether the relationship between BP traits and Body-Mass Index (BMI) changed with corrections.

The corrections for antihypertensive treatment did not significantly affect the heritability of BP measurements in VETSA data. However, corrections for antihypertensive treatments resulted in higher correlations between BP and BMI.

We also analyzed demographic data on twins to compare prevalence of hypertension, prescribed BP medications, and BMI in regions across the United States, stratified by (1) geographic location, (2) political affiliation and (3) stress levels. The prevalence of hypertension significantly differed between regions of high stress and regions of low stress, suggesting a correlation between stress and hypertension.

Chapter 1
Background of Blood Pressure and Introduction to Antihypertensive Treatments

1.1 Background

Blood pressure (BP) is the pressure that blood exerts on the walls of blood vessels. BP varies between a maximum pressure (systolic) and a minimum pressure (diastolic) during every heartbeat. It is standardly written as systolic blood pressure (SBP) over diastolic blood pressure (DBP) and measured in mmHg units.

Normal BP is when SBP is between 120 and 90 mmHg and DBP is between 80 and 60 mmHg. If BP exceeds 140/90 mmHg, it is classified as high blood pressure, a condition medically referred to as *hypertension*. If a BP falls between the range of normal and hypertensive (e.g. 130/85 mmHg), the individual is considered prehypertensive and at high risk for hypertension. The various classifications are listed in **Table 1**[1].

Table 1: Classification of BP for adults[1]

Blood Pressure Classification	SBP mmHg	DBP mmHg
Normal	90-120	60-80
Prehypertension	120-139	80-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	>160	>100

1.2 General Introduction

Hypertension is a chronic disease that is a risk factor for impaired cognition, stroke, heart attacks and various other diseases[2, 3]. Hypertension affects approximately 1 billion individuals worldwide and more than 75 million Americans. There are 7.1 million deaths from hypertension-related diseases per year[1].

Due to its prevalence, intense efforts have been made to identify the causes of hypertension, yet our understanding of the etiology of hypertension is still far from complete, primarily due to the complexity of BP regulation and the polygenic nature of hypertension[4]. Although direct causes have not yet been identified, factors such as drugs, stress, obesity, diet (e.g. salt and sugar intake), and inactivity are known to increase the risk of hypertension[5].

There are two treatments for hypertension: (1) lifestyle changes and (2) blood pressure-lowering medication. For some patients, lifestyle changes including, diet modification, exercise and weight loss are recommended first. If these changes are insufficient to reduce BP, BP drugs, also known as antihypertensive treatments, are prescribed[6]. The goal of antihypertensive treatment is to reduce BP to less than 120/80 mmHg for most individuals[1].

Antihypertensive treatments are generally categorized into several classes, each having a different mechanism of controlling BP. The most widely used drug classes are thiazide diuretics, beta-blockers, alpha-blockers, calcium channel blockers (CCBs), Angiotensin II Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)[5].

Diuretics work on the kidneys to flush excess sodium and water from the body. Beta-blockers weaken the sympathetic nerve impulses to the heart and blood vessels, decreasing the speed and force of the heartbeat. Alpha-blockers also weaken the nerve impulses, but instead act on the alpha-receptors of the muscle, widening the arteries and allowing for smooth blood flow. CCBs prevent calcium from entering the muscle

cells of the heart and blood vessels. The blood vessels then relax and pressure goes down[7].

There are a series of BP drug classes that deal with the renin-angiotensin system (RAS)[8]. In RAS, juxtaglomerular cells of the kidney first secrete the *renin* enzyme in response to low BP. *Renin* converts angiotensinogen from the liver into angiotensin I; Angiotensin Converting Enzyme (ACE) converts angiotensin I into angiotensin II. Angiotensin II causes blood vessels to narrow[8].

An ACE-inhibitor will retard the formation of angiotensin II, preventing the constriction of blood vessels and decreasing the BP. Angiotensin Receptor Blocker (ARBs) shield the blood vessels from angiotensin II. The blood vessels become wider and BP goes down[7].

Various drug classes exist, yet no universal system currently exists for prescribing BP medications, primarily because the effects of each medication differ by ethnicities[9], gender[10] and age[11]. Nonetheless, prescription protocols do exist. Generally, the first-line of antihypertensive therapy is a beta-blocker, ACE-inhibitor or a diuretic, since all have been found to reduce morbidity and mortality[2]. Recent evidence, however, has found that a thiazide diuretic is both safer and more effective than beta-blockers[12].

If the patient suffers from a pre-existing condition, different BP drug classes are prescribed as first-line therapy. For instance, if the patient has diabetes, heart disease or LVH, then ARBs or ACE-inhibitors are recommended. If the patient has difficulty lowering sodium intake or is African American, then CCBs are prescribed[13].

In approximately 50 percent of hypertension patients[14], the first-line of therapy is inadequate. Therefore, multiple medications from different classes are used to achieve BP control[15]. If a second drug is needed, it is usually chosen by the patient's underlying disease mechanism[13], as previously referred. Another way to combine drugs is to merge 2 drug classes into one medication. These "combo drugs" are effective and enhance compliance since the patient no longer has to take 2 pills[14].

After a thorough review of the efficacy of certain combinations, Swift et al.[11] in 2002 proposed a method to prescribe medications that accounted for both ethnicity and age. Their method is summarized in the **Figure 1** below. Swift proposed that African Americans and elders should begin with a diuretic or CCBs, while younger individuals and non-African Americans begin on a beta-blocker, ACE-inhibitor, or ARBs. If those medications prove inadequate, Swift's system provides suggestions for second-line and third-line therapy.

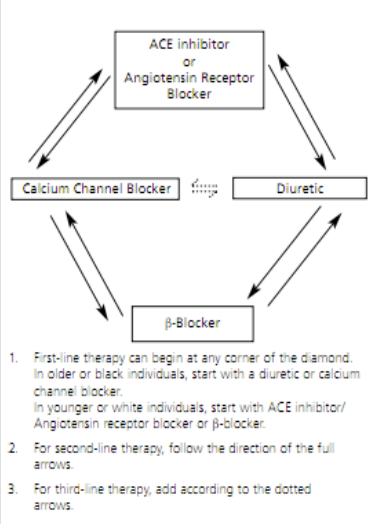

Figure 1: Swift et al.'s (2002)[11] proposed method for prescribing BP medications in antihypertensive therapy. Figure taken from *The frequent need for three or more drugs to treat essential hypertension* (Swift 2002).

Our study assessed BP and antihypertensive medications in 1,237 male twins from the Vietnam Era Twin Study of Aging (VETSA). The VETSA study has collected prescription medication information on this cohort and measured BP on each participant during an 8-hour clinical examination day. The VETSA study has data on a number of other physiological and neurocognitive phenotypes. The VETSA cohort is useful for our study because twin studies are a unique tool that helps differentiate the genetic and environmental influences on traits[16]. We used this population to carry out the three aims of this project. (1) Test whether correcting for BP-lowering medication affects the results of genetic analyses. For the first aim of the study, I used previously published methods to correct for BP medication and developed a third model based on Wu et al.'s[24] drug class-based corrections. I then assessed the impact of correcting for blood pressure-lowering medications on genetic influences (heritability) of the BP trait.

(2) Test how the corrected BP measures affect correlation with other traits. I looked at the correlation between BMI and BP after corrections. (3) Conduct an epidemiological study of the hypertension, BP medication use, and BP correlated traits with US geographic regions.

Chapter 2

Correcting measured BP for BP Lowering Medication

2.1 Introduction

Many genetic and epidemiological studies look at the relationship of measured BP with genes and other phenotypes[18, 19]. The problem with such studies is when study participants are on medication that lower BP. The dilemma is whether to analyze data with the measured BP, or account for the lowering effect of antihypertensive treatments and other BP lowering drugs. To address this dilemma, we identified and developed models to correct for BP lowering medication and explored the effects of correcting for medication on genetic and epidemiological analyses.

2.1.1 Various Corrections

In 2003, Cui et al.[20] proposed two corrections to medicated BP. The first correction was a *fixed addition,* in which a fixed value of 10 mmHg and 5 mmHg was added to measure SBP and DBP respectively, for subjects on any antihypertensive medication. This addition did not depend on how many medications the subject was taking.

