



RUTGERS

**Hypercalcemia and Its Effects on the Cardiovascular Diseases-A Retrospective
Analysis**

By

Riaz Basha Shaik

**A Dissertation Submitted to Faculty of the School of Health Related
Professionals, Rutgers State University of New Jersey in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy in Biomedical Informatics**



**DEPARTMENT OF HEALTH INFORMATICS
SPRING 2016**

APPROVAL PAGE

**HYPERCALCEMIA AND ITS EFFECTS ON THE CARDIOVASCULAR
DISEASES-A RETROSPECTIVE ANALYSIS**

**BY
RIAZ BASHA SHAIK**

Dissertation Committee:

Syed Haque, Ph.D., Ph.D. Committee Chair

Dinesh Mittal, Ph.D., Committee Member

Shankar Srinivasan, Ph.D., Committee Member

Fredrick D. Coffman, Ph.D., Committee Chair

Approved by the Dissertation Committee:

_____ Date:

_____ Date:

_____ Date:

_____ Date:

ABSTRACT

Recent increase in health awareness has led to substantial increase in dietary Calcium intake and supplements. Americans spend more than \$1 billion a year on calcium supplements in hopes of staying off Osteoporosis". Osteoporosis has been common in elderly women and men.

There is the increase need to find if increase intake of calcium is doing more harm than good. The study objective is to determine the incidence of Hypercalcemia and its relation to calcium rich diet based on gender, race, ethnicity and socioeconomic status. All patients with serum calcium ≥ 14 mg/dl (≥ 3.5 mmol/l) are considered Hypercalcemia patients. Pathological role of calcium in calcification of the arteries increase the emphasis to find if it accentuates the process with its increase in availability. In this research, we plan to do a Retrospective analysis of Hypercalcemic patients and its association with cardiovascular diseases like Hypertension, Myocardial Infarction, Coronary Artery Occlusion, Coronary artery atherosclerosis and Stroke and overall mortality.

NIS 2006 -2102 data and NHANES 2006- 2010 data used for analysis. SAS (version 9.4, SAS Institute) has been used to calculate utilization and mean of calcium intake from both diet and supplements. Tabulating it independently based on gender, race and ethnicity and socioeconomic status.

Descriptive analysis and Linear regression used to determine an association of Hypercalcemia and Cardiovascular diseases, and if any increase in mortality during the Years. Non-Hispanic white used more supplemental calcium in comparison to Hispanic and African American population. 28% of men and 38% of women used throughout the recent study. Study of regression analysis has to be carried out for Association of

hypercalcemia and CVD. Results showed no significant association between the two and found an association with Diabetes Mellitus.

The study emphasized areas that can be directed for designing health intervention plans that will be targeted to particular subgroups of the American population

Dedicated

To

My inspiring parents, my brother, sisters,

And my nephews and Nieces

*For being the pillows of comfort, role models for motivation,
launching pad for success, cheerleading squad and sounding
boards forever ending happiness , joy and love I needed .*

***"Say: Come. I will recite unto you that which you're Lord has made a sacred duty for
you; that you ascribe nothing as partner unto Him and that you do good to parents..."***

(Quran 6:151)

Acknowledgement

My journey in obtaining my Ph.D. has been eventful. This thesis has been kept on track and been seen through to completion with the support and encouragement of numerous people including my well-wishers, my friends, colleagues and various institutions. At the end of my thesis I would like to thank all those people who made this thesis possible and an unforgettable experience for me. At the end of my thesis, it is a pleasant task to express my thanks to all those who contributed in many ways to the success of this study and made it an unforgettable experience for me.

Firstly, I would like to express my sincere gratitude to my advisor Prof. Syed Haque and Prof. Shankar Srinivasan for the continuous support of my Ph.D. study and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my Ph.D. study. This would not be possible without your support and assistance. Special Thanks to Dr. Shankar being my mentor and bearing with me and pushing me forward to achieve my goals.

Besides my advisor, I would like to thank the rest of my thesis committee: Prof. Dinesh Mittal, Prof. Fredrick D. Coffman, Ph.D., Prof. Shibata. For their insightful comments and encouragement, but also for the hard question which incited me to widen my research from various perspectives.

I owe a great deal of appreciation and gratitude to all my **friends and well-wishers** who have supported me during this phase of my life and I am indebted to Allah for giving such beautiful people in my life. Things would not have been smooth sailing.

Last but not the least, I would like to thank my family: my parents and to my brothers and sister for supporting me spiritually throughout writing this thesis and my life and for their never ending love and support.

Table of Contents

ABSTRACT.....	iii
DEDICATION	v
ACKNOWLEDGEMENTS.....	vi
Table of Contents	viii
List of Tables	ix
List of Figures	xii
CHAPTER 1	1
INTRODUCTION	1
1.1 Statement of the Problem.....	1
1.2 Nature of the Study	5
1.2.1 Assumptions.....	6
1.2.2 Significance of the Study	6
1.2.3 Goals and Objectives	7
1.3 Hypothesis	9
CHAPTER 2	19
LITERATURE REVIEW	19
2.1 Literature Search Strategies	19
2.2 Calcium Distribution	20
2.3 Calcium Homeostasis	22
2.3.1 Parathyroid hormone (PTH)	22
2.3.2 Vitamin D	25
2.4 Pathophysiology of Calcium	27
2.4.1 Mechanisms Of Arterial Calcification	27
2.4.2 Clinical Impact Of Arterial Calcifications	29
2.4.3 Calcium And Heart Failure	33
2.4.4 Calcium And Cardiac Hypertrophy	33
2.5 HYPERCALCEMIA	34
2.5.1 Symptoms.....	37
2.5.2 Incidence Of Hypercalcemia	40
2.5.3 Treatment.....	44

2.5.4 Prevention.....	45
2.6 PREVALENCE AND BURDEN OF CVD IN THE UNITED STATES	46
2.6.1 Incidence and Mortality	46
2.6.2 Traditional Risk Factors and Common Pathologic Mechanisms for CVD	47
2.6.3 Heart Disease facts on mortality and morbidity	51
2.6.4 Death by ethnicity	52
2.7 OBSERVATIONAL STUDY	53
CHAPTER 3	57
METHODOLOGY	57
3.1 Research Design	57
3.1.1 NIS and NHANES Data Set and Data Elements	58
3.1.2 Study Group/ Inclusion/ Exclusion Criteria	60
3.2 Disease and Procedures Coding for NIS and NHANES data	61
3.3 Data Collection Methods	63
3.3.1 Statistical Analysis and Data Cleaning	67
3.4 Modeling Techniques Overview	67
3.5 Descriptive statistics	67
3.6 Inferential statistics	68
3.7 Cox Proportional Hazards Regression	69
3.8 C-Statistic	70
3.9 Linear Regression	70
3.10 Kolmogoro Smirnov Test	71
3.11 Logistic Regression	71
3.12 Alternative Analysis Methods	71
3.13 Special Notes on Using the Dataset	73
CHAPTER 4	74
RESULTS	74
4.1 Descriptive analysis of NHANES data	74
4.1.1 Calcium Intake and it's a significant effect on Blood Pressure based on Gender and Race	77

4.1.2 Incidence of Hypertension from year 2005- 2103	80
4.2 Distribution of Hypercalcemia cases based on age from year 2006 -2012	80
4.3 Distribution of Hypercalcemia cases based on the Race	84
4.4 Hypercalcemia Distribution by Gender	91
4.5 Logistic Regression of Hypercalcemia CVD.....	97
CHAPTER 5	106
DISCUSSIONS AND LIMITATIONS	106
5.1 DISCUSSIONS	106
5.2 LIMITATIONS	114
CHAPTER 6	116
SUMMARY AND CONCLUSIONS	116
6.1 FUTURE STUDIES	114
REFERENCES	121

LIST OF TABLES

Table 1: Number of High Blood Pressure Mortality cases by Gender and Race	24
Table 2: Calcium Intake Trends by Age and Gender Groups over 5 NHANES Cycles.....	25
Table 3: Demographic Variables and Sample Weight	56
Table 4: The variables obtained from the dietary data file	58
Table 5: The variables obtained from the total nutrients data file.....	59
Table 6: The variables obtained from the examination data file	60
Table 7: The variable obtained from the laboratory data file	61
Table 8: Classification of the variables used in the analysis	64
Table 9: Means of the Variables NHANES 2005-2012	68
Table 10: Weighted Demographics Characteristics persons 20years and older	74
Table 11: Collinearity Check for Continues Variables	75
Table 12: Cross tabulations of Calcium Consumption and Blood Pressure using NHANES data 2005-2012	82
Table 13: Results of Chi-Square test for the association between Races Calcium Intake and Blood Pressure NHANES 2005-2012	88
Table14: Regression of Calcium and Race from Blood Pressure	89
Table 15: Cross tabulations of Education and Calcium Consumption NHANES data 2005-2012	93
Table 16: Education by Blood Pressure NHANES 2005-2012	94
Table 17: The Effects of Education and Calcium on Blood Pressure 2005-2012	95
Table 18: House Hold Income by Blood Pressure.....	97
Table 19: Cross tabulations of Household Income and Blood Pressure Consumption NHANES data 2005-2012	98
Table20: Effect of Calcium on Blood Pressure Controlling for Income on NHANES 2005-2012.....	99
Table 21: Cross tabulations of Sex and Blood Pressure Consumption NHANES	100

Table 22: Cross tabulations of Sex and Calcium Intake Consumption NHANES data 2005-2012.....	100
Table 23: Significance of Gender/Sex and Calcium on Blood Pressure NHANE 2005-2012	101
Table 24: Cross tabulations of BMI and Blood Pressure NHANES data 2005-012.....	103
Table 25: Cross tabulations of BMI and Calcium Intake Consumption NHANES data 2005-2012	104
Table 27: The Effect of Body Mass Index and Calcium on Blood Pressure	105
Table 28: Significance of Age and Calcium on Blood Pressure NHANES 2005-2012.....	107
Table 29 Systolic Isolated Blood Pressure by Gender	109
Table 30: Systolic Isolated Blood Pressure by Age	109
Table 31: Cross tabulations of Isolated Blood Pressure by Calcium intake.....	109
Table 32: Risk Estimate for Significant Independent Variables Using Logistic Regression	110
Table 33: Test for Association of the Categorical Variables to the Dependent Variable	115
Table 34: Risk Estimate for Significant Independent Variables Using Logistic Regression	115

LIST OF FIGURES

Figure 1: How the body regulates blood pressure	22
Figure 2: The cluster of co-morbidities associated with and aggravated by obesity.....	27
Figure 3: A flow chart showing the link between daily calcium, blood pressure	29
Figure 4: The paleolithic diet vs modern diet	32
Figure 5: The Mean Dietary Calcium Intake among U.S. Men and Women Ages 18-74 years – NHANES 1971-2010	34
Figure 6: The Amount of Calcium Contained in a Ham Sandwich.....	35
Figure 7: Global Calcium Consumption	38
Figure 8: Break down of the data used in the study	51
Figure 9: Distribution of blood pressure by Gender/sex NHANES 2005-2012	79
Figure 10: Distribution of Calcium Consumption by Sex NHANES 2005-2012	80
Figure 11: Calcium Intake and Blood Pressure NHANES 2005-2012	83
Figure 12: Calcium intake and Blood Pressure NHANES 2005-2012	85
Figure 13: The effect of calcium on Blood Pressure NHANES 2005-2012	86
Figure 14: Effects of Calcium by Blood Pressure Controlling for Race NHANES 2005-2012	87
Figure 15: Calcium Consumption, Education by Blood Pressure	96
Figure 16: Subgroup Analysis of Calcium Intake, Blood Pressure by Household Income NHANES 2005-2012	98
Figure 17: Analysis of Calcium Intake Blood Pressure by Sex/Gender NHANES 2005-2012	101

Figure 18: Analysis of Calcium Intake, Blood Pressure by BMI NHANES 2005-2014	103
Figure 19: Comparing Calcium Intake by Blood Pressure in Age 20 and Older NHANES 2005-2012	106
Figure 20: Analysis of Systolic Isolated Blood Pressure by Gender by Age	110
Figure 21: Distribution of Blood pressure by Calcium	111
Figure 22: Distribution of Blood pressure by Race	112
Figure 23: Distribution of Blood pressure by Education	112
Figure 24: Distribution of Blood pressure by Income	113
Figure 25: Distribution of Blood pressure by Gender	113
Figure 26: Distribution of Blood pressure by BMI	114
Figure 27: Distribution of Blood pressure by Age	114
Figure 28: Prevalence of Blood Pressure NHANES 2005-2015 Ages 20 Years and Older	117
Figure 29: Incidence of Blood Pressure among Adults Ages 20 and Older NHANES 2005 2014	118

CHAPTER 1

INTRODUCTION

1.1 Statement of the Problem

Americans consumers spent more than \$21 billion on Vitamins and herbal supplements in 2105 in hopes of staying off osteoporosis, the brittle bone disease that cripples many elderly women and some men. Scott, C. (2015). Americans are wasting billions of dollars every year on health supplements that don't even work.

According to the Council for Responsible Nutrition the U.S. dietary-supplement market totals about \$28 billion, ^[1]7.8% increase in general US Retail Sales of Vitamins and dietary supplements to \$2.476 billion. 70% of grown-ups in the United States with Internet access utilize the Web to search out wellbeing and health data, as per the Pew Research Center, 42% of adults age 20 and more established used a supplement as a part of the previous month as indicated by NHANES

Recently all around the world, a calcium and Vitamin D supplementation a micronutrient intake have been overemphasized because of its proposed advantage on bone health. The calcium supplementation has turned out to be over utilized, specifically among the elderly. A study reported more than 50% of men around 70% of women above 50 years in the USA use some the other supplemental calcium ^[2] as dairy products are not palatable to older people. In recent decades, calcium intake to prevent postmenopausal osteoporosis and maintain serum phosphate levels use have been increased quite

drastically Already known that excessive consumption leads to renal calculi and gastrointestinal symptoms including cardiovascular health. This potential risk remains obscure and has turned out to be progressively growing^[2-3]Excess calcium intake causes Hypercalcemic emergency is an uncommon life-undermining condition auxiliary to decompensated hypercalcemia prompting renal disorders and altered mental status. The dominant part of cases are brought on by primary hyperparathyroidism ^[1]. Extreme hypercalcemia clinical not known till the serum calcium level is above 15 mg/dL (3.74 mmol/L), which might present with manifestations of stubborn sickness, retching and obstruction, lethargy, and unconsciousness, electrocardiographic (ECG) finding of abbreviated QTc interim and additionally sudden heart failure. Hyperparathyroidism and hypercalcemia due to malignancy cause are known for the hypercalcemic crisis are more clinical prevalent and diagnosed. Hypercalcemia caused due to excessive use of calcium and vitamin D supplements third most typical reason for hospital admissions for hypercalcemia ^[2-3].However, there are increasing concern about the potential adverse effects of excessive dietary calcium intake and calcium and Vitamin D supplementation on cardiovascular health.

Hypercalcemia had been depicted dominatingly in men as a metabolic disorder coming about because of over-enthusiastic treatment of peptic ulcer infection (PUD) with calcium-containing antacids agents and milk in the mid-twentieth century ^[6]. The commonness of the condition declined gradually after the advent of histamine blockers

and proton-pump inhibitors for the treatment of PUD, and as of late the disorder has been principally reported in more established people getting treatment for osteoporosis ^[2, 3, 4]. As the name no more shows the etiology of the confusion, the milk-alkali base disorder has been renamed 'calcium-antacid disorder' ^[3]. We report an uncommon instance of Hypercalcemic emergency in an elderly male coming about because of ingestion of calcium supplements mirroring the calcium-alkali base disorder ^[3].

Epidemiological studies have reliably reported an inverse relationship between dietary calcium intake and the danger of Blood Pressure, Type 2 diabetes and obesity ^[5-13], proposing that a sensibly higher intake of this mineral may at lead to the reduction of cardiovascular diseases. Such a conceivable medical advantage has evidently appeared. In epidemiological and clinical studies, dietary calcium intake was fundamentally contrarily connected with the ischemic stroke ^[14-16]. A fourth study additionally found a measurably huge inversely relationship between dietary calcium admission and mortality from ischemic coronary illness ^[16] In a Swedish male cohort, the relationship between dietary calcium intake and general cardiovascular ailment (CVD) mortality was inverse and of marginal statistical significance^[17] However, these strong discoveries are the larger part of observational studies reported invalid associations^[18-25].

Calcium supplements, which are regularly prescribed to elderly individuals, especially postmenopausal women, to keep up their bone health, have additionally been recommended as the important substance to enhance serum cholesterol profile ^[26-28] and to control Blood Pressure^[25] However, no solid epidemiological

confirmation proposes that calcium supplementation may give cardiovascular advantages [16 18 20 22]. Rather, two meta-analysis of clinical trials have encouraged a notice that calcium supplements may increase the risk of having a myocardial infarction (MI)^[52,53,54 53].

An extensive number of studies have researched the potential connection between serum calcium levels and cardiovascular demise^[5,6,7,8,9,10,11,12]. As of now in 1996, Reunanen and associates^[7] found an expanded danger of sudden passing in men (<50 years) with expanding serum calcium levels. They inspected death rate in connection to a solitary serum calcium estimation acquired at the screening of 33,346 persons amid a mean subsequent time of 10.8 years^[7]. Interestingly, a meta-examination concentrated on perpetual kidney infection patients found no relationship between all-cause mortality and serum levels of calcium [6], yet a German investigation of 1206 patients with coronary illness found a stable positive correlation between serum calcium and all-cause mortality

Daily Calcium Requirement

Age	Milligram (mg)/day	Tolerable Upper Intake Level (UL) mg/day
4 - 8	1,000	2,500
9 - 18	1,300	3,000
19 - 50	1,000	2,500
Males 51 - 70	1,000	2,000
Females 51 - 70	1,200	2,000
> 70	1,200	2,000
<u>Pregnancy and Lactation</u>		
14 - 18	1,300	3,000
19 - 50	1,000	2,500

FOOD SOURCE SERVING SIZE CALCIUM (mg)

Milk & Yogurt 8 oz or 1 cup 300 - 450

Cheese 3 ounces 300 - 450

Bones in canned sardines and salmon 3 ounces 181 - 325

Calcium fortified foods (i.e. orange juice, soy milk, tofu) 8 ounces 200 - 300

Dark green, leafy vegetables 1/2 cup cooked, 1 cup raw 50 - 100

Nuts and Seeds 1 ounce 25 - 75

[Source: Institute of Medicine, National Academy of Science, 2011]

Table 1: Daily Calcium Requirement

1.2 Nature of the Study

The study is based on the NATIONWIDE Inpatient Sample which is an Annual inpatient information from a stratified method example of releases from all hospitals across United States in HCUP, equivalent to around 20 percent of all releases in U.S. community health centers, excluding rehab and acute care clinics. Information is accessible from 1988 forward, and another database is released every year, roughly year and a half. The NIS Overview and the NIS Database Documentation pages of the HCUP-US Web website contain extra data. Overhaul of the 2012 NIS: From 2012, another sampling strategy was achieved to enhance NATIONWIDE estimates. Healthcare Cost and Utilization Project – (HCUP)

Nationwide Health and Nutrition Examination Survey (NHANES) data collected by the Centers for Disease Control (CDC); a cross - sectional sample of non-institutionalized U.S. populations. NHANES data is designed to assess the health and nutritional status of adults and children in the United States. NHANES data collection started in the 1960s and contains information on health and nutrition on the sample reflecting changing nutritional and health trends among Americans. This research used the NHANES data from 2005 to 2010. NHANES data is available in the public domain and is free. The survey design was a stratified, multistage probability sample of the target population. Data collection was done in accordance with the NHANES procedures and protocols.

1.2.1 Assumptions

This research assumes the following:

- All data was collected using the NIS and NHANES data collection procedures and protocols.
- All the study participants fell within the NHANES eligibility.
- All data was handled and stored in satisfactory manner.

1.2.2 Significance of the Study

Does everyone need Calcium supplements?

You really can't know without a blood chemistry test There is 7 times more calcium than magnesium In our dietary intake Some people have plenty of calcium, they just need to push that calcium into their bone Some people just need more protein or need to improve protein Metabolism

Does hypercalcemia cause comorbidity of CVD?

This study is essential and important for a variety of reasons. Review of literature shows that a comprehensive analysis of the 2005-2010 NHANES data on the impact of Calcium intake on high blood pressure in adult American subpopulations has not been done. This research will help to disclose the relationship of calcium and Blood Pressure based on the 2005-2010 NHANES data about calcium consumption in the USA sub populations and trend of calcium consumption among the subpopulations during the years covered by the study .NIS data used to explore the association of the Hypercalcemia and Cardiovascular diseases. If in-patient mortality and morbidity of CVD could be correlated with Hypercalcemia Then in-hospital mortality could be reduced by finding the causative factor of Hypercalcemia Thus, a method for reducing in-hospital mortality becomes available. Some patient-related characteristics are known to influence in-hospital mortality rates.

The findings of these analyses will be a significant addition to the understanding of the impact of calcium on blood pressure and Hypercalcemia and CVD.

1.2.3 Goals and Objectives

In this study, we aimed to prospectively examine the associations of dietary calcium intake, in total or separated from dairy sources and from non-dairy sources like supplements.

This research focused on assessing the relationship between calcium intake and Blood pressure and identify the solutions for following queries:

- 1) Is Calcium Intake a significant determinant of Blood Pressure?
- 2) Is there a significant relationship between Calcium and Blood Pressure in all ethnic groups available from NHANES data from 2006 – 2010?
- 3) Is there a significant relationship between Calcium and Blood Pressure in all education groups from NHANES data from 2006 – 2010?
- 4) Is there a significant relationship between Calcium consumption and Blood Pressure in all income groups NHANES data from 2006 – 2010?
- 5) Is there a significant relationship between Calcium and Blood Pressure based on sex?
- 6) Has Calcium consumption, and Blood Pressure, or the relationship between Calcium
- 7) Consumption and Blood Pressure changed in any of the groups studies between 2005 -2010?

8) Increase Calcium consumption leads to Hypercalcemia?

Using data from the Nationwide Inpatient Sample (NIS) of HCUP, and Centers for Disease Control and Prevention (CDC):

1. To determine association between Calcium supplementation and Hypercalcemia
2. To determine the associations between demographics, socioeconomic status, education level and calcium supplementation usage.
3. To relate Hypercalcemia to Cardiovascular disease incidence and prevalence
4. To determine the costs and in-hospital mortality associated with Hypercalcemia
5. To determine the comorbidities associated with Hypercalcemia

1.3 HYPOTHESIS

1. Calcium has a significant effect on Blood Pressure

Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

2. There a significant relationship between Calcium and Blood Pressure in all Ethnic Groups of NHANES data from 2006 – 2010

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

3. There is a significant relationship between Calcium and Blood Pressure in all education groups NHANES data from 2006 – 2010

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

4. There is a significant relationship between Calcium consumption and Blood Pressure in all income groups NHANES data from 2006 – 2010

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

5. There a significant relationship between Calcium and Blood Pressure based on sex

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

6. Hypercalcemia has a significant effect on comorbidity Chronic Heart Failure (CHF)

Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

7. Hypercalcemia has a significant effect on comorbidity Malignant Hypertension(HTN)

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

8. Hypercalcemia has a significant effect on comorbidity Valvular Heart Diseases (Valve)

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

1. Hypercalcemia has a significant effect on comorbidity Perivascular Hear disease (Perivasc)

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

AS control group we used Diabetes Mellitus and Arthritis as comorbidity

9. Hypercalcemia has a significant effect on comorbidity Diabetes Mellitus (DM)

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

10. Hypercalcemia has a significant effect on comorbidity Arthritis
(Arth)

Null Hypothesis: $H_0 = H_1$

Alternative Hypothesis: $H_0 \neq H_1$

Focuses and Techniques to solve the Research Requisitions

1. Is Calcium a significant determinant of Blood Pressure?

This query is for building up a reasonable comprehension on the Effect of Calcium on Blood Pressure with the support of literature and the NHANES data from 2005 to 2010.

By answering this question, the researchers will conduct chi-square to determine whether there is a significant association between Calcium and Blood Pressure variables. The chi-square test will be followed by logistic regression.

The following guiding questions can be deduced from it:

Guiding Questions

2. Significance in Calcium to Blood Pressure?

❖ Is there a change in the results over the years?

These are not unique questions to determining the study relevance in the area of interest. The guiding questions are not necessarily to be solved or answered. It gave better navigation for the study to make more productive and predict the issues that may have to emerge in the analysis.

❖ Is there a significant relationship between Calcium consumption and Blood Pressure in all ethnic groups NHANES data from 2006 – 2010?

This question is aimed at determining the impact of race on Calcium consumption. The race is a coefficient of the determinant of high blood Pressure.

This research informed by literature that shows that different races have different genetic backgrounds consume different traditional staple foods and exist in various Cultural environments. This question will investigate the effects of these factors on Calcium consumption.

To answer this research question, the researchers will compare the Calcium intake across the various races. By drawing these statistical inferences, chi-square test will be used to assess the relationship between race, Calcium consumption, and blood Pressure.

The following guiding questions have been understood from it:

Guiding Questions

- What is the relationship between race and Calcium consumption?
- What is the relationship between Calcium consumption and Blood Pressure for each ethnic group?
- ❖ Is there a significant relationship between Calcium and Blood Pressure in all education groups NHANES data from 2006 – 2010?

The aim of the third research question is to generate a link between the

The interpretative paradigm of the preliminary results showed a positive association between education and Calcium and the rest of the data. Chi-square tests used to test for the association between Calcium consumption and Blood Pressure among different educational attainment levels and the amount of dietary Calcium that the study population consumed.

Guiding Questions

- What is the percentage of highly educated individuals who take calcium have elevated blood Pressure?
- How does level of education correlate with Calcium consumption in all populations?
- ❖ 4. Is there a significant relationship between Calcium consumption and Blood pressure in all income groups NHANES data from 2006 – 2010?

The purpose this question is to develop an understanding of the relationship between household income and calcium consumption. To answer this the research question, the researchers was used chi-square to assess the relationship, compare the Calcium intake and blood Pressure between different income levels.

The following guiding questions can be understood from it:

Guiding Questions

- What income level consumers use Calcium?
- Is income a determinant of high blood Pressure?
- Does income have an effect on blood Pressure level?

- ❖ Is there a significant relationship between Calcium and Blood Pressure based on gender?

The research question is aimed at determining the impact of sex/gender on Calcium consumption and Blood Pressure. This research informed by literature that shows that different men and women have a different biological effect on Calcium consumption and Blood Pressure. This question will investigate the effects of gender on Calcium consumption.

To solve this problem, Chi-square tests used. The relationship further accessed by using, logistic regression.

The following guiding questions inferred from it:

Guiding Questions

- What is the relationship between sex and Calcium consumption?
- How Calcium consumption and Blood Pressure does vary among male and females?

The following guiding questions can be deduced from it:

7. Has Calcium Consumption, Blood Pressure, or the relationship between Calcium consumption and Blood Pressure changed in any of the group studies between 2005 - 2010?

The purpose of the last research question is to develop an understanding of the relationship between Calcium consumption and blood Pressure over the years.

Calcium Consumption, Blood Pressure, or the relationship between Calcium consumption and Blood Pressure will be assessed in different years histogram will be used to check the changes over the years.

The following guiding questions can be understood from it:

- What is the change in Calcium consumption and Blood Pressure over the years?

