Examination of diabetes as a risk factor for osteoporosis among older adults in Korea: A population-based cohort study

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ABSTRACT

With population aging worldwide, the prevalence of diabetes has significantly risen, leading to various complications. Recent evidence suggests there could be potential associations between diabetes as osteoporosis risk. This thesis aimed to examine whether diabetes represents an independent risk factor for osteoporosis onset in Korean adults aged 50 years and older.

The analysis utilized longitudinal data from the Korean National Health Panel Survey from 2008-2018, following 7304 participants aged 50+ years at baseline. Among them, a total of, 1616 individuals with diabetes and 5688 without diabetes were followed for up to 11 years to identify new clinically diagnosed osteoporotic events, including osteoporosis or osteoporotic fractures, based on Korean Standard Disease Classification codes. Kaplan-Meier curves displayed visual comparison of survival over time between diabetes groups and other different risk factors for osteoporosis events, and Cox proportional hazards models calculated adjusted hazard ratios (HRs) of different risk factors.

Over the study period, 794 new osteoporotic events were documented. Diabetes status did not significantly impact osteoporosis risk in multivariate analysis. Older age (70+ years) (vs. 50-60 years) (HR=10.32, 95% CI: 3.25–32.80) and female sex (vs. male) (HR=9.05, 95% CI: 5.32–15.40) emerged as key factors independently associated with greater osteoporosis hazards. Unexpectedly, people with hypertension (vs no hypertension) and previous smokers (vs non-smokers) had lower osteoporosis risk. There was a significant interaction of sex and age, with 60–70-year-old females having higher risk than their male counterparts.

In summary, while diabetes itself was not implicated as an independent predictor, this thesis identified critical demographic and clinical factors for osteoporosis onset in Korean adults aged 50+ years. These findings can guide screening initiatives and future research on underlying mechanisms.

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DEDICATION

This thesis is dedicated to my cousin brother, Shwapnil Sarker, a beautifully kind, loving, and caring soul.

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List of Abbreviations

CI= Confidence Interval

PH= Proportional hazard

ICDS= International Classification of Diseases

BMD= Bone Mineral Density

DM= Diabetes Mellitus

T1DM= Type 1 Diabetes Mellitus

T2DM= Type 2 Diabetes Mellitus

BMI= Body Mass Index

RA= Rheumatoid Arthritis

PD= Parkinson's Disease

DEXA= Dual-energy X-ray Absorptiometry

WHO= World Health Organization

GDM= Gestational Diabetes Mellitus

IDF=International Diabetes Federation

SBP=Systolic Blood Pressure

KSCD= Korean Standard disease sign classifications

NIH= National Institutes of Health

P.D.F =Probability Density Function

C.D.F=Cumulative Distribution Function

KM= Kaplan Meier

HF= Hip Fractures

CVD= cardiovascular disease

SPA= Single photon absorption spectroscopy

CAPI=Computer-assisted personal interviewing

Chapter 1 Introduction

1.1 Background

As the population ages, the prevalence of diabetes mellitus has risen substantially worldwide. Diabetes has increased significantly across all geographic regions and is currently estimated to affect approximately 415 million adults globally [1]. This represents a major public health concern that is expected to impose a substantial healthcare burden in coming decades if the current trends continue unabated [1].

Diabetes can adversely impact numerous organs throughout the human body, including the liver, kidneys, brain, eyes, feet, and nervous system, resulting in an array of debilitating complications that reduce the quality of life [2]. For instance, it can lead to several diseases, including liver dysfunction, kidney failure, cognitive deficits, vision loss, foot ulcerations, and peripheral neuropathy. Thus, diabetes often profoundly disrupts normal physiological functioning in multiple organ systems [2].

In recent years, the complex interrelationship between diabetes and development of osteoporosis has garnered increased research attention, as both represent highly prevalent metabolic diseases. Osteoporosis involves progressive deterioration of bone tissue microarchitecture over time, resulting in reduced bone mineral density (BMD), compromised bone strength, and increased skeletal fragility [3]. Moreover, osteoporosis is a common cause of broken bones among older adults [3], the most vulnerable bones being those in the spine, lower arm, and hip [4]. Osteoporosis often remains undiagnosed until a fracture occurs, which can happen with even minor pressure or sudden movements such as sneezing at which point the presence of reduced bone density becomes

evident. Fractures most often affect the bones of the spine, hips, and wrists, which are particularly vulnerable to osteoporotic damage [4]. Sometimes, even after bone healing, individuals may experience persistent pain and diminished ability to perform daily activities. These debilitating fractures can severely impact mobility and independence. Vertebral fractures are especially common in osteoporosis, often causing back pain, height loss, and spinal deformities [4].

Globally, over 200 million individuals are estimated to have osteoporosis [4], which affects approximately 15% of white North Americans in their 50s. However, the prevalence is disproportionately higher in postmenopausal women compared to that in men of similar age, highlighting sex differences in fracture risk [3]. Furthermore, postmenopausal women face an increased risk of osteoporosis and bone fractures compared to older men [4]. This heightened risk can be linked to a significant reduction in estrogen production among women after menopause. Estrogen plays a crucial role in maintaining bone strength. However, in postmenopausal women, estrogen production decreases, which, in turn, contributes to the risk of reduced bone density and an elevated rate of osteoporosis [4]. In fact, osteoporosis causes almost 8.9 million bone fractures worldwide each year, with one out of every three women and one out of every five men older than 50 years eventually experiencing a fracture due to the disease [5]. According to the National Institutes of Health (NIH), more than 53 million individuals in the United States are either affected by osteoporosis or are at high risk of developing the disease [6]. However, North American Caucasians are at a lower risk of developing osteoporosis compared to Europeans and Asians [3]. Conversely, the African Americans have a lower risk of bone fractures due to osteoporosis compared to Native Americans, Asians, Hispanic and white, but a higher risk of death from osteoporotic fractures [6].

In Canada and the United States, approximately 10% of all postmenopausal women have osteoporosis [7,8]. However, in Asia, the prevalence of osteoporosis is expected to increase, with an anticipated 50% of osteoporotic hip fractures occurring in Asian women by 2050 [9].

Patients with osteoporosis have a major risk of hip bone fracture, possibly leading to morbidity and mortality [10]. Therefore, early detection through screening and treatment is critical for preventing osteoporotic fractures [11].

However, osteoporosis rates in Korea remain prevalent, with an incidence comparable to that in other East Asian nations but higher than that in North America [5]. This highlights the need for studies on osteoporosis risk factors such as diabetes in Asian populations. To address this issue, Korea introduced a National Screening Program in 1988, focusing on chronic diseases such as diabetes mellitus and hypertension. To advance the program, the Service of Health and Welfare of Korea introduced a modern national screening initiative known as the "Screening Program for Transitional 3 Ages," which has focused on those aged 40 and 66 years. As a part of the program since 2007, the BMD estimations for women have been conducted exclusively for those in the 66-year-old age group [12].

1.2 Rationale

With the aging of the global population, the prevalence of chronic diseases such as osteoporosis and diabetes mellitus has risen substantially and is expected to increase further [13]. Diabetes involves several metabolic abnormalities that can alter bone homeostasis, including elevated insulin levels, hypercalciuria, worsened kidney function, weight gain, micro- and macrovascular changes, and systemic inflammation [14,15]. These metabolic derangements may accelerate bone loss [16]. Diabetes complications such as retinopathy, cataracts, peripheral neuropathy, and

impaired proprioception can also increase susceptibility to falls and fractures in individuals who have osteoporosis [17]. While preventing debilitating bone fractures is the primary goal of osteoporosis screening and management, monitoring bone health and quality in diabetes patients, even in the absence of evident fractures, is also important to facilitate early prevention. Researchers have identified improving bone health as essential for preventing osteoporosis events, regardless of sex [17]. Changes in bone metabolism and architecture potentially differ between type 1 and type 2 diabetes mellitus, given different underlying disease mechanisms [18]. In patients with type 1 diabetes mellitus (T1DM), BMD reductions appear modest based on current evidence [18]. It remains unclear whether patients with type 2 diabetes mellitus (T2DM) are at higher risk for osteoporosis than are those with T1DM [18]. Findings are inconsistent in T2DM, with studies showing decreased, unchanged, or even increased BMD measurements [18]. Further studies are needed to clarify the diabetes-osteoporosis association, given these discrepancies. This thesis aims to help address this knowledge gap by analyzing national cohort data to determine whether diabetes would be a significant risk factor for osteoporosis development in Korean adults.

1.3 Study Objectives: The objectives of the study are:

Objective 1. To compare the probability of osteoporotic events among individuals with or without diabetes using the Korean Health Panel study data.

Objective 2. To determine whether diabetes represents a significant independent risk factor for osteoporosis development.

Objective 3. To compare the probability of osteoporosis event difference between men and women.

Chapter 2 Literature review

In this chapter, I will describe the epidemiology of diabetes and osteoporosis, their pathophysiology, and risk factors.

2.1 Literature review for diabetes

Diabetes mellitus involves chronically elevated blood glucose levels resulting from insufficient insulin production in the pancreas, reduced tissue sensitivity to insulin, or a combination of both defects [18]. Insulin is responsible for converting sugar from food into energy. Diabetes can be classified into T1DM and T2DM [19].