The second correction, the *stepped addition*, factored in the number of drug classes the individual was taking. They proposed an addition of 8/4 mmHg, 14/10 mmHg and 20/16 mmHg to the SBP and DBP of participants on 1, 2, and 3 drug classes, respectively.

In 2005, after a careful review of clinical trials literature, Wu et al.[24] proposed a correction. They found that antihypertensive medications had significantly different

effects on African Americans when compared to other races, primarily due to less plasma renin activity[24]**.** As a result, they suggested accounting for ethnicity and specific drug class in correcting measured BP for medication. They also recommended an algorithm that calculates corrections for participants on 2 drug classes. However, a large proportion of U.S. patients on antihypertensive treatment are on more than 2 drug classes. New drug classes have also become popular treatments since Wu et al.'s original report in 2005. Thus, an updated model based on Wu et al.s' correction was necessary.

2.1.2 Literature Review

BP has been traditionally corrected by regression methods for covariates such as age and gender[20]. Other methods included excluding those who were on antihypertensive medications from analysis. Cui et al. (2003) [20] and Hunt et al. (2002)[22] found that these methods did not appropriately compensate for the effects of antihypertensive treatment on BP.

In 2002, Hunt et al.[22] compared 4 methods of managing medicated individuals in a cohort: (1) the exclusion of all medicated individuals, (2) using the participants' medicated BPs (3) assigning a fixed BP (140/90 mmHg) for all medicated participants, and (4) a random assignment between 140 and 160 mmHg for SBP and between 90 and 100 mmHg for DBP. Hunt discovered that excluding medicated measurements or use of uncorrected BP (methods 1 and 2) lowered logarithm of the odds, a degree of alikeness, when compared to correcting BP (methods 3 and 4).

Cui et al. (2003)[20] also compared 5 different methods of handling participants on antihypertensive medications in a family study: (1) exclusion of medicated individuals, (2) using the individual's medicated BPs, (3) the methods of Hunt et al. (4) Cui's *fixed addition* and (5) Cui's *stepped addition*. His team tested for heritability, the proportion of phenotypic variation due to genetic variance. A high heritability would provide solid evidence that BP variation is due to genetics. Cui et al. found that the genetic variance components in families increased when the BP was corrected for antihypertensive treatments (methods 3,4 and 5). On the other hand, when medicated individuals were excluded or medicated BP was used, the genetic variance component decreased.

In 2005, Tobin et al.[23] analyzed various corrections in simulated data sets, comparing the estimation bias and the loss of power. They found that two correction methods consistently performed well in statistical tests, the (1) *fixed addition* and (2) a normal regression model that assumes BP follows a normal distribution curve. They also discovered a few methods inherently flawed, including (1) ignoring the effects of antihypertensive medications and (2) excluding medicated individuals from the study.

A 2005 study by Wu et al.[24] did focus on ethnicity and its effect on BP medication. He first suggested to separate the cohort into African and non-African Americans. For people on 1 BP medication, he suggested to add effects according to Table 2a and 2b.

Table 2a: Wu's suggested addition to SBP and DBP for BP Drugs taken by African Americans

Different Drugs	Systolic Addn	Diastoli Addn
ACE-inhibitor	6.8	7.7
Alpha-Blocker	17.9	12
Beta-Blocker	9.1	10.5
Calcium Channel Blockers - D	20.2	13
Calcium Channel Blockers -ND	14.8	13.1
Loop Diuretic	26.7	10.1
Thiazide Diuretic	19.1	12.4

Table 2b: Wu's suggested addition to SBP and DBP for BP drugs taken by Non-African Americans

Different Drugs	Systolic Addn	Diastolic Addn
ACE-inhibitor	14.3	10.4
Alpha-Blocker	18.6	12.5
Beta-Blocker	14.6	12.1
Calcium Channel Blockers - D	17.1	10.4
Calcium Channel Blockers -ND	13.9	14.6
Loop Diuretic	12.3	6.1
Thiazide Diuretic	15	9.5

In computing the BP effect of 2 BP meds, Wu et al. suggested that the second drug would not have the full monodrug effect. They defined the first drug as the drug with a greater monodrug effect. Wu et al. then proposed that we take a proportion of the second drug's monodrug effect and add it to the full monodrug effect of the first

drug. This proportion varied, depending on: (1) whether any of the drugs were diuretics and (2) whether the individual was African-American or not.

There are a few major limitations to the corrections mentioned above. First, they did not address subjects on 3 or more drug classes. Second, Wu et al. did not list the monodrug effects of several drug classes; however, they did provide a suggested average effect for these missing drug classes. This average effect was used for the following drug classes: ARBs, potassium diuretics, central agonist and angiotensin receptor antagonist drug classes. Finally, they did not address "combo drugs," the combination of 2 BP Drug Classes into one pill. Thus, we propose a new model, a *Correction By Drug Class*, which addresses these gaps in present studies.

2.2 Methods

2.2.1 VETSA Data

VETSA[27] is a longitudinal study that examines the genetic and environmental influences on cognitive aging from midlife onwards. In VETSA 1, neuropsychological, cognitive, physical and biological data were collected for 1237 male twin subjects (over 600 pairs of twins) who had served in some branch of military service during the Vietnam era (1965-1975). These data will be recollected and reevaluated every 5 years by teams under 2 Principal Investigators (William Kremen, UCSD; Michael Lyons, Boston Univ.).

From the large quantity of data provided, only a few variables were isolated for each participant: mean SBP, mean DBP, BMI, medications, ethnicity and state

location. Mean SBP and mean DBP are an average of 4 BP measurements–2 taken in the morning and 2 in the afternoon.

2.2.2 Preparation of VETSA data for Analysis

Creating A Master List of all BP Medications in Cohort

VETSA had compiled and coded all the medications in their cohort. This list included over 3000 different medications categorized and organized by function. The BP medications had to be extracted from this list. Once extracted, the BP medications also had to be classified into their respective drug class. **Figure 2** outlines the method by which this was accomplished.

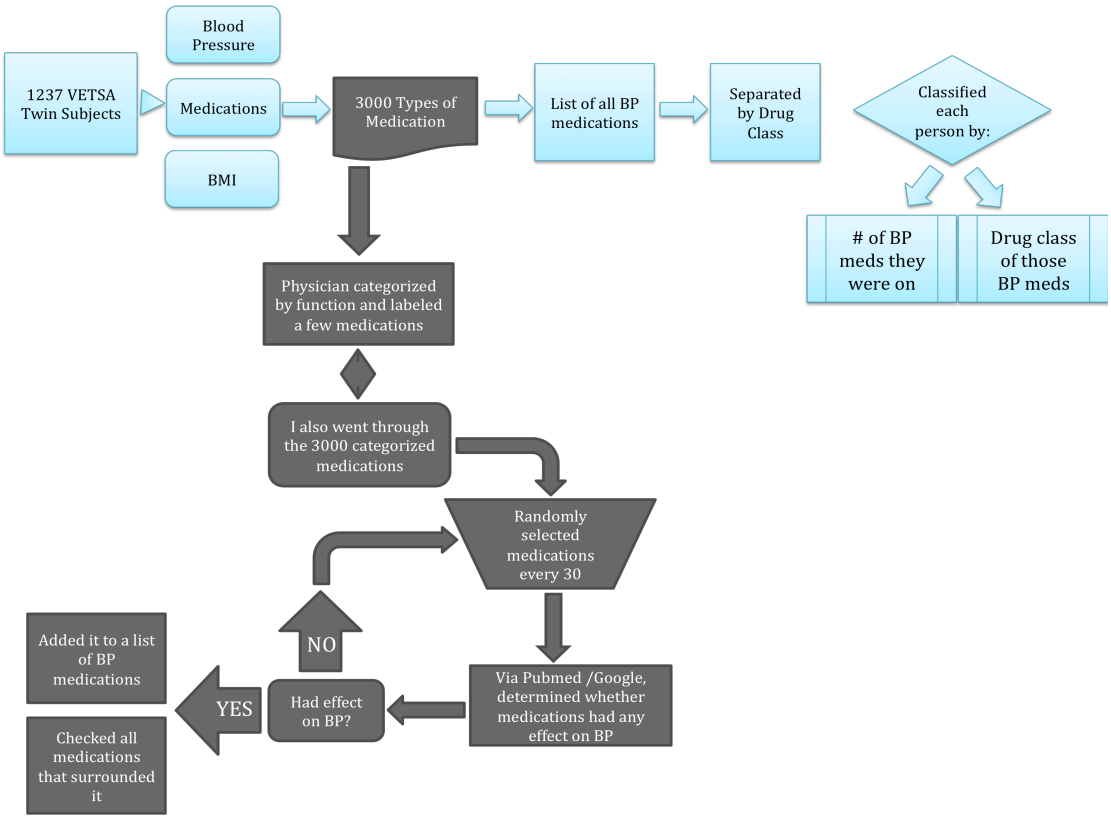

Figure 2: Flowchart of how BP medications were selected and classified

A physician had categorized and labeled ~60% of medications by function; however, this labeling was incomplete. Therefore, I went through the 3000 categorized medications and randomly selected a medication within the first 30. This medication was then entered into PubMed search engine to determine if it reduced BP. If a BP effect was found, its BP drug class was identified via PubMed, and that medication and their respective drug classes were then added to a *master list* of BP medications.