The outcomes of interest as indicated in the goals and hypotheses above are the comorbidity. Datasets from the NIS database appropriate descriptive and inferential statistics will be affected. The factors associated with the research outcome, the length of stay and the costs multiple regression models set up and validated. Predictive models such as logistic regression will be employed to determine the risks and ratios for the various factors influencing mortality such as race, age groups, number and types of procedures and comorbidities. Details as to the state of art knowledge and research

CHAPTER 2

LITERATURE REVIEW

2.1 Literature Search Strategies

Review of literature was conducted to identify articles on the impact of calcium on blood pressure. Relevant studies were obtained from NJEM, PubMed, Medline EBCOS, BMJ, NJEM, JSTOR, Google Scholar search and Web of Science, including books. The selection processes was done according to significance to the topic. Exclusion and inclusive criteria was done as follows: The articles that were closely related to the study topic (topic sentence) were reviewed and summarized for the inclusion and exclusion criteria. Search words included: blood pressure and calcium, dietary intake and blood pressure, blood pressure, Blood Pressure, prospective study, and calcium chloride. Medical Subject Headings (MeSH) key words. Abstracts were read to make sure each article was related to the topic sentence and only full text articles were included in the review. There was no age cutoff for the articles as long as they were relevant to the topic.

2.2 Calcium Distribution

Calcium plays a vital role in a wide range of biologic functions, "either in the form of its free ion or bound complexes. One of the most important functions as bound calcium is in skeletal mineralization. The vast majority of total body calcium (99%) is present in the skeleton as calcium-phosphate complexes, primarily as hydroxyapatite, which is

responsible for much of the material properties of bone" (36).

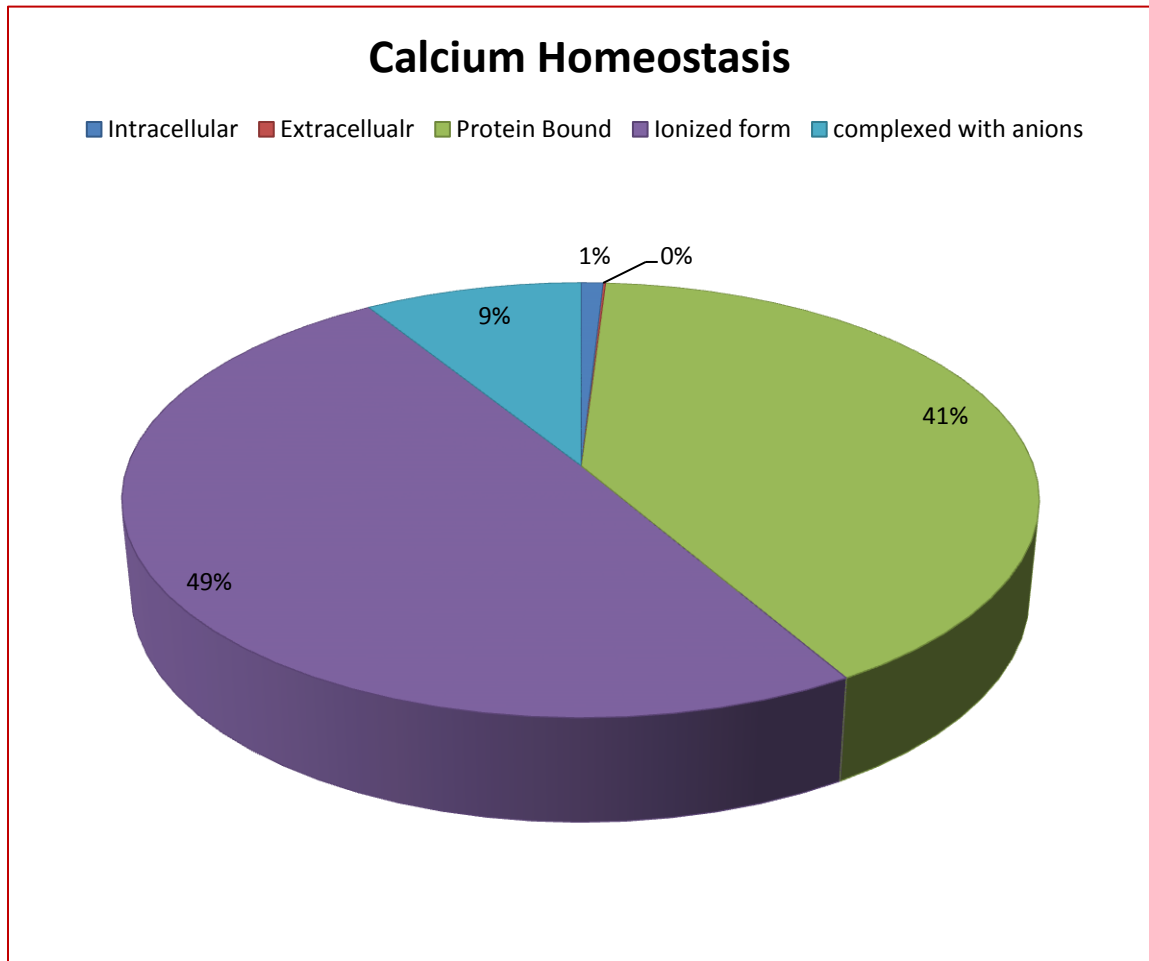


Figure 1: Calcium Homeostasis

In bone, calcium fills two principle needs: it gives skeletal quality and, simultaneously, gives a dynamic store to keep up the intra-and extracellular calcium levels. Non-bone calcium constitute to 1% of aggregate body calcium (10 g in an adult). Be that as it may, it is inconsistent and fast trade inside the different calcium pools and is in charge of an extensive variety of vital capacities, including additional and intracellular maintained, nerve conduction, and muscle constriction ^(18,19).

Serum calcium ranges from 8.8 to 10.4 mg/dl (2.2 to 2.6 mM) in solid subjects. It includes free particles (51%), protein-bound (40%), and ionic edifices (9%) ⁽²⁰⁾. to keep away from calcium bad quality, the convergence of serum ionized calcium is firmly kept up inside a physiologic scope of 4.4 to 5.4 mg/dl (1.10 to 1.35 mM).

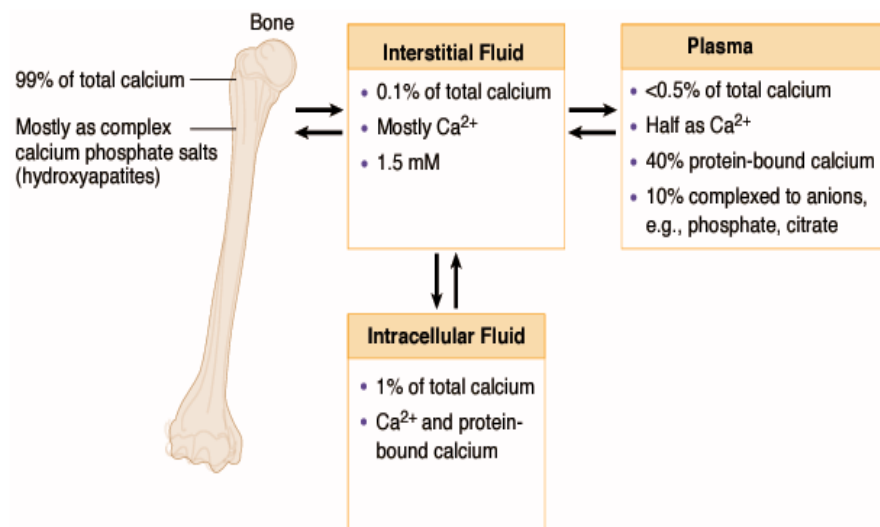


Figure 2 : Distribution of Calcium in the body

Non-ionized calcium is bound to proteins and anions in both the new and intracellular pools. The major calcium tying proteins incorporate egg whites and globulin in serum

and calmodulin and other calcium-tying proteins in the cell. The real ionic buildings in serum are calcium phosphate, calcium carbonate, and calcium oxalate.

2.3 Calcium Homeostasis

Calcium homeostasis is a mind boggling process including the accompanying four key parts: serum calcium, serum phosphate, 1,25-dihydroxyvitamin D-3, and parathyroid hormone (PTH).^[21] More than 99% of the aggregate body calcium is put away in bone as phosphate and hydroxide salts, prevalently as hydroxyapatite. Ordinarily, a little parcel of this calcium is accessible for trade in the serum.

2.3.1 Parathyroid hormone (PTH)

Parathyroid hormone (PTH) is a polypeptide containing 84 amino acids that are emitted by the parathyroid organs after cleavage from preproparathyroid hormone (115 amino acids) to genius parathyroid hormone (90 amino acids) to the full grown hormone. The significant target end organs for parathyroid hormone (PTH) activity are the kidneys, skeletal framework, and digestive tract.^[21]

The essential reaction to parathyroid hormone (PTH) by the kidney is to increment renal calcium resorption and phosphate discharge. In the kidney, parathyroid hormone (PTH) squares reabsorption of phosphate in the proximal tubule while advancing calcium reabsorption in the rising circle of Henle, distal tubule, and gathering tubule.^[21,22]

Parathyroid hormone (PTH) promotes absorption of calcium from the bone in 2 ways. The fast stage achieves an ascent in serum calcium inside minutes and seems to happen at the level of the osteoblasts and osteocytes. Despite the fact that it might appear to be

outlandish that the cells that advance testimony of bone included in resorption, these cells frame an interconnected system known as the osteocytic film overlying the bone lattice, however with a little layer of intervened liquid termed bone liquid. At the point when parathyroid hormone (PTH) ties to receptors on these cells, the osteocytic film pumps calcium particles from the bone fluid into the extracellular fluid [22].

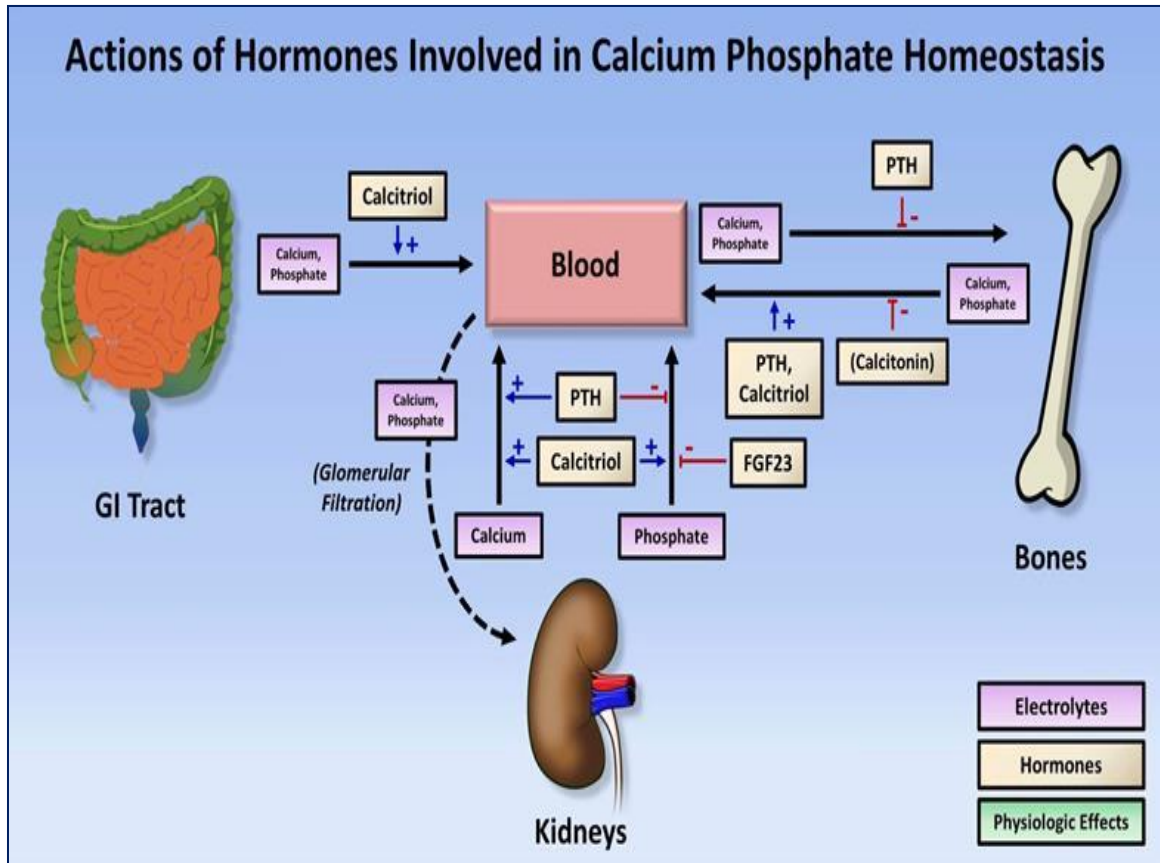


Figure 3: Action of Hormones Involved In Calcium Phosphate Homeostasis

The reasonable period of bone resorption happen more than a few days and has two parts. To start with, osteoclasts are actuated to process framed bone, and second, multiplication of osteoclasts occurs. Interestingly, develop osteoclasts need parathyroid hormone (PTH) layer receptors; enactment and expansion give off an impression of being stimulated by

cytokines discharged by actuated osteoblasts and osteocytes or by separation of juvenile osteoclast precursors that have parathyroid hormone (PTH) and vitamin D receptors.

The last critical capacity of parathyroid hormone (PTH) is a change of 25-hydroxyvitamin D to its most dynamic metabolite, 1,25-dihydroxyvitamin D-3 [1,25-(OH)₂ D₃], by actuation of the protein 1-hydroxylase in the proximal tubules of the kidney.

Criticism restraint of parathyroid hormone (PTH) discharge happens mainly by the direct impact of calcium at the level of the parathyroid organ. Despite the fact that not all around illustrated, 1-25-(OH)₂ D₃ seems to apply a gentle inhibitory impact on the parathyroid organ too.^[21]

2.3.2 Vitamin D

Vitamin D-3 (cholecalciferol) is formed in the skin when a cholesterol precursor, 7-dehydroxycholesterol, is exposed to bright sun light. Enactment happens when the substance experiences 25-hydroxylation in the liver and 1-hydroxylation in the kidney.^[23]

The essential activity of 1,25-(OH)₂ D₃ is to advance gut retention of calcium by stimulating the development of calcium-tying protein inside the intestinal epithelial cells.

Vitamin D likewise promotes intestinal absorption of phosphate particle, despite the fact that the particular component is vague. Adversely charged phosphate particle may latently move through the intestinal cell on account of a flux of the emphatically charged calcium particle. In bone, vitamin D may assume a synergistic part with parathyroid hormone (PTH) in stimulating osteoclast multiplication and bone resorption.

[23]Contrasted with parathyroid hormone (PTH), vitamin D applies a much slower

administrative impact on calcium equalization.

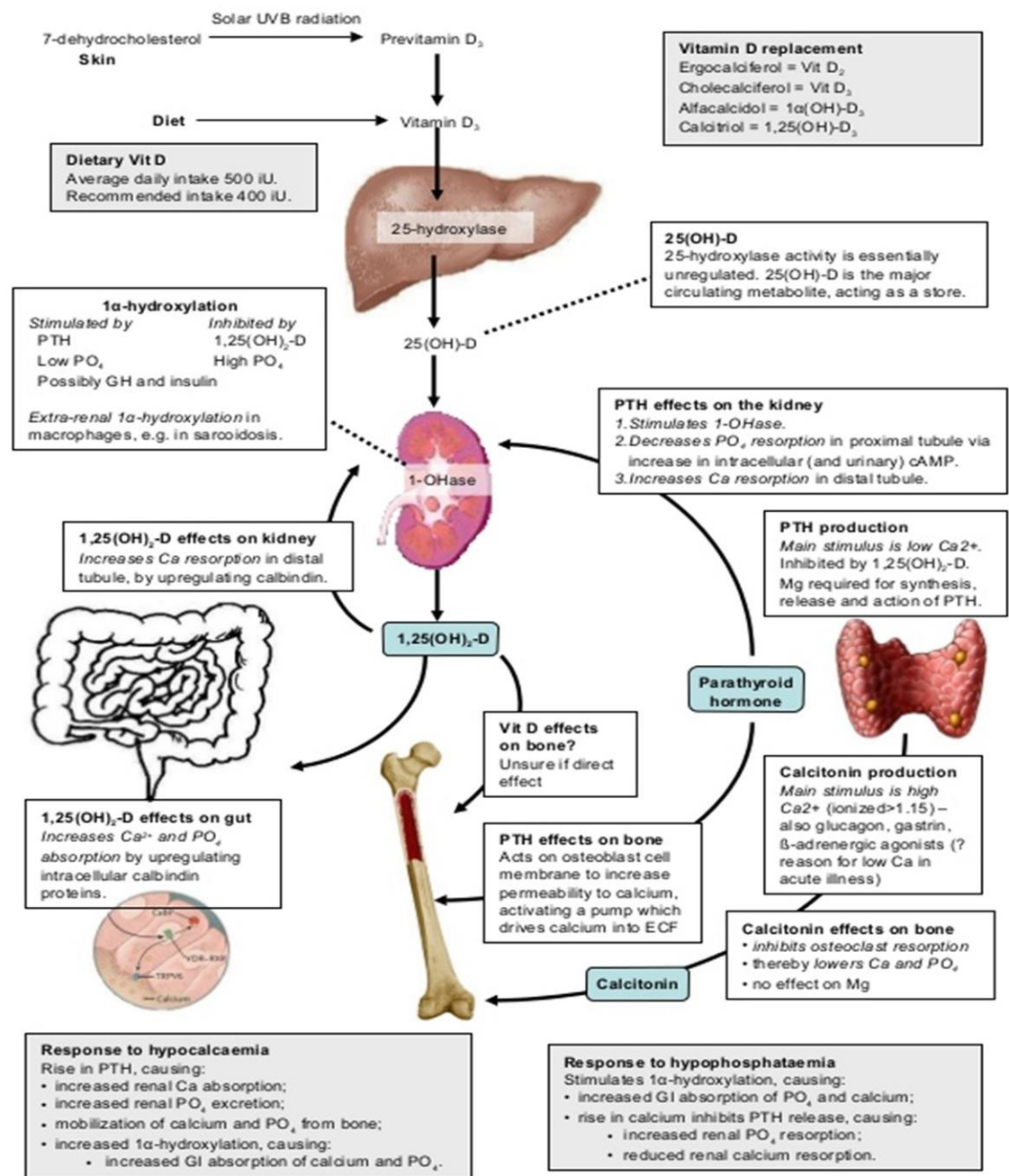


Figure 4 :Calcium and Vitamin D Metabolism

2.4 PATHOPHYSIOLOGY OF CALCIUM

2.4.1 Mechanisms of Arterial Calcification

The dystrophic calcification in the blood vessel occurs in response a reaction to tissue injury, scar tissue is formed due to repair process^[41] Test and clinical studies have demonstrated that AC is a procedure reflecting changes of the vascular smooth-muscle cells (VSMC) and pericytes from contractile to secretory phenotype). VSMC combine bone-related proteins, including soluble phosphatase, osteocalcin, osteopontin and a layer of collagen-rich extracellular framework, what's more, incorporates the development of lattice vesicles, knobs and apoptotic bodies, which serve as start locales for apatite crystallization^[42,43]

In vitro, VSMC separation towards osteoblast-like cells, with consequent mineralization, is controlled by the harmony amongst promoters and inhibitors of calcification and results from interruption of this equalization for promoters.

The secretory phenotype is started by the actuation of Runx2 (Cbfa1) and osterix (Osx), transcription figures that advance the separation of mesenchymal cells into the osteoblastic lineage^[24,25]

The Runx2 and Osx are actuated upstream by a few variables including Msx2, Wnt and catenin signaling^[24] The boosts are starting this "osteogenic course" incorporate bone morphogenic proteins (BMP 2, 4) and endless damaging jolts and metabolic toxicities including the era of receptive oxygen species (ROS)^[46-48] The outcome could be either

VSMC apoptosis or incitement of NF κ -B and initiation of incendiary middle people TNFa, IL-1, IL-6, and enactment of macrophages^[25,26]

Exploratory studies utilizing sub-atomic imaging plainly demonstrated that calcifications create in parallel with irritation in two stages: early actuation of macrophages and aggravation and calcification at later stage²² (figure 1).

Pooled uremic serum with high phosphate focus, impelled articulation of Runx²²⁴ and obstructs the declaration of qualities in charge of articulation of contractile molecules^[24] In vitro, the phosphate-activated calcification procedure can be hindered by including pyrophosphates that estrange the cell sodium-phosphate cotransport framework (PIT-1).[49]

The Late study has demonstrated that phosphate affects the calcification process through a typical pathway: expanding mitochondrial ROS and actuation of NF κ -B pathway and interpretation of osteogenic project with the articulation of Msx2-Wnt-Runx2.[50]

In the nearness of typical serum, VSMC don't calcified and can restrain unconstrained calcium and phosphate precipitation in arrangement, showing that systemic calcification inhibitors, for example, fetuin-An are available in the serum [51] Furthermore in VSMCs who constitutively express intense nearby inhibitors of calcification, for example, lattice GLA protein^[32,33,34] which may constrain AC by tying to bone morphogenic proteins (BMP-2).Osteopontin and osteoprotegerin are powerful inhibitors of AC in vivo, and inactivation of their quality upgrades the calcification process^[34,35]

Types and Characteristics of Vascular Calcification

Types of Vascular Calcification	Location and Features	Associated Condition(s)
Calcific atherosclerosis	Intimal; ossification	Atherosclerosis, hyperlipidemia; osteoporosis; hypertension; inflammation
Calcific medial vasculopathy (Mönckeberg's medial calcific sclerosis)	Tunica media	Type 2 diabetes mellitus; end-stage renal disease; hyperphosphatemia; amputation
Elasto calcinosis	Internal elastic lamina	Pseudoxanthoma elasticum; Marfan syndrome
Calcific uremic arteriolopathy	Microvessels; amorphous	End-stage renal disease; warfarin (?)
Calcific aortic valvular stenosis	Aortic face of the leaflets	Hyperlipidemia; congenital bicuspid valve; rheumatic heart disease
Portal vein calcification	Portal vein thrombus or venous wall	Portal hypertension; liver disease

Table 2 : Vascular Calcification

2.4.2 CLINICAL IMPACT OF ARTERIAL CALCIFICATIONS

Intimal calcification happens with regards to primary atherosclerosis, advances in parallel with the plaque development. The blood vessel brokenness result from narrowing of the blood vessel lumen with ischemia influencing the tissues and organs downstream. The intense coronary occasions and dead tissue are more identified with the biomechanical dependability of atherosclerotic plaques and the burst of the plaque's flexible top. This outcome from mechanical irregularity between the consideration of stiff material (calcium gems) into the distensible material (lipid center) bringing about plaque weakness and break. Despite the fact that a higher coronary AC score is connected with a poorer cardiovascular visualization, the impact of calcification on plaque solidness is

dubious. The consequences of a few studies demonstrated that AC does not expand plaque weakness, which appears to be more inferable from a vast lipid pool, thin flexible top, and force of neighborhood inflammation.^[36,37]

Media calcification (Mönckeberg's sclerosis or media calcinosis) is portrayed by diffuse mineral stores inside the blood vessel tunica media. While media calcification is much of the time saw with maturing in the overall public, it is essentially more announced in patients with metabolic disorders

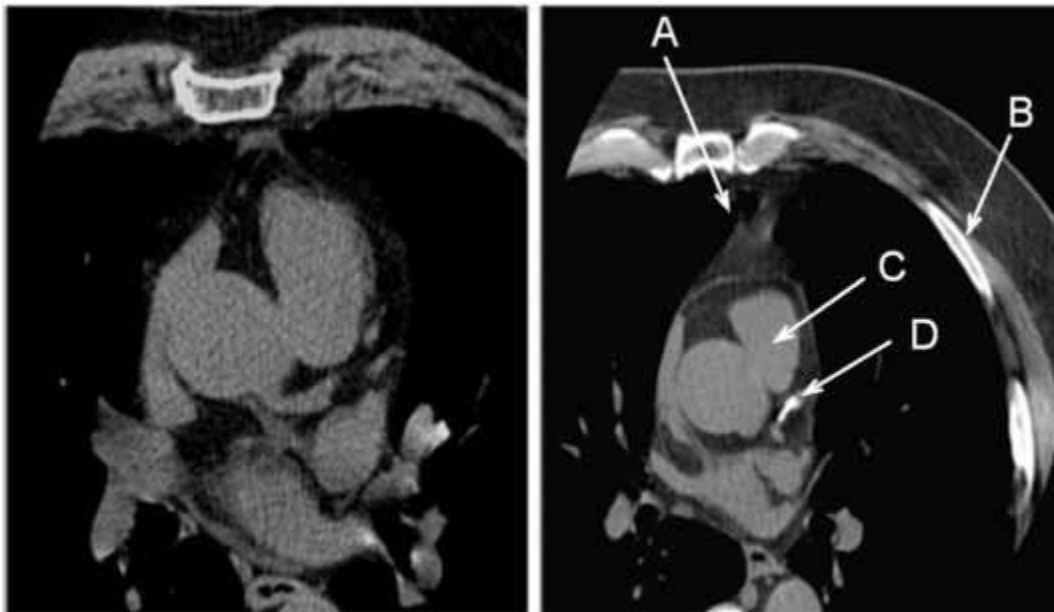


Figure 5 CT of Normal Coronary Artery

(Right) Abnormal CT showing calcium in the left coronary artery.