2.1.1 Epidemiology of Diabetes

Individuals with T1DM are unable to produce insulin and is considered an autoimmune disorder because it involves the immune system mistakenly attacking and destroying the insulin-producing beta cells in the pancreas [20]. The term T1DM is also commonly used to refer to insulin-dependent diabetes or juvenile diabetes [20]. T2DM is more strongly linked to lifestyle factors, including poor diet and low physical activity, which contribute to insulin resistance rather than absolute insulin deficiency [21,22]. According to the International Diabetes Federation, approximately 643 million individuals worldwide are expected to suffer from diabetes by 2030 [23]. Without intervention, this number is anticipated to increase to approximately 783 million people by 2045 [24]. T2DM accounts for a significant portion of all cases of diabetes worldwide and is causing an increasing healthcare burden [25]. Due to lifestyle changes such as an unhealthy diet and lack of physical activity [23], T2DM is now affecting younger people, including children and adolescents. Moreover, around one-third to half of all T2DM cases remain undiagnosed due to the slow onset of the disease and the absence of symptoms for several years [23]. It is important

to routinely screen for T2DM in the general population, particularly for individuals aged > 40 years, with or without symptoms. New cases of microvascular complications in T2DM patients can lead to social problems and mortality [26]. T2DM is more common in older age groups, especially in individuals over the age of 40. This is often because of factors like reduced physical activity, weight gain, and age-related changes in insulin sensitivity. However, it's essential to note that Type 1 Diabetes can also develop at any age, including in older adults, although it is less common in this age group [26].

2.1.2 Risk factors for diabetes

Numerous risk factors contribute to the development of diabetes. These risk factors can be categorized into two categories: modifiable and non-modifiable. Non-modifiable risk factors include genetics, environment, age, and culture, while modifiable risk factors include unhealthy dietary habits, physical inactivity, obesity, and sleep apnea [27,28]. While non-modifiable factors cannot be changed, we can focus on the modifiable factors to prevent diabetes [28]. For example, a healthy diet and regular exercise can help prevent T2DM and maintain overall health and well-being [29].

T1DM is heavily influenced by genetic predisposition; however, environmental factors, viral infections, and diet can also trigger autoimmune disease [30]. Since T1DM cannot be prevented, proper management is essential [31]. Individuals with T2DM are at a higher risk of developing hyperlipidemia and hypertension, and high blood sugar levels can also lead to stroke, blindness, and heart failure [32]. To prevent T2DM, it is important to maintain a healthy weight, exercise regularly, and consume a nutritious diet [32]. Awareness of these risk factors and initiatives to prevent and manage diabetes can improve our overall health and well-being [32].

2.2 Epidemiology of osteoporosis

The World Health Organization (WHO) identifies osteoporosis as a disease that causes deterioration and low bone density, leading to an increased risk of bone fractures [33]. The WHO diagnostic criteria consider a bone density of 2.5 standard deviations below the average of young adults as osteoporosis [33]. This condition is caused by a metabolic disorder that reduces BMD and leads to brittle and weak bones. Dual-energy X-ray absorption or bone density measurements are used to measure BMD [33].

Osteoporosis is often asymptomatic until the first fragility fracture occurs, which indicates the disease's presence [34]. Clinical guidelines prioritize the prevention of fragility fractures over-treating low BMD. Osteoporosis and related fractures are commonly associated with aging, and the term "fragility fracture" refers to fractures that occur spontaneously or due to minor trauma, sneezing, or coughing [35,36]. Papaioannou et al. found that postmenopausal women are more susceptible to fragility fractures [34].

Osteoporosis has significant economic impact worldwide [34]. The disability caused by osteoporosis is higher than disability caused by cancers (excluding lung cancer) and is comparable to or greater than that caused by chronic non-communicable diseases such as rheumatoid arthritis (RA), asthma, and cardiovascular diseases (CVDs) due to high blood pressure [35]. Fractures are a significant concern globally, with estimated costs of 37.5 billion in Europe alone in 2017 [35]. These costs are expected to increase 27% by 2030 [35]. In Asia, China is projected to have the highest cases of hip fractures, with an estimated increase of over one million by 2050, from 411,000 in 2015 [35]. Additionally, Latin America is anticipated to experience an increase in hip fracture cases, with a projected total of 655,648 by 2050, incurring a direct cost of $13 billion [35]. Hip fractures are also associated with a high mortality rate following the injury [35]. Alarmingly,

this fracture burden is rising steadily as populations age, underscoring the need for preventive strategies. Several demographic, lifestyle, and clinical factors influence osteoporosis development and fracture risk.

2.2.1 Risk factors for osteoporosis

Studies have assessed community members worldwide and found that osteoporosis is associated with various clinical and individual factors, including alcohol consumption [36] and smoking [37]. Moreover, further evidence suggests that clinical factors such as high body mass index (BMI) [38], T2DM [39], RA [40], dementia [41], and Parkinsonism [42,43] contribute to osteoporosis [21,22].

2.2.2 Other risk factors for osteoporosis

Fractures in older men and women are also associated with various physiological, demographic, and lifestyle factors. A hip fracture (HF) is a break in the upper quarter of the femur, near the hip joint. It is one of the most devastating consequences of osteoporosis and is an important health indicator for osteoporosis severity [44].

Sex

Women are more likely to have compromised bone health than men [45]. The incidence of marked bone loss with age is relatively higher among women than among men. A variety of physiological factors, such as hormonal deprivation of estrogen and demographic variation (e.g., socioeconomic status), may contribute to the risk of HF [45]. Men and women of advanced age generally have lower levels of calcium and vitamin D [46]. Among individuals over 65 years old, women exhibit a disproportionately higher incidence of fragility fractures compared to that in men [47]. Canadian data indicates that from 1985 to 2005, women represented 72.3% of hospitalizations for hip

fractures compared to only 27.7% in men [48]. According to data collected by Osteoporosis Canada, the number of women who suffer from HFs has been increasing [45,48].

This sex difference in fracture risk may reflect several factors, including hormonal changes after menopause, smaller bone size, longer life expectancy, lower calcium intake, and reduced physical activity in women [49]. HF is proportionally more prevalent in women due to their tendency to live longer than men, with a 2:1 ratio of women to men in terms of HF incidence [50].

Bone architecture is also associated with HF [51]. Loss of estrogen during menopause can accelerate bone deterioration, while testosterone decline in aging men has less pronounced effects on bone [52].

Cortical thickness tends to decrease as bone size increases during aging, partly owing to the process of endocortical resorption surpassing periosteal apposition. This causes tubular bones to become more fragile due to a decrease in bending strength [52]. The mechanical properties of bones are generally stronger in men than in women, regardless of their age, body weight, or body height [53]. HF patients with lower elasticity, smaller sectional modulus, and higher buckling ratios have been found to have bones with relatively less cortical thickness, lower sectional modulus, and higher buckling ratios [54,55]. A fracture in an older woman with these bone characteristics was observed in the present study [51]. Women who sustain high-femur fractures have thinner femoral neck cortices, longer hip axes, greater neck-shaft angles, narrower femoral shafts, and higher acetabular widths than those of women who do not sustain HFs [51]. The differential epidemiology between the sexes may be explained by these characteristics.

Age

Age exhibits a strong correlation with fracture risk, as well as with BMD [44]. As individuals age, other factors such as medical comorbidities, muscular impairment, balance deficits, and physical inactivity may heighten fall and fracture risks [50].

Since HF is associated with aging, care plans, resources, and research are naturally affected [57]. In Canada, HF increases from 3.9% in adults aged > 50 years to 21% in those aged 50–74 years [58]. By age 75 and older, HF incidence surge dramatically to 75%, highlighting the steep trajectory of fracture risk with aging [58]. Consequently, the health resource allocation for fracture prevention, treatment, and rehabilitation is affected by its close relationship with aging [57].

Educational Level

Educational attainment can play a pivotal role in influencing an individual's understanding of healthy behaviors, including the importance of bone health. Those with higher levels of education are often better equipped to comprehend and appreciate the value of preventive measures against osteoporosis, such as maintaining a well-balanced diet and engaging in regular physical exercise [59].

To substantiate this connection between education and osteoporosis, empirical evidence from various studies supports the notion that educational attainment is independently associated with bone health. For example, a population-based observational study conducted among postmenopausal Chinese women aged 48-63, encompassing 685 participants, revealed a compelling link [59]. This study demonstrated that a higher level of education was independently associated with better Bone Mineral Densities (BMDs) and a lower prevalence of osteoporosis

among postmenopausal Chinese women [59]. These findings emphasize the significant role education can play in promoting bone health awareness and fostering healthier practices [59].

Similarly, a study conducted in the United States reinforced the correlation between education and osteoporosis [60]. The research indicated that osteoporosis was more prevalent among U.S. adults who were non-citizens, less educated, unemployed, and had lower incomes [60]. This highlights the socioeconomic disparities that exist and how they can contribute to a higher risk of osteoporosis, particularly among older adults [59,60].

Income

Higher-income individuals often benefit from improved access to healthcare resources, which, in turn, can lead to the early diagnosis and effective management of osteoporosis risk factors [61]. Additionally, their socioeconomic advantage provides them with better access to dietary options and lifestyle resources that are conducive to maintaining bone health. In contrast, lower-income individuals may confront various challenges [61]. They may encounter barriers to accessing nutritious foods, encounter limitations in engaging in physical activities, and potentially reside in environments with heightened stressors. Collectively, these factors contribute to a heightened risk of osteoporosis among individuals with lower incomes [61].