I then checked all the medications that surrounded BP-lowering medication. If a medication did not have an effect on BP, I continued to randomly select medications every 30. This process was repeated until the entire list of 3000 medications had been finished.

Therefore, the entire list of medications was narrowed down to a list of those that only affect BP. It was discovered that BP-lowering meds included not only antihypertensive meds but also other prescription meds. While some studies ignore these other drugs, I included them. Each of those BP medications was then categorized into a specific BP drug class. This list of BP medications became the *master list*, essentially consisting of BP drug classes and the drugs that fell under that respective drug class.

Identifying the BP Medications For Each Participant

Most of the 1237 subjects were taking medications, but it was unclear if some of these were BP medications or not. Using the *master list*, a code was written that (1) found if a medication was a BP drug and then (2) replaced that medication with its BP

drug class. Another code tallied how many BP drugs they were taking. As a result, each participant was now classified by (1) the number of BP meds they were taking and (2) the drug class of those BP Meds.

2.2.3 Corrections

Each subject was now labeled by their average BP, their BP medications, and the number of BP medications they were taking. The corrections to the blood pressure needed to be made.

Fixed Addition Correction

The first correction applied was the *Fixed Addition*. A code automatically added 10/5 mmHg to anyone on BP medication. This was independent of the number of BP medications that individual was taking.

Stepped Addition Correction

Unlike Fixed Addition, the *Stepped Addition* correction depended on the number of BP drugs that person was taking. More specifically, the addition to BP varied directly with the number of BP drug classes that individual was on.

Cui[7] proposed that 8/4, 14/10, 20/16 be added to individuals on 1, 2, and 3 drug classes, respectively. However, no values were indicated for individuals on 4,5, or 6 drug classes. From extrapolation and other studies[12], it was decided that there would be a 24/20, 26/22, 27/23 mmHg addition to BP for those on 4,5 and 6 drug

classes, respectively. **Table 3** summarizes the corrections that were made in the Stepped Addition.

Table 3: Corrections suggested by Cui et al (2003)[1] and by extrapolation.

# of Drug Classes	Addition to the Blood Pressure (SBP/DBP)
1	+8/4 mmHg
2	+14/10 mmHg
3	+20/16 mmHg
4*	+24/20 mmHg
5*	+26/22 mmHg
6*	+27/23 mmHg

**determined by extrapolation*
*Corrections depend on the number of drug classes the individual is on.

Correction by Drug Class

The final correction applied was *Correction by Drug Class*, an addition to Wu's correction. According to Wu's correction, BP medications have different effects on African Americans than Non-African Americans. Therefore, the cohort was first separated into African Americans and non-African Americans. These categories were further divided by the number of BP meds participants were taking, resulting in a total of 6 categories: (1) African Americans on 0 BP meds; (2) African Americans on 1 BP med; (3) African Americans on 2 or greater BP meds; (4) Non-African Americans on

0 BP meds; (5) Non-African Americans on 1 BP med; (6) Non-African Americans on 2 or greater BP meds.

Subjects on 0 or 1 BP medication

For individuals on 0 BP meds, no BP correction was made. For subjects on 1 BP medication, the addition to BP depended on the drug class and participant's ethnicity. If the individual was African American, then effects were added according to **Table 4a**; if the individual was non-African American then effects were added according to **Table 4b**. These tables include effects for "combo drugs" and new drugs that Wu et al. had not addressed. A code matched the individuals' BP drug class with the drug class in the tables below, subsequently adding the corresponding *monodrug effect.*

Table 4a: A modified table of BP medication effects on African Americans that includes combo drugs and some drug classes that Wu did not include. The differences are highlighted in blue.

Different Drugs	Systolic Addition	Diastolic Addition
ACE Inhibitor	6.8	6.6
Alpha-Blocker	17.9	12
Beta-Blocker	9.1	10.5
Calcium Channel Blockers - D	20.2	13
Calcium Channel Blockers -ND	14.8	13.1
Thiazide Diuretic	19.1	12.4
Loop Diuretic	26.7	10.1
Angiotensin Receptor Blocker	15.4	11.2
Potassium Diuretic	15.4	11.2
Beta-Blocker + Thiazide Diuretic	30.8	19.9
ACE + Thiaizide Diuretic	27.9	17.1
Potassium Diuretic + Thiazide Diuretic	39	20.4
Alpha-Blocker + Beta-Blocker	22.5	18.1
ACE + Calcium Channel Blocker	23.6	16.8

Table 4b: A modified table of BP medication effects on Non-African Americans that includes combo drugs and some drug classes that Wu did not include. The differences are highlighted in lavender

Different Drugs	Systolic Addition	Diastolic Addition
ACE Inhibitor	14.3	10.4
Alpha-Blocker	18.6	12.5
Beta-Blocker	14.6	12.1
Calcium Channel Blocker - D	17.1	10.4
Calcium Channel Blocker - ND	13.9	14.6
Loop Diuretic	12.3	6.1
Thiazide Diuretic	15	9.5
Potassium Diuretic	15.7	10.5
Angiotensin Receptor Blockers (ARBs)	15.7	10.5
Beta-Blocker + Thiazide Diuretic	22.7	16.3
ACE Inhibitor + Thiazide Diuretic	22.6	14.6
Potassium Diuretic + Thiazide Diuretic	23.7	14.7
Alpha + Beta-Blocker	25.9	19.6
ACE Inhibitor + Calcium Channel Blocker-D	24.3	16.5

Subjects on 2 BP medications

A code identified the 2 BP drugs that the participant was taking and determined which of these drugs had a higher monodrug effect according to **Table 4a** or **4b**. Similar to Wu et al., the drug with the higher effect was labeled as the first drug; the drug with the lower effect was labeled as the second drug. Another code took the proportion of this 2nd drug. Wu claimed that this proportion varied, depending on: (1) Whether the individual was African American or non-African American, and (2) whether any of the drugs were diuretics. The proportions are listed in **Table 5**:

Table 5: Proportion taken of 2nd drug. Proportion depended on ethnicity (left column) and drug class (top row).

Proportion	If 1 of the 2 drugs is Diuretic (SBP/DBP)	If None are a Diuretic (SBP/DBP)
African Americans	1.29/.71	.5/.58
Non-African Americans	.53/.44	.5/.59

Different proportions were applied to SBP and DBP.

This proportion of the 2nd drug was then added to the full monodrug effect of the 1st drug. This number was then added to the individual's average BP. There is a computed example of the BP correction for 2 drugs in the "*combo drugs*" section.

Subjects on more than 2 BP Meds

The VETSA cohort had 71 people on 3 or more drug classes, but Wu did not mention any corrections for individuals on 3 or more drug classes. Additional drugs have a diminished effect lower than its monodrug or second drug effect[12]. The second drug effect was approximately .5. Therefore, we chose to decrease the effect by a factor of 0.1 for each additional drug. This correction factor is within the range observed in clinical trials[12].

- If an individual is on ≥ 3 drugs, the monodrug effect of the 3rd drug class is multiplied by .4.