A: sternum

B: rib

C: heart

D: calcium in the coronary artery

Potential Biologic Mechanisms for the Beneficial Cardiovascular Effects of Calcium Intake	
Decreases cholesterol	Intestinal binding of calcium with fatty acids and bile acids decreases fat absorption
Lowers blood pressure	Down-regulates the renin-angiotensin-aldosterone system. Improves sodium-potassium balance
Promotes weight loss	Inhibits fatty acid synthase and activates lipolysis
Improves insulin secretion	Intracellular calcium increases insulin secretion and sensitivity, which stimulates glucose transport
Has antithrombotic effects	Inhibits platelet aggregation and prevents intravascular thrombosis
Induces vasorelaxation	Opens calcium-activated potassium channels, increases sensitivity to nitric oxide, and decreases superoxide production

Table 3 Cardiovascular Effects of Calcium Intake

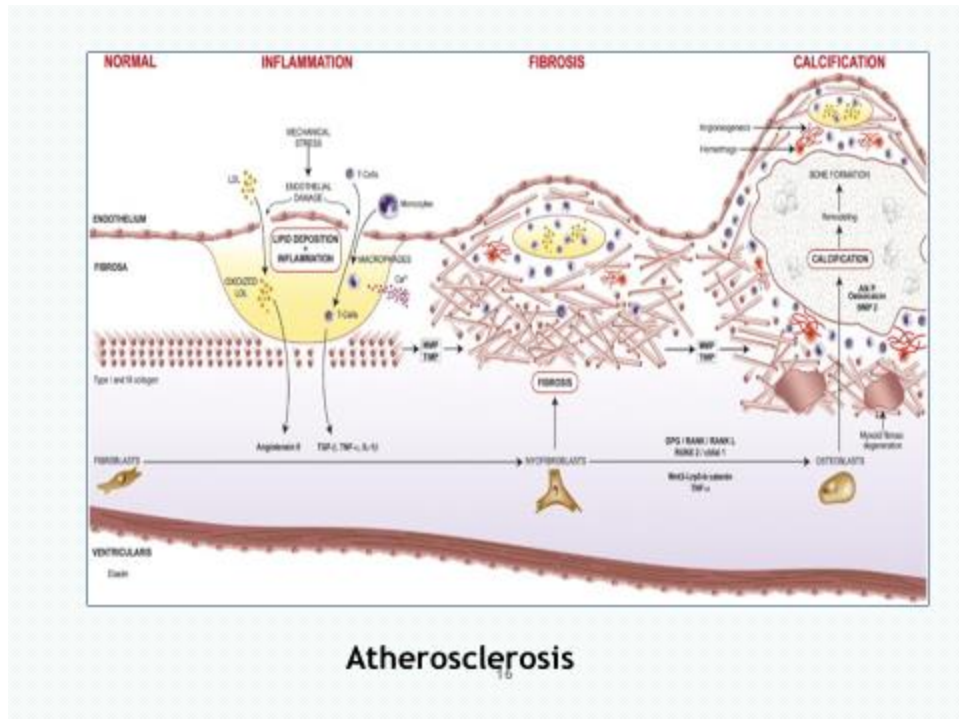


Figure 6 Atherosclerosis of Artery

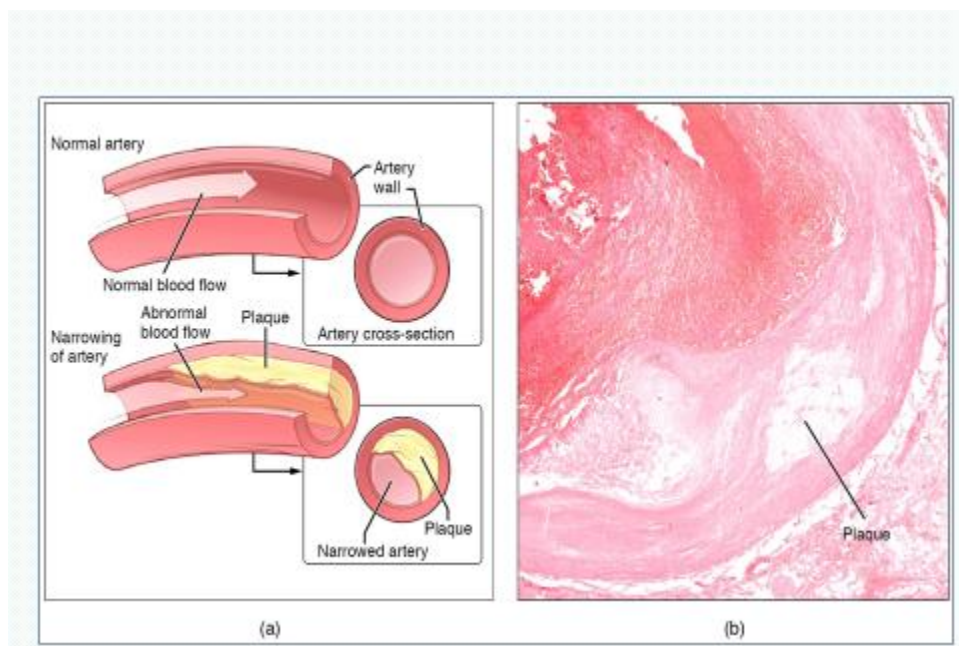


Figure 7 Cross section of Atherosclerosis of artery(plaque formation)

2.4.3 CALCIUM AND HEART FAILURE

For sure, an appealing theory for the component basic cardiovascular muscle brokenness amid heart disappointment, the main source of mortality in the created world, is that impeded calcium discharge causes diminished muscle withdrawal (systolic brokenness) and faulty calcium evacuation hampers unwinding (diastolic brokenness). Given that the estimation of cell calcium is generally direct, the undeniable examination required to address this vital issue is to quantify calcium in heart muscle cells from fizzling hearts. Such estimations have been done in confined cardiomyocytes and, however, there is a considerable lot of variability in the distributed reports, the information tend to bolster the idea of an abatement in SR calcium discharge and an imperfection in the end of discharge. These outcomes infer that there are probably absconds in SR calcium discharge in vivo. In any case, there is no information demonstrating that calcium levels are constantly hoisted in heart muscle in coming up short hearts. Such studies anticipate the improvement of solid strategies utilizing calcium markers with sufficient sign to clamor proportions and discovery frameworks that will allow estimations of intracellular calcium in the living heart in place living beings^[38,39,40,41,42,45]

2.3.4 CALCIUM AND CARDIAC HYPERTROPHY

Another disease in which disorders of calcium signaling have been related to cardiac hypertrophy. Calcium elevation via the calcium-activated phosphatase calcineurin has been the trigger for cardiac hypertrophic signaling. , research studies found a role for calcineurin in hypertrophic signaling in the heart, combining invitro and in vivo studies that clearly demonstrated a physiologically important signaling system [58]

A captivating inquiry is whether or not there are any clinical conditions in which one would want to treat (i.e. prevent) cardiac hypertrophy. Adds some intensity for cardiac hypertrophy by linking it to cardiac failure which, as mentioned above, is a leading cause of mortality (over 500,000 deaths per year in the US alone). Cardiac hypertrophy, death is usually due to cardiac arrhythmias, not the hypertrophy per se. deaths linked to cardiac hypertrophy occur in individuals with inherited forms of the disease associated with mutations in one of the contractile proteins. They exhibit abnormal pathology well-ordered arrays of cardiac muscle fibers, suggesting an electrical instability. However, the molecular mechanisms underlying the hypertrophy and the arrhythmias in both the inherited and acquired forms of cardiac hypertrophy remain to be studied. Also some types of cardiac hypertrophy are a completely normal physiological response, such as that seen in well-trained athletes or during pregnancy. Hypertrophy are pathologic in the sense that they ultimately lead to heart failure”^[45,47,48]

2.5 HYPERCALCEMIA

Hypercalcemia is a condition in which the calcium level in your blood is above normal. Too much calcium in your blood can weaken your bones, create kidney stones, and interfere with the way your heart and brain works.

Hypercalcemia most commonly results from overactive parathyroid glands. These four tiny glands are each about the size of a grain of rice and are located on or near the thyroid gland. Other causes of hypercalcemia include cancer, certain other medical disorders, some medications, and excessive use of calcium and vitamin D supplements^[22]

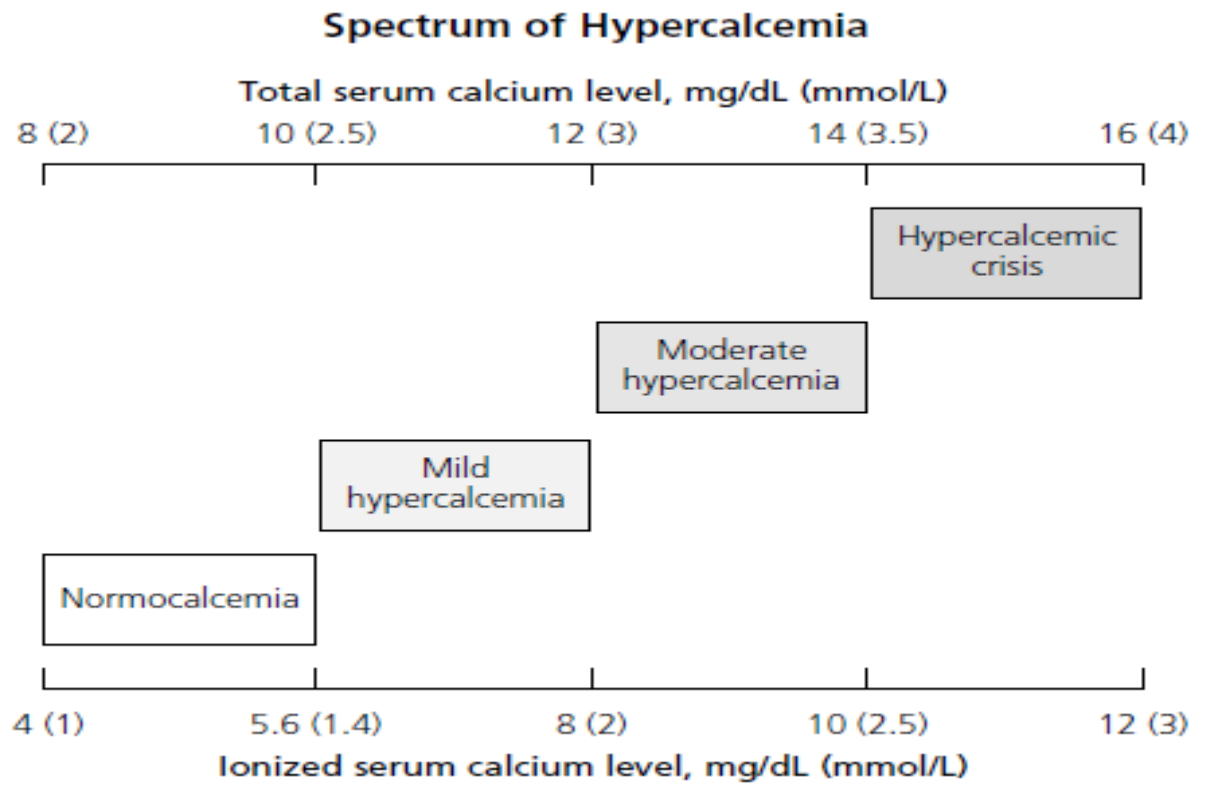


Figure 8 Spectrum of hypercalcemia with Serum Calcium level

Cause:

Mostly intake of calcium carbonate supplements (1–1.5 g of elemental calcium/day) with or without vitamin D analogues, like ergocalciferol or calcitriol (2, 3), rarely antacids like magnesium oxide (2, 5]

- Gender:

Mostly females, post-menopausal, pregnant or bulimic (4)

Rare reported cases of middle to elderly aged males

- Co-morbid condition:

Gastritis, Dyspepsia

Osteoporosis

Chronic kidney disease, hypertension

Hypercalcemia, often severe

Diuretic therapy, few cases with ACE-Is or ARBs

Varying degree of renal insufficiency and metabolic alkalosis

- Lab Findings:

Normal or low normal serum phosphorus

Hypercalcemia affects fewer than 1 in 100 people. The condition is most often diagnosed at an early stage by lab diagnosis, not many patients present with any clinical symptoms.

Women 50 years or older (after menopause) are most likely to have hypercalcemia. In most cases, this is due to primary hyperparathyroidism. ^[49, 50,51]

2.5.1 Symptoms

Abdominal symptoms:

- Constipation
- Nausea
- Pain
- Poor appetite
- Vomiting

Kidney symptoms:

- Flank pain
- Frequent thirst
- Frequent urination

Muscle symptoms:

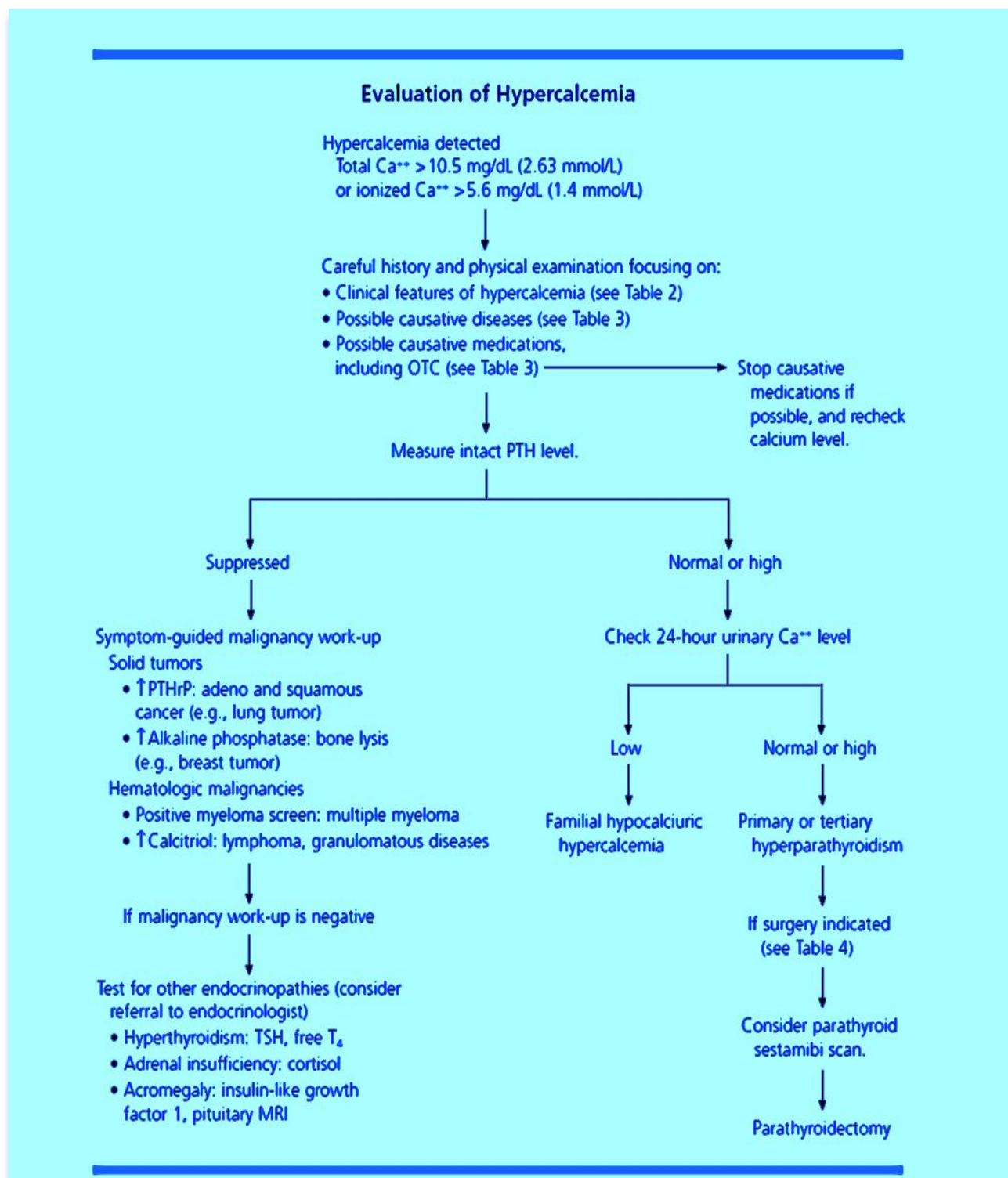
- Muscle twitches
- Weakness

Psychological symptoms:

- Apathy
- Dementia
- Depression
- Irritability
- Memory loss

Skeletal symptoms:

- Bone pain
- Bowing of the shoulders
- Fractures due to disease (pathological fractures)
- Loss of height



2.4.2 INCIDENCE OF HYPERCALCEMIA

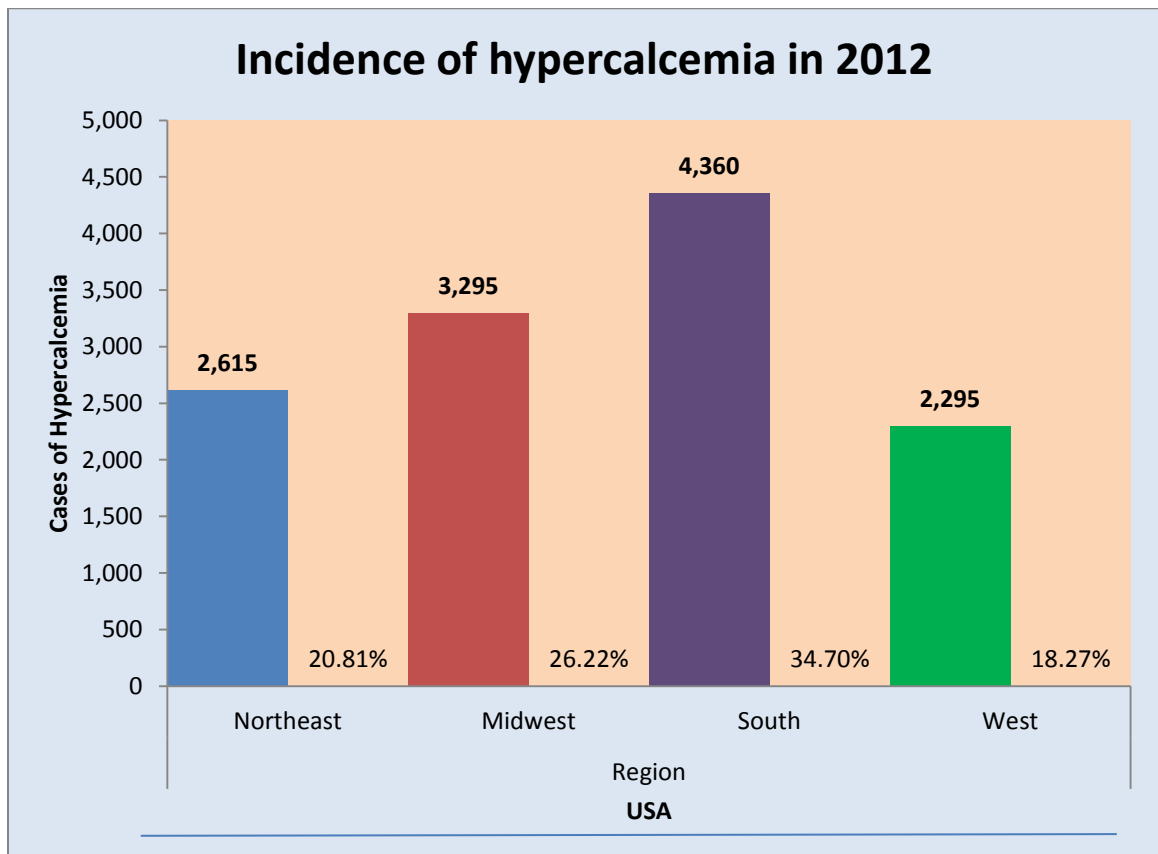


Figure 4 :Incidence of Hypercalcemia in USA

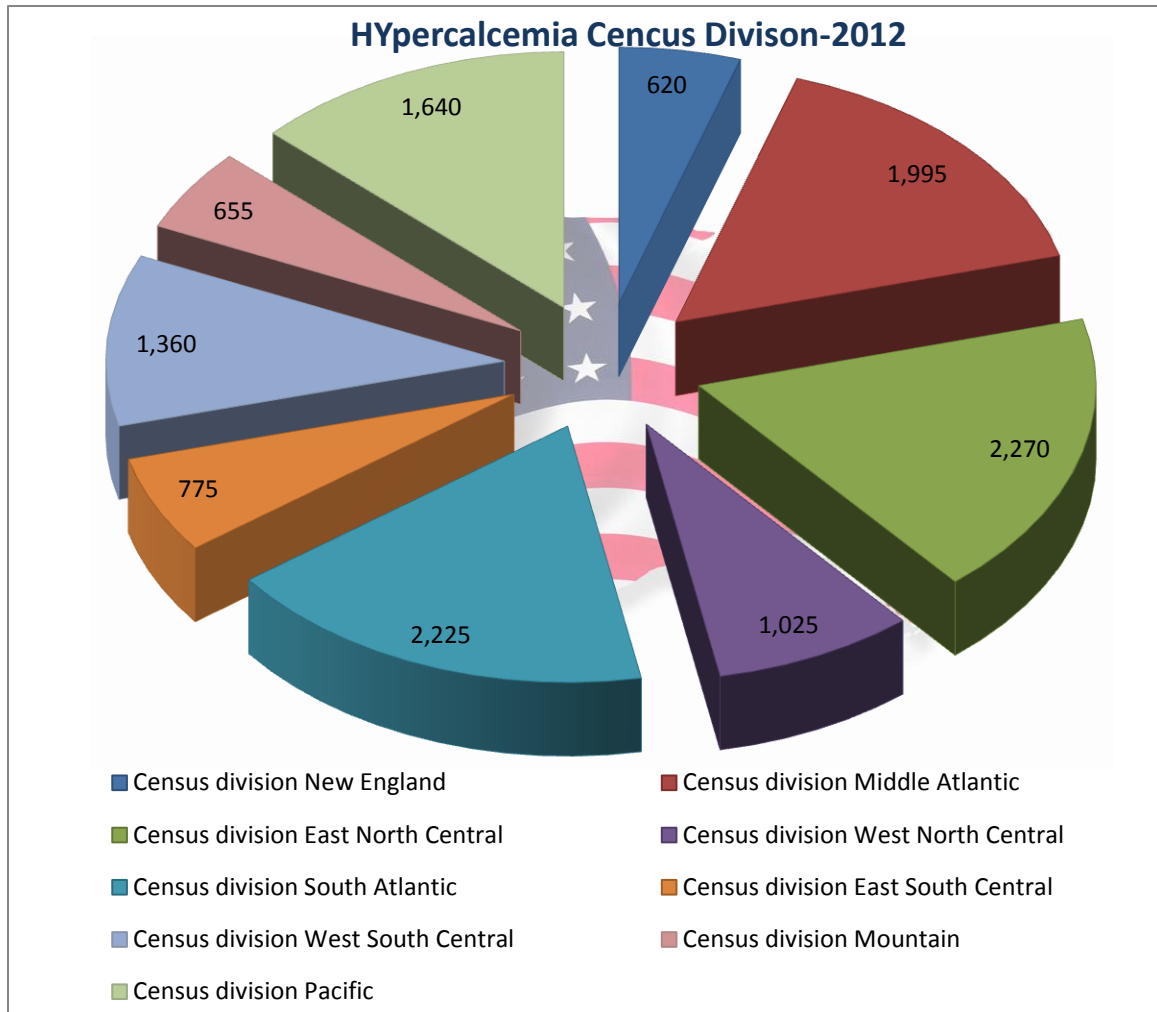


FIGURE:5 PIE CHART OF HYPERCACEMIA

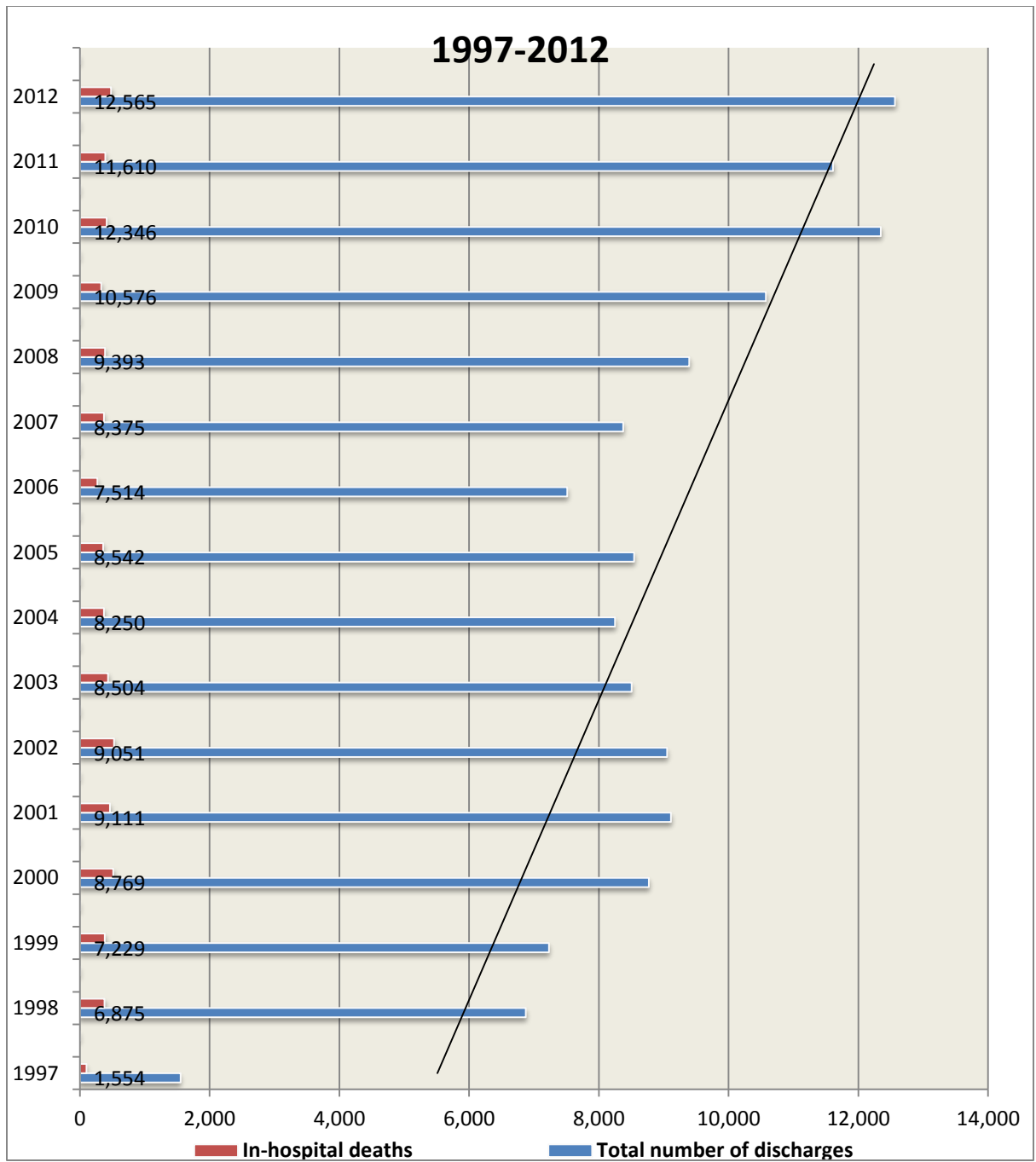


Figure 6: Total number of discharges and in hospital deaths from 1997-2012

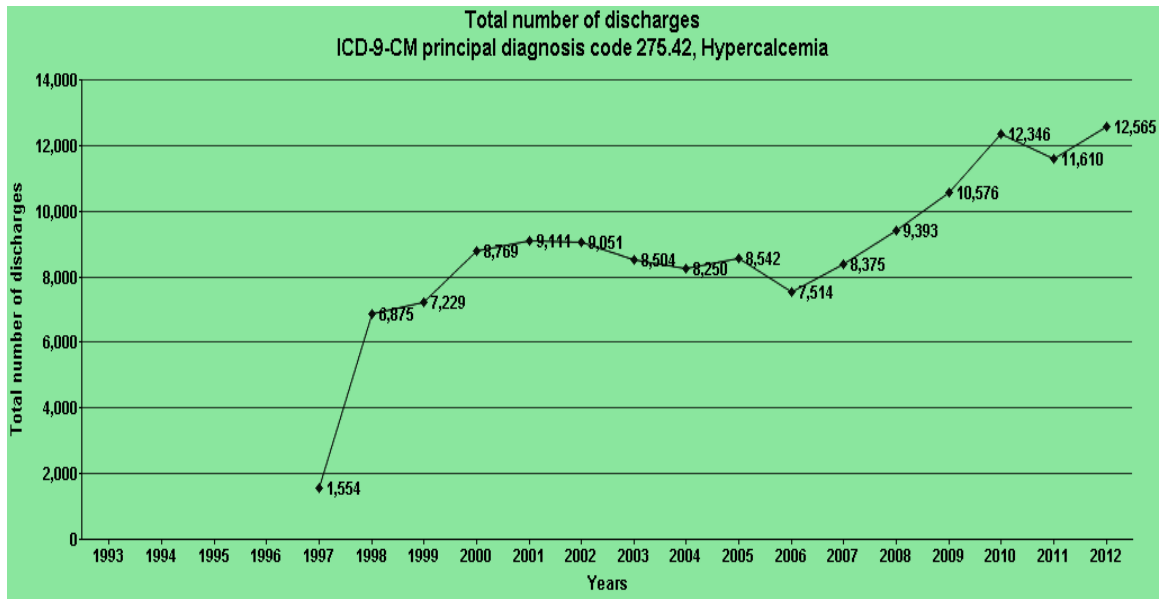


Figure 7: DataSource: HCUP NATIONWIDE Inpatient Sample(NIS)