Empirical evidence further supports the link between income and osteoporosis risk. An observational study conducted among older adults in the United States, involving a sample size of 3,901, reveals that osteoporosis risk tends to be relatively low for Non-Hispanic Black males [61]. This study underscores how income disparities can intersect with other demographic factors to influence osteoporosis risk [61].

Similarly, an observational study involving 1,477 postmenopausal women over the age of 50 in Korea presents compelling insights [62]. This study demonstrates that older individuals with lower socioeconomic status face a notably higher risk of developing osteoporosis [62]. These findings underscore the global implications of economic disparities in the context of osteoporosis risk among older adults [61,62].

Low body weight and BMI

Fracture risk in postmenopausal women is associated with low body weight and BMI [33,44,63,64]. While BMI is associated with fracture risk even after adjusting for BMD, it is not a reliable predictor for fractures, except for HF in patients with a BMI of 20 kg/m^2 or less [65]. Therefore, BMI is most useful as a clinical risk factor when BMD is unknown [65].

Weight loss has been identified as a predictor of fracture risk. In a group of women aged 50–65 years, a weight loss of over 10% within ten years was found to be a strong risk factor for osteoporosis and fractures [66].

Physical activity

Insufficient physical activity is associated with worsened physical function, falls, and fractures [63]. Aside from the risks of balance issues, falls, and fractures, studies showed a correlation between inadequate physical activity and declining physical health [63,64]. For people with osteoporosis, physical activity can enhance muscle strength, diminish pain, and enhance balance [34]. Weight-bearing exercise strengthens lower extremity muscles, improves balance, and stimulates bone formation, which reduces fracture risks in patients with osteoporosis [34].

Alcohol consumption

Excessive alcohol intake is recognized as a risk factor for bone loss and fragility fractures, which can be mitigated by changing alcohol consumption habits [67]. Excessive alcohol consumption can negatively impact bone strength, increasing the risk of fractures [33,66]. This could be attributed to the effects of alcohol on protein and calcium metabolism, mobility, gonadal function, and the osteoblast [33]. Furthermore, heavy drinking can lead to loss of motor control, confusion, and memory, indirectly contributing to changes in HF epidemiology [68,69,70]. Alcohol has been identified as a significant risk factor for global healthcare due to its disease burden [67]. However, a study in Italy revealed contradictory evidence, highlighting that moderate beer consumption renders protection against osteoporosis [71].

Smoking

Smoking is a risky behavior that can have negative consequences on health and reduce life expectancy; however, it can be changed with effort. Both women and men are at greater risk for osteoporosis when they smoke cigarettes, as indicated by various studies [63,67]. Despite the evidence, the exact physiological effects of smoking on BMD remain controversial [72].

Multiple studies have cited smoking history as a risk factor for fractures [63,67,69]. This is because cigarette smoking can lead to earlier onset of menopause, reduced body weight, and increased metabolic breakdown of estrogen in women, all of which are independent risk factors for fractures [33,73].

Additionally, the long-term consequences of smoking on BMD should be considered to comprehensively understand the impact of smoking on bone health. Cheng et al. studied the relationship between BMD and smoking among men and women aged >75 years [74]. Single

photon absorption spectroscopy has been used to measure the BMD of the right calcaneus (i.e., weight-bearing trabecular bone site), revealing that neither among current, ex-smokers, nor non-smokers differed significantly in BMD, supporting the findings of May et al. [75]. The relationship between BMD and lifelong smoking habits was significant only among current smokers, regardless of sex [75]. This suggests that in relation to bone mass, the total number of cigarettes smoked over a lifetime may be more critical than current smoking levels [75].

In a study of older men, dual-energy x-ray absorption (DXA) was used to measure the BMD of the lumbar spine and proximal femur, while smoking status was divided into three groups [74]. Among those who had smoked fewer than 100 cigarettes in their lifetime were classified as never-smokers, while ex-smokers are those that had quit smoking for at least three months before the study [74]. In this study current smokers had lower BMD than ex-smokers and never-smokers. However, these findings became non-significant when weight was considered. Therefore, cigarette smoking may not affect the BMD of the hip or spine in this group of older men [74].

Using DXA, Huuskonen et al., evaluated 140 men aged 54–63 years to assess how smoking affected their spinal and femoral BMD [76]. Resultantly, smoking did not influence spinal and proximal femur BMD. Moreover, May et al. found no correlation between smoking and BMD [75]. Notably, only 17% of that study's cohort included current smokers, potentially influencing its results. Furthermore, Glynn et al., found no significant association between cigarette smoking and BMD due to low statistical power [77]. Specifically, smoking was not linked with proximal femoral BMD after analyzing the DXA measurements of 523 men with a mean age of 66.6 years, suggesting that smoking is not significantly associated with femoral BMD [77].

Moreover, current smokers have lower BMD than that of former smokers (9% vs. 63%), primarily due to smaller number of current smokers, as demonstrated by Bendavid et al [78]. The Bernhards et al cohort study showed that smoking was associated with lower hip, spine, and forearm BMD; however, this significance was lost after adjusting for age and BMI [79]. The authors suggested that the observed differences in BMD may be explained by the low number of current smokers and their lower BMI [79].

Furthermore, smoking significantly reduces BMD, especially in the lumbar spine and proximal femur. Ortego-Centeno et al. compared the smoking status of 57 healthy men aged 20–45, classified into three groups [80]. In contrast to previous studies, more than half of the participants in this study were smokers (n=31), while only 26 were non-smokers. Compared to non-smokers, heavy smokers had significantly lower lumbar spine BMDs (p=0.05) while light smokers did not show significant differences. Thus, in this study smoking negatively affects lumbar spine BMD but is more severe in heavy than in light smokers [80]. Taken together, the current data suggest that avoiding smoking is beneficial for bone health, although further clarification is warranted [66].

Hypertension

Researchers found an association between hypertension and osteoporotic fracture risk in both women and men in a recent meta-analysis [81]. Specifically, individuals with hypertension showed an increased risk of osteoporotic fractures than those without hypertension [odds ratio (OR)= 1.33 (95% CI: 1.25–1.40; P = 0.001]. Hypertension and fracture risk were slightly more prevalent in women than in men, with pooled ORs of 1.35 (95% CI 1.26–1.44) and OR=1.32 (95% CI 1.30–1.79) respectively [81]. The results were similar in Asian and European studies. The evidence suggests that hypertension increases the risk of osteoporotic fractures [81].

Additionally, a cross-sectional cohort study involving 5566 women and 2187 men aged 50 and above, as part of the population-based Canadian Multicentre Osteoporosis Study, aimed to investigate the potential associations between documented prior medical conditions and bone mineral density or prevalent vertebral deformities [82]. In this study, researchers observed that hypertension was similarly linked to higher bone mineral density measurements in both women and men [82].

Furthermore, clinical investigations conducted in diverse regions of China also established a correlation between systolic blood pressure (SBP) and BMD T-scores among postmenopausal women with Type 2 diabetes in Tibet [83]. This Tibetan study reached the conclusion that lower SBP was correlated with higher BMD among the Tibetan women in their study [83].

Hyperlipidemia

Lipid deposits may directly stimulate osteoclast maturation and bone resorption, providing a pathophysiological link between hyperlipidemia and osteoporosis [84]. Research suggests that elevated cholesterol levels can stimulate osteoclasts, which are cells responsible for breaking down bones [84]. This effect was observed in mice and humans with osteoporosis with lipid deposits in their bones [84]. The study suggests that high cholesterol levels may contribute to bone breakdown and increase the risk of osteoporosis [84]. Thus, identifying and managing hyperlipidemia to reduce the risk of bone loss and osteoporosis is necessary.

In summary, a multitude of risk factors, including sex, age, educational level, income, smoking, excessive alcohol consumption, hypertension, and hyperlipidemia, significantly influence osteoporosis risk among older adults.

Chapter 3 Methods and Materials

This chapter outlines the methods, describing the data source, study design, variables, study population, data collection procedures and statistical analysis approach. Research ethics board approval was obtained from the University of Saskatchewan (Exemption request, E308).

3.1 Study design and Data Source

This thesis utilized the Korea Health Panel Study (KHPS), which was a nationally representative survey conducted annually from 2008 to 2018, examining healthcare utilization, costs, and other variables related to public health services in South Korea [85,86]. The data collection procedures for the KHPS involve conducting computer-assisted personal interviews with trained staff. The survey covers a variety of domains, including demographics, socioeconomics, health behaviours, chronic conditions, healthcare service utilization, and medical expenditures. Households were selected for participation in the KHPS using a rigorous stratification and clustering sampling strategy designed to allow robust national estimates through sufficient geographic and demographic representation. Trained staff conduct computer-assisted personal interviews with household members. The interviews are divided into three sections: household, individual, and case based [85]. The household section collects information on the household composition, income, and assets. The individual section collects information on the individual's demographics, health status, and healthcare utilization. The case-based section collects information on any chronic conditions or disabilities that the individual has. [86].