- If an individual is on ≥ 4 drugs, the monodrug effect of the 4th drug class is multiplied by .3.
- If an individual is on ≥ 5 drugs, the monodrug effect of the 5th drug is multiplied by .2.
- If an individual is on ≥ 6 drugs, the monodrug effect of the 6th drug is multiplied by .1.

These proportions were totaled and added to the previous calculations of the 1st and 2nd drug class. **Figure 3** is a summary of our model, *Correction by Drug Class.*

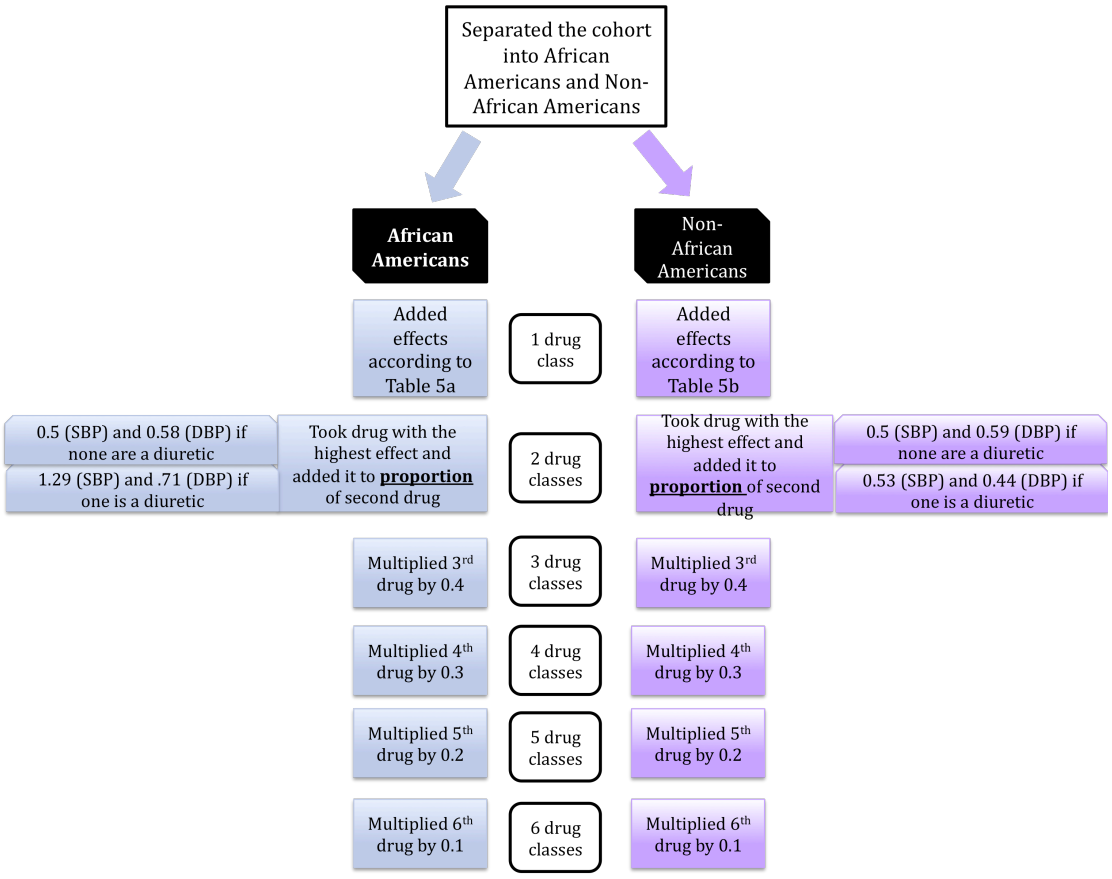

Figure 3: A summary of *Correction by Drug Class.*

"Combo Drugs"

Studies[14] suggest that "combo drugs" have the same effect as 2 different drugs; therefore, they were treated the same as subjects on 2 BP medications in Wu's method. For instance, if an African American participant takes an ACE-inhibitor and a thiazide diuretic (ace+td) combo drug, then overall BP effect can be calculated by taking the drug with the highest effect (1st drug) and adding it to a proportion of the 2nd drug.

According to **Table 4a,** ACE has an effect of 6.8/6.6 mmHg, while the thiazide diuretic has an effect of 19.1/12.4 mmHg on BP. If only SBP is considered, thiazide's effect of 19.1 is greater than ACE's SBP effect of 6.8; thus, thiazide is the first drug and ACE is the second drug. A proportion of ACE must be taken. **Table 5** states that if one of the 2 drugs is a diuretic and the individual is African-American, we multiply 1.29 by the systolic effect of the 2nd drug.

$$1.29 \times 6.8 \text{ mmHg} = 8.772 \text{ mmHg}$$

This is the effect that the 2nd drug, the ACE-inhibitor, has on the BP. This effect is added to the systolic effect of the 1st drug (19.1 for the thiazide diuretic).

$$19.1 \text{ mmHg} + 8.7 \text{ mmHg} = 27.9 \text{ mmHg}$$

Therefore, 27.9 mmHg will be added to the average SBP if an individual is only on an ace+td diuretic combo drug.

2.3 Results

2.3.1 Results from the Preparation of VETSA Data

Initially, the data were prepared and the BP Drug Classes were identified. Through the procedures outlined in *Preparation of VETSA data for Analysis*, a master list was created. This master list was then later used to identify the BP drug classes that each individual was taking.

Table 6 specifies the different BP drug classes present in the VETSA data. The bold titles in the top row are the various drug classes. Below these Drug Classes are specific medications that fall into that drug class. At the very bottom is the number of people that have BP drugs in that BP drug class. For instance, 187 and 71 subjects are taking ACE-inhibitors and Combo Drugs, respectively. The table also reveals that the majority of BP medications were both ACE-inhibitors (27.4%) and beta-blockers (26.5%). Diuretics are found to be quite prevalent, but are commonly used in "combo drugs."

There are a few "less common" drug classes that were found to affect BP. These drugs, listed in the last column, were not specified, as only 12 individuals were taking them. An exception is fish oil, which does affect BP[28], but is not considered a BP drug and not included in our analysis.

Table 6: Specific BP drug classes and medications of VETSA individuals. Number of people in each drug class are also noted.

ACE Inhibitor	Alpha 1-blockers	Beta blockers	Calcium Channel Blockers	Diuretic (non-thiazide)	Thiazides	Angiotensin Receptor Blockers	Combo Drugs	Other Drug Classes
Captopril	Terazosin	Atenolol	Nifedipine	Spironolactone	Hydrochlorothiazide	Losartan potassium	Carvedilol	Clonidine
Enalapril	Prazosin	Timolol	Felodipine	Furosemide/ Torasemide	Chlorothalidine	Valsartan	Enalapril maleate/ Felodipine	Telmisartan
Lisinopril	Alfuzosin HCL	Metoprolol	Isradipine	Bumetamide	Hydroflumethiazide	Irbesartan	Amlodipine/ Benazepril	Methyldopa
Fosinopril		Nadolol	Amlodipine			Candesartan	Bendroflumethiazide/ Nadolol	Fish Oil (62)
Benazepril HCl		Acebutolol	Diltiazem				Bisprolol/ HCTZ	
Ramipril		Propranalol	Verapamil				Captopril/ HCTZ	
Quinapril HCl		Bisoprolol					Lisonopril/ HCTZ	
Moexipril							Enalapril/HCTZ	
Trandolapril							Triamterene/ HCTZ	
Cilazapril							Spironolactone/ HCTZ	
							Irbesartan/ HCTZ	
							Losarten/HCTZ	
187	17	181	71	26	64	54	71	12

Through the procedures outlined above, a number of subjects were also found to be on more than 1 BP drug class. Multiple drug classes complicate the effects of the medication and overall BP corrections. **Table 7** depicts the number of people on multiple drug classes. About 36% of the VETSA population was taking a BP drug. Approximately 16% of those on BP drugs were on 3 or more different drug classes.

Table 7: The number of people on BP Drugs in VETSA Cohort

Number of Drug Classes	Number of People
0	791
1	236
2	139
3	52
4	12
5	5
6	2

2.3.2 Results from the Corrections

There were 3 different corrections made: fixed addition, stepped addition, and *Correction By Drug Class*. **Table 8** shows the differences in mean SBP and mean DBP due to each correction. The standard deviation is also noted.