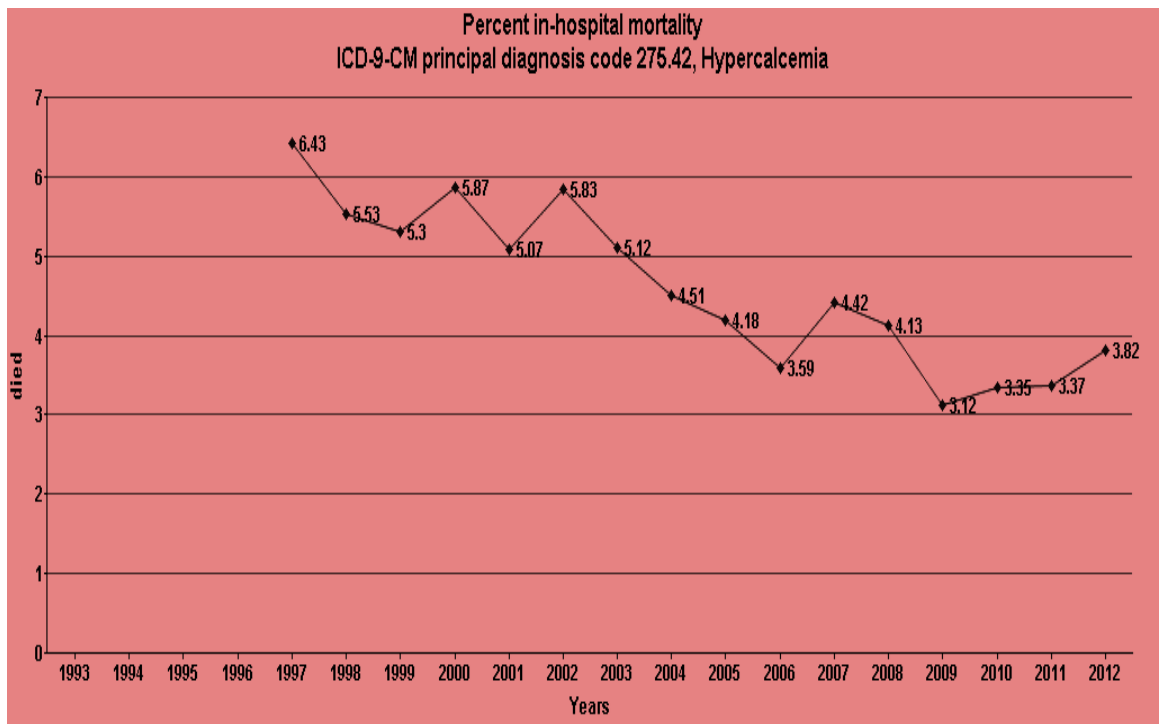


Figure 8: Data Source: HCUP NATIONWIDE Inpatient Sample (NIS)

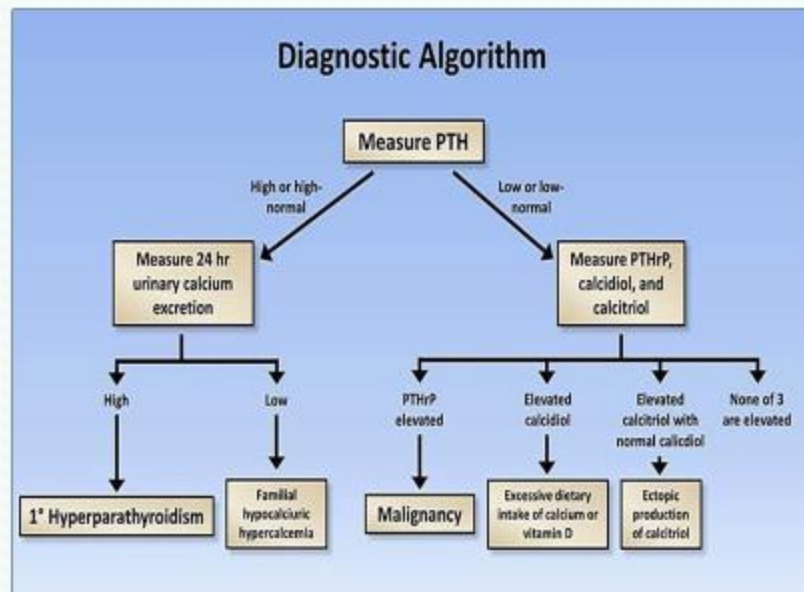
2.5.3 Treatment

Treatment is aimed at the cause of hypercalcemia whenever possible. People with primary hyperparathyroidism (PHPT) may need surgery to remove the abnormal parathyroid gland. This will cure the hypercalcemia.

People with mild hypercalcemia may be able to monitor the condition closely over time.

Severe hypercalcemia that causes symptoms and requires a hospital stay may be treated with the following: [67 68]

- Calcitonin
- Dialysis
- Diuretic medication, such as furosemide
- Drugs that stop bone breakdown and absorption by the body, such as pamidronate or etidronate (bisphosphonates)
- Fluids through a vein (intravenous fluids) - this is the most important therapy
- Glucocorticoids (steroids)



12

Figure 10 Diagnostic Algorithm

2.5.4 Prevention

Most causes of hypercalcemia cannot be prevented. Women over age 50 should see their health care provider regularly and have their blood calcium level checked if they have symptoms of hypercalcemia.

Talk to your health care provider about the correct dose for calcium and vitamin D supplements if you are taking these medicines.[67 68]

2.6. Prevalence and Burden of CVD in the United States

2.6.1 Incidence and Mortality

Every year, the American Heart Association (AHA), in conjunction with the Centers for Disease Control and Prevention, the National Institutes of Health, and other government organizations, contribute most recent and reliable statistical data on all CVD, and their risk factors and exhibits them its Heart Disease and Stroke Statistical Update^[70]

More than 1.2 million individuals encounter a first or intermittent coronary occasion and almost 800,000 have a stroke every year in the United States ^[69,70,71] CVD is progressively influencing the elderly (age 65 years and more established) and influences a larger number of men than women. ^[69, 70,71] Additionally, the commonness of coronary illness is most prominent among American Indians/Native Americans (11.6%), trailed by blacks (6.5%), Hispanics (6.1%), and whites (5.8%).¹⁸ Asians and Pacific Islanders have the least predominance (3.9%) ^[71]

Coronary disease is one of the primary cause of death in the United States across over both genders and all races and ethnicities In 2009, CVD (i.e., coronary disease, hypertensive coronary illness, heart disappointment, and stroke) represented around one in each three deaths in the United States (age-balanced death rate, 243.9 for each 100,000).¹⁷ Over 33% (34%) of CVD death happened in individuals more youthful than age 75 years.^[71,72] coronary illness (myocardial localized necrosis [MI], angina, and

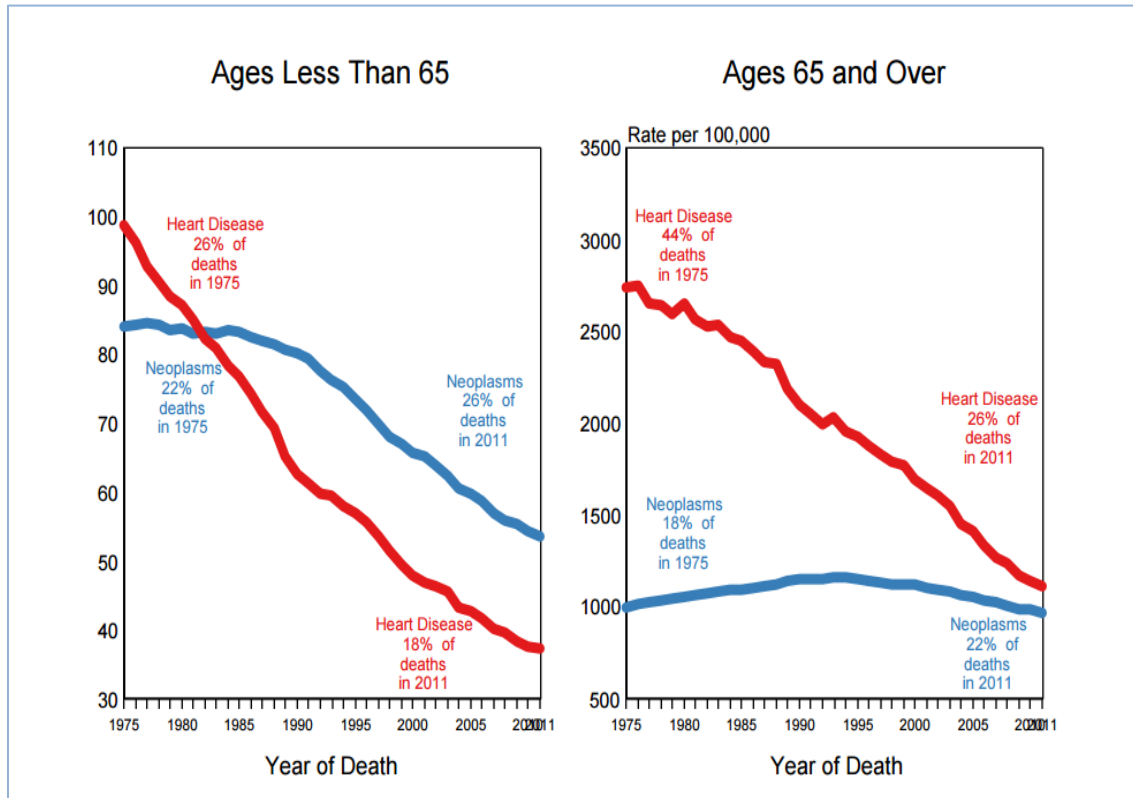


Figure 11 Deaths due to Heart Diseases

2. 6.2 Traditional Risk Factors and Common Pathologic Mechanisms for CVD

The risk factors for CVD are well known which include

- Age,
- Sex
- Blood Pressure
- Smoking Status
- Blood Cholesterol Level.

The effects of age and gender are related to each other. Women develop CVD when they are about ten years older than men. There are well established Randomized, controlled

trials (RCTs) proving the causal relationship between elevated blood pressure and cholesterol levels and CVD. Other factors that affect CVD risk, including genetic variation. The major risk factors for high blood pressure, abnormal lipid levels, and smoking, plus other lifestyle factors are

- Diabetes
- Obesity
- Sodium
- Alcohol
- Psychosocial Factors
- Regular Physical Activity

These above account for about 90 percent of the variance in CVD rates worldwide.^[73]

Cancer risk considered more complicated because both environmental factors and genetics are critically involved. CVD and cancer share same risk and etiologic factors.

- Cigarette Smoking,
- Poor Nutrition,
- Physical Inactivity
- Obesity

All the above associated with both CVD and many types of cancer (particularly breast and colorectal) despite the differences in their clinical manifestations, Inflammation and oxidative stress, both primary targets of vitamin and mineral supplements. Cigarette smoke has many oxidative compounds while dietary fruits and vegetables have high amounts of antioxidant compounds and regular physical activity associated with lower

levels of inflammatory markers^[74] Inflammation and high oxidative potential causes arterial wall damage and increase the chances of hypertension and dyslipidemia.^[75] The most atherogenic forms of low-density lipoprotein (LDL) are highly prone to oxidation, and only oxidized LDL particles stimulate atherosclerosis.^[76] Oxidative damage to DNA causes the formation of multiple aberrations, including DNA adducts, single strand breaks, methylation and genomic instability, that lead to mutagenesis and oncogenesis^[74]

Another pathway for CVD and cancer etiology is methionine metabolism. Methionine is a sulfur-containing amino acid from dietary sources (especially animal protein) and intracellular turnover of proteins. Methionine metabolism results in the generation of S-adenosylmethionine, a significant methyl donor to RNA, DNA, proteins, and other compounds. Methylation may interfere with tumor suppressor genes and causes chromosomal aberrations that lead to oncogenesis.^[77,78]

The methionine cycle has homocysteine, a cytotoxic compound that's risk factor for CVD^[79] Interestingly, the conversion of homocysteine to methionine is the pathway for eliminating the compound from cardiovascular cells and is dependent on all B vitamins not limited to, B12 and folate

Table 1: Top 10 leading causes of death trends from the year 2008-2012

1	Heart diseases	616,828	599,413	597,689	596,339	599,711
2	Cancer	565,469	567,628	574,743	575,313	582,623
3	Chronic Lower respiratory Diseases	141,090	137,353	138,080	143,392	143,489
4	Stroke	134,148	128,842	129,476	128,931	128,546
5	accidents	121,902	118,021	120,859	122,777	127,792
6	Alzheimer's	82,435	79,003	83,494	84,691	83,637
7	Diabetes	70,553	68,705	69,071	73,282	73,932
8	Influenza and Pneumonia	56,284	53,692	50,476	53,667	50,636
9	Nephritis, Nephrotic syndrome and Nephrosis	48,237	48,935	50,097	45,731	45,622
10	Intentional self-harm(suicide)	36,035	36,909	38,364	38,285	40,600
Total		1,872,981	1,838,501	1,852,349	1,862,408	1,876,588

Table 4 Top 10 leading causes of death

Both the table and figure in the above and below represent the top leading causes of death in United states from year 2008 to 2012. Among the Cardiovascular disease has been remained top the leading causes of the death followed by the cancer. These numbers indicate that CVD remained top the charts in spite being identifying the risk factors to control and with simultaneous improvement in the methods of treatment. **Source: Nationwide Inpatient Sample**

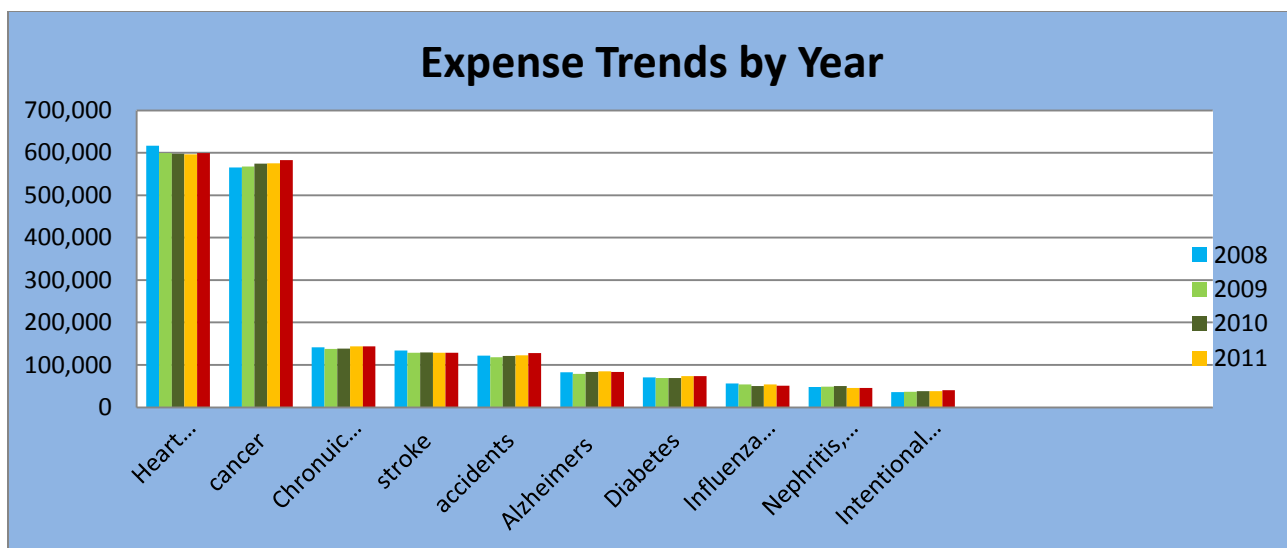


Figure 12Top 10 Leading Causes of Death Trends from Year 2008-2012

2.6.3 Heart Disease facts on mortality and morbidity

- ❖ In the United States every year—About 600,000 people die of heart disease that's 1 in every four deaths.
- ❖ CVD is the leading cause of death for both men and women. More than half of the deaths due to heart disease in 2009 were in men^[80,81]
- ❖ Coronary heart disease is the most common type of heart disease, killing more than 385,000 people annually. ^[80,81]
- ❖ Heart attack kills about 715,000 Americans. Of these, 525,000 are a first heart attack and 190,000 happen in people who have already had a second heart attack. ^[80,82]
- ❖ Coronary heart disease alone costs the United States about \$108.9 billion each year. ^[80,83] This total includes the cost of health care services, medications, and lost productivity.

2.6.4 Death by ethnicity

In most ethnicities in the United States, Heart disease leads cause of death among people including African Americans, Hispanics, and whites. Heart disease is second only to cancer in American Indians or Alaska Natives and Asians or Pacific Islanders; below is the percentages of all deaths caused by heart disease in 2008, listed by ethnicity.⁸⁴

Race of Ethnic Group	% of Deaths
African Americans	24.5
American Indians or Alaska Natives	18.0
Asians or Pacific Islanders	23.2
Hispanics	20.8
Whites	25.1
All	25.0

Table 5 : Death by Race/Ethnicity

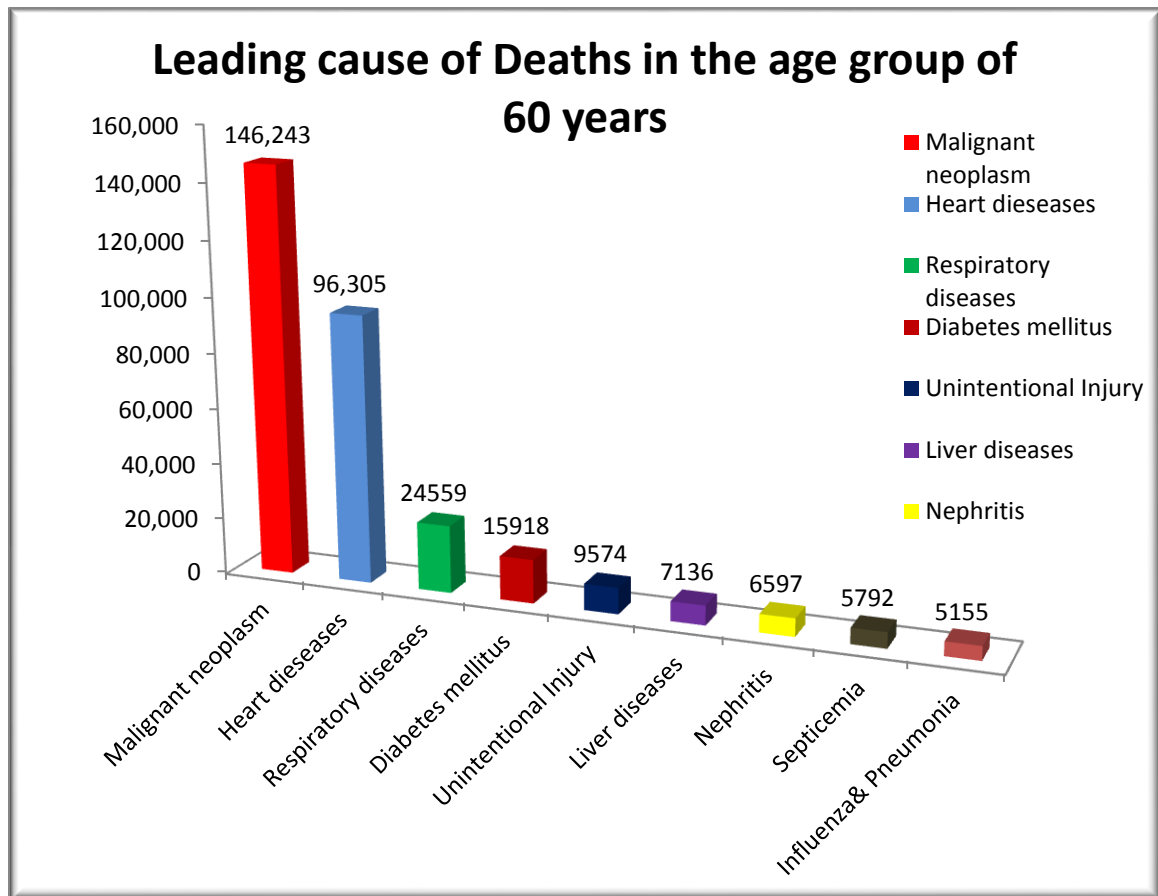


Figure 13: Leading Causes of Death by age 60 yrs.

Malignant Neoplasm is the leading cause of the death above 60yrs in both males and females followed CVD.

2.7 Observational study.

Different research studies have been carried out regarding the role of calcium and dietary calcium induced hypercalcemia and its effects on CVD

Dietary calcium modulation of intracellular calcium, mediated by suppression of calcitropic hormones, has previously been demonstrated to attenuate the risk of hypertension and possibly type II diabetes as well. Intracellular calcium plays a key role

in multiple related metabolic disorders, including hypertension, cardiac hypertrophy, insulin resistance, and hyperinsulinemia, all of which are commonly associated with obesity^[58,59]

In a Nurses Health prospective cohort study of 74,245 women with 24 years of follow-up, They found no independent associations between supplemental calcium intake and risk of incident coronary heart disease (CHD) and stroke^[60].

Randomized study of 36 282 postmenopausal women between 50 to 79 years age at 40 clinical sites given calcium carbonate 500 mg with Vitamin D 200 IU twice daily or to placebo. Calcium/vitamin D supplementation did not show any effects, it neither increased nor decreased coronary or cerebrovascular risk in healthy postmenopausal women over a 7-year use period^[61]

During follow-up of 7904 and 3874 CVD deaths in men and women for a mean of 12 years, researchers identified that Supplements containing calcium used by 51% of men and 70% of women. Calcium supplements intake associated with an increased risk of CVD death (RR>1000 vs 0 mg/d, 1.20; 95% CI, 1.05-1.36), more specifically with heart disease death (RR, 1.19; 95% CI, 1.03-1.37) but not with cerebrovascular disease death (RR, 1.14; 95% CI, 0.81-1.61).^[62]

According to Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), utilizing the WHI dataset, and conducted the meta-analysis of calcium supplements and cardiovascular danger. Calcium supplements with or without vitamin D unobtrusively expand the risk of cardiovascular occasions, particularly

myocardial dead tissue, a finding clouded in the WHI CaD Study by the across the board utilization of individual calcium supplements.^[63]

Population-based Kuopio Osteoporosis Risk Factor (OSTPRE) and Prevention Study Prospective study with 10,555 women between 52-62-year-old ladies roughly 2723 women reported current utilization of calcium or calcium+ Vit D supplementation. Amid the preliminary, CHD was diagnosed in 513 women. Contrasted with study group who didn't consume calcium/calcium+ Vit D supplements.^[64]

Information from 3,139 Chinese men and women in a population-based forthcoming companion study, older ≥ 65 years and free of heart disease or stroke at benchmark, were examined. Higher admission of dietary calcium was connected with decreased risk of all-cause mortality and potentially cardiovascular mortality in Chinese more established individuals with moderate chronic calcium intake^[65]

A Korean cross-sectional study performed in 23 652 participants (40.8 ± 7.3 years, male 83.5%) without chronic kidney disease (estimated glomerular filtration rate ≥ 60 mL/min per 1.73 m²) or clinically overt cardiovascular disease. Elevated serum levels of calcium, phosphorus, and calcium–phosphorus product but not dietary consumption are associated with increased CAC. ^[66].

A prospective cohort study of 34,486 postmenopausal Iowa women 55–69 years old and without a history of ischemic heart disease who completed a dietary questionnaire in 1986. Through 1994, 387 deaths due to ischemic heart disease were documented ^[67]

Decreased and Inadequate vitamin D3 and calcium consumption could play a role in the pathogenesis and progression of hypertension and cardiovascular disease in older women. According to 8-week short-term supplementation with calcium and vitamin D3 is more effective in reducing Systolic Blood Pressure than calcium alone.

Worldwide distribution of dietary calcium intake.

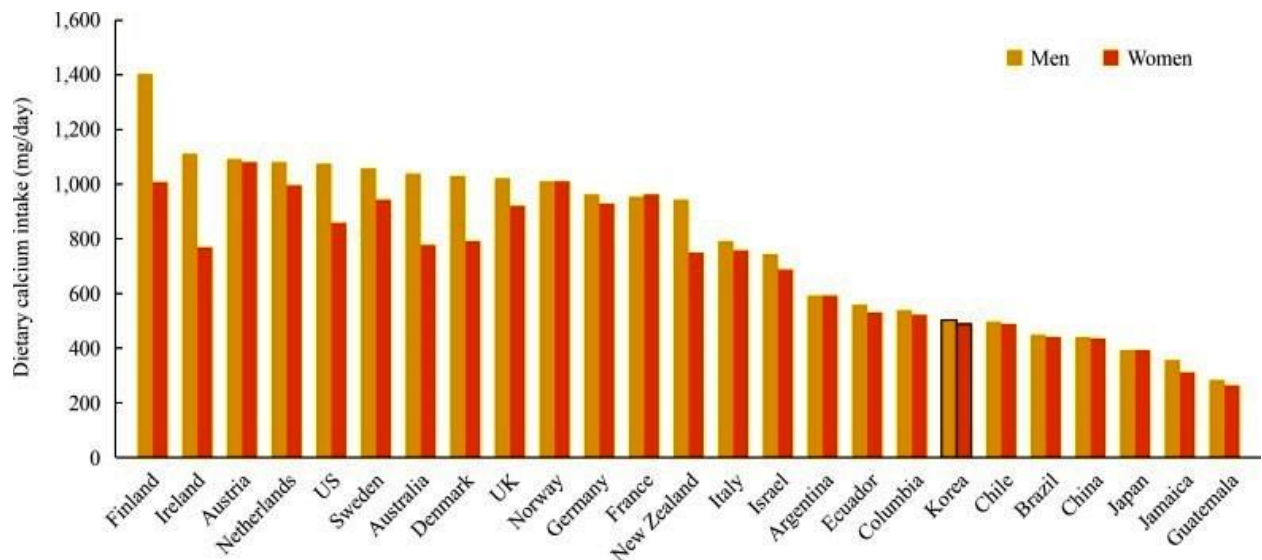


Table 6 Worldwide distribution of Dietary Calcium Intake

Source: Data obtained from the EFSA Panel on Dietetic Products -Weaver and Heaney, Wang and Li, and Pinheiro et al.