3.2 Study population

This study utilized a subset of an eleven-year longitudinal survey within the KHPS. The KHPS is collected by the Korean Institute for Health and Social Affairs in collaboration with the National Health Insurance Service. The survey employs a robust stratified sampling frame derived from the Korean Population and Housing Census in 2000 [87]. Furthermore, to ensure the representation of the South Korean population and the reliability of the data, sample weights for the KHPS were calculated. This involved adjusting for unequal selection probabilities and non-responses while making population distribution disclosures via post-stratification corresponding to the sample distribution [85]. In 2008, the initial study year, a total of 29,142 individuals participated in the study. In 2014, 5,424 additional participants identified using the original 2008 sampling frame and weights, were recruited to replace dropouts and maintain statistical reliability [87]. The study sample was restricted to adults aged 50 years or older at baseline to target those at highest osteoporosis risk, yielding 9,077 eligible individuals. After excluding 1,002 with pre-existing osteoporosis diagnoses, the final analytic sample comprised 8,075 participants. From this group of participants, 771 had missing observations. Subsequently, this cohort was divided into diabetes (n=1,616) and non-diabetes control (n=5,688) groups, from the final analytic sample comprised 7,304 participants. The study followed until 2018 to ascertain new osteoporosis onset using standard diagnosis codes. Figure 1 shows the study flowchart.

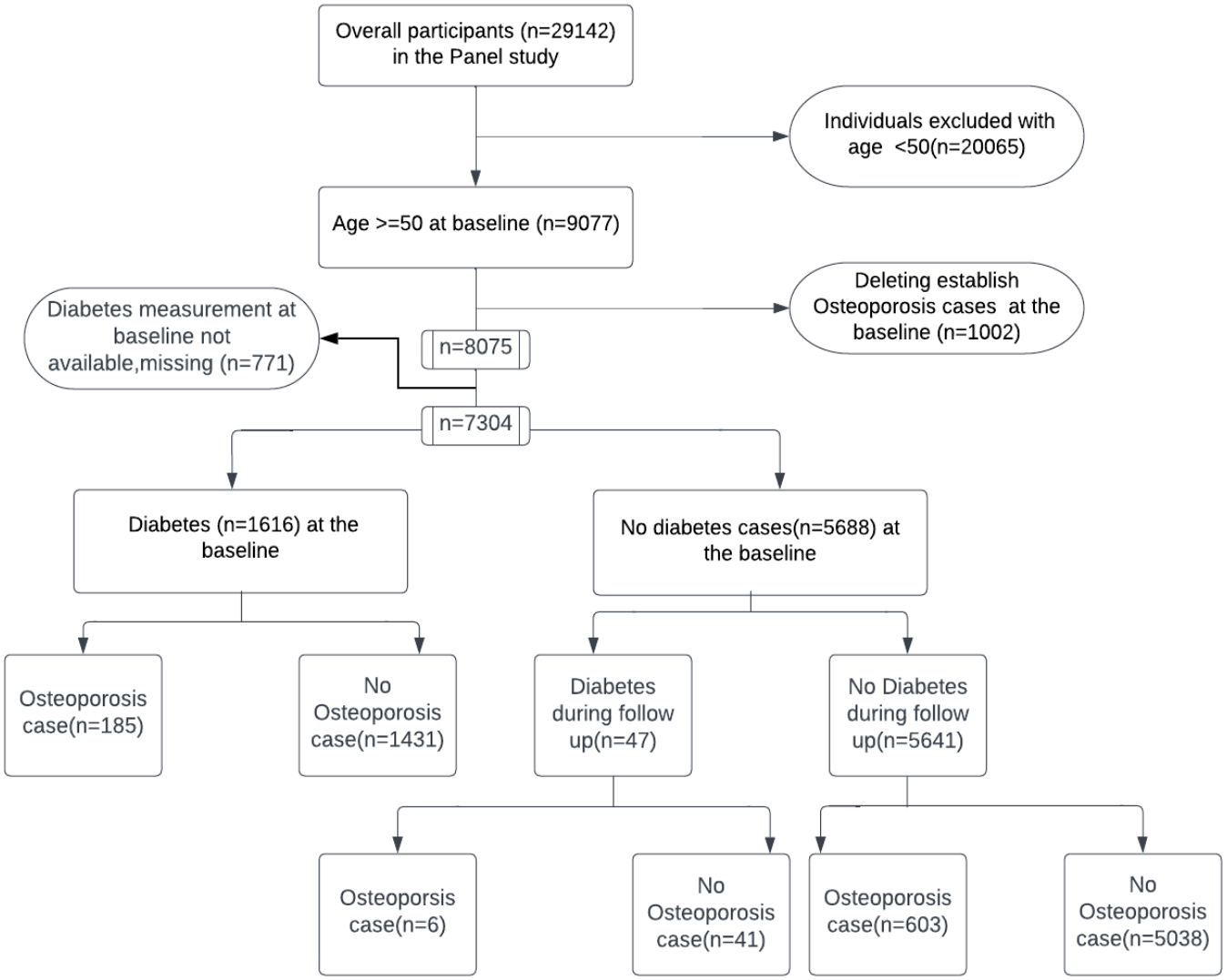


Figure 1: Study flow chart

3.3 Variables

3.3.1 Outcome variable

The KHPS collected data across numerous domains including demographics, socioeconomics, health behaviors, chronic conditions, healthcare service utilization, and medical expenditures [86]. Diagnosis coding encompassed annual International Classification of Diseases (ICDs) codes until

2011, thereafter the Korean Standard Classification of Diseases (KSCD) codes were adopted through 2018 [85]. Time to osteoporosis diagnosis was the primary outcome of this study. Participant records were reviewed for KSCD osteoporosis or fracture codes to determine the diagnosis dates. For the diagnosis date of osteoporosis, each patient's records were reviewed for osteoporosis codes (23091, M81.9). The earliest reported date was taken as the definitive diagnosis time. Participants meeting osteoporosis criteria during follow-up were classified as cases, while those without recorded diagnoses were censored. The follow-up extended from study entry until osteoporosis diagnosis, censoring, or the study closure on December 31, 2018.

For the diagnosis date of diabetes, each patient's records were reviewed for diabetes codes (14021, E10) according to the KSCD.

3.3.2 Covariates

Comprehensive evaluations of healthcare service utilization associated costs, and potential influencing factors have been conducted on an annual basis since the year 2008. The survey's fundamental inquiries encompassed thirteen primary sectors and an additional ten sectors, encompassing data related to household items, household member details, health insurance particulars, chronic health conditions, pharmaceutical usage records, long-term care information for adult household members, and data on emergency medical utilization. In the case of medical data, annual records included disease diagnosis codes and adhered to the KSCD system [87].

Data collection procedures involved field investigators visiting designated households and employing computer-assisted personal interviewing (CAPI) methods [87]. Baseline covariates were established in the initial survey year of 2008. These covariates encompassed demographics (sex, age, education, income, and private pension or life insurance status), health behaviors

(smoking, alcohol use, physical activity), and comorbidities (hypertension, hyperlipidemia). In sex, 1 was assigned for “male” and 2 for “female.” Age was divided into three groups: 50–60 years, 60–70 years, and 70 years and older. BMI was categorized as 1 for BMI (< 18.5 kg/m^2), 2 for BMI (18.5 to 24.9 kg/m^2), 3 for BMI (25 to 29.9 kg/m^2), and 4 for BMI (≥30 kg/m^2). Marital status was coded as 1 for married, 2 for separated, and 3 for single. Education was classified as 0 for no education, 1 for elementary school and middle school (grades 1–9), 3 for high school (grades 9–12), and 4 for university or higher. The household income quintile was divided into five categories every 20%. Smoking status was coded as 0 for non-smokers, 1 for current smokers, and 2 for previous smokers. The drinking (alcohol consumption) variable was scored on an 8-point Likert scale that asked how often they drank in the past year. Based on their answers, scores were re-categorized as 0 for never, 1 for almost daily, 2 for 2–3 times/week, 3 for once/week, and 4 for monthly. The ability to exercise variable was coded as 1 for no problem exercising, 2 for some problem exercising, and 3 for cannot exercise (always lying down). Hyperthyroidism, hypertension, hyperlipidemia, CVD, and acute pancreatic disease were selected as baseline comorbidities. Baseline comorbidities were coded as 1 for yes and 0 for no diseases according to their chronic disease record. All baseline covariates were measured in 2008 for initial participants or 2014 for added participants. The operationalization of independent variables is shown in Table 1.