Table 8: The differences in average SBP and average DBP due to corrections.

	Average SBP	Standard Deviation	Average DBP	Standard Deviation
No adjustment	134.2	15.04	83.6	9.4
Fixed Addition	137.8	16.18	85.4	9.85
Stepped Addition	138.5	16.96	86.5	10.9
Correction by Drug Class	141.3	19.06	88.8	12.3

*Statistical Significance determined by one-sample t-test

The *Correction by Drug Class* had a significantly large effect on the SBP and DBP when compared to non-adjusted BP. It also had the greatest standard deviation, indicating that the blood pressures in that correction were further spread out from the mean. All 3 corrections increased the average SBP and DBP.

2.4 Discussion

The aim of this project was to develop a refined method for correcting for BP-lowering medication. The new method and existing methods described in this chapter will be used to estimate heritability and correlations with BMI in the next chapter.

2.4.1 Limitations

There are a few limitations to this study. First, the diseases in this cohort are self-reported; therefore, people who report being hypertensive may actually not be. Second, the dosage of the antihypertensive medications was unknown and not considered in calculations. Third, the medication is self-reported and there is no way to estimate adherence to treatment regimen.

Without more clinical trials or longitudinal studies, it is difficult to come up with an accurate model for predicting underlying BP, but we hypothesize that our model is more refined because it extends to more than 2 drugs and "combo drugs," while the other methods fall short.

Chapter 3

The Effect of Correcting for BP Lowering Medication on Heritability Estimates and BMI Correlations

3.1 Introduction

3.1.1 Heritability and BMI

Estimating heritability is important in identifying the genetic causes of hypertension. Heritability is the proportion of phenotypic variation in a population that is due to the genetic variation between individuals[21]. For example, a heritability of 0.5 indicates that 50% of the variation found in a phenotype in a given population is due to genetic variation.

Antihypertensive medications lower BP, confounding the phenotype (BP). It is believed that predicting the original (untreated) BP will yield a more accurate heritability[24]. Many researchers have set out to find the appropriate BP corrections for those participants on antihypertensive treatment.

The body mass index (BMI) is a measure of body fat based on the weight and height of an individual. To calculate, the weight in kg is divided by the square of his height in meters. High BMI (25-100) has been associated with hypertension[35]. This study will examine whether correcting for BP medication will unmask the expected (positive) correlation between BMI and HBP.

3.1.2 The Aims of the Study

The goal of the present study is to provide a more refined model for correcting for BP-lowering medications in order to better estimate the heritability of BP and obtain more meaningful correlations of BP with other measures. Using the model in my study on the VETSA cohort should provide a more accurate estimate for

heritability for four reasons: (1) The VETSA twin cohort will be more powerful to estimate heritable effects than family studies since the twins are age-matched and do not include cross-generation or cohort effects[25]. (2) The age range of VETSA participants (51-60 years) is narrow, limiting BP variability and confounding effects of cohorts which include children and adolescents in which HBP may not yet be expressed[26]. (3) BP measurements corrected for the BP lowering effects of medications is more accurate than not correcting for medication[23].

It is predicted that the most refined correction for BP would yield the highest heritability of BP. Heritability measures how much *genetic* factors are responsible for the phenotypic variation. Phenotypic variation among individuals may be due to *genetic* or *environmental* factors. If BP medications are an environmental influence, then correcting for BP medications would reduce an environmental factor. Hypothetically, this increases the relative contribution of genetic factors to the phenotypic variance, which by definition, increases heritability. Thus, correcting for BP medication is predicted to increase the heritability estimate of BP. In addition, the most accurate BP correction is predicted to increase heritability by the greatest amount.

It is believed that the more refined the corrections are the better the correlations are with a known correlated trait. There is a positive correlation[17] that exists between BMI and HBP. In this study, we predicted that Correction by Drug Class would result in the highest correlation between BMI and BP. The corrections increase BP, and thus it is expected that this correlation would become stronger.

In summary, this project will compare the effects that 3 models for BP medication correction, stepped addition, fixed addition and Correction By Drug Class, would have on (1) heritability estimates and (2) the correlation of BP with BMI, in order to determine the best model for use in subsequent studies of BP.

3.2 Methods

3.2.1 Estimating Heritability

After the three corrections were made, heritability was then estimated using *Falconer's estimate of Heritability*[42]. The formula is $h_b^2 = 2(r_{mz} - r_{dz})$, in which h^2 is heritability, rmz is the correlation of BP between monozygotic twins and rdz is the correlation of BP between dizygotic twins. Identical (monozygotic) twins are estimated to be twice as genetically similar as fraternal (dizygotic) twins, so heritability is approximately twice the difference in correlation between monozygotes and dizygotes.

The monozygotic twins were first separated from the dizygotic twins with the SPSS Filter. For each category, the SBP and DBP for each BP correction were correlated to see how alike they are.

In monozygotic twins, correlations were calculated for 4 different SBPs: (1) non-corrected SBP, (2) Fixed addition SBP, (3) Stepped addition SBP, and (4) Correction by Drug Class SBP. These values served as the *rmz* in the heritability calculation. The same was done for the SBP of dizygotic twins, which provided the *rdz* for the heritability calculation. After calculating the four rmz's and four rdz's for

systolic BP, the heritability h^2 was calculated. The heritabilites for DBP were estimated in the same way.

3.2.2 Correlations with BMI

BP has a positive correlation with BMI[13]. I calculated the correlation of BMI with SBP and DBP for each BP correction to test if corrections increased the magnitude of correlations.

A summary of the entire method and analysis is shown in **Figure 4** below.

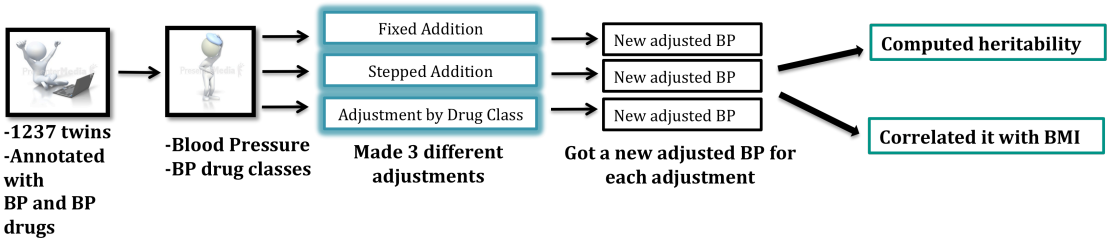

Figure 4: A summary of the Chapter 3 methods.

3.3 Materials

Microsoft Excel was used for organizing, evaluating and coding. SPSSStatistics 17.0 was used to calculate correlations, heritability and significance.

The formulas applied were Pearson's correlation and Falconer's Estimate of heritability = h^2= 2(rmz-rdz). Significance for the correlation was calculated with a two-tailed test. **Table 9** lists the analyses performed and the formulas used for calculations.

Table 9: Summarizes how heritability and correlations were calculated

Analyses	SPSS Data Analysis	Formula
Heritability	Falconer's Estimate of Heritability	$h^2 = 2(rmz-rdz)$
Correlation	Pearson's Correlation;	$r = (\sum z_x z_y)/N$

The VETSA data was partially compiled by Dr. Kremen's team at the University of California, San Diego, Department of Psychiatry at 9500 Gilman Dr., La Jolla, CA 92093-0603. Dr. Kremen can be contacted at wkremen@ucsd.edu.

3.4 Results

3.4.1 Results for Heritability Estimates

The heritability of BP is generally suggested to be around 41 to 82% for SBP and 51 to 66% for DBP[29]. The heritability values calculated for each correction are in **Table 10.**

Rmz and rdz are components to calculate heritability and are calculated for both SBP and DBP. In the top section of **Table 10**, rmz is the correlation of SBP in monozygotic twins, while rdz is the correlation of SBP in dizygotic twins. Heritability is the Falconer's estimate of heritability found for each correction. The rmz and rdz increase, and the heritability h^2 decreases for each correction. The bottom section lists the values of rmz and rdz for DBP. The correlations between DBP in monozygotic/dizygotic twins are then calculated to yield h^2.