CHAPTER 3

METHODOLOGY

3.1 Research Design

The NHANES is a NATION Widely representative, cross-sectional survey that samples noninstitutionalized, civilian U.S. residents using a complex, stratified, multistage probability cluster sampling design ⁽⁶⁸⁾. The NHANES data are collected by the NATIONWIDE Center for Health Statistics of the CDC. Written informed consent was obtained from all participants or proxies and the survey protocol was approved by the Research Ethics Review Board at the NATIONWIDE Center for Health Statistics. ⁽⁶⁸⁾. NATIONWIDE Center for Health Statistics. About the NATIONWIDE Health and Nutrition Examination Survey. 2009. [cited 2008 Aug 17]. Available

The sample data consist of inpatient hospital stay file from the HCUP Nationwide Inpatient Sample (NIS). The NIS is the nationwide database of community hospital inpatient stays. Research and policymakers use NIS data to identify, track and analyze trends in health care utilization, access, charges, quality, and outcome. The NIS is NATIONWIDE INPATIENT SAMPLE represented by all community hospitals (i.e. short-term, non-federal, non-rehabilitation hospitals). The NIS is a sample of hospitals and includes all patients from each hospital, regardless of payer including uninsured. Data were drawn from a sampling frame that contains hospitals comprising about 95 percent of all discharges in the United States. NIS has more than 100 clinical and nonclinical data elements of hospital stay. Which Include data elements like:

- Primary and secondary diagnoses

- Primary and secondary procedures
- Admission and discharge status of patients
- Patient demographics (gender, age, race, median income for ZIP code)
- Payment source
- Total charges
- Length of hospital stay
- Hospital characteristics (size, ownership, teaching status)

Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK97358/>

3.1.1 NIS and NHANES Data Set and Data Elements

NIS Dataset:

There are two parts: the core file and the hospital file. The core file has the data elements depicted the first core part of DXn deal with ICD-9 diagnostic and repair procedural codes respectively. Other factors relate to mortality and patient classifications. The patient classifications include age, gender, race, insurance type, admission type as source and the calendar year to which the data pertains.

Table. Data Variables Used for Analysis:

The NIS data set on different variables covering the period of 2006-2012 were used in this project.

Study Variables	Original Variable Name in the NIS Data Set	Variable Description
Age	AGE	Age in years, Numerical Variable
Mortality	DIED	Patient did not die during hospitalization (DIED=0); Patient died during hospitalization (DIED=1), Categorical (binary) Variable
GENDER	FEMALE	Gender of patient FEMALE = 1 is Male; FEMALE=0 is female, Categorical (binary) Variable
TOTAL CHARGE	TOTCHG	Total charges , Numerical Variable
RACE	RACE	1 = White, 2 = Black, 3 = Hispanic, 4 = Asian/Pacific, 5 = Native Am., 6 = Other, Categorical Variable
NUMBER OF DIAGNOSES	NDX	The number of diagnoses on the patient record, Numerical Variable
REGION	REGION	Four regions are included Northeast = 1, Midwest =2, South = 3, west =4 , Categorical Variable

440.1	ATHEROSCLEROSIS OF RENAL ARTERY
-------	---------------------------------

NIS Data variables Used for Analysis

3.1.2 Study Group/ Inclusion/ Exclusion Criteria

This research will analyze the NIS data from 2006-2012 by HCUP and NHANES data collected by the Centers for Disease Control (CDC), from 2005-2010. The analysis used Statistical Analysis Software (SAS version 9.4), SPSS ,Excel Microsoft and R programing. This study utilized a series of processing methods on both NIS and NHANES data, data mining techniques and statistical procedures to attain its goals. Data cleaning, recoding, extraction were used to arrange the raw data for the analysis. The NHANES data set contains respondents aged a few months to over 80. In order to be included in the study, participant of all ages were included to avoid missing out any possible new outcomes. Recoding and truncation strategies were conducted to control outliers in the variables to keep the individual in the data set and at the same time minimize the harm to statistical inference.¹ Weighting was done to ensure that the means can be compared to the NATIONWIDE population. Participants with whose serum calcium level were above **10 mg** (2.5 mmol/L) moderate Hypercalcemia included in the study and looked for any significant association with rise in Blood Pressure.

The prevalence of use and mean contribution of calcium and vitamin D from supplemental sources was calculated. Mean calcium and vitamin D intake were calculated from the estimated usual intake distributions (dietary and total). Each adjusted intake was compared with the AI and tolerable upper intake level (UL) [55] appropriate to the individual, and the fraction of individuals above the cutoffs was used as the estimate of the proportion of the population that is meeting the DRI recommendations. The variables of interest were organized and merged and more frequencies were done on the selected variables to make sure they were similar to frequencies. Some variables were

coded into categorical variables (age, blood pressure, calcium consumption, education and income). Other variables such as ethnicity and gender were also recoded.

3.2 Disease and Procedures Coding for NIS and NHANES data

The ICD-9 CM codes and clinical classification codes for co-morbidities are given in

HYPERCALCEMIA	
275.42	HYPERCALCEMIA
COMORBIDITY DISEASES BELOW	
Hypertensive heart disease	
402.00	MALIGNANT HYPERTENSIVE HEART DISEASE WITHOUT HEART FAILURE
402.01	MALIGNANT HYPERTENSIVE HEART DISEASE WITH HEART FAILURE
402.10	BENIGN HYPERTENSIVE HEART DISEASE WITHOUT HEART FAILURE
402.11	BENIGN HYPERTENSIVE HEART DISEASE WITH HEART FAILURE
402.90	UNSPECIFIED HYPERTENSIVE HEART DISEASE WITHOUT HEART FAILURE
402.91	UNSPECIFIED HYPERTENSIVE HEART DISEASE WITH HEART FAILURE
Ischemic heart disease	
411.89	OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE OTHER
414.8	OTHER SPECIFIED FORMS OF CHRONIC ISCHEMIC HEART DISEASE
414.9	CHRONIC ISCHEMIC HEART DISEASE UNSPECIFIED
437.1	OTHER GENERALIZED ISCHEMIC CEREBROVASCULAR DISEASE
Coronary artery occlusion	
411.81	ACUTE CORONARY OCCLUSION WITHOUT MYOCARDIAL INFARCTION
414.2	CHRONIC TOTAL OCCLUSION OF CORONARY ARTERY
414.4	CORONARY ATHEROSCLEROSIS DUE TO CALCIFIED CORONARY LESION

Myocardial infarction	
410.00	ACUTE MYOCARDIAL INFARCTION OF ANTEROLATERAL WALL EPISODE OF CARE UNSPECIFIED
410.01	ACUTE MYOCARDIAL INFARCTION OF ANTEROLATERAL WALL INITIAL EPISODE OF CARE
410.02	ACUTE MYOCARDIAL INFARCTION OF ANTEROLATERAL WALL SUBSEQUENT EPISODE OF CARE
410.10	ACUTE MYOCARDIAL INFARCTION OF OTHER ANTERIOR WALL EPISODE

	OF CARE UNSPECIFIED
410.11	ACUTE MYOCARDIAL INFARCTION OF OTHER ANTERIOR WALL INITIAL EPISODE OF CARE
410.12	ACUTE MYOCARDIAL INFARCTION OF OTHER ANTERIOR WALL SUBSEQUENT EPISODE OF CARE
410.20	ACUTE MYOCARDIAL INFARCTION OF INFEROLATERAL WALL EPISODE OF CARE UNSPECIFIED
410.21	ACUTE MYOCARDIAL INFARCTION OF INFEROLATERAL WALL INITIAL EPISODE OF CARE
410.22	ACUTE MYOCARDIAL INFARCTION OF INFEROLATERAL WALL SUBSEQUENT EPISODE OF CARE
410.30	ACUTE MYOCARDIAL INFARCTION OF INFEROPOSTERIOR WALL EPISODE OF CARE UNSPECIFIED
410.31	ACUTE MYOCARDIAL INFARCTION OF INFEROPOSTERIOR WALL INITIAL EPISODE OF CARE
410.32	ACUTE MYOCARDIAL INFARCTION OF INFEROPOSTERIOR WALL SUBSEQUENT EPISODE OF CARE
410.40	ACUTE MYOCARDIAL INFARCTION OF OTHER INFERIOR WALL EPISODE OF CARE UNSPECIFIED
410.41	ACUTE MYOCARDIAL INFARCTION OF OTHER INFERIOR WALL INITIAL EPISODE OF CARE
410.42	ACUTE MYOCARDIAL INFARCTION OF OTHER INFERIOR WALL
410.50	ACUTE MYOCARDIAL INFARCTION OF OTHER LATERAL WALL EPISODE OF CARE UNSPECIFIED
410.51	ACUTE MYOCARDIAL INFARCTION OF OTHER LATERAL WALL INITIAL EPISODE OF CARE
410.52	ACUTE MYOCARDIAL INFARCTION OF OTHER LATERAL WALL SUBSEQUENT EPISODE OF CARE
411.81	ACUTE CORONARY OCCLUSION WITHOUT MYOCARDIAL INFARCTION
412	OLD MYOCARDIAL INFARCTION
Atherosclerosis	
414.00	CORONARY ATHEROSCLEROSIS OF UNSPECIFIED TYPE OF VESSEL NATIVE OR GRAFT
414.4	CORONARY ATHEROSCLEROSIS DUE TO CALCIFIED CORONARY LESION
437.0	CEREBRAL ATHEROSCLEROSIS
440.0	ATHEROSCLEROSIS OF AORTA

3.3 Data Collection Methods

The NHANES computer-assisted (CADI) framework is collected the data automatically that was created utilizing Power Builder™. Food tests that employed as a part of past NHANES and USDA overviews turned out to be a piece of the inherent components of the framework, created utilizing RoboHelp™. The CADI gives a standardized procedure to gather NHANES dietary interview information.

The NHANES computer-assisted (CADI) framework is collected the data automatically that was created utilizing Power Builder™. Food tests that employed as a part of past NHANES and USDA overviews turned out to be a piece of the inherent components of the framework, created utilizing RoboHelp™. The CADI gives a standardized procedure to gather NHANES dietary interview information.

NHANES collects data using

- Interviews
- Physical Examinations
- Questionnaires

All participants complete an in-person

- Household Interview.
- Complete A Health Examination.

- All participants may complete additional interviews and questionnaires following the health examination,

This an ongoing long-term health study of general population focused on preventing adverse effects on chronic heart diseases due to increasing use of **calcium** supplementation.

During the household interview, information contains:

- Dietary Modifications Due To Health Conditions
- Dietary Supplement Use
- Demographic
- Socioeconomic And
- Other Health-related Questions Are Also Administered.

24-hour Recalls

Survey participants

- 12 years and older complete the dietary interview on their own.
- Proxy respondents report for children who are five years and younger and for other persons who are not capable of self-reporting.
- Proxy-assisted interviews are done with kids 6-11 years of age.

The NHANES data files are accessible to the public and they contain the following data:

The following variables selected from the data files for the study:

DR1IVD - Vitamin D (D2 + D3) (mcg)

DR2IVD - Vitamin D (D2 + D3) (mcg)

DR2ICALC - Calcium (mg)

DR1TCALC - Calcium (mg)

DR1TVD - Vitamin D (D2 + D3) (mcg)

DR2TVD - Vitamin D (D2 + D3) (mcg)

DR2TCALC - Calcium (mg)

DS1ANTA - Antacid containing calcium/magnesium

DS1IVD - Vitamin D (D2 + D3) (mcg)

DS1ICALC - Calcium (mg)

DS2ANTA - Antacid containing calcium/magnesium

DS2IVD - Vitamin D (D2 + D3) (mcg)

DS2ICALC - Calcium (mg)

DS1TVD - Vitamin D (D2 + D3) (mcg)

DS1TCALC - Calcium (mg)

DS2TVD - Vitamin D (D2 + D3) (mcg)

DS2TCALC - Calcium (mg)

RXQ215A - Antacid, calcium supplement or both?

DSQIVD - Vitamin D (D2 + D3) (mcg)

DSQICALC - Calcium (mg)

DSQTVD - Vitamin D (D2 + D3) (mcg)

DSQTCALC - Calcium (mg)

In the Demographic data file, the variable selected were:

- Years at screening, (adults 20+ years)
- Gender,
- Race,
- Education level 20 years and older
- Adults 20 years and older
- Annual household income.

In the Dietary data file: Dietary interview - individual foods second day data file was selected. Variable selected were: Cholesterol (mg), Calcium (mg), Potassium (mg).

In the Examination data file:

-Body Measure, Body Mass Index, Blood Pressure,

In the Laboratory data file:

Calcium and Vitamin intake and total of serum Calcium levels.

We used a variable name called SEQN to merge the files for the analysis.

3.3.1 Statistical Analysis and Data Cleaning

Effectively collected de-distinguished observational clinical information will be inspected to be accepted as valid data. It will be ordered as proper to explore research questions. All calculations performed with SAS® Release 9.4 running on an IBM PC with the Windows/XP and ten working framework. Every invalid data accounted for and a reason was given for why the information is viewed as invalid (case –missing value). Where distant information watched, investigations will be performed with and without the peripheral information. Sound factual proof that the information are remote (i.e. peripheral information is more than 4 standard deviations past the mean of practically identical information) will be archived. Peripheral information can be expelled from an investigation in the event that it can be appeared to enhance the force of the actual tests or if not evacuating it would skew the outcome.

3.4. Modeling Techniques Overview:

The following is a brief summary of some major statistical modeling techniques such as Cox regression, c-statistic, linear regression, Kolmogoro Smirvov test and Logistic regression were frequently mentioned for predicting outcome models.

3.6. Descriptive statistics

Descriptive statistics that were used to summarize the demographic data include means, standard deviations, percentages and frequency counts. Percentage and frequencies tables were used to describe the categorical and ordinal variables. We recoded the variables to account for outliers. The PROC frequencies showed missing cases and outliers. In this study, missing cases and outliers were dropped.

Proc means used to calculate the mean values, determine the mean number of missing values, identify outliers and compare estimates with and without outliers. Sample weight applied to the recording of the variables. Therefore, the means calculated for this multistage probabilistic sample is weighted arithmetic mean.

3.6. Inferential statistics

Inferential statistics used in the study were chi-square and regression analysis. Chi-square test of association was used to test for the presence of the systematic relationship between the dependent variables (blood pressure) and the independent variables (subgroups). There after the significant variables from the chi-square test were the only factors included for the ordinal regression. The logistic regression and Cramer's V statistic were further used to identify if calcium is determinant of Blood Pressure..

Descriptive and distribution analyses will be performed for all appropriate variables. Continuous variables will be assessed for normality. If the data is normally distributed, parametric methods will be used to analyze data otherwise non-parametric

methods will be used. Non-parametric methods will be used to analyze score data. Categorical analyses with the appropriate methods will be used to compare categorical variables. Cochran-Mantel-Haenszel tests (for categorical variables) or linear models (for continuous variables) will be used to compare the baseline clinical characteristics. Relationships between outcome and clinical characteristics will be tested by using Pearson correlations. When data are not normally distributed, nonparametric tests such as Spearman correlation will be used. Also nonparametric tests (Wilcoxon rank sum test) will be used where appropriate. Categorical variables will be analyzed using the chi-square test or Fisher exact test where appropriate to compare groups. A two-sample student's t test will be used to compare difference in scores between clinical groups. Pearson correlation or the Spearman rank correlation coefficient will be used where appropriate to test independence between variables. Spearman rank correlation coefficients between categorical factors and the continuous research outcomes (length of stay, total charges and mortality) will be calculated. All means will be provided with the standard deviation (SD). For comparison of means, the Student t-test will be used, and where appropriate, a paired t-test will be performed.

The following SAS procedures will be used to perform the analyses: The CORR Procedure, The CATMOD Procedure, The FREQ Procedure, The GLM Procedure, the LOGISTIC Procedure and The MEANS Procedure.

3.8. Cox Proportional Hazards Regression:

The Cox proportional hazards model describes the relationship the time that passes before some event occurs to one or more covariates that may be associated with that quantity of time using the hazard function, $\lambda_0(t)$. Three central assumptions exist in this

regression technique²⁰. The linearity assumption states that the relationship between a predictor and the outcome takes a linear functional form. For variables that have a skewed distribution, as laboratory values commonly do, the axis may be transformed by a square root or logarithmic function so that the transformed variable may adhere better to the linearity assumption.

Further assumption states that the total effect of different predictors may be estimated simply by summing the individual effects. In cases where a more complex variable interaction is believed to exist, the experimenter may create a composite variable by joining two individual variables together in a single term. The proportional hazards assumption states that the impact of each predictor on survival does not change over time. Extensions to the Cox model exist, such as the use of time-dependent covariates, to allow for situations where this assumption does not hold²¹.

In summary, the Cox assumptions are not rigid, and some methods exist to account for situations when they are violated. These methods tend to require a priori preference for some functional form by the experimenter.

3.8. C-Statistic:

Concordance (C) statistic model translates into a graphical plot which demonstrates the performance of a two-classifications; true positive versus false positive or sensitivity versus specificity. It is also known as a “receiving operating characteristic” or simply ROC curve and used during WWII for radar signals analysis. US military utilized ROC to predict Japanese aircraft from their radar signals¹⁹. Currently, c-statistic analysis is commonly used in the evaluation of diagnostic tests.

3.9. Linear Regression:

Linear regression is modeling the relationship between two variables using the least squares approach. A fitted linear regression model can be used to identify the relationship between a single predictor x and the response variable y .

3.10. Kolmogoro Smirnov Test:

Kolmogoro Smirvov (K-S) test is a nonparametric test for the equality of continuous, one dimensional probability distribution that can be used to compare a sample with a reference distribution or to compare two samples. It is commonly being used to standardize and compare with a standard normal distribution.

3.12. Logistic Regression:

Logistic model is used to predict the outcome of a categorical dependent variable based on one or more predictor variables. Logistic regression can be binomial or multinomial, i.e. dead versus alive, success versus failure, yes versus no, better versus no change versus worse. Generally, the outcome is coded as “0” and “1”. Logistic model was developed by Boyd et al in 1987⁹.

Logistic regression is a type of regression analysis used for predicting the outcome of a categorical dependent variable (a dependent variable that can take on a limited number of categories) based on one or more predictor variables. The probabilities describing the possible outcome of a single trial are modeled, as a function of explanatory variables, using a logistic function. Logistic function or logistic curve is a common sigmoid function, given its name in 1844 by Pierre Francois Verhulst who studied it in relation to

population growth. A simple logistic function is defined as $P(t) = 1 / (1 + e^{-t})$, where variable P is considered a population, variable e is Euler's number and variable t is time.

This is a standard logistic sigmoid function with $\beta_0 + \beta_{1x} + e$ on the horizontal axis and $\pi(x)$ on the vertical axis. The input is $\beta_0 + \beta_{1x}$ and the output is $\pi(x)$. Logit function is useful because it can take as an input any value from negative to positive infinity, whereas the output is confined to values between 0 and 1. In the above equations, $\ln$ denotes the natural logarithm, $\pi(x)$ is the probability of being a case, β_0 is the intercept from the linear regression equation, β_{1x} is the regression coefficient multiplied by some value of the predictor and base e denotes the exponential function.

The portion of the output labeled Model Fit Statistics describes and tests the overall fit of the model. This model includes AIC, SC and -2 Log L fit models.

Akaike information criterion (AIC) was developed by Hirotugu Akaike in 1974². It is grounded in the concept of information entropy, in effect offering a relative measure of the information lost when a given model is used to describe reality. It describes the tradeoff between bias and variance in a model, i.e. accuracy and complexity of the model. The formula for $AIC = 2k - 2\ln(L)$, where k is the number of parameters and L is the maximized value of the likelihood function for the estimated model.

Schwarz criterion (SC) or Bayesian information criterion (BIC) was developed by Gideon Schwarz³⁹ in 1978 to predict the likelihood function by adding penalty term of the number of parameters in the model when results are over-fitting. The formula for $SC = -2 \cdot \ln L + k \ln(n)$, where x = the observed data, n = the number of data points in x , k = the number of free parameters to be estimated, $p(x/k)$ = the probability of the observed data and L = the maximized value of the likelihood function for the estimated model.

Wilks' theorem was developed by Samuel Wilks in 1938⁴⁵ to compute the likelihood for the data and compare $-2\text{Log}(L)$ to the chi squared value corresponding to a desired statistical significance as an approximate statistical test.

3.13. Alternative Analysis Methods:

The statistical analyses described in this document are predicted to give maximal statistical efficacy and power. However, analyses planning are based on assumptions that require verification. In the event that the critical underlying assumptions for particular statistical methods are not met, it will be necessary to select alternative statistical methods. Supplemental statistical methods may be selected if they are shown to be more powerful and discriminating than those originally proposed. The rationale for the use of alternative and/or supplemental statistical analyses will be documented.

3.13 Special Notes on Using the Dataset

The Individual Foods File has included food records. As a rule, there are different records per review member in the document. This document connected with different NHANES records by the mix of the respondent succession number (SEQN) and food number (DRXILINE). A status code (DRDDRSTS) is utilized as a part of the current NHANES dietary meeting segment to demonstrate the quality and fulfillment of reaction to the dietary review area. The dietary review segment status is coded as takes after:

Chapter 4

Results

4.1 Descriptive analysis of NHANES data

Cumulative calcium Intake by Age and Gender NHANES 2005-2010

Analysis of Calcium consumption of American population based on the age.

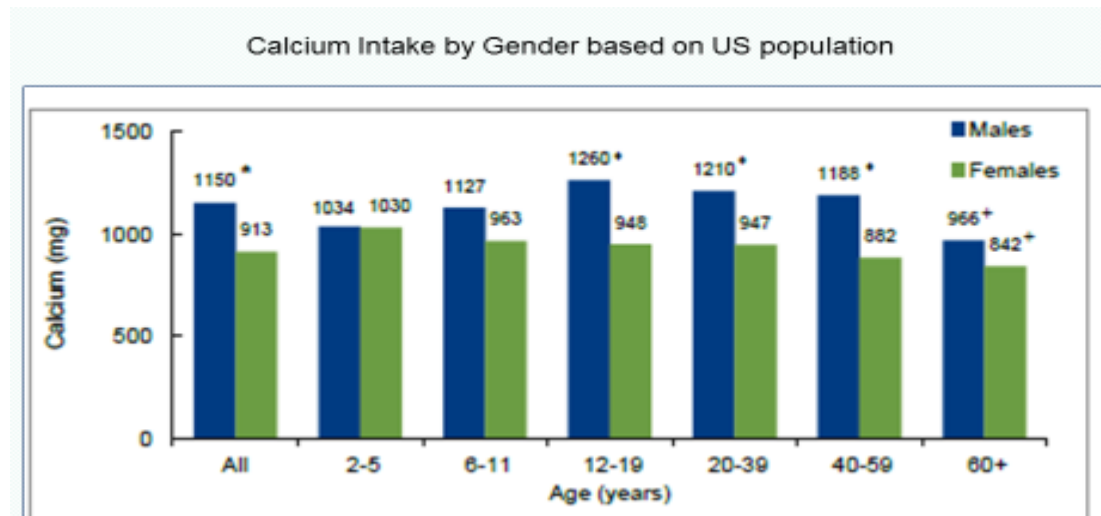


Figure 14 Calcium Intake by Gender and Age of USA Population

Fig 14 shows the age wise distribution of calcium intake in between both Males and Females between all age groups collectively and from age 2-60yrs and older.

Results show that's there significant amount of calcium intake in the age group of 12-19 yrs. and 20—39 yrs. There's significant drop of calcium intake in 60Yrs and older in comparison to other age group. In Males its 966 mgs of the daily requirement consumption and in females its 842mgs of daily requirement

Distribution of calcium Consumption by Race/Ethnicity and Income NHANES 2005-2010

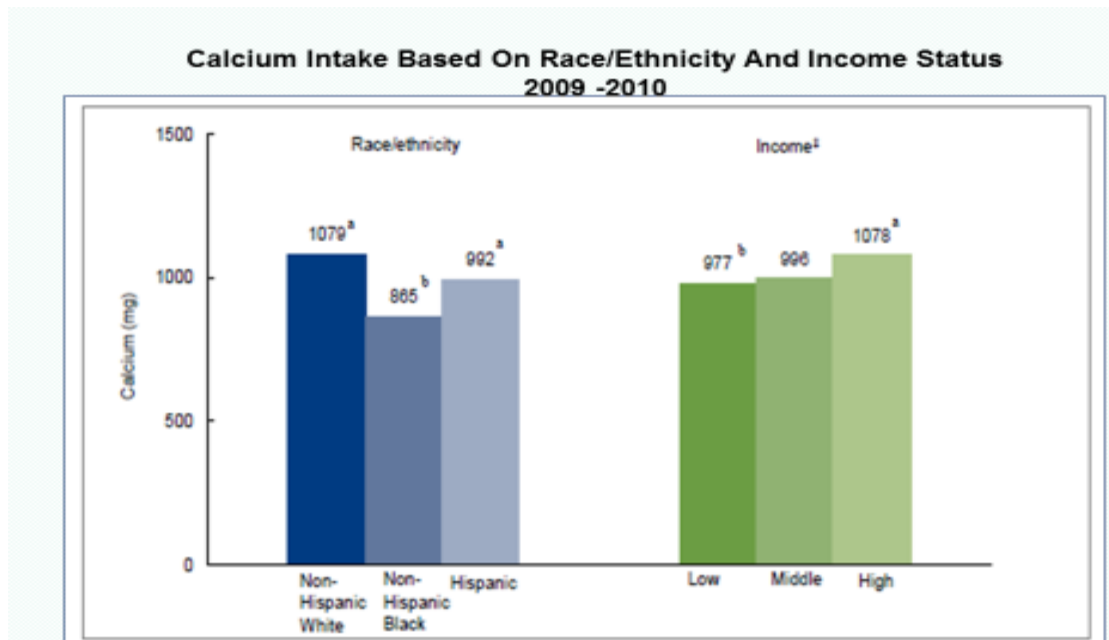


Figure 15 Calcium Intake based on Race /Ethnicity and Income

Non-Hispanic white consumed more dietary calcium of age groups and gender when compared to other Race or Ethnicity.

Fig 15 show there is significant amount calcium intake among higher income come compared to rest of the middle and low income group.

Contribution of diet and supplements to total calcium intake on a given day

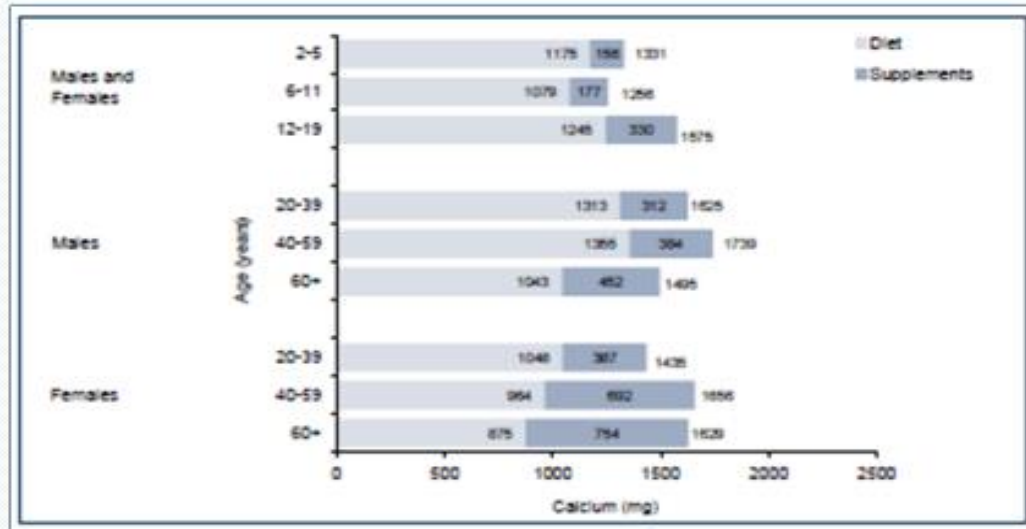


Figure 10: Distribution of Calcium Consumption on given day

This Fig 10 shows the amount of calcium intake through diet and supplements.

There is significant amount of supplemental calcium intake in female over 60 yrs. and older in comparison with males of same age group. In spite of this the dietary calcium intake is low in females in comparison to males.