Table 1 : The operationalization of independent variables

	Variable	Original question and response options	Category of variables
Demographic	**Sex**		
			1. Male 2. Female
	Age		
			1. (50-60) 2. (60-70) 3. (70+)
	Marital status	**Marital status**	
		What is your marriage status? (1) marriage (including putative marriage) (2) separate (Divorce premise) (3) widow/disappearance (4) divorce (5) none (-1) NA (-6) not surveyed	1.Married 2.Separated 3.Never Married
Socioeconomic	**Household income**	**Total household income 5%tile (weight applied) total sample.**	
		(1) 1st quintile (2) 2nd quintile (3) 3rd quintile (4) 4th quintile (5) 5th quintile (-9) unknown	< 20 20 - 40 40 - 60 60 - 80 80 - 100
	Education		
		How far did you (household members name) go to school, or are you attending?	0.No Education

	Variable	Original question and response options	Category of variables
		(1) preschool (under 7 years old) (2) no education (Illiteracy) (3) no education but literacy (11) ~ (16) 1~ 6 elementary school (21) ~ (23) 1~3 middle school (31) ~ (33) 1~3 high school (41) ~ (46) 1~6 university (51) master in graduate school (52) PhD in graduate school Have you (household members names) joined private company's (banks, insurers and asset managers and securities) private pension or life insurance?	1. Elementary &Middle 2.High School 3. University
	Private Pension /Life insurance		
		(1) Only Private Pension join (2) only Life Insurance join (3) both join (4) both Not included (9) not know	1.Only Private Pension 2.Only Life insurance 3.Both 4.Nothing
Personal	**Ability to exercise.**		
		What do you think of your athletic ability? (1) no problem with walking (2) some problem with walking (3) always lay down (-1) NA (-9) no response/refusing response.	 1.No problem to exercise 2.Some problem to exercise 3. Can not Exercise
	BMI [88]	**Body mass index (BMI) = weight in kg/ height in m^2**	
		Underweight- <18.5 kg/m^2 Normal weight -18.5 to 24.9 kg/m^2 Overweight-25 to 29.9 kg/ m^2 Obese ≥30 kg/ m^2	1. Underweight 2. Normal 3. Overweight 4. obese
	Alcohol drinking status	**How often have you been drinking in the last year?**	

	Variable	Original question and response options	Category of variables
		(1) Never (7) 2-3 times per week (8) almost daily (-9) unknown/no respond (6) once a week (3) less than once per month (4) once a month (5) 2-3 times per month (2) recently non-drink	(0) Never (1) Almost daily (2) Weekly (3) Monthly (4) Recently quit drinking
	Smoking Status	**Are you currently smoking?**	
		(1) current daily smoking (2) occasionally smoking (3) smoked but not smoking now (4) Never (-9) unknown/no respond (-1) NA	1. currently smoking 2. previously smoking 0. Never smoked
	Weight change	**Have you gained or lost more than 5kg in the last two years? (except for changes in weight due to pregnancy)**	
		(1) 5kg above gain (2) 5kg above lose (3) almost no change	1. 5 kg above gain 2. 5 kg above loss 3. Almost No change
Comorbid conditions	**Comorbid conditions**	**Doctor diagnosed disease.**	
		Heart problem (CVD) Hyperlipidemia Hyperthyroidism Hypertension Acute Pancreatic disease	1. Yes 0. No 1. Yes 0. No 1. Yes 0. No 1. Yes 0. No 1. Yes 0. No

3.4 Statistical Analysis

3.4.1 Survival data

Survival analysis was used to measure the time that passes between a given time origin and a particular event. This category of data is commonly referred to as lifetime, failure time, or survival

data [89]. The major focus of survival analysis is time-to-event data analysis. Survival analysis encompasses a range of methodologies for determining event time such as:

- Time until death
- Time until a machine fails
- Time from treatment initiation to cure
- Time from remission until disease recurs
- Time from HIV infection until AIDS is diagnosed
- Time until osteoporosis diagnosis

In survival analysis, it is frequently beneficial to identify the characteristic features of the time-to-event distribution for a population and contrast time-to-event across different groups (e.g., treatment vs control arms in clinical trials). The Kaplan–Meier estimator is commonly used to estimate the time-to-event distribution of a cohort, providing insight into the impact of certain factors. Modeling approaches are often used by researchers to study time-to-event and other covariates [90]. Cox proportional hazards models are often used to quantify the effects of covariates on time-to-event.

Statistical analysis of survival data is particularly relevant and important for analyzing the data in my thesis for several key reasons:

- The primary outcome of interest was time to diagnosis of osteoporosis. This represents a survival time or failure time outcome that requires specialized statistical techniques designed for this type of data.

- Standard statistical methods like linear or logistic regression are inappropriate for modeling time-to-event data where the outcome variable is a length of time before an event occurs.
- My data included right censoring of survival times, meaning the exact event time was unknown for participants who did not experience osteoporosis during the study period. Censoring must be appropriately accounted for through survival analysis methods.
- I wanted to compare survival between groups defined by covariates like diabetes status. Survival analysis provides the appropriate statistical tools for modeling and testing group differences.
- Factors like age and comorbidities were expected to influence hazard rates for osteoporosis over time. Survival models like Cox regression can estimate covariate effects on hazard functions.
- Quantifying how hazard rates vary over time and across patient subgroups provides clinically useful insights for risk stratification and prevention. This required a time-to-event analytical approach.

In summary, because the research question involved investigating predictors of time to diagnosis of a disease endpoint, using statistical approaches specialized for survival data was essential for modeling the temporal relationships and producing valid results. The presence of censoring further dictated the need for survival analysis tools like Kaplan-Meier and Cox regression.

3.4.2 Terminology

This section will provide overview of some important terminology, notation, and fundamental concepts.

Survival function

The probability of an event occurring by a certain time t can be determined using a continuous, non-negative random variable T, which has a probability density function (pdf) f(t) and cumulative distribution function (cdf) F(t) [89]. The survival probability, S(t), represents the likelihood of surviving past a certain timepoint, either just before or after t [89].

$$\boldsymbol{S(t) = \mathrm{P\,r}\,(T \geq t) = 1 - F(t) = \int_t^{\infty} f(x)\,dx}$$

Based on t, the survival function has these traits:

- It does not rise
- S(0) equals 1 when t = 0
- S(∞) = 0 when t = ∞

3.4.2.1 Hazard function

The hazard function, h(t), represents the probability of failure within a short timeframe, assuming endurance up to that timepoint. It has also been termed as the instantaneous failure rate. The hazard function is a vital metric in survival analysis. [89].

$$\boldsymbol{h(t) = \lim_{\Delta t \to 0} \frac{Pr(t \leq T < t + dt + dt | T \geq t)}{\Delta t} = \frac{f(t)}{s(t)}}$$

Additionally, cumulative hazard, H(t), denotes the accumulated risk up to time t and is:

$$\boldsymbol{H(t) = \int_0^t h(u)\,du}$$

The cumulative hazard function assists in determining failure rate over time and can be utilized to calculate survival probability within a given timeframe. According to the cumulative hazard function, the survival function can be defined as follows:

$$\boldsymbol{S(t) = \exp\big(-H(t)\big) = \exp\left(-\int_0^t h(u)\,du\right)}$$

3.4.3 Kaplan-Meier estimate of the survival function

One of the nonparametric approaches for estimating survival functions and comparing survival functions between two or more groups is the Kaplan–Meier estimator [90]. Alternatively, it is called the product limit estimator. Consider an n-sample with k (k ≤ n) distinct lifetimes $t_1 < t_2 < \cdots < t_k$ where the mortality occurs. It is also allowed to include more than one death at $\boldsymbol{t_j}$, where j = 1, 2, ..., k. For example, if dj is the number of individuals who have died at $\boldsymbol{t_j}$, then the Kaplan–Meier estimator $\boldsymbol{\hat{s}(t)}$is:

$$\boldsymbol{\hat{s}(t) = \prod_{j:t_j \le t} \left(1 - \frac{dj}{n_j}\right)}$$

where $\boldsymbol{n_j}$ represents the number of individuals with a lifespan longer than $\boldsymbol{t_j}$, and $\boldsymbol{dj}$ refers to the individual data values. As per the Kaplan–Meier estimator, the probability of an event between consecutive observations is assumed constant.

Log-rank test

Based on visual examination of Kaplan–Meier curves, we can approximately determine which group has better survival. However, statistical testing is required to analyze whether Kaplan–Meier

curves differ significantly [90]. The log-rank test is commonly used as a nonparametric test to compare survival curves based on the proportional hazards' assumption, contrasting estimated hazard functions at each observed event time. A chi-square distribution table was used to determine the p-value for equivalence under the null hypothesis [90]. When proportionality was satisfied, the log-rank test exhibited greater statistical power [91].

Wilcoxon test

The Wilcoxon test determines whether two survival curves are equivalent. Unlike the log-rank test which equally weights all event times, the Wilcoxon test provides more emphasis to early events versus late events. [92]. Compared to the log-rank test, it is appropriate when proportionality is violated. The Wilcoxon test can substitute for the log-rank test when evaluating multiple survival curves, especially when hazard functions are nonproportional, since it emphasizes early hazard rates rather than late hazard rates in the survival curves.

Cox hazards regression model

Identifying associations between potential covariates and time-to-event outcome is an important research interest in health sciences. For lifetime data, conventional regression methods are inappropriate due to censoring and nonnormality. Consequently, the Cox proportional hazards models are often preferred for analyzing failure time since they do not require assumptions about the survival distribution [93].

The Cox proportional hazards model is widely utilized to assess the impact of different factors on failure time. This model is typically applied with time-independent covariates and is unsuitable for covariates that vary over time. The model described the probability of failure time based on covariate vectors and corresponding coefficients.

Cox models are commonly used with time-independent covariates. The proportional hazards (PH) model characterizes covariate vectors X as predictors of failure time T:

$$\boldsymbol{h(t) = h_0(t)\, exp\{\beta^T X\}}$$

where, $X = \left(X_1, X_{2,\ldots\ldots,} X_P\right)^T$ contains a baseline hazard p vector of covariates.

and $\beta_1 = \left(\beta_1, \beta_{2,\ldots,} \beta_p\right)^T$ represents the corresponding coefficient vector.