Table 10: Heritability calculated for SBP/DBP for each correction

Blood Pressure	rmz	rdz	h^2
Average BP SBP	.425	.209	.432
Fixed Addition SBP	.497	.289	.416
Stepped Addition SBP	.524	.331	.386
Adjustment by Drug Class SBP	.560	.368	.384
Average BP DBP	.431	.209	.444
Fixed Addition DBP	.481	.276	.41
Stepped Addition DBP	.508	.340	.336
Adjustment by Drug Class DBP	.537	.371	.332

The heritability estimates decrease away from the non-adjusted values of heritability with each correction. More specifically, the heritability of SBP decreases

from 43% to 38%, and the heritability estimates for DBP decrease from 44% to 33%. The heritability for *Correction By Drug Class* is .384, which indicates that 38.4% of the variability in SBP is due to genetics. This is not significantly different from the non-corrected SBP (Average SBP) heritability of 43.2%. In the DBP corrections, the h^2 also drops from 44.4% in the non-corrected BP to 33.2% in the *Correction by Drug Class*.

Significance of heritability was calculated using *MZ* with a more precise formula for heritability. The heritability estimates were found to not statistically differ. Therefore, although the heritability estimates do decrease, the statistics indicate that no real decrease exists because none are significantly different.

3.4.2 Results from BMI Calculations

For each correction, I calculated the correlation between BMI and SBP and the correlation between BMI and DBP. The results and statistical significance are displayed in **Table 11**. A two-tailed t-test was used to calculate significance, providing a $p < 0.01$ for the *Correction by Drug Class*.

Table 11: Correlation between BMI and SBP/DBP for each adjustment. Significance values are also noted

Blood Pressure	Change to the Blood Pressure	Correlation of Systolic with BMI	Correlation of Diastolic with BMI
Average BP Measurement	0	.169	.209
Fixed Addition	+10/5mmHg	.231 (p=.0548)	.260 (p = .0901)
Stepped Addition	+ 8/4 -1 DC +16/10 -2 DC +20/14 -3 DC	.246 (p=.0228)	.286 (p=.0207)
Adjustment by Drug Class	See explanation above	.272 (p=.0036)	.314 (p=.0026)

The correlation between BMI and SBP without any corrections, .17, was significantly lower than the correlation between BMI and DBP, .21. All the corrections significantly increased these correlations. The *Correction By Drug Class* resulted in the highest correlations, as the correlation between BMI and SBP increased to .27, while the correlation between BMI and DBP increased to .31.

3.5 Discussion

3.5.1 Corrections and BP Heritability

It was hypothesized that heritability estimates would increase with BP corrections. Contrary to this prediction, BP corrections decreased heritability non-significantly. Thus, it can be concluded that in our population, BP corrections did not affect heritability. More specifically, the amount that BP medications lower BP does not significantly affect heritability in this population.

Why Heritability Estimates Did not Increase with Corrected BP Values

A plausible explanation is that heritability is lower for BP than previously understood. A lower heritability implies that the trait is more impacted by environmental factors (such as stress, diet, etc.) relative to genetic factors. The heritability estimates obtained would then improve the accuracy of genetic analyses of hypertension.

Conversely, another explanation could be that BP corrections are simply unnecessary. This could only be justified by further research and data analysis.

It is important to note that the correlations rmz and rdz increased for each correction. This supports the hypothesis that corrections improve the correlation of BP between twins.

Why Results Were Non-Significant

The first serious consideration is that the effect being measured simply does not exist. In that case, our results would support DeStefano et al.'s[31] idea that antihypertensive medications do not have a significant effect on heritability.

Nonetheless, two studies are not sufficient evidence that there is not an effect.

It is also possible that there really is some effect, but that the study was inadequately powered to detect it reliably, prompting a Type II error. A large number of subjects provide power to detect a real effect, but the magnitude of the effect of interest also significantly affects power. The power with 1237 subjects to detect any large effect will be close to 1; however, the power decreases since only a small effect is being detected.

Another explanation could be the lack of precision in measurements. Noisy measures of BP and medication can substantially affect the power of a hypothesis test. Perhaps knowing the dosages of medications, in addition to the medications, would be beneficial. Also, perhaps more accurate measurements of BP would improve significance. For example, averaging 10 measurements of BP over a few weeks would provide a more precise measure of each person's true BP.

The results could also suggest that a more refined correction may be needed to produce significant results. This theory would not agree with Cui's findings[20] who found that both *fixed* and *stepped addition* increased heritability significantly.

3.5.2 Corrections and BP correlation with BMI

According to various studies, there is a modest correlation between BP and BMI[17]. **Table 11** above shows that the correlations with BMI significantly increase with the various corrections from .169 to .272 in the SBP and from .209 to .314 in DBP. These agree with the accepted theory that individuals with higher BMI have a greater likelihood of having a higher BP[17]. They also support my prediction that the corrections would increase the correlation of SBP and DBP with BMI.

There are several reasons why BMI could cause hypertension. The most reasonable explanation is that the excess adipose tissue secretes substances that the kidneys then act upon, resulting in hypertension[32]. Obesity also tends to produce higher amounts of insulin. Excess insulin also elevates blood pressure[32]. As evident, BMI is a risk factor for high BP, and so it is a good measure to compare BP corrections.

Correction By Drug Class most significantly impacted correlations between BP and BMI. This certainly could be valid, considering that this correction accounts for ethnicity, diuretic effects, drug class and specific effects of the 2nd drug. Therefore, the more refined the corrections are the better the correlations were with a known correlated trait.

3.5.3 Conclusions

The corrections for antihypertensive medication did not affect heritability estimates in this population. However, the model *Correction By Drug Class* did increase the correlations between the BP of both monozygotic and dizygotic twins. Also, correlations with BMI were most impacted by the *Correction by Drug Class* model. Therefore, we recommend the *Correction By Drug Class* model for future BP corrections.

3.5.4 Future Work

Some suggestions for future work include the following:

- An additional BP correction based on a literature search of specific BP drug classes.
- A multivariate regression to predict BP from health-related variables that would suggest the specific effects of a BP drug class.
- This same study but including the effects of fish oil, which has been found to lower BP 4.4/3.2 mmHg[28].

Chapter 4

Prevalence of Hypertension, BMI, and Prescribed BP Medication Distribution by U.S. Regions

4.1 Introduction

A number of different environmental factors have been identified as risk factors for hypertension. These include (1) geographic residence, (2) high BMI, and (3) a stressful lifestyle[34, 35, 36, 37]. In order to explore the relationship of BP in the VETSA cohort with risk factors for hypertension, I examined BP distribution in different regions of the U.S. I partitioned the U.S. into regions according to stress index, election maps and geography.

Several geographic studies have confirmed that Southern United States has a greater prevalence of hypertension[34]. High BMI (BMI 25-100) has also been associated with hypertension[35], and is most prevalent in the Southern and Southeastern regions of the US [36]. Stress has also been found to be associated with increases in BP, although it has not yet been identified as a direct cause of hypertension[37]**.** Moriarty et al. (2009) also noted that stress levels are highest in the South and lowest in the Midwest regions of the United States[38]. They classified stress by the prevalence of frequent mental distress (FMD) within states. FMD is defined as having at least 13 mentally distressed days during the previous 30 days and was measured over a span of 12 years. This is the stress level measurement I used to partition the US.

No report exists on the distribution of BP medications across geographic regions. In addition, no studies have addressed a relationship between political classification and hypertension prevalence.

The purpose of the present study is to explore a relationship between the geographic subdivision that the study participant lives in and BP. This will provide insight into how environmental factors, such as (1) geography (2) political

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classification of their state of residence and (3) stress levels, relate to the prevalence of hypertension, BMI and prescribed medications. VETSA's comprehensive data set allowed us to statistically analyze the following questions: Will the prevalence of hypertension, BMI, and prescribed BP medications differ among geographic regions across the United States? Political regions? States with varying levels of stress?

There were 3 a priori predictions made prior to statistical analysis. It is predicted that (1) the prevalence of hypertension will be greater in Southern regions, Red (Republican) States (because most Red states are in the South) and stressed states, (2) BMI will be greatest in Southern Regions, Red States and Stressed states and (3) the BP medications will remain relatively constant in all regions of the United States because no differences in prescription have yet been found.