4.1.1 Calcium Intake and it's a significant effect on Blood Pressure based on Gender and Race

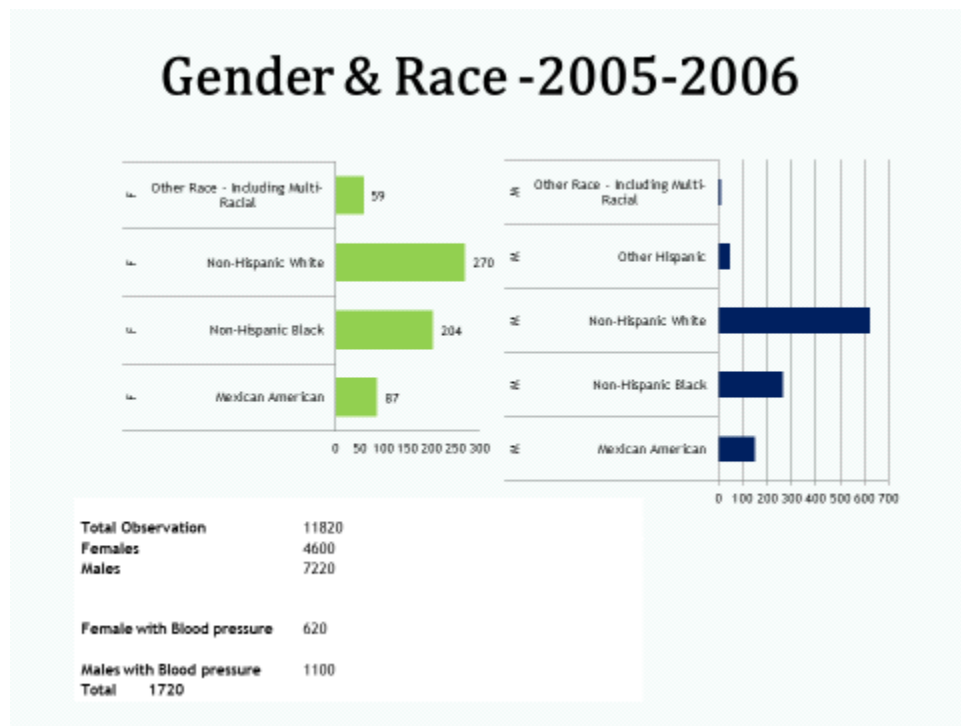


Figure 16 Calcium Intake and it's a significant effect on Blood Pressure based on Gender and Race 2005-2006

Total observation who had serum calcium levels over 10mgs/dL based on the laboratory data where 11820 both males and female together. Females 4600 and Males were 7220 numbers of cases of which 620 cases of females showed rise in blood pressure and males with blood pressure 1100. Total of 1720 cases were found with increase blood pressure and Increase serum calcium. Based on the same information Non-Hispanic white showed significant number of cases compared to other ethnicity in year 2005-2006

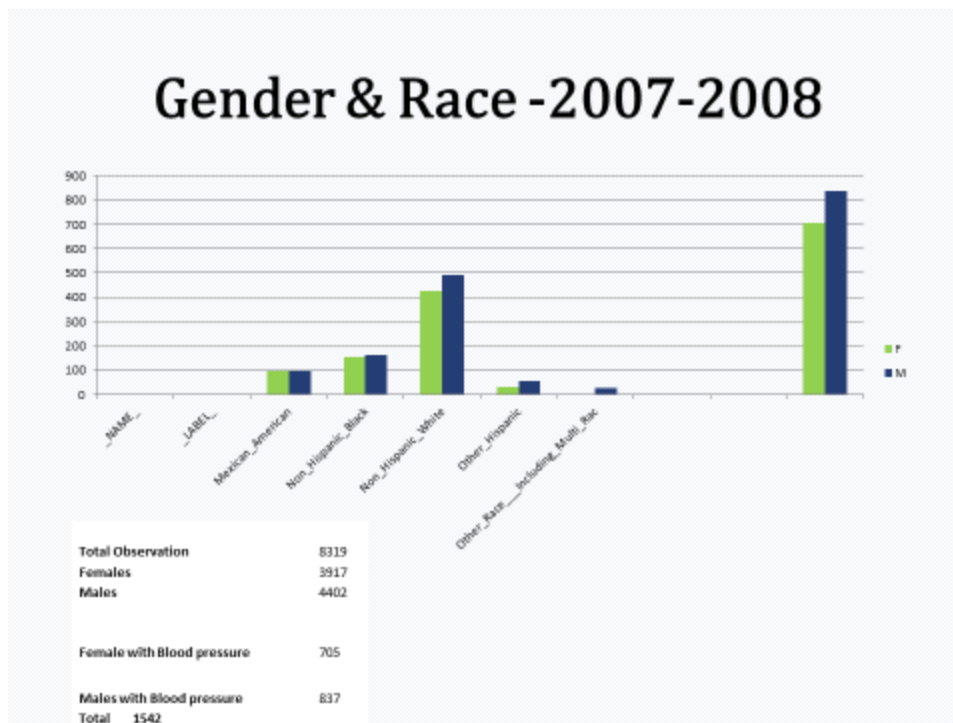


Figure 17 Calcium Intake and it's a significant effect on Blood Pressure based on Gender and Race 2005-2006

Total observation who had serum calcium levels over 10mgs/dL based on the laboratory data where 8319 both males and female together. Females 3917 and Males were 4402 numbers of cases of which 750 cases of females showed rise in blood pressure and males with blood pressure 837. Total of 1542 cases were found with increase blood pressure and Increase serum calcium. Based on the same information Non-Hispanic white showed.

significant number of cases compared to other ethnicity in year 2007-2008.

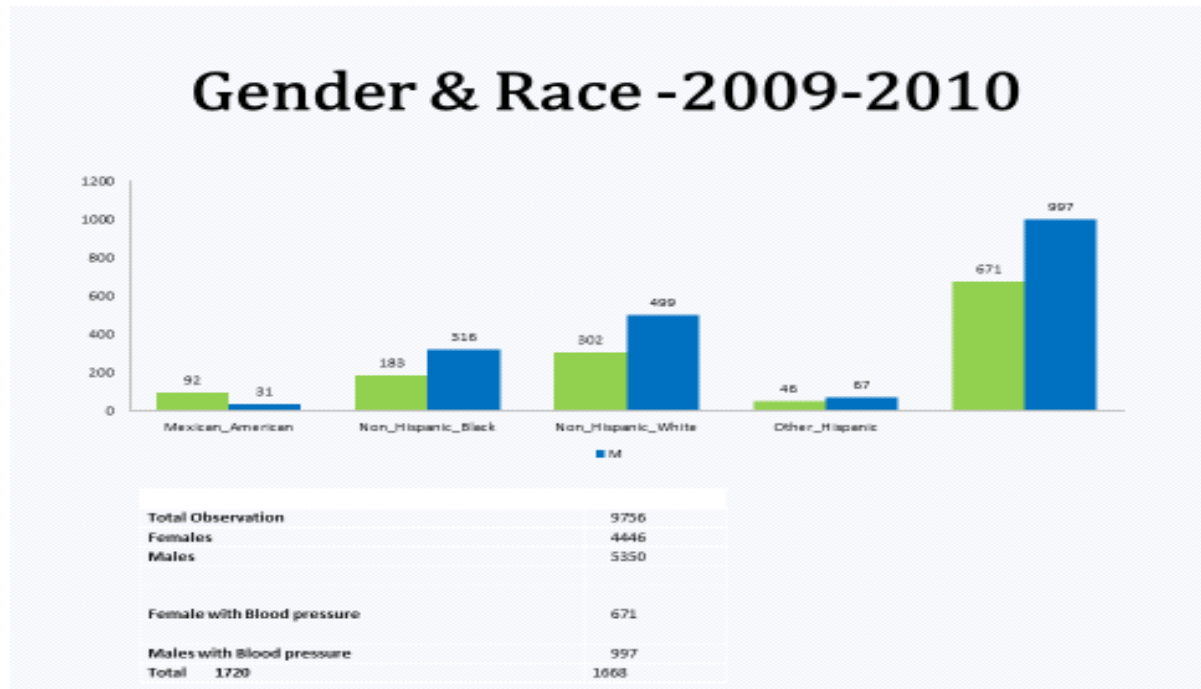


Figure 18 Gender & Race 2009-2010

Total observation who had serum calcium levels over 10mgs/dL based on the laboratory data where 9756 both males and female together. Females 4646 and Males were 5350 numbers of cases of which 671 cases of females showed rise in blood pressure and males with blood pressure 997. Total of 1668 cases were found with increase blood pressure and Increase serum calcium. Based on the same information Non-Hispanic white showed significant number of cases compared to other ethnicity in year 2009-2010

4.1.2 Incidence of Hypertension from year 2005- 2103

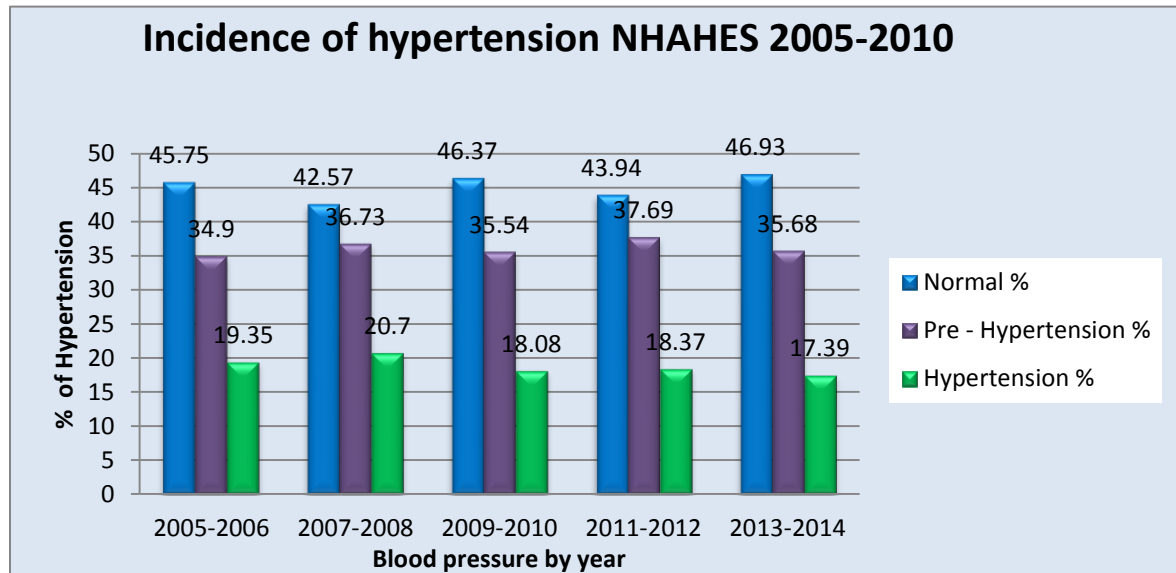


Figure 19 Incidence of Hypertension from year 2005- 2103

There are consistent number hypertensive cases in every year from 2005 to 2010 from normal cases to Hypertension.

4.2 Distribution of Hypercalcemia cases

4.2.1 Distribution of Hypercalcemia cases based on age from year 2006 -2012

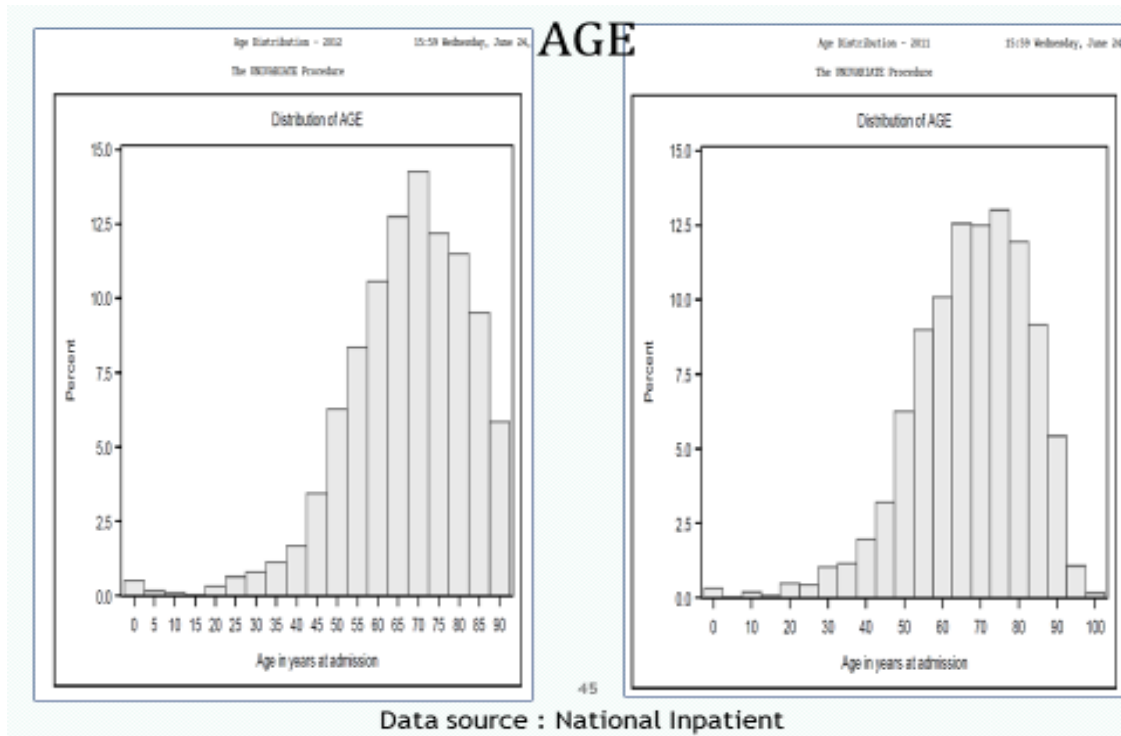


Figure 20 Hypercalcemia distribution by age 2011-2012

Based on the Fig 20 there is increase in cases of Hypercalcemia between the age groups 60 and older in both males and females in year 2012 and 2011 from NIS Data.

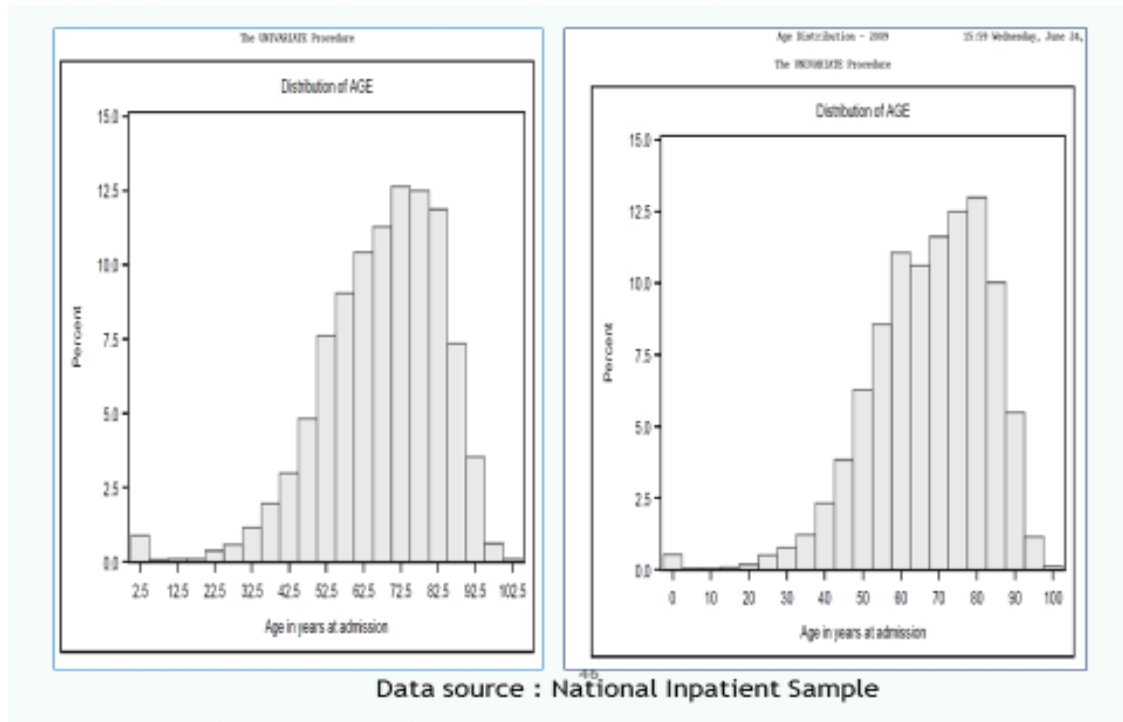


Figure 21: Figure 14 Hypercalcemia distribution by age 2009-2010

Based on the Fig 20 there is increase in cases of Hypercalcemia between the age groups 60 and older in both males and females in year 2009 and 2010 from NIS Data.

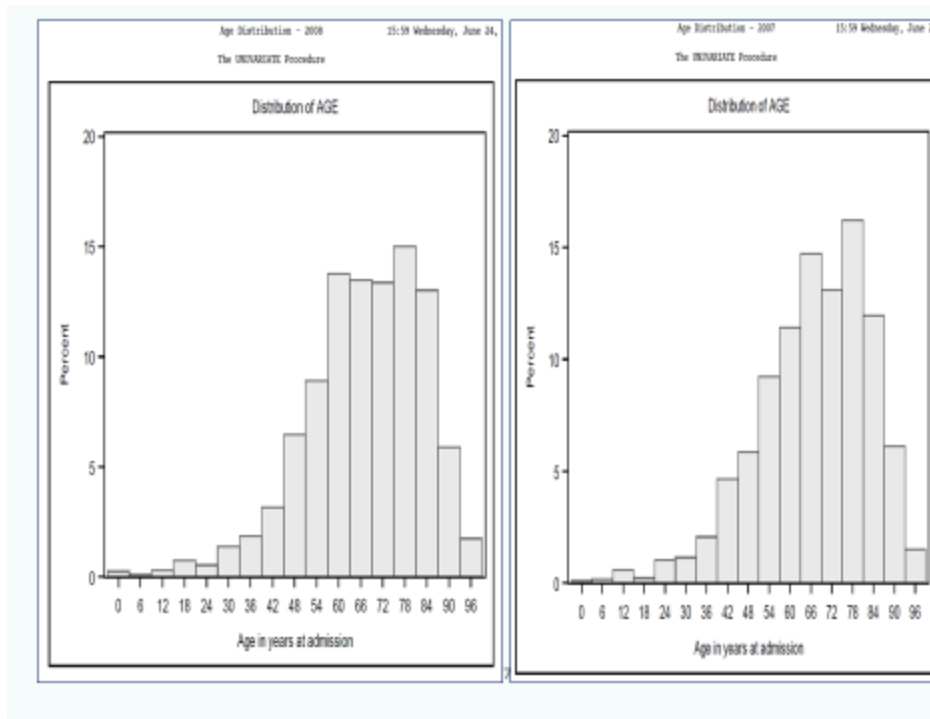


Figure 22 : Figure 14 Hypercalcemia distribution by age 2006-2007

Based on the Fig 20 there is increase in cases of Hypercalcemia between the age groups 60 and older in both males and females in year 2006 and 2007 from NIS Data.

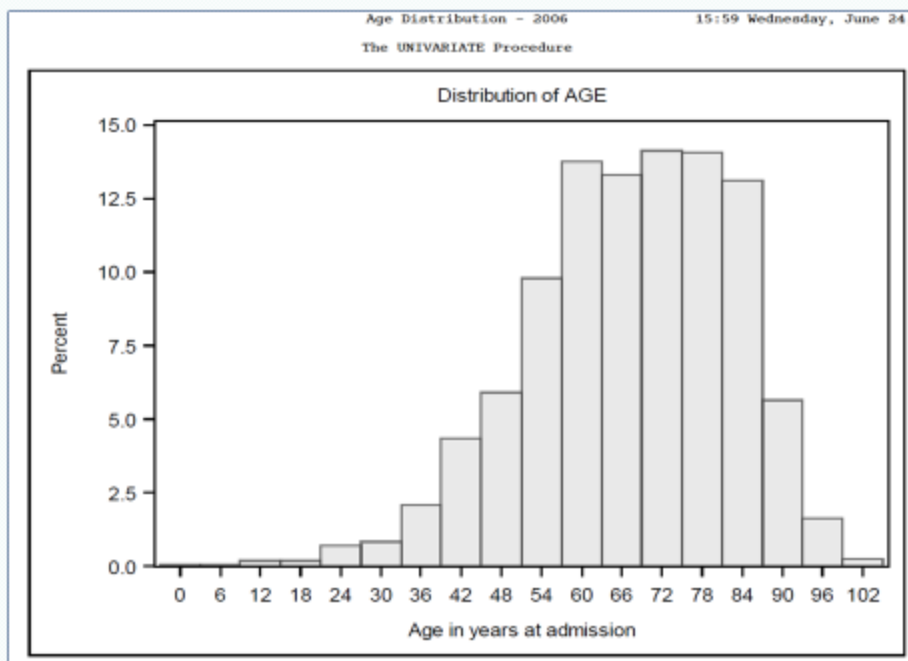


Figure 23: Figure 14 Hypercalcemia distribution by AGE 206

4.3 Distribution of Hypercalcemia cases based on the Race

Race

Year 2006 14:43 We

The FREQ Procedure

Frequency Percent Row Pct Col Pct		Table of HyperCal by RACE						
		RACE(Race (uniform))						Total
HyperCal		1	2	3	4	5	6	
1=White	0	302	125	71	9	3	10	520
		17.54	7.26	4.12	0.52	0.17	0.58	30.20
		58.08	24.04	13.65	1.73	0.58	1.92	
		25.51	40.32	44.94	28.13	75.00	29.41	
2= Black	1	882	185	87	23	1	24	1202
		51.22	10.74	5.05	1.34	0.06	1.39	69.80
		73.38	15.39	7.24	1.91	0.08	2.00	
		74.49	59.68	55.06	71.88	25.00	70.59	
5=N.American	Total	1184	310	158	32	4	34	1722
		68.76	18.00	9.18	1.86	0.23	1.97	100.00
6=Other		Frequency Missing = 551						

Table 7: Hypercalcemia distribution by RACE 2006

0= Indicates Hypocalcemia and 1 = Hypercalcemia

Total number of Hypercalcemia cases 1202

White = 882, Black = 185, Hispanic =87, Other= 24

There are significant number case of White Race and Ethnicity in comparison with rest of the races in 2006.

Year 200714:43 Wed

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of HyperCal by RACE							
	HyperCal	RACE (Race (uniform))						Total
		1	2	3	4	5	6	
1=White	0	347 18.56 57.36 27.34	145 7.75 23.97 39.94	83 4.44 13.72 58.45	11 0.59 1.82 25.58	4 0.21 0.66 57.14	15 0.80 2.48 32.61	605 32.35
2= Black	1	922 49.30 72.89 72.66	218 11.66 17.23 60.06	59 3.16 4.66 41.55	32 1.71 2.53 74.42	3 0.16 0.24 42.86	31 1.66 2.45 67.39	1265 67.65
3= Hispanic	Total	1269 67.86	363 19.41	142 7.59	43 2.30	7 0.37	46 2.46	1870 100.00
4=Asia/Pacific	Frequency Missing = 693							
5=N.American								
6=Other								

50

Table 8: Hypercalcemia distribution by RACE 2007

0= Indicates Hypocalcemia and 1 = Hypercalcemia

Total number of Hypercalcemia cases 1870

White = 922, Black = 218, Hispanic =59, Asia = 30Other= 31

There is significant number case of White Race and Ethnicity in comparison with rest of the races in year 2007

Year 2008							
14:43 Wed							
The FREQ Procedure							
Table of HyperCal by RACE							
Frequency Percent Row Pct Col Pct	HyperCal	RACE(Race (uniform))					
		1	2	3	4	5	6
1=White	0	360	134	71	16	3	17
2= Black		16.22	6.04	3.20	0.72	0.14	0.77
		59.90	22.30	11.81	2.66	0.50	2.83
		22.83	35.36	47.97	39.02	18.75	28.81
3= Hispanic	1	1217	245	77	25	13	42
4=Asia/Pacific		54.82	11.04	3.47	1.13	0.59	1.89
		75.17	15.13	4.76	1.54	0.80	2.59
		77.17	64.64	52.03	60.98	81.25	71.19
5=N.American	Total	1577	379	148	41	16	59
6=Other		71.04	17.07	6.67	1.85	0.72	2.66
Frequency Missing = 509							

Table 9 Hypercalcemia distribution by RACE 2008

0= Indicates Hypocalcemia and 1 = Hypercalcemia

Total number of Hypercalcemia cases 2220

White = 1217, Black = 245, Hispanic =77, Asia = 13 Other=42

There are significant number cases of White Race and Ethnicity in comparison with rest of the races in year 2008

Year 2009

14:43 We

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of HyperCal by RACE							
		RACE(Race (uniform))						
	HyperCal	1	2	3	4	5	6	Total
1=White	0	358 14.55 58.50 20.68	135 5.49 22.06 33.75	73 2.97 11.93 39.25	11 0.45 1.80 28.21	7 0.28 1.14 26.92	28 1.14 4.58 35.90	612 24.88
2= Black								
3= Hispanic	1	1373 55.81 74.30 79.32	265 10.77 14.34 66.25	113 4.59 6.11 60.75	28 1.14 1.52 71.79	19 0.77 1.03 73.08	50 2.03 2.71 64.10	1848 75.12
4=Asia/Pacific								
5=N.American	Total	1731 70.37	400 16.26	186 7.56	39 1.59	26 1.06	78 3.17	2460 100.00
6=Other								
Frequency Missing = 447								

52

Table 10 Hypercalcemia distribution by RACE 2009

0= Indicates Hypocalcemia and 1 = Hypercalcemia

Total number of Hypercalcemia cases 1731

White =1373, Black = 265, Hispanic =113, Asia = 28 Other= 50

There are significant number case of White Race and Ethnicity in comparison with rest of the races in year 2009

Year 2010 14:43 Wed

The FREQ Procedure

Frequency Percent Row Pct Col Pct		Table of HyperCal by RACE						
		RACE(Race (uniform))						
HyperCal		1	2	3	4	5	6	Total
1=White	0	379	158	77	20	2	16	652
		12.65	5.28	2.57	0.67	0.07	0.53	21.77
2= Black		58.13	24.23	11.81	3.07	0.31	2.45	
		18.34	27.05	35.98	37.74	15.38	25.00	
3= Hispanic	1	1688	426	137	33	11	48	2343
		56.36	14.22	4.57	1.10	0.37	1.60	78.23
4=Asia/Pacific		72.04	18.18	5.85	1.41	0.47	2.05	
		81.66	72.95	64.02	62.26	84.62	75.00	
5=N.American	Total	2067	584	214	53	13	64	2995
6=Other		69.02	19.50	7.15	1.77	0.43	2.14	100.00
Frequency Missing = 326								

53

Table 11: Hypercalcemia distribution by RACE 2010

0= Indicates Hypocalcemia and 1 = Hypercalcemia

Total number of Hypercalcemia cases 2067

White = 1688, Black = 426, Hispanic =137, Asia = 33, Other= 48

There are significant number case of White Race and Ethnicity in comparison with rest of the races in year 2010

Year 2011							
14:43 Wed							
The FREQ Procedure							
Frequency Percent Row Pct Col Pct	Table of HyperCal by RACE						
	HyperCal	RACE(Race (uniform))					
		1	2	3	4	5	6
		Total					
1=White	0	462	198	97	22	3	26
		14.94	6.40	3.14	0.71	0.10	0.84
2= Black		57.18	24.50	12.00	2.72	0.37	3.22
		21.93	31.78	44.70	35.48	18.75	38.81
3= Hispanic	1	1645	425	120	40	13	41
		53.20	13.75	3.88	1.29	0.42	1.33
4=Asia/Pacific		72.02	18.61	5.25	1.75	0.57	1.80
		78.07	68.22	55.30	64.52	81.25	61.19
5=N.American	Total	2107	623	217	62	16	67
6=Other		68.14	20.15	7.02	2.01	0.52	2.17
Frequency Missing = 324							

Table 12 :Hypercalcemia distribution by RACE 2011

0= Indicates Hypocalcemia and 1 = Hypercalcemia

Total number of Hypercalcemia cases 2107

White = 1645, Black = 425, Hispanic =120, Asia = 40, Other= 41

There are significant number case of White Race and Ethnicity in comparison with rest of the races in year 2011

Year 2012

14:43 Wed

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of HyperCal by RACE							
HyperCal	RACE(Race (uniform))							
	1	2	3	4	5	6	Total	
1=White	0	450 14.46 60.48 20.45	171 5.50 22.98 31.67	76 2.44 10.22 36.02	14 0.45 1.88 25.45	8 0.26 1.08 40.00	25 0.80 3.36 29.41	744 23.92
2= Black								
3= Hispanic	1	1750 56.25 73.93 79.55	369 11.86 15.59 68.33	135 4.34 5.70 63.98	41 1.32 1.73 74.55	12 0.39 0.51 60.00	60 1.93 2.53 70.59	2367 76.08
4=Asia/Pacific								
5=N.American	Total	2200 70.72	540 17.36	211 6.78	55 1.77	20 0.64	85 2.73	3111 100.00
6=Other		Frequency Missing = 183						

55

Table 13: Hypercalcemia distribution by RACE 2012

0= Indicates Hypocalcemia and 1 = Hypercalcemia

Total number of Hypercalcemia cases 2200

White = 1750, Black = 369, Hispanic =135, Asia = 41, Other= 60

There are significant number cases of White Race and Ethnicity in comparison with rest of the races in year 2012

4.3. Hypercalcemia Distribution by Gender.

Year 2006				
The FREQ Procedure				
Frequency Percent Row Pct Col Pct	Table of HyperCal by FEMALE			
	FEMALE (Indicator of sex)			
	HyperCal	0	1	Total
0=Male 1 = Female	0	188 8.28 27.65 24.26	492 21.66 72.35 32.89	680 29.94
	1	587 25.85 36.90 75.74	1004 44.21 63.10 67.11	1591 70.06
	Total	775 34.13	1496 65.87	2271 100.00
	Frequency Missing = 2			

Table 14 : Hypercalcemia distribution by Gender -2006

0= Indicates Hypocalcemia and 1 = Hypercalcemia

0= Males and 1 = Females

Total number of Hypercalcemia cases 1591

Males = 587, Females = 1004.