This equation contains a baseline hazard function h_0(t) that is generally unspecified. In this model, the effect measure must be estimated using the hazard ratio (HR), $\boldsymbol{e^{\beta}}$, to find the effect of exposure. Regardless of time t, the HR are assumed to remain constant over time. The HR was used to estimate the measure of effects in this model. Explanatory variables or exposure were determined in this way.

Goodness-of-fit

Various aspects of the multiplicative hazards model can be inspected to assess model adequacy, including evaluating the PH assumption [89,94]. The most popular methods are Cox-Snell residuals [95], martingale residuals, and deviance residuals.

3.5 Data Analysis

The chi-square test was used for categorical variables, while a t-test was used for continuous variables. The Kaplan–Meier survival curves, log-rank test and/or Wilcoxon test were conducted to compare the two groups regarding osteoporosis events. Person-years of follow-up were calculated for each participant extending from the date of completion of their baseline either 2008 or 2014. KHPS survey was conducted until December 31,2018. Person-years were calculated for

each participant from the study start date for the participants to the occurrence of the outcome osteoporosis diagnosis, death, or the study conclusion, whichever occurred first.

Clinically relevant variables were selected for inclusion in the univariate models based on a threshold p-value <0.20 in descriptive analyses, indicating a significant association. Variables deemed to be of theoretical importance were also retained for additional testing.

PH regression techniques were utilized to estimate the associations between diabetes, other covariates, and time to osteoporosis diagnosis. Univariate Cox regression models were constructed first to obtain an unadjusted HR for each predictor. Statistically significant or borderline significant variables ($p<0.10$) were further included in the multivariable Cox model to determine independent effects. Non-significant covariates were discarded from the final model. However, hypothesized risk factors such as diabetes were retained irrespective of significance level to specifically test their effects after multivariable adjustment.

Confounding and interaction between covariates from the multivariable model were examined. Likelihood ratio tests were used to assess whether the addition of interaction terms improved model fit. If the interaction p-value was significant at $\alpha=0.05$, it was retained in the final model. The PH assumption was checked using log-log survival plots and Schoenfeld residuals. The final model covariates were tested for multicollinearity or significant confounding effects. The Akaike Information Criterion (AIC) provided a supplementary metric for comparing competing multivariate Cox regression models, with lower values indicative of enhanced model parsimony and fit. We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, NC) and a two-tailed alpha level of 0.05 was used to indicate statistical significance. For KM analysis, we used SAS macro program. All the SAS programs used for this thesis are presented in the Appendix.

To further investigate the associations between potential risk factors and osteoporosis onset, univariate Cox PH regression models were constructed. The Cox PH model is used for a statistical test to examine the relationship between patient survival time and several predictor variables. This computational technique offers researchers insights into HR, comparing the event occurrence in one population compared to that in another [96,97].

To determine the likelihood of developing osteoporosis between two distinct groups in my sample, such as diabetes versus non-diabetes patients, the hazard ratio (HR) is a valuable measurement [97]. Using Cox proportional hazards regression analysis, my multivariable model considered the effects of different predictor variables like age, sex, and comorbidities on the occurrence of osteoporosis events based on their estimated HRs. The HR quantifies the size of each variable's effect on osteoporosis risk over follow-up. Meanwhile, the standard error determines the extent of uncertainty around the HR estimate. The chi-square value and p-value then indicate whether each variable's influence is statistically significant. Finally, 95% confidence limits were established around the HRs to delineate a range of values within which we can be confident the true HR lies for my study population. This allowed me to make inferences about where the actual osteoporosis risk effect size likely resides for a given predictor in my sample.

Chapter 4 Results

This chapter presents the study descriptive statistics, survival analysis findings, and PH regression outputs.

4.1 Descriptive statistics

Demographic characteristics

This chapter presents extensive descriptive analyses profiling the baseline characteristics of diabetic and normoglycemic participants in a large cohort study of 7,304 older adults aged 50 years and over.

Overall, 1,616 participants (22% of the total sample) had diabetes at baseline, compared to 5,688 normoglycemic individuals (78% of participants). Delving into the diabetic subgroup, their mean age was 64.6 years with a standard deviation of ±8.65 years, indicating variability around the mean. The diabetic participants comprised 829 men (51.3% of this subgroup) and 787 women (48.7%). Stratifying diabetic patients by age revealed that the majority (612 individuals or 38% of diabetic patients) were aged 60-70 years.

Regarding socioeconomic factors, most diabetic participants were married (1,238 or 76.6% of diabetic patients), suggesting potential social support. However, they had lower educational attainment, with 898 participants or 55.5% of diabetics having completed only elementary and middle school (grades 1-8). Another 402 diabetic patients (24.8%) had finished high school (grades 9-12). For income distribution, 335 diabetic participants (20.7% of this group) were in the lowest

income quintile, while 215 (13.3%) were in the middle-income quintile. This indicates that a substantial proportion of diabetic individuals were in the lower income strata.

Examining health behaviors revealed that less than a quarter of diabetic participants were non-smokers (23% or 313 individuals) and only 9.4% (136 patients) were non-drinkers. Just 17% (273 patients) had private pension or insurance. However, most diabetics (64.3% or 1,040 people) reported no problems with exercising, suggesting preserved physical function despite having overall poorer health behaviors.

In terms of clinical profile, comorbidities were common among diabetic patients, especially hypertension (76.6% or 1,238 patients), CVD (23.5% or 381 individuals), and hyperlipidemia (54.9% or 887 people). However, substantial weight changes were rare - only 2.2% (37 patients) had gained over 5kg and 3.6% (59) lost over 5kg in the preceding two years.

In comparison, the normoglycemic group (5,688 participants or 78% of the cohort) was slightly younger with a mean age of 63.4 years (SD ±9.82 years) and comprised more women (52% or 2,955). They had higher educational attainment and income levels, along with better health behaviors including more non-smokers (20% or 958), non-drinkers (9% or 448), and participants with insurance (20% or 1,129). Rates of clinical comorbidities were lower than the diabetic group (hypertension 47.5%, CVD 12.1%, hyperlipidemia 26.9%).

In summary, these extensive descriptive analyses revealed diabetic participants had a higher-risk profile at baseline across demographic, socioeconomic, behavioral, and clinical characteristics compared to their normoglycemic counterparts. These multidimensional baseline differences

likely influence downstream diabetes complications and outcomes. The analyses provide necessary context for interpreting subsequent survival models examining these two groups.

4.1.1 Clinical characteristics

Examining clinical comorbidities among patients with diabetes, hypertension was most common, affecting 1,238 (76.6 % of the overall participants) individuals. Other conditions included CVD (23.5% of patients with diabetes), hyperthyroidism (1.4%), hyperlipidemia (54.9%), and acute pancreatic disease (1.5%). Assessing weight changes, markedly few diabetic patients had gained (2.2% of diabetes patients) or lost (3.6% of diabetes patients) more than 5 kg in the last two years prior to baseline measurements.

In summary, the baseline clinical profile revealed that comorbidities such as hypertension, CVD, and hyperlipidemia were more prevalent among patients with diabetes compared to the prevalence in their normoglycemic counterparts. However, substantial weight changes in the two years preceding baseline measurements were rare occurrences in both diabetic and normoglycemic participants. These findings characterize the baseline health status and comorbidity burden of the study population, which may influence their future risk of developing osteoporosis.

Table 2 : Baseline characteristics of the study participants(N=7304) Mean (± SD) and n (%)

Variables	**With diabetes (n = 1616)**	**Without diabetes (n=5688)**	**P-value**
	Mean (SD) Total N%	**Mean (SD) Total N%**	
Sex Male Female	829(51.3) 787(48.7)	2733(48) 2955(52)	<.0001
Age (as continuous)	64.60(±8.65)	63.36(±9.82)	<.0001

Variables	With diabetes (n = 1616)	Without diabetes (n=5688)	P-value
Age (50-60 years) Age (60-70 years) Age (70 + years)	515(32) 612(38) 489(30)	2406(43) 1767(31) 1515(26)	<.0001
BMI **(as continuous)**	24.39(±3.19)	23.15(±2.85)	<.0001
BMI < 18.5 (kg/m^2) 18.5 <BMI < 24.9kg/ m^2 25 < BMI < 29.9kg/ m^2 BMI>30 kg/ m^2	126(0.07) 894(55.2) 533(33.8) 63(0.03)	729(13) 3702(65) 1194(21.9) 63(0.01)	<.0001
Marital Status Married Separated Never Married	 1238(76.6) 371(23) 7(0.4)	 4435(77.9) 1197(21.4) 54(0.7)	<.0001
Educational level No Education Grade 1-8 Grade 9-12 Higher than grade 12	 141(8.9) 898(55.5) 402(24.8) 175(10.8)	 532(9.3) 2899(50.9) 1500(26.3) 757(13.5)	<.0001
Income Quintile <20 20-40 40-60 60-80 80-100	 442(27.3) 425(26.2) 335(20.7) 215(13.3) 199(12.5)	 1249(21.9) 1277(22.4) 1129(19.8) 988(17.3) 1031(18.6)	<.0001
Smoking status Current Smokers Previous Smokers Non-Smokers	 313(22.9) 412(27.4) 799(49.7)	 958(19.8) 1228(24.5) 3002(55.7)	<.0001
Drinking(alcohol) Habits Non-Drinker Almost Daily 2-3 times per week once a week Monthly	 704(44.5) 136(9.4) 173(11.7) 82(5.3) 438(29.1)	 2212(40.8) 448(8.8) 615(12.8) 327(6.7) 1617(30.9)	<.0001
Physical activity No problem to exercise	1040(64.3)	3816(67)	<.0001