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4.2 Methods

4.2.1 Preparation

Five variables were extracted from the VETSA database for each individual: (1) Presence or absence of hypertension (2) BP drug classes (3) the non-BP medications that individual was taking, (4) state of residence and (5) BMI.

4.2.2 Geographic Divisions of the US

The United States was partitioned in 3 different ways: (1) geographically, (2) election map and (3) by stress levels. These various separations will be called "divisions." Thus, there are three divisions: a geographical division, political division, and a stress division.

Each division is separated into several regions. These divisions are explained in more detail below. Geographical division was partitioned into West, South, Midwest, East Coast and Southeast regions. Political division was partitioned into Red states, Purple states and Blue states[39]. In the stress division, the regions were separated using a stress map from Moriarty et al.[38] into stressed and less-stressed states. Stressed States were experiencing frequent mental distress in 14 of the past 30 days over a span of 12 years.

Geographic Division

The U.S. was separated into 5 different geographic regions based on geographic location: West, South, Midwest, East Coast, and Southeast. **Table 12** displays the states included in each of these geographic regions.

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Table 12: The states in the various geographic regions

Region	States Included
Region 1 -West	California
Region 2 -South	Texas
Region 3-Midwest	Ohio, Minnesota, Illinois, Wisconsin, Indiana
Region 4-East Coast	Pennsylvania, New York
Region 5-Southeast	Florida

The individuals in these states were then isolated to their respective region (e.g. all Californians in the data set were grouped as Region 1). Analyses were then done on these regions, as detailed later.

Region 5 only contained Florida because Florida is commonly perceived as a low-stress environment. We wanted to determine whether the results of Florida's low-stress environment differed from other geographic regions.

Political Division

Political affiliations of the study participants were not recorded for individuals in our study. The states were instead classified into Red States (Republican), Purple States (Swing) and Blue States (Democratic) by compiling the average margins of victory in the five presidential elections between 1992 and 2008[39]. **Table 13** lists the states that were included in each region.

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Table 13: The states included in the various political regions

Region	States Included
Red States	AK, AL, AZ, GA, ID, IN, KS, KY, LA, MS, MT, NC, ND, NE, OK, SC, SD, TN, TX, UT, VA, WY
Purple States	AR, CO, FL, MO, NV, OH, WV
Blue States	CA, CT, DE, HI, IA, IL, MA, MD, ME, MI, MN, NH, NJ, NM, NY, OR, PA, RI, VT, WA, WI

Study participants were categorized within the Red, Purple, Blue States solely based on their state of residence.

Stress Level Division

A stress map[6] was used to identify 2 regions: (1) "stressed" states and (2)"less-stressed" states**.** The table below lists the states classified in each of these regions. **Figure 5** is the map that highlights geographic patterns of mental distress. **Table 14** is a list of the states classified in each region.

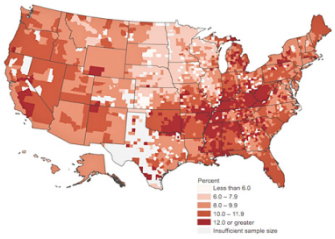

Figure 5: A visual depiction of the stress division. Darker colors = regions of high stress; lighter colors = regions of lower stress

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Table 14: The states classified as stressed and less-stressed states

Region	States Included
Stressed States	KY, MS, AR, TN, MO, AL, WV
Not Stressed States	WI, NE, IA, HI, MN, TX

The individuals in these states were separated into lower or higher stressed regions for later analyses.

4.2.3 Analyses: Comparing Four Factors Within Each Region

Prevalence of Hypertension

Hypertension prevalence was calculated using the number of subjects that responded "Hypertensive," "Prehypertensive," or "Neither." For each region, the number of individuals that responded "hypertensive" was divided by the total number of individuals in that region. The equation is below:

$$\frac{\text{\# Of individuals that are hypertensive}}{\text{Total \# of individuals in that regions}}$$

The result was converted into a percentage and labeled as "prevalence of hypertension" for that particular region. Analysis was also done on those categorized as prehypertensive (>130/85 mmHg) in the same way—the number of individuals that responded "prehypertensive" was divided by the total number of individuals in that region.

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BP Drug Class

The next method discusses the issue of BP drug distribution across the US. The most common BP drug classes in each geographic region were compared and discrepancies were noted.

For these calculations, the number of BP drugs in a specific BP Drug Class was first tallied. This number was then divided by the total number of BP drugs in that region. The equation is below:

$$\frac{\text{\# Of individuals on a specific BP Drug Class}}{\text{Total \# of BP drugs in that region}}$$

For example, 21 subjects were taking ACE-inhibitor BP Drugs in Geographic Division Region 1 (CA). There were a total of 61 BP drugs in that region. Therefore, 32.31% of the BP drugs in that region were of the ACE-Inhibitor drug class.

Most common medications

I discovered the 4 most common medications of all the subjects in each region. These top 4 medications were compared in each division with a code.

BMI Data

VETSA had recorded the BMI for each subject. The average BMI of all the individuals in a particular region was then compared with the average BMI of all other regions.

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Analysis

Each region will have a set of the 4 factors above: Hypertension Prevalence, most common BP Drug Classes, most common medications and BMI data. These 4 factors are compared with all the other regions in its division.

A summary of the Ch. 4 method is shown in **Figure 6**.

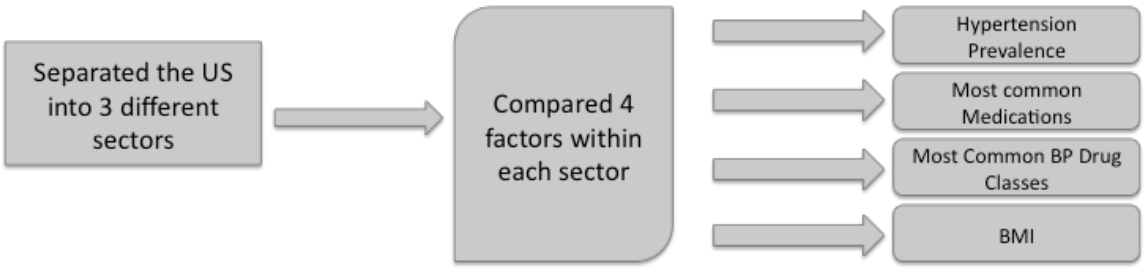

Figure 6: Summary of the methods of Chapter 3

4.3 Materials

Microsoft Excel was used to isolate the variables and manipulate the data for statistical analysis. SPSSStatistics 17.0 was used to analyze the data and determine if there were any significant results.

Dr. James Nieh of University of California, San Diego, Department of Biology suggested the stress overlay study[38]. CDC tracked self-perceived mental stress through the Behavioral Risk Factor Surveillance System (BRFSS) during 1993-2006 to determine geographic patterns of mental stress.

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The VETSA data were partially compiled by Dr. Kremen's team at the University of California, San Diego, Department of Psychiatry at 9500 Gilman Dr., La Jolla, CA 92093-0603. Dr. Kremen can be contacted at wkremen@ucsd.edu.

4.4 Results: Difference in Hypertension Prevalence, BP Meds, Medications and BMI within divisions.

Hypertension prevalence, BP drug classes, most common medications and BMI were compared within the regions of each division. The results below are separated by division. Only significant results are listed.

4.4.1 Geographic Division

There were 5 regions in the geographic division. **Table 15a** below lists the various regions and the percentage of those prehypertensive and hypertensive in the respective region. The final column (>130/85) includes subjects that are hypertensive or prehypertensive.

About 82% of the subjects from Region 4 – EC (East Coast) are prehypertensive or hypertensive, significantly greater than any other region.

Table 15a: The prevalence of hypertension in geographic regions across the US. Prehypertension (130/85) prevalence is also noted.

Region	# of subjects	High Blood Pressure (>140/90)	>130/85
Region 1 -CA	125	55.20%	68.00%
Region 2 -TX	66	**63.64%**	74.24%
Region 3-MW	293	53.58%	74.40%
Region 4-EC	93	59.14%	**81.72%**
Region 5-FL	54	53.70%	68.52%

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Additional results from the geographic division are presented in **Table 15b**. Participants in Region 2- TX (South) were prescribed the ace and thiazide (ace+td) "combo drug" significantly more often (10.81%) than participants in any other region.

Table 15b: The popularity of particular drug classes across geographic regions of the US. Significant differences are bolded.