There are significant number cases of Female cases of Hypercalcemia in comparison with males in year 2006

Year 2007			
The FREQ Procedure			
Frequency Percent Row Pct Col Pct	Table of HyperCal by FEMALE		
	HyperCal	FEMALE(Indicator of sex)	
		0	1
		Total	
0=Male 1 = Female	0	231	573
		9.02	22.37
		28.73	71.27
		25.11	34.92
	1	689	1068
		26.90	41.70
		39.21	60.79
		74.89	65.08
	Total	920	1641
		35.92	64.08
			2561
			100.00
Frequency Missing = 2			

Table 15: Hypercalcemia distribution by Gender -2007

0= Indicates Hypocalcemia and 1 = Hypercalcemia

0= Males and 1 = Females

Total number of Hypercalcemia cases 1757

Males = 689, Females = 1068.

There are significant number cases of Female cases of Hypercalcemia in comparison with males in year 2007

Frequency Percent Row Pct Col Pct	Table of HyperCal by FEMALE			
		FEMALE (Indicator of sex)		
	HyperCal	0	1	Total
	0	193 7.07 26.40 20.53	538 19.71 73.60 30.07	731 26.79
	1	747 27.37 37.39 79.47	1251 45.84 62.61 69.93	1998 73.21
	Total	940 34.44	1789 65.56	2729 100.00

58

Table 16: Hypercalcemia distribution by Gender -2008

0= Indicates Hypocalcemia and 1 = Hypercalcemia

0= Males and 1 = Females

Total number of Hypercalcemia cases 1998

Males = 747, Females = 1251.

There are significant number cases of Female cases of Hypercalcemia in comparison with males in year 2008

Year 2009				
The FREQ Procedure				
Frequency Percent Row Pct Col Pct	Table of HyperCal by FEMALE			
	HyperCal	FEMALE (Indicator of sex)		
		0	1	Total
	0	200 6.88 28.13 21.10	511 17.59 71.87 26.11	711 24.48
0=Male	1	748 25.75 34.09 78.90	1446 49.78 65.91 73.89	2194 75.52
1 = Female	Total	948 32.63	1957 67.37	2905 100.00
Frequency Missing = 2				

Table 17: Hypercalcemia distribution by Gender -2009

0= Indicates Hypocalcemia and 1 = Hypercalcemia

0= Males and 1 = Females

Total number of Hypercalcemia cases 2194

Males = 748, Females = 1446.

There are significant number cases of Female cases of Hypercalcemia in comparison with males in year 2009

Year 2010				
The FREQ Procedure				
Frequency Percent Row Pct Col Pct	Table of HyperCal by FEMALE			
	HyperCal	FEMALE (Indicator of sex)		
		0	1	Total
	0	207	522	729
		6.23	15.72	21.96
		28.40	71.60	
		18.19	23.92	
	1	931	1660	2591
		28.04	50.00	78.04
		35.93	64.07	
		81.81	76.08	
	Total	1138	2182	3320
		34.28	65.72	100.00
Frequency Missing = 1				

60

Table 18: Hypercalcemia distribution by Gender -2010

0= Indicates Hypocalcemia and 1 = Hypercalcemia

0= Males and 1 = Females

Total number of Hypercalcemia cases 2591

Males = 931, Females = 1660.

There are significant number cases of Female cases of Hypercalcemia in comparison with males in year 2010

Year 2011				
The FREQ Procedure				
Frequency Percent Row Pct Col Pct	Table of HyperCal by FEMALE			
	FEMALE (Indicator of sex)			
	HyperCal	0	1	Total
0=Male 1 = Female	0	264 7.73 29.73 22.00	624 18.27 70.27 28.16	888 26.00
	1	936 27.40 37.03 78.00	1592 46.60 62.97 71.84	2528 74.00
	Total	1200 35.13	2216 64.87	3416 100.00

61

Table 19: Hypercalcemia distribution by Gender -2011

0= Indicates Hypocalcemia and 1 = Hypercalcemia

0= Males and 1 = Females

Total number of Hypercalcemia cases 2528

Males = 936, Females = 1592.

There are significant number cases of Female cases of Hypercalcemia in comparison with males in year 2011.

Year 2012

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of HyperCal by FEMALE			
	HyperCal	FEMALE(Indicator of sex)		
		0	1	Total
	0	238 7.23 30.47 19.85	543 16.48 69.53 25.92	781 23.71
	1	961 29.17 38.24 80.15	1552 47.12 61.76 74.08	2513 76.29
	Total	1199 36.40	2095 63.60	3294 100.00

62

Table 20: Hypercalcemia distribution by Gender -2012

0= Indicates Hypocalcemia and 1 = Hypercalcemia

0= Males and 1 = Females

Total number of Hypercalcemia cases 2513

Males = 961, Females = 1552.

There are significant number cases of Female cases of Hypercalcemia in comparison with males in year 2012.

4.5. Logistic Regression of Hypercalcemia and CVD

Logistic regression analysis done for finding the likelihood of comorbidity of

Hypercalcemia and Cardiovascular diseases from year 2006 to 2012

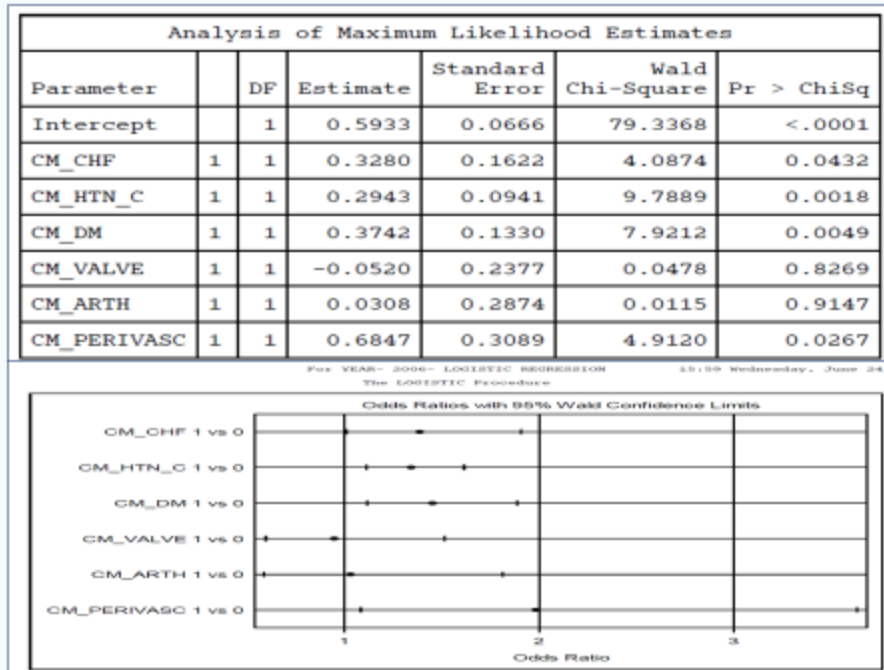


Table 21: Analysis of likelihood Estimates between Hypercalcemia and CVD -2006

No significant association is found in the Table 21 for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant

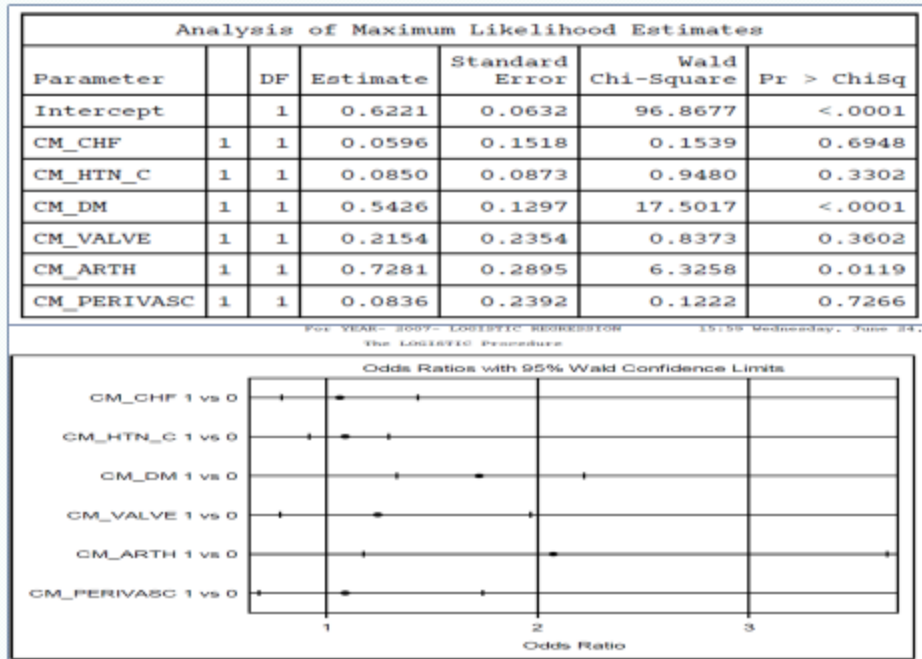


Table 22: Analysis of likelihood Estimates between Hypercalcemia and CVD -2007

No significant association is found in the Table 22 for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant in 2007 data

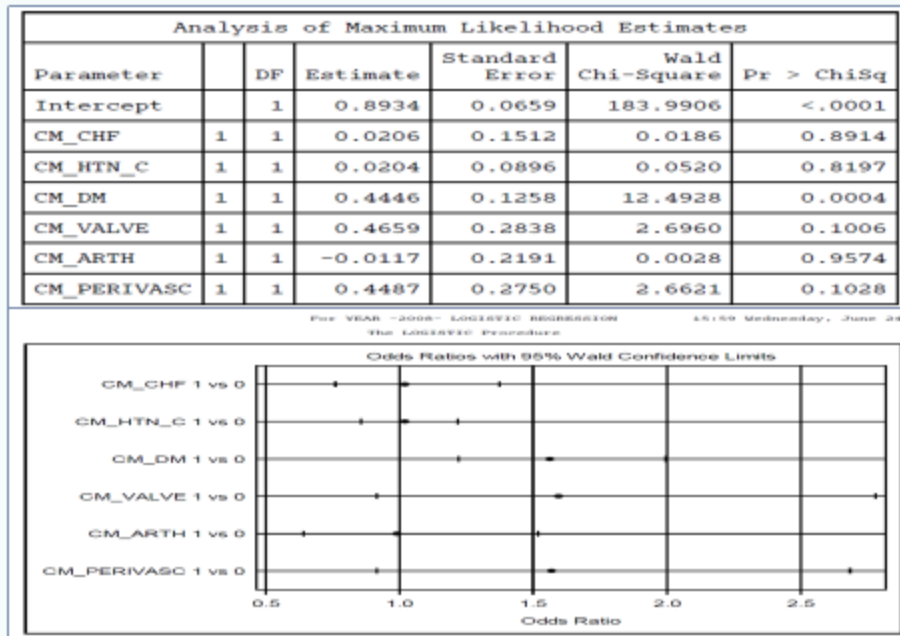


Table 23: Analysis of likelihood Estimates between Hypercalcemia and CVD -2008

No significant association is found in the Table 23. for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant in 2008 data

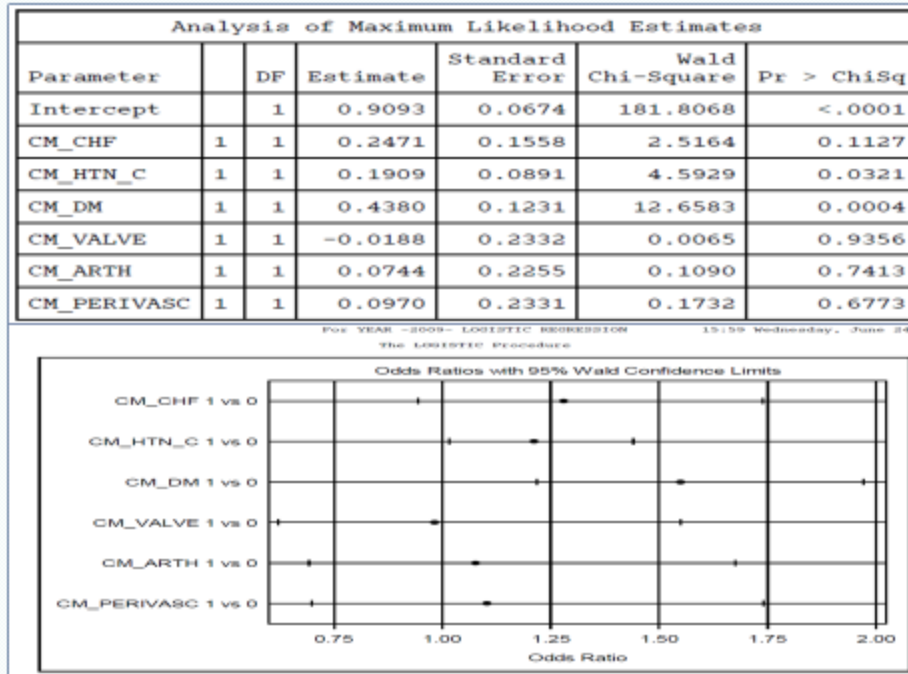


Table 24: Analysis of likelihood Estimates between Hypercalcemia and CVD -2009

No significant association is found in the Table 24 for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant in 2009 data

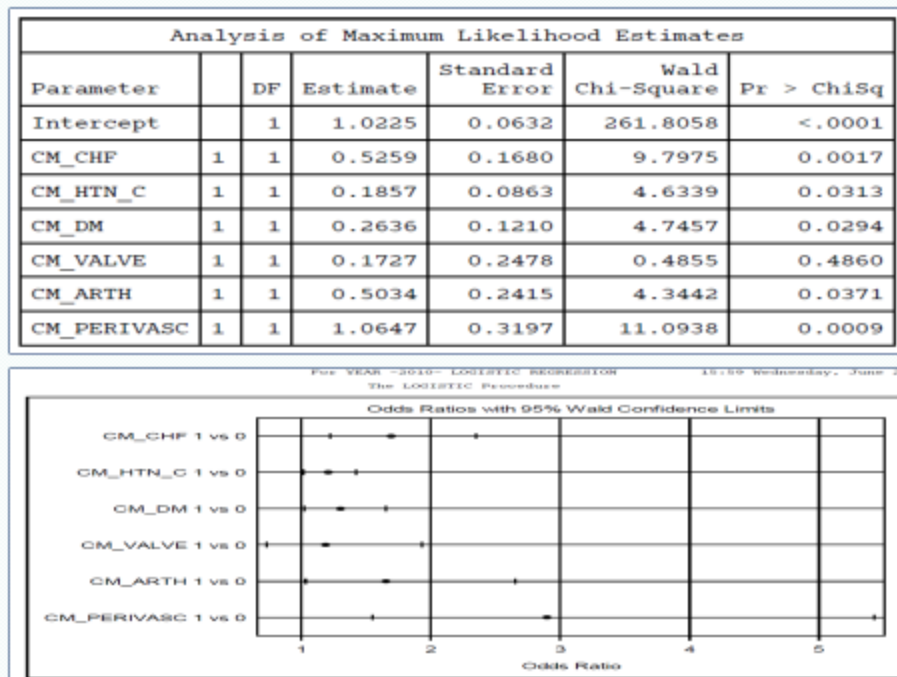


Table 25: Analysis of likelihood Estimates between Hypercalcemia and CVD -2010

No significant association is found in the Table 25. for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant in 2010 data

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	0.8289	0.0631	172.3737	<.0001
CM_CHF	1	1	0.2239	0.1361	2.7074	0.0999
CM_HTN_C	1	1	0.2241	0.0814	7.5761	0.0059
CM_DM	1	1	0.2480	0.1032	5.7827	0.0162
CM_VALVE	1	1	0.0582	0.2006	0.0843	0.7715
CM_ARTH	1	1	0.0385	0.1959	0.0387	0.8441
CM_PERIVASC	1	1	0.1829	0.2227	0.6748	0.4114

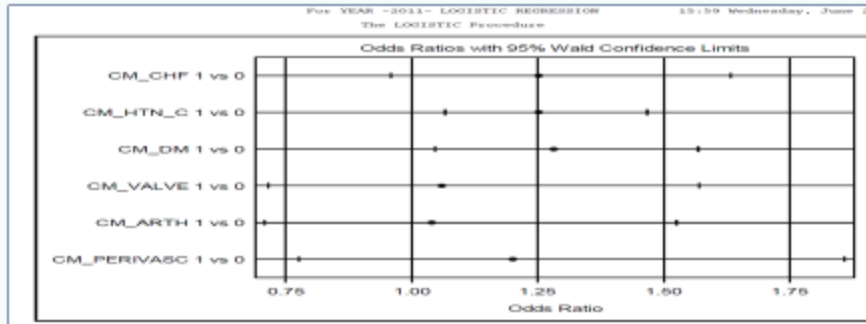


Table 26: Analysis of likelihood Estimates between Hypercalcemia and CVD -2011

No significant association is found in the Table 26.. for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant in 2011 data

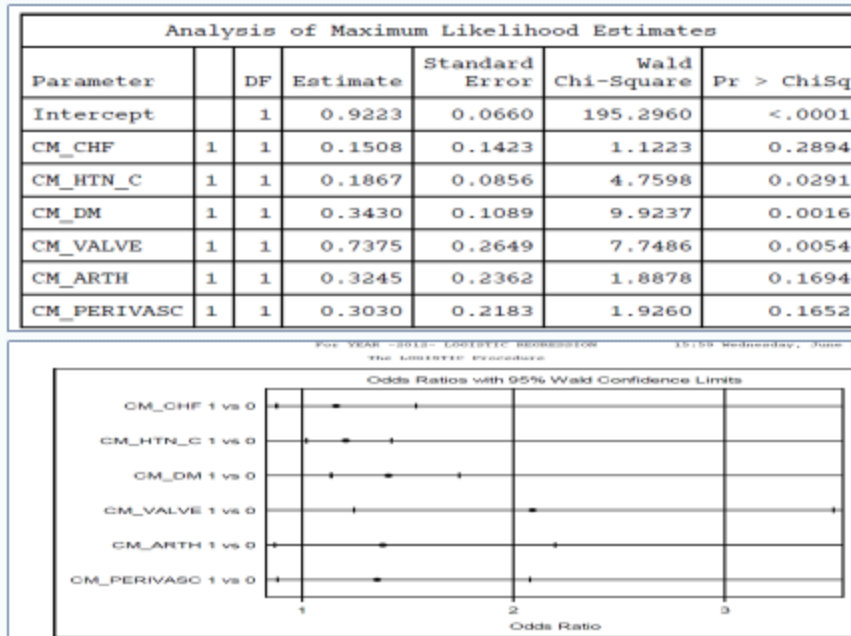


Table 27: Analysis of likelihood Estimates between Hypercalcemia and CVD -2012

No significant association is found in the Table 27. for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant in 2012 data

Year 2012	Analysis of Maximum Likelihood Estimates					
	Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
	Intercept	1	-7.7780	0.0204	145463.831	<.0001
	Ischemic	1	-0.4079	0.1788	5.2045	0.0225
	Coronary	1	-2.1986	1.0006	4.8280	0.0280
	Myocardial	1	-0.5966	0.1282	21.6385	<.0001
Year 2011	Analysis of Maximum Likelihood Estimates					
	Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
	Intercept	1	-7.8699	0.0203	150229.848	<.0001
	Hypertensive	1	-0.9151	0.3785	5.8444	0.0156
	Ischemic	1	-0.6082	0.2017	9.0924	0.0026
	Coronary	1	-10.7215	78.7828	0.0185	0.8918
Year 2006	Analysis of Maximum Likelihood Estimates					
	Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
	Intercept	1	-8.3103	0.0255	106030.541	<.0001
	Hypertensive	1	-0.6959	0.3544	3.8552	0.0496
	Ischemic	1	-0.8296	0.3030	7.4982	0.0062
	Myocardial	1	-0.7200	0.1689	18.1629	<.0001

Table 28: Cumulative Analysis of likelihood estimates

No significant association is found in the Table 25. for Hypercalcemia and rest of cardiovascular diseases like Congestive Heart failure, Malignant Hypertension, Valvular diseases and Perivascular heart diseases. As P value of <0.001 is not significant in 2012 data

CHAPTER 5

DISCUSSIONS AND LIMITATIONS

- ❖ Calcium has a significant effect on Blood Pressure

- Hypothesis: $H_0 = H_1$
- Alternative Hypothesis: $H_0 \neq H_1$

Results are in the favor the primary hypothesis stating the significant number of cases showed rise in blood pressure in comparison with cases with increase calcium intake

- ❖ There a significant relationship between Calcium and Blood Pressure in all Ethnic Groups of NHANES data from 2006 – 2010

- Null Hypothesis: $H_0 = H_1$
- Alternative Hypothesis: $H_0 \neq H_1$

Results showed that there is significant relationship .Non-Hispanic Whites showed increase incidence of cases compared to other races and ethnicity.

- ❖ There is a significant relationship between Calcium and Blood Pressure in all education groups NHANES data from 2006 – 2010

- Null Hypothesis: $H_0 = H_1$
- Alternative Hypothesis: $H_0 \neq H_1$

Results showed significant relationship between Calcium and Blood Pressure in education groups. Educated group had more intake of calcium in comparison to other group and increase in the awareness might be the reason and increase in Blood Pressure.

- ❖ There is a significant relationship between Calcium consumption and Blood Pressure in all income groups NHANES data from 2006 – 2010

- Null Hypothesis: $H_0 = H_1$
- Alternative Hypothesis: $H_0 \neq H_1$

Results showed there significant relationship between Calcium consumption and Blood Pressure in income groups. Higher income group showed increased calcium intake and increase in blood pressure in comparison with low income group

- ❖ There a significant relationship between Calcium and Blood Pressure based on sex

- Null Hypothesis: $H_0 = H_1$
- Alternative Hypothesis: $H_0 \neq H_1$

Results showed significant relationship between Calcium and Blood Pressure based on sex. Male counterpart has higher incidence of rise in blood pressure in comparison to

females IN spite of female mandatorily take calcium supplements after menopause. Reason might be due increase in both dietary and supplemental intake by males.

- ❖ Hypercalcemia has a significant effect on comorbidity Chronic Heart Failure (CHF)

- Hypothesis: $H_0 = H_1$
- Alternative Hypothesis: $H_0 \neq H_1$

Results showed no significant effect of hypercalcemia on comorbidity of CHF all the consecutive years from 2006 to 2012 based on analysis of NIS data. Proving Alternative Hypothesis

- ❖ Hypercalcemia has a significant effect on comorbidity Malignant Hypertension(HTN)

- Null Hypothesis: $H_0 = H_1$
- Alternative Hypothesis: $H_0 \neq H_1$

Results showed no significant effect of hypercalcemia on comorbidity of Malignant Hypertension (HTN) all the consecutive years from 2006 to 2012 based on analysis of NIS data. Proving Alternative Hypothesis

- ❖ Hypercalcemia has a significant effect on comorbidity Valvular Heart Diseases (Valve)

- Null Hypothesis: $H_0 = H_1$

- Alternative Hypothesis: $H_0 \neq H_1$

Results showed no significant effect of hypercalcemia on comorbidity of Valvular Heart Diseases (Valve) all the consecutive years from 2006 to 2012 based on analysis of NIS data. Proving Alternative Hypothesis

- ❖ Hypercalcemia has a significant effect on comorbidity Perivascular Hear disease (Perivasc)

- Null Hypothesis: $H_0 = H_1$

- Alternative Hypothesis: $H_0 \neq H_1$

Results showed no significant effect of hypercalcemia on comorbidity of Perivascular Hear disease (Perivasc) all the consecutive years from 2006 to 2012 based on analysis of NIS data. Proving Alternative Hypothesis

AS part of the research control group used Diabetes Mellitus and Arthritis as comorbidity to check the reliability and any errors in the data consistency.

- ❖ Hypercalcemia has a significant effect on comorbidity Diabetes Mellitus (DM)

- Null Hypothesis: $H_0 = H_1$

- Alternative Hypothesis: $H_0 \neq H_1$

- Results showed significant effect of hypercalcemia on comorbidity of Diabetes Mellitus (DM) all the consecutive years from 2006 to 2012 based on analysis of NIS data. Proving Primary Hypothesis.