Variables	With diabetes (n = 1616)	Without diabetes (n=5688)	P-value
Some problem to exercise	404(25)	944(16.5)	
No Exercise	9(0.05)	24(0.04)	
Private Pension/Life insurance			
Private Pension	36(0.2)	141(0.2)	<.0001
Life insurance	96(0.5)	518(0.9)	
Both	9(0.05)	76(0.1)	
Nothing	1407(87)	4557(80)	
Hyperthyroidism			
NO	1594(98.6)	5621(98.8)	<.0001
YES	22(1.4)	67(1.2)	
Hypertension			
NO	378(23.4)	2988(52.5)	<.0001
YES	1238(76.6)	2700(47.5)	
CVD			
NO	1235(76.5)	5003(87.9)	<.0001
YES	381(23.5)	685(12.1)	
Hyperlipidemia			
NO	729(45.1)	4158(73.1)	<.0001
YES	887(54.9)	1530(26.9)	
Acute Pancreatic disease			
NO	1592(98.5)	5654(99.4)	<.0001
YES	24(1.5)	34(0.6)	
Weight Change			
5 kg above gain	37(2.2)	70(1.2)	<.0001
5kg above loss	59(3.6)	133(2.3)	
Almost No change	1008(62.3)	2989(52.5)	

*t-test for continuous and chi-square test for categorical variable was conducted

4.2 Survival analysis for time-to-osteoporosis

Survival analysis techniques were employed to identify risk factors associated with the primary study outcome of osteoporosis onset. The outcome of interest was time-to-event, measured in years from baseline until diagnosis of osteoporosis or the end of the study on Dec 31,2018.

4.2.1 Kaplan-Meier (K-M) estimates

Over the 11-year follow-up period, 794 (9.8%) participants were diagnosed with osteoporosis. Kaplan–Meier survival curves were constructed to depict time to osteoporosis diagnosis based on key exposure variables including sex (stratified by diabetes status) (Figure 2.8), age group (Figure 2.1), education level (Figure 2.9), income category (Figure 2.10), smoking status (Figure 2.5), alcohol use (Figure 2.7), and other important factors. Log-rank tests and/or the Wilcoxon test were used to assess differences in survival probability between strata of each exposure variable.

Examination of the Kaplan–Meier survival estimates revealed several noteworthy patterns. Participants in the youngest age group (50–60 years), men, those with higher educational attainment, and those in the highest income categories demonstrated significantly improved osteoporosis-free survival compared to that of those of their respective counterparts (i.e., older ages, females, less education, lower incomes, smoking status). However, the probability of having Osteoporosis did not differ significantly between diabetic and nondiabetic participants over the follow-up period (Figure 2.6). In subgroup analyses restricted to female participants, non-smokers had lower survival compared to that of smokers (Figure 2.12), while male drinkers exhibited higher survival compared to that of non-drinkers (Figure 2.11).

Specifically for sex, the survival curves revealed significantly improved osteoporosis-free survival for men compared to that of women, regardless of diabetes status ($p<0.0001$). For example, approximately 80% of men remained osteoporosis-free at 130 months follow-up compared to only 30% of women. This highlights the substantially increased risk faced by women (Figure 2.2).

Stratifying by age group, participants aged 50–60 years had significantly longer osteoporosis-free survival compared to that of participants aged 60–70 and 70+ years ($p<0.0001$). By 130 months,

over 80% of participants aged 50–60-years were event-free, versus approximately 50% of 60–70 years and only 20% of those 70+ years. This illustrates the dramatically higher risks experienced by older adults (Figure 2.1).

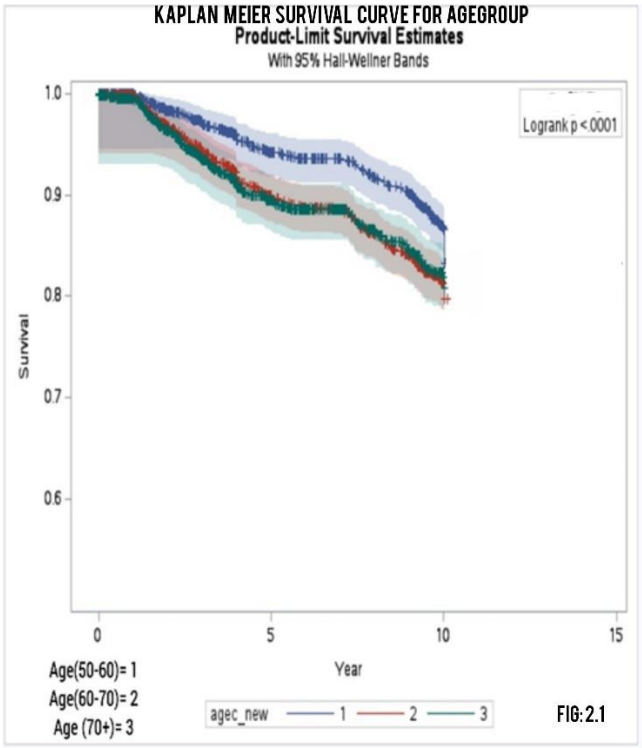
Examining education level (Figure 2.9), participants who completed high school or attended university had enhanced osteoporosis-free survival relative to those with only elementary/middle school education or no education ($p<0.0001$). Approximately 70% of highly educated participants were event-free at 130 months compared to only 40% of those with less education.

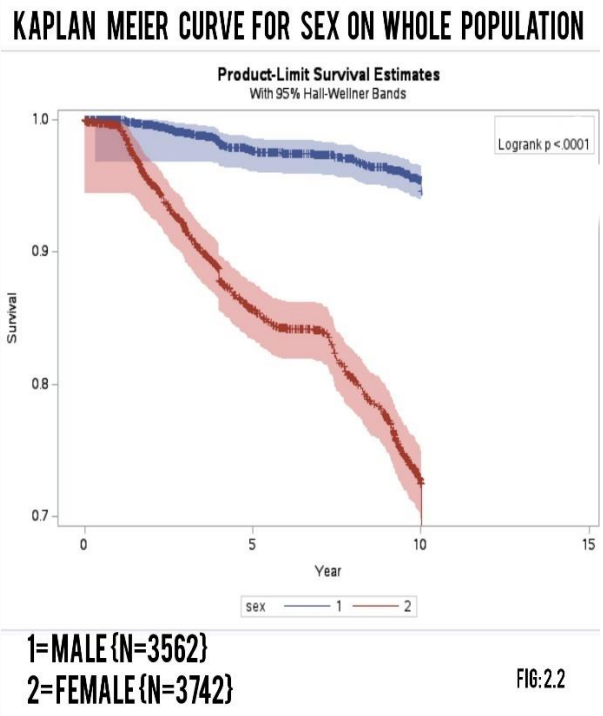
Regarding income (Figure 2.10), higher quintiles were associated with significantly improved osteoporosis-free survival versus lower income quintiles ($p=0.0279$). By 130 months, 70% of top earners were event-free compared to only 50% of bottom earners. This demonstrates the protective effects of a higher socioeconomic status.

In summary, Kaplan–Meier analyses clearly demonstrated that female sex confers a substantially and significantly higher risk of developing osteoporosis than that in men, regardless of diabetes status. Conversely, other comorbid conditions such as hypertension (Figure 2.4) did not significantly impact risk of osteoporosis events. These Kaplan–Meier curves helped characterize the risk profiles for osteoporosis within this sample of middle-aged and older adults with and without diabetes.

Figure 2.1 to 2.12, Results of Kaplan-Meier analysis

Figure 2 : Kaplan–Meier survival estimates for age category, sex, hyperlipidemia, hypertension, diabetes, smoking status, drinking status, diabetes status based on sex, education, income quintile and subgroup analyses of drinking and smoking habits restricted to female and male participants, and we derived the p-value from log-rank test