Class	Region 1	Region 2	Region 3	Region 4	Region 5
# of BP meds	65	37	132	29	25
beta	24.62%	24.32%	31.82%	31.03%	24.0%
ace	32.31%	29.73%	28.03%	31.03%	44.0%
Ace + thiazide	1.54%	**10.81%**	0.76%	0%	0%
diuretics	16.92%	8.11%	12.88%	12.0%	12.0%
CCBs	16.92%	10.81%	12.88%	10.34%	12.0%

4.4.2 Political Division

In the political division, **Table 16** shows that subjects from Red states (Republicans) were more likely (60%) to have hypertension than those from Blue states (53.1%) or Purple states (55.1%). This difference in hypertension prevalence was the only significant result in the political division.

Table 16: The prevalence of hypertension in political regions

Region	# of subjects	High Blood Pressure (>140/90)	>130/85
Red States	380	60.0%	74.7%
Blue States	625	53.1%	72.3%
Purple States	198	55.1%	73.2%

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Interestingly, the purple states had results between those of the Red and Blue States.

4.4.3 Stressed vs. Less-Stressed States

There was a significant difference in the prevalence of hypertension between stressed and less-stressed states. In stressed states, 57.4% of the subjects had HBP, while only 40.6% of the people in less-stressed states had HBP.

There is a large disparity between the proportion of individuals with a BP>130/85. 76.5% of the individuals in stressed states were prehypertensive or hypertensive, in comparison to only 54% of the individuals in less-stressed states. More participants were also on Insulin in stressed states than less-stressed states.

Table 17: The prevalence of hypertension in different stress levels across the US. Prehypertension (130/85) prevalence is also noted.

Region	States Included	# of subjects	High Blood Pressure (>140/90)	>130/85
Stressed States	KY, MS, AR, TN, MO, AL, WV	115	57.4%	76.5%
Not Stressed States	WI, NE, IA, HI, MN, TX	128	40.6%	53.9%

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4.4.4 Less pertinent results:

- Region 1, Region 4 and Blue States had a greater number of participants on *Atenolol* as Beta-blocker
- Region 3, Red States, and Purple States had a greater number of participants on *Lepressor* as Beta-Blocker
- Region 2 has a significantly greater number of subjects on *Glucophage* for Diabetes
- Region 4 has a significantly greater number of subjects on *Desyrel* for Depression

4.5 Discussion

The aim of this chapter was to explore the relationship of environmental factors, specifically geography, political affiliation and stress, to the prevalence of hypertension, BMI, and drug distribution. Tests were done on a geographical division, political division and stress level division of the United States. We will discuss each division separately.

4.5.1 Geographical Division

Prevalence of hypertension

Studies have found that the prevalence of hypertension is highest in the South and Southeast geographic regions of the United States[34]. Conversely, Gillum et al (2004)[40] argues that prevalence of hypertension does not significantly vary within

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geographic regions for larger studies. I aimed to resolve this conflict and confirm which claim is true.

About 64% of subjects from the Southern region (Region 2) are classified as hypertensive—a larger proportion than any other geographic region. However, this result and all other differences were found to be non-significant. Therefore, the VETSA data validates the study by Gillum et al (2004) [40] that no geographic region has a significantly higher prevalence of hypertension than others.

The results could be non-significant for several reasons. First, only a few participants from Texas were included in the Southern geographic region. To obtain more accurate results, all Southern States should be included in a cohort that is a more faithful representation of the demographics. Further studies of region and hypertension incidence are needed to verify this relationship.

Current research on the relationship between prehypertension and geographic regions is limited. In our study, 82% of the subjects from East Coast are prehypertensive, significantly greater than any other region, possibly indicating that the East Coast has a greater risk of hypertension. Future research should focus on the prehypertensive population to perhaps provide some insight on causes and factors of hypertension.

BP Drugs Prescribed

No research to our knowledge compares the distribution of antihypertensive medications across the United States. The VETSA data were arranged to note any difference in the prescription of BP medication across the United States.

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More participants in Texas took a combo drug of ace+td in comparison to other regions. California and the East Coast favored *Atenolol* as Beta-blocker, while the Midwest preferred *Lepressor* as their Beta-Blocker. Apart from those, the results were fairly non-signficant and constant—consistent with the prediction that BP medication prescription is relatively constant throughout the United States.

Medications Prescribed

Although BP medications remained constant, some discrepancy was found among the most common medications in each region. Texas had a significantly greater number of people on *Glucophage* (diabetes), while the East Coast had a significantly greater number of people on *Desyrel* (depression). This knowledge provides unique insight into the distribution of medication that afflict a particular region.

BMI

No significant differences in BMI were found across the geographic regions, clashing with studies[35] that show that most Southern States suffer from above-average BMIs. This disparity likely exists because our Southern population only consisted of subjects from Texas.

Conclusions

According to our data, geography is not significantly related to hypertension or BMI, but is linked with prehypertension and the distribution of certain medications. There were significantly more people with BP> 130/85 on the East Coast. Texas had

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significantly more participants taking Glucophage (diabetes), while the East Coast had significantly more participants on Desyrel (depression).

Suggestions for Future work

Future studies should aim to improve accuracy of conclusions and test efficiency of these methods. This implies including more subjects in each region and obtaining data from a more representative cohort.

4.5.2 Political Division

Hypertension Prevalence

No studies to our knowledge have investigated the relationship between political affiliation and hypertension prevalence. VETSA data was analyzed to explore this possible association. Political allegiances of the subjects were not recorded; instead, the states were classified into Red States (Republican), Purple States (Swing) and Blue States (Democratic).

Significantly more subjects in Republican states had hypertension than subjects in Democratic or swing states, possibly because (1) many Republican States are Southern States, and (2) Republicans, on average, are older[41], a proven risk factor for hypertension. No significant prehypertensive differences were observed.

BP drugs prescribed, medications prescribed and BMI

BP Drugs were fairly constant among the political division; however, participants in Blue States more commonly used *Atenolol* as Beta-blocker, while

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participants in Red and Purple states more commonly used *Lepressor* as Beta-Blocker. BMI and the medications prescribed were also fairly constant across all political divisions.

Conclusion

Political affiliation is not significantly related to prehypertension, medication distribution or BMI, but is linked with hypertension. Republican States have a significantly higher prevalence of hypertension than both Democratic and Swing States.

Suggestions for future work

Since research is limited, there is much potential for development and expansion. Future studies should examine a subject's political allegiances rather than state classification. Another possibility is a psychological study that examines the association between certain strongly held beliefs and hypertension.

4.5.3 Stress Level Division

Hypertension Prevalence

An unclear link exists between stress and hypertension[37]. Our data strengthens this link—57% of VETSA participants in stressed states have hypertension, compared to only 40.6% in less-stressed states; 76.5% of participants in stressed states suffer from prehypertension or hypertension, compared to only 54% of participants in less-

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stressed states. An association is known to exist, but these drastic differences should encourage researchers to investigate this topic even further.

BP Drugs Prescribed, medications prescribed and BMI

The BP Drugs prescribed and BMI were relatively constant between stressed and less-stressed states. Insulin, a medication generally prescribed for diabetes, was much more commonly prescribed in stressed states. This confirms the common association between stress and diabetes[42].

Conclusions

Stress is significantly related to hypertension and insuilin distribution. Subjects in stressed states both had a higher prevalence of hypertension and were prescribed insulin for diabetes more often. These conclusions support former studies on the link between stress and (1) hypertension and (2) diabetes, respectively. No significant relationship was found between stress and BMI.

Suggestions for Future Work

Using the subjects' stress levels, rather than a stress map, would provide more accurate conclusions. Also, a clinical trial following prehypertensive and hypertensive patients as they experience a stress relief course (e.g. Mindfulness-Based Stress Reduction) could help us understand the role of stress in hypertension.

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4.5.4 Summary of Conclusions

The objective was to explore how three environmental factors relate to hypertension, prehypertension, BMI and distribution of medications.

- Geography is not related to hypertension or BMI, but is linked with prehypertension and the distribution of Desyrel, Glucophage and ace+td combo drug
- Political Affiliation is *possibly* associated with hypertension.
- Stress is significantly related to hypertension and distribution of Insulin.

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