This study assessed the relationship between calcium consumption, serum calcium levels leading to hypercalcemia and distinctive sorts of cardiovascular diseases in both men and women while considering many confounders, including serum vitamin D levels. We found an significant association of rising of blood pressure when serum calcium levels were >2.5 mmol/L (10mg/dl) contrasted with 1.16–1.31 mmol/L, yet for women, there was an expanded CVD mortality among women with high serum calcium levels (>1.31 mmol/L). Association found between a rise in blood pressure and dietary and calcium supplement consumption. Notwithstanding, there was a defensive impact for aggregate calcium admission of 1300–2000 mg/day and passing from CVD among men.

While the analyzes confirmed one of our primary study hypotheses, that baseline risk status of CVD modified with the association hypercalcemia did not strong evidence to reject the null hypothesis that the intervention

Additionally, contrary to the study's hypothesis that the intervention associated with an increase in blood pressure in the population with consumption of dietary and Calcium supplements based on NHANES data

Calcium is known not part of the etiological pathways of cardiovascular s. For example, coronary conduit calcium scores determine the proximity of calcium in coronary courses and are characteristic of atherosclerotic plaques and in this way the danger of cardiovascular sickness ^[86]. By the by, calcium has fundamentally been considered in connection to bone wellbeing and just all the more as of late cardiovascular security was brought as a worry up in osteoporosis administration ^[89]. Two meta-investigations demonstrated an expanded danger of up to 31% for episode AMI when contrasting calcium supplement clients versus placebo treatment ^[87,88]. Notwithstanding calcium supplements, additionally dietary admission and serum levels of calcium have found a connection to episode cardiovascular disease. The latest study, in light of the Heidelberg associate of EPIC, demonstrated an opposite relationship in the middle of dietary and dairy calcium admission and danger of AMI, however, an expanded risk among clients of calcium supplements ^[90].

All the above studies concentrated on cardiovascular diseases and recommend a part for calcium, by discoveries for a relationship with cardiovascular mortality have been less steady with not very many studies examining both serum levels and also dietary and supplement admission in both men and women ^[90,87]. According to the American Association of Clinical Endocrinologists, it was as of late complete survey of all pertinent articles distributed somewhere around 1992 and 2011, that there is conflicting confirmation for a relationship between calcium supplementation ≥ 500 mg/day and expansion in cardiovascular mortality rate ^[92]. Additionally, in a companion of patients with stable coronary illness, it was demonstrated that high serum calcium levels firmly

connected with mortality (HR for fourth versus the first quartile: 2.39 (95% CI: 1.22–4.66))^[91]. Dietary calcium and CVD association was assessed in a group of 23,366 Swedish men between the age of 45–79 years who did not take any nutritional supplements and demonstrated critical lower rate of cardiovascular diseases.[93]

Our concentrate in this way surveyed three distinct estimations of calcium and partially certifies past discoveries. As far as serum calcium, we found a positive relationship between high serum calcium levels and rise in blood pressure, restricted to more in men compared to women might be because of cumulative increase consumption, and additionally abnormal states and IHD passing for ladies. This finding in past studies of bigger serum calcium classifications or the emphasis on a particular patient populace, We didn't locate a general relationship between dietary or supplement calcium admission and cardiovascular mortality, which is converse with the latest NIH AARP-Diet and Health study^[94]. This study and our study both balanced for an extensive variety of potential confounders and have similarly long preliminary, yet it is conceivable that distinctions in an appraisal of supplement admission clarify the conflicting discoveries between both studies.

The key quality of this study is its generalizability as it uses broadly descriptive information including both men and women. Also, we could consider numerous potential puzzling components and perform stratified examinations by sex and vitamin D levels. Repeated estimation could have reinforced the accuracy of various calcium estimations as

a solitary evaluation might be inclined to estimation error and inside individual variety. Dietary calcium admission was evaluated utilizing a separate 24-hour review, which may not mirror a member's periodic eating regimen. Supplement intake in NHANES is self-reported however the recording of the supplement name from the name is a quality contrasted and numerous different studies, given the complexity of supplements information accumulation might be liable to some mistake and the explanatory confirmation of the supplement's genuine substance would be required to device specifically the levels of calcium intake .In spite of its relative specimen size, we needed force for a percentage of the laminated investigations and couldn't perform a examination of the relationship between dietary or supplement calcium consumption and cardiovascular mortality by serum calcium levels as indicated by the compelling shorts utilized.

The U.S. Nutritional Supplements business sector is going to keep up its normal development rate of a little more than 6% every year through 2018, hitting sales of \$16.4 billion in that year^[85] Development in the business sector moderated in 2013 and the first piece of 2014 because of negative press scope of supplement safety and adequacy, and the expansion in customer utilization of foods and drinks. Omega-3/fish oil and calcium/bone supplements have been hardest hit, with deals declining by twofold digits in 2013. Then again, digestive wellbeing and probiotic deals have been sound to be sure, posting a just about 25% expansion in offers of such supplements in the multi-outlet (MULO) direct in 2013. Looking ahead, offers of nourishing supplements will encounter an expanded development rate somewhere around 2014 and 2018, with deals extending because of a maturing populace, rising customer contribution in individual wellbeing, and

a developing desire of personalization for all intents and purposes all administrations and items^{.85]}

LIMITATIONS

The study relied on diagnosis and procedure of only the ICD-9 coding registered in NIS dataset. NIS data does not include all the sophisticated diagnostic procedure codes. Differentiation of hypercalcemia caused due to endocrinal or due to malignancy or excessive intake or due to idiopathic is not available in ICD-9 codes and is not indicated in NIS data. Disadvantage due to small sample size and inability to detect the progression associated with it. It would not be possible to differentiate the characteristic and particular association with CVD. These kind of studies require large cohort study and extensive data with the most detailed history of the inpatients. This study was limited to the study of most Hypercalcemic in patients missing out the ambulatory cases

The present discoveries for the thesis were liable to confinements; despite the fact that four cycles of NHANES data gave substantial example estimate that calls for accuracy in result estimation. Dietary review can be over - evaluated or under assessed when giving record of caloric admission and calcium. What's more, self-reported calcium admission can bring about under estimation which can make reporting inclination since one can't estimate for calcium that was included while cooking or calcium that added through other kind supplements. NHANES being a cross-sectional study does not permit easy going deduction in the study. Further, 2013-2014 calcium information is not accessible which implies the investigation with calcium was liable to 8 years rather than 10 years.

NHANES information has beforehand been utilized for estimations of pervasiveness as a part of a few concentrates: Meanwhile, principally NHANES information are confined to non-organized members. Besides, inquire about discoveries on non-systematized populace don't speak to hundred percent of the populace. Additionally, individuals eat distinctively on various days; individuals swing to eat more eatery foods on weekends and to rely upon the day that the meeting was done can likewise influence the calcium admission report. At long last, notwithstanding the previously stated constraints, the multi-stage likelihood nature of NHANES does not address time. Examining parameters can change after some time.

- (NIS) data which is the only source for hospital inpatient related information such as costs, LOS, insurance and demographic data.
- The NIS data is only for US Community Hospitals and does not include Private Hospitals.
- Study does not include Genetic Profiles of patients which may play an important role in the etiology and progression of Hypercalcemia.

To turn away these restrictions, the administration and strategy producers ought to meet up to work with food and commercial ventures and the Multivitamin Supplement businesses to set benchmarks for calcium usage and providing the information about the adverse effects of over dosage. The prevalence of CVD is increasing as population ages. The use of Oral calcium supplements is also increasing drastically with increase in awareness of health and too much information available on the internet. Large prospective randomized studies are needed to support these findings.

CHAPTER 6

SUMMARY AND CONCLUSIONS

These discoveries have made contention and worry among doctors and consumers since calcium is used by a substantial number of older men and women to avert osteoporosis and bone cracks. Taking into account the techniques for patient self-reporting of calcium admission and cardiovascular occasions, the conclusions drawn from the studies may not be entirely substantial. Subsequently, until more affirmative information is accessible, doctors ought not to be deterred from endorsing calcium supplements to their patients. The best competitors are patients with low calcium consumption, yet their calcium supplementation ought not to surpass the suggested 1200 mg/d to 1500 mg/d.

Further review of the literature on the impact of calcium on blood pressure was conducted. This review look at the different data sets used in investigating the relationship between calcium intake leading to hypercalcemia and high blood pressure, analysis procedures used and the list of variables used.

6.1 FUTURE STUDIES

The goals for the study were contradictory in comparison with other studies supporting one school of research studies compared to other. . NHANES data is valuable in accessing the NATIONWIDE disease prevalence. Meanwhile in the future studies can

look at the impact of calcium on children and adolescents. Instead of 10 years, future studies can focus on one NHANES cycle (two years) and limit the subgroups to just two groups such as race and education.

Future studies can include cholesterol as an independent variable to see if it has any influence on the impact of calcium on Blood Pressure.

Additional studies are needed to investigate the effect of supplemental calcium use beyond bone health.

- ❖ Role of Nano bacteria in renal stones and arterial calcification.
- ❖ Hypercalcemia and its association with Diabetes Mellitus. Also, one can use two dependent variables such as Blood Pressure and diabetes to predict if there is a correlation between Blood Pressure and diabetes and the other independent variables.
- ❖ Calcium supplements and its possible role in the outcome of breast cancer. To study the association between consumption of dairy products and calcium intake and risk of breast cancer risk according based age, ethnicity and region
- ❖ Calcium supplement users and its effects on Calcium Coronary score.

REFERENCES

1. Bailey RL, Dodd KW, Goldman JA, et al. Estimation of Total Usual Calcium and Vitamin D Intakes in the United States. *Journal of Nutrition* 2010;140(4):817–22
2. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *Bmj* 2010;341(dec01 2):c6923–c6923
3. Picolos MK, Lavis VR, Orlander PR. Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. *Clin Endocrinol Clinical Endocrinology* 2005;63(5):566–76.
4. Kapoor K, Saha A, Dubey NK, Nandan D, Jilowa S. Hypercalcemic crisis in the pediatric emergency department: Questions. *Pediatr Nephrol Pediatric Nephrology* 2014;30(11):1939–40
5. Grandi NC, Brenner H, Hahmann H, Wusten B, Marz W, et al. (2012) Calcium, phosphate and the risk of cardiovascular events and all-cause mortality in a population with stable coronary heart disease. *Heart* 98: 926–933
6. Leifsson BG, Ahren B (1996) Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab* 81: 2149–2153
7. Lundgren E, Lind L, Palmer M, Jakobsson S, Ljunghall S, et al. (2001) Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. *Surgery* 130: 978–985
8. Marco MP, Craver L, Betriu A, Belart M, Fibla J, et al. (2003) Higher impact of mineral metabolism on cardiovascular mortality in a European hemodialysis population. *Kidney Int Suppl*: S111–114
9. Ogaard CG, Petersen J, Jorgensen T, Almdal T, Vestergaard H (2006) Serum ionised calcium and cardiovascular disease in 45-years old men and women followed for 18 years. *Eur J Epidemiol* 21: 123–127

10. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, et al. (2011) Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 305: 1119–1127

11. Reunanen A, Knekt P, Marniemi J, Maki J, Maatela J, et al. (1996) Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. *Eur J Clin Nutr* 50: 431–437

12. Xiao Q, Murphy R, Houston D, Harris T, Chow W-H, et al.. (2013) Dietary and Supplemental Calcium Intake and Cardiovascular Disease Mortality The National Institutes of Health–AARP Diet and Health Study. *AMA Intern Med* published online 4 Feb.

13. Li K, Kaaks R, Linseisen J, Rohrmann S (2012) Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* 98: 920–925

14. Bonthuis M, Hughes MC, Ibiebele TI, Green AC, van der Pols JC (2010) Dairy consumption and patterns of mortality of Australian adults. *Eur J Clin Nutr* 64: 569–577

15. Kaluza J, Orsini N, Levitan EB, Brzozowska A, Roszkowski W, et al. (2010) Dietary calcium and magnesium intake and mortality: a prospective study of men. *Am J Epidemiol* 171: 801–807

16. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR (2011) Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 342: d2040.

17. Shaping Our Food – an Overview of Crop and Livestock Breeding. Edited by A. Lehrman. Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden. Published in 2014, Pp. 176. ISBN 978-91-637-5757-0 Available at [Http://tr.anpdm.com/track?t=c&mid=11856281&uid=603295709&&&http://www.slu.se/shapingourfood/en.](http://tr.anpdm.com/track?t=c&mid=11856281&uid=603295709&&&http://www.slu.se/shapingourfood/en.) "Animal Genetic Resources/Ressources Génétiques

18. Animales/Recursos Genéticos Animales Anim. Genet. Resour. 55 (2014): 143. Web.
19. Campbell AK: Calcium as an intracellular regulator. Proc Nutr Soc 49: 51–56, 1990
20. Bootman MD, Collins TJ, Peppiatt CM, Prothero LS, MacKenzie L, De Smet P, Travers M, Tovey SC, Seo JT, Berridge MJ, Ciccolini F, Lipp P: Calcium signalling—An overview. Semin Cell Dev Biol 12: 3–10, 2001
21. Robertson WG, Marshall RW: Calcium measurements in serum and plasma—Total and ionized. CRC Crit Rev ClinLab Sci 11: 271–304, 1979
22. "Parathyroid Physiology." Parathyroid Physiology: Calcium Homeostasis, Disorders of Parathyroid Hormone Metabolism, Pathophysiology. Web. Apr. 2015.
23. "Harrison's Manual of Medicine, 18e." AccessMedicine. Web. 25 Feb. 2014.
24. Guyton-hall-textbook-medical-physiology-13/chapter-80/vitamin-d."Student Consult. Web. 25 Apr. 2014.
25. Shao J-S, Cheng SL, Sadhu J, Towler DA. Inflammation and the osteogenic regulation of vascular calcification. A review and perspective. Hypertension 2010;55:579-92.
26. Mody N, Parhami F, Sarafian TA, Demer LL. Oxidative stress modulates osteoblastic differentiation of vascular and bone cells. Free Radic Biol Med 2001;31:509-19
27. Tintut Y, Patel J, Territo M. Monocyte macrophage regulation of vascular calcification in vitro. Circulation 2002;105:650-5.

28. Moe SM, Duan D, Doehle BP. Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. *Kidney Int* 2003;63:1003-11.
29. Schafer C, Heiss A, Schwarz A. The serum protein alpha 2- Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. *J Clin Invest* 2003;112:357-66
30. Sweatt A, Sane DC, Hutson SM, Wallin R. Matrix Gla protein (MGP) and bone morphogenetic protein-2 in aortic calcified lesions of aging rats. *J Thromb Haemost* 2003;1:178-85.
31. Arterial Calcification:Cardiovascular Function and Clinical Outcome."ResearchGate. Web. Nov.-Dec. 2014.
32. Luo G, Ducky P, McKee MD. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature* 1997;386:78-8.
33. Sweatt A, Sane DC, Hutson SM, Wallin R. Matrix Gla protein (MGP) and bone morphogenetic protein-2 in aortic calcified lesions of aging rats. *J Thromb Haemost* 2003;1:178-85.
34. Wada T, McKee MD, Steitz S, Giachelli CM. Calcification of vascular smooth muscle cells: inhibition by osteopontin. *Circ Res* 1999;84:166-78.
35. Price PA, June HH, Buckley JR, Williamson MK. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. *Arterioscler Thromb Vasc Biol* 2001;21:1610-6.
36. Lin TC, Tintut Y, Lyman A, Demer LL, Hsiai TK. Mechanical response of a calcified plaque model to fluid shear force. *Ann Biomed Eng* 2006;34:1535-41.
37. Hoshino T, Chow LA, Hsu JJ. Mechanical stress analysis of rigid inclusion in distensible material: a model of atherosclerotic calcification and plaque vulnerability. *Am J Physiol Heart Circ Physiol* 2009;297:H802-H810.

38. Molkenstein JD, et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell*. 1998;93:215–228.
39. Marks AR, Reiken S, Marx SO. Progression of heart failure: is protein kinase a hyperphosphorylation of the ryanodine receptor a contributing factor? *Circulation*. 2002;105:272–275.
40. Chidsey CA, Harrison DC, Braunwald E. Augmentation of plasma norepinephrine response to exercise in patients with congestive heart failure. *N. Engl. J. Med*. 1962;267:650.
41. Marx SO, et al. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell*. 2000;101:365–376.
42. Zhu W-Z, et al. Linkage of β_1 -adrenergic stimulation to apoptotic heart cell death through protein kinase A-independent activation of Ca^{2+} /calmodulin kinase II. *J. Clin. Invest*. 2003;111:617–625. doi:10.1172/JCI200316326.
43. Luttrell LM, et al. Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. *Science*. 1999;283:655–661.
44. Zaccolo M, Magalhaes P, Pozzan T. Compartmentalisation of cAMP and Ca^{2+} signals. *Curr. Opin. Cell. Biol*. 2002;14:160–166.
45. Marks, Andrew R. "Calcium and the Heart: A Question of Life and Death." *Journal of Clinical Investigation*. American Society for Clinical Investigation. Web. July 2015.
46. Calcium–calcineurin Signaling in the Regulation of Cardiac Hypertrophy. "Calcium–calcineurin Signaling in the Regulation of Cardiac Hypertrophy. Web. Jan. 2015.
47. Zhu W-Z, et al. Linkage of β_1 -adrenergic stimulation to apoptotic heart cell death through protein kinase A-independent activation of Ca^{2+} /calmodulin kinase II. *J. Clin. Invest*. 2003;111:617–625.

48. Zaccolo M, Magalhaes P, Pozzan T. Compartmentalisation of cAMP and Ca(2+) signals. *Curr. Opin. Cell. Biol.* 2002;14:160–166.
49. Hypercalcemia: MedlinePlus Medical Encyclopedia." U.S National Library of Medicine. U.S. National Library of Medicine. Web. Feb.-Mar. 2015.
50. Bringhurst R, Demay MB, Kronenberg HM. Hormones and disorders of mineral metabolism. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia, Pa: Saunders Elsevier; 2011:chap 28.
51. Wysolmerski JJ, Insogna KL. The parathyroid glands, hypercalcemia, and hypocalcemia. In: Goldman L, Schafer AI, eds. *Cecil Medicine*. 24th ed. Philadelphia, Pa: Saunders Elsevier; 2011:chap 253
52. Cardiovascular complications of calcium supplements. Reid IR, Bristow SM, Bolland MJ *J Cell Biochem.* 2015 Apr; 116(4):494-501
53. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis.
54. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR *BMJ.* 2011 Apr 19; 342():d2040.
55. Shin, Chan Soo, and Kyoung Min Kim. "The Risks and Benefits of Calcium Supplementation." *Endocrinology and Metabolism*. Korean Endocrine Society. Web. 25 Dec. 2014.
56. Food and Nutrition Board. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, DC: National Academy Press; 1997
57. "U.S. Food and Drug Administration." Qualified Health Claims: Letter Regarding Calcium and Colon/Rectal, Breast, and Prostate Cancers and Recurrent Colon Polyps -(Docket No. 2004Q-0097). Web. 10 June 2015.

58. Public Health Reviews." Public Health Reviews. Web. Dec. 2015.
59. Zemel, M. B., Kim, J. H., Zemel, M. B., Moore, W., Woychik, R. P., Moustaid, N., Wilkison, W. O. (1995) Agouti gene product regulation of intracellular free calcium results in stimulation of fatty acid synthase. *Obesity Res.*3,338sabstr.
60. Resnick, L. (1999) The cellular ionic basis of hypertension and allied clinical conditions. *Prog. Cardiovasc. Dis.* 42,1-22
61. 2014 Guideline for Management of High Blood Pressure." JAMA Network. Web. Jan.-Feb. 2015.
62. "Calcium/Vitamin D Supplementation and Cardiovascular Events."Calcium/Vitamin D Supplementation and Cardiovascular Events. Web. Jan.-Feb. 2015.
63. Xiao, Qian, Rachel A. Murphy, Denise K. Houston, Tamara B. Harris, Wong-Ho Chow, and Yikyung Park. "Dietary and Supplemental Calcium Intake and Cardiovascular Disease Mortality." *JAMA Internal Medicine* JAMA Intern Med173.8 (2013): 639. Web. 2015.
64. Bolland, M. J., A. Grey, A. Avenell, G. D. Gamble, and I. R. Reid. "Calcium Supplements with or without Vitamin D and Risk of Cardiovascular Events: Reanalysis of the Women's Health Initiative Limited Access Dataset and Meta-analysis." *Bmj* 342.Apr19 1 (2011): D2040. Web. 2015.
65. "Result Filters." National Center for Biotechnology Information. U.S. National Library of Medicine. Web. 12 May 2015.
66. Chan, Ruth, Jason Leung, and Jean Woo. "A Prospective Cohort Study Examining the Associations of Dietary Calcium Intake with All-Cause and Cardiovascular Mortality in Older Chinese Community-Dwelling People." Ed. Yoshihiro Fukumoto. *PLoS ONE* 8.11 (2013): e80895. PMC. Web. 26 Apr. 2016.
67. Dietary intake of calcium and phosphorus and serum concentration in relation to the risk of coronary artery calcification in asymptomatic adults.Kwak SM, Kim

JS, Choi Y, Chang Y, Kwon MJ, Jung JG, Jeong C, Ahn J, Kim HS, Shin H, Ryu S. *Arterioscler Thromb Vasc Biol.* 2014 Aug;34(8):1763-9. doi: 10.1161/ATVBAHA.114.303440. Epub 2014 Jun 12. PMID:24925973

68. "Relation of Calcium, Vitamin D, and Dairy Food Intake to Ischemic Heart Disease Mortality among Postmenopausal Women." *Relation of Calcium, Vitamin D, and Dairy Food Intake to Ischemic Heart Disease Mortality among Postmenopausal Women.* Web. Apr. 2014.
69. Papanikolaou, Yanni et al. "U.S. Adults Are Not Meeting Recommended Levels for Fish and Omega-3 Fatty Acid Intake: Results of an Analysis Using Observational Data from NHANES 2003–2008." *Nutrition Journal* 13 (2014): 31.PMC. Web. 26 Apr. 2016.
70. National Institutes of Health, National Heart, Lung, and Blood Institutes. *Morbidity and Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases.* http://www.nhlbi.nih.gov/resources/docs/2012_ChartBook_508.pdf Accessed June 7, 2013.
71. Roger, Véronique L. et al. "Heart Disease and Stroke Statistics—2011 Update: A Report From the American Heart Association." *Circulation* 123.4 (2011): e18–e209. PMC. Web. 2016..
72. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, et al. *Circulation.* 2014 Jan 21; 129(3):399-410
73. "Executive Summary: Heart Disease and Stroke Statistics-2014 Update." *Executive Summary: Heart Disease and Stroke Statistics-2014 Update.* Web. 2 Mar. 2016.
74. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937–52.
75. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature.* 2011;473(7347):317–25.

76. Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. *J Mol Med (Berl)* 1996;74(6):297–312.
77. Steinberg D, Parthasarathy S, Carew TE, et al. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med*. 1989;320(14):915–24.
78. Davis CD, Uthus EO. DNA methylation, cancer susceptibility, and nutrient interactions. *Exp Biol Med (Maywood)* 2004;229(10):988–95.
79. Das PM, Singal R. DNA methylation and cancer. *J Clin Oncol*. 2004;22(22):4632–42.
80. Robinson K, editor. *Homocysteine and Vascular Disease*. Norwell, MA: Kluwer Academic Publishers; 2000.
81. "Heart Disease Facts." Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, 2015. Web. 6 Dec. 2015.
82. CDC, NCHS. Underlying Cause of Death 1999-2013 on CDC WONDER Online Database, released 2015. Data are from the Multiple Cause of Death Files, 1999-2013, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed Feb. 3, 2015.
83. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-322.
84. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933-44. Epub 2011 Jan 24.
85. Heart Disease Prevention & Wellness." Emory Healthcare. Web. 5 Mar. 2015.

86. "U.S. Food and Drug Administration." Qualified Health Claims: Letter Regarding Calcium and Colon/Rectal, Breast, and Prostate Cancers and Recurrent Colon Polyps -(Docket No. 2004Q-0097). Web. 2 July 2015.
87. Yeboah, Joseph et al. "Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate Risk Individuals. The Multi-Ethnic Study of Atherosclerosis." JAMA : the journal of the American Medical Association 308.8 (2012): 788–795. PMC. Web. 2015
88. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, et al. (2010) Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 341: c3691
89. Wang L, Manson JE, Song Y, Sesso HD (2010) Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med 152: 315–323
90. "Calcium Supplements: Bad for the Heart?" -- Reid and Bolland 98 (12): 895. Web. Feb.-Mar. 2015.
91. "Associations of Dietary Calcium Intake and Calcium Supplementation with Myocardial Infarction and Stroke Risk and Overall Cardiovascular Mortality in the Heidelberg Cohort of the European Prospective Investigation into Cancer and Nutrition Study (EPIC-Heidelberg)." Associations of Dietary Calcium Intake and Calcium Supplementation with Myocardial Infarction and Stroke Risk and Overall Cardiovascular Mortality in the Heidelberg Cohort of the European Prospective Investigation into Cancer and Nutrition Study (EPIC-Heidelberg). Web. May-June 2015
92. Grandi NC, Brenner H, Hahmann H, Wusten B, Marz W, et al. (2012) Calcium, phosphate and the risk of cardiovascular events and all-cause mortality in a population with stable coronary heart disease. Heart 98: 926–933
93. Miller PD (2011) Vitamin D, calcium, and cardiovascular mortality: a perspective from a plenary lecture given at the annual meeting of the American Association of Clinical Endocrinologists. Endocr Pract 17: 798–806

94. Kaluza J, Orsini N, Levitan EB, Brzozowska A, Roszkowski W, et al. (2010) Dietary calcium and magnesium intake and mortality: a prospective study of men. *Am J Epidemiol* 171: 801–807
95. Xiao Q, Murphy R, Houston D, Harris T, Chow W-H, et al.. (2013) Dietary and Supplemental Calcium Intake and Cardiovascular Disease MortalityThe National Institutes of Health–AARP Diet and Health Study. *AMA Intern Med* Published online 4 Feb.

LIST OF ABBREVIATIONS

AHA	American Heart Association
ANOVA	Analysis of Variance
ATP	Adult Treatment Panel III
BMI	Body Mass Index
CAPI	Computer Assisted Personal Interview
CI	Confidence Interval
DASH	Dietary Approach to Stop Blood Pressure
DBP	Diastolic Blood Pressure
EBSCO	Elton B. Stephen Co.
FDA	Food and Drug Administration
GDP	Gross Domestic Product
HBM	Health Believe Model
HCUP	Healthcare Cost and Utilization Project
IOM	Institutes of Medicine
JNC 7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

JSTOR	Journal Storage
MEC	Mobile Examination Center
MeSH	Medical Subject Headings
mRFEI	Modified Retail Food Environment Index
NCDs	Non- Communicable Diseases
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHF	National Heart Foundation
NIS	Nationwide Inpatient Sample
OR	Odd Ratio
SAS	Statistical Analysis Software
SPSS	Statistical Package for the Social Sciences
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
SCT	Social Cognitive Theory
TOHP	Trials of Blood Pressure Prevention
TPB	Theory of Planned Behavior

US	United States
USA	United States of America
WHO	World Health Organization
R1	Research question one
R2	Research question two
R3	Research question three
R4	Research question four
R5	Research question five
R6	Research question six
R7	Research question seven
H1	Hypotheses one
H1	Hypotheses two
H1	Hypotheses three
H1	Hypotheses four
H1	Hypotheses five
H1	Hypotheses six

H1 Hypotheses seven

ISH Isolated Systolic Blood Pressure

IDH Isolated Diastolic Blood Pressure