SURVIVAL CURVE FOR HYPERLIPIDEMIA

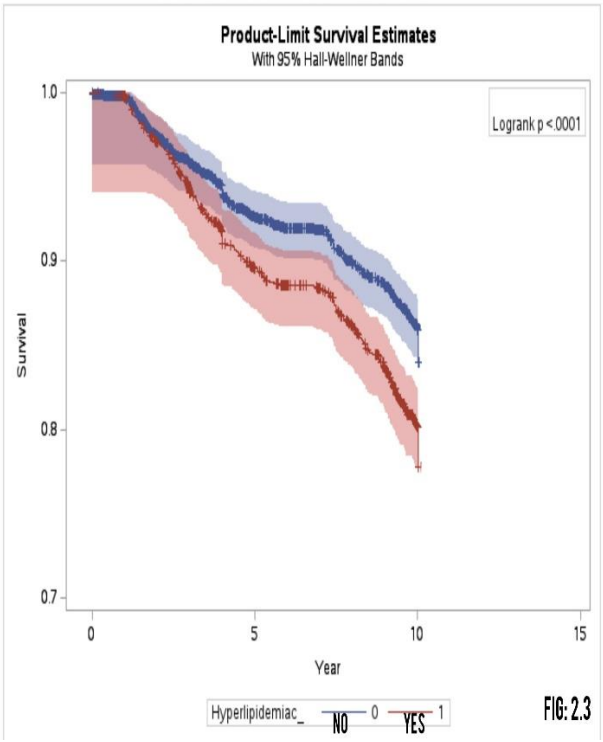


FIG: 2.3

SURVIVAL CURVE FOR HYPERTENSION

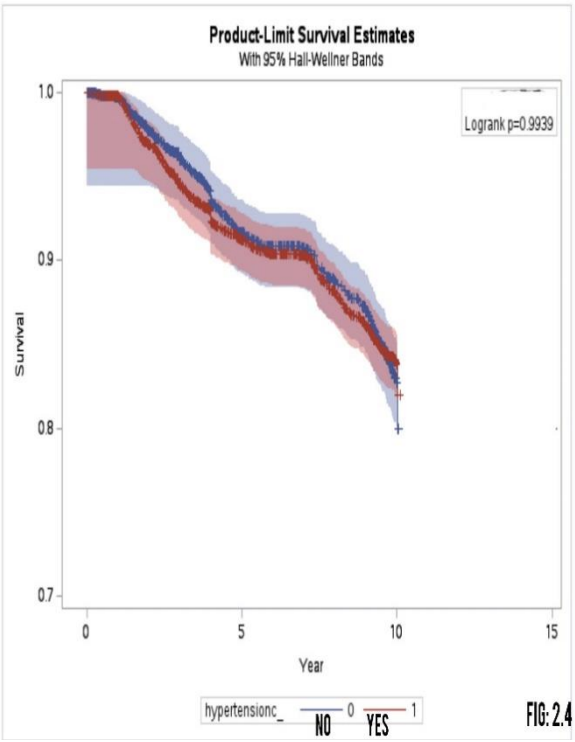
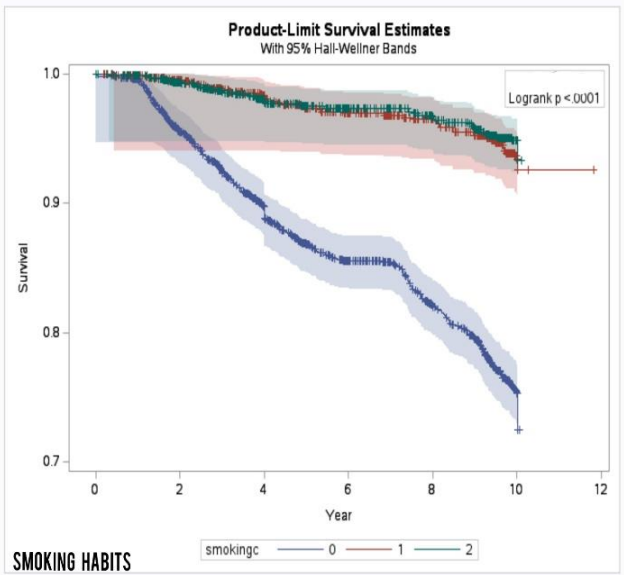


FIG: 2.4

SURVIVAL CURVE FOR SMOKING STATUS



SMOKING HABITS
1= CURRENT DAILY SMOKERS (N=1271)
2= OCCASIONAL SMOKERS (N=1640)
0= NON-SMOKERS (N=3801)

FIG: 2.5

SURVIVAL CURVE FOR DIABETES

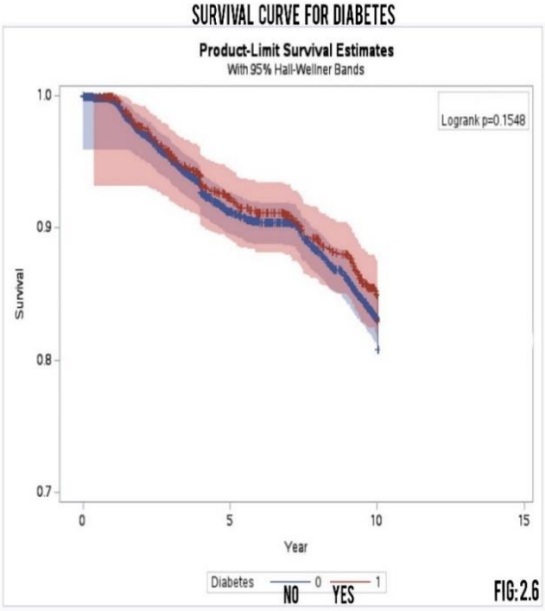
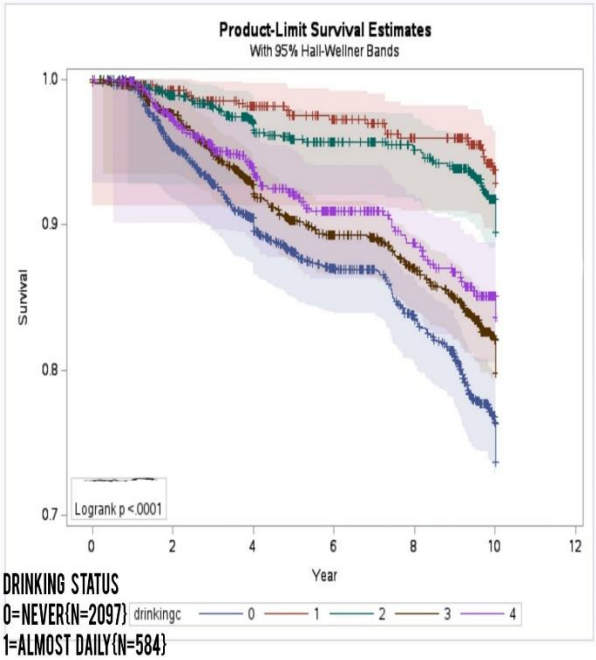


FIG: 2.6

SURVIVAL CURVE FOR DRINKING STATUS



DRINKING STATUS
0=NEVER{N=2097}
1=ALMOST DAILY{N=584}
2=WEEKLY{N=1197}
3=MONTHLY{N=2055}
4=RECENTLY NOT DRINKING{N=819}

FIG: 2.7

KAPLAN MEIER SURVIVAL CURVE FOR SEX ON DIABETES STATUS

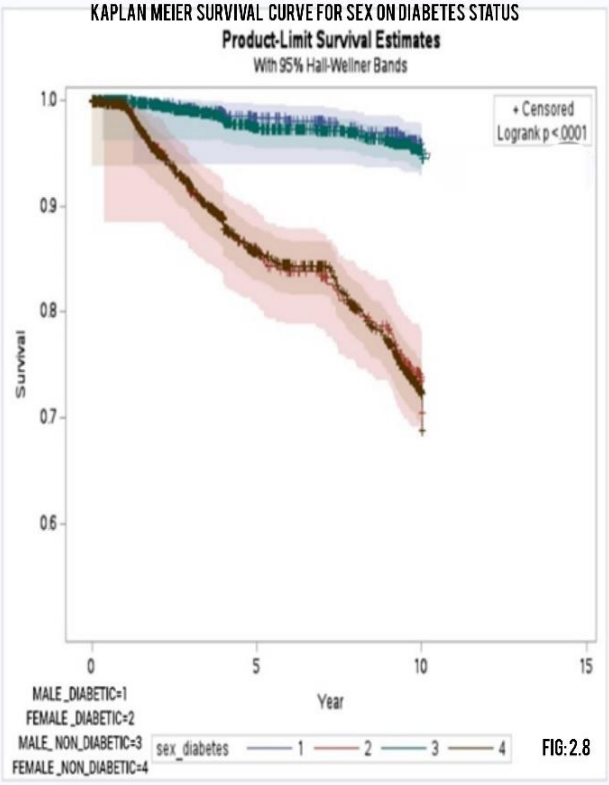
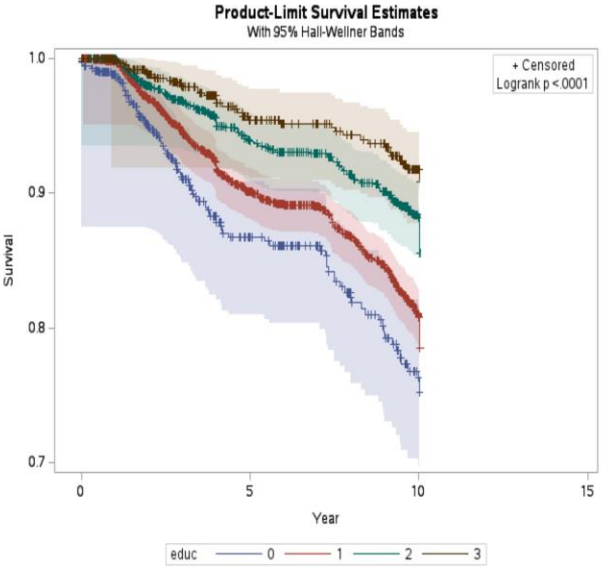


FIG: 2.8

KAPLAN-MEIER CURVE BY EDUCATION



NO EDUCATION=0
ELEMENTARY AND MIDDLE SCHOOL=1
HIGH SCHOOL=2
UNIVERSITY=3

FIG: 2.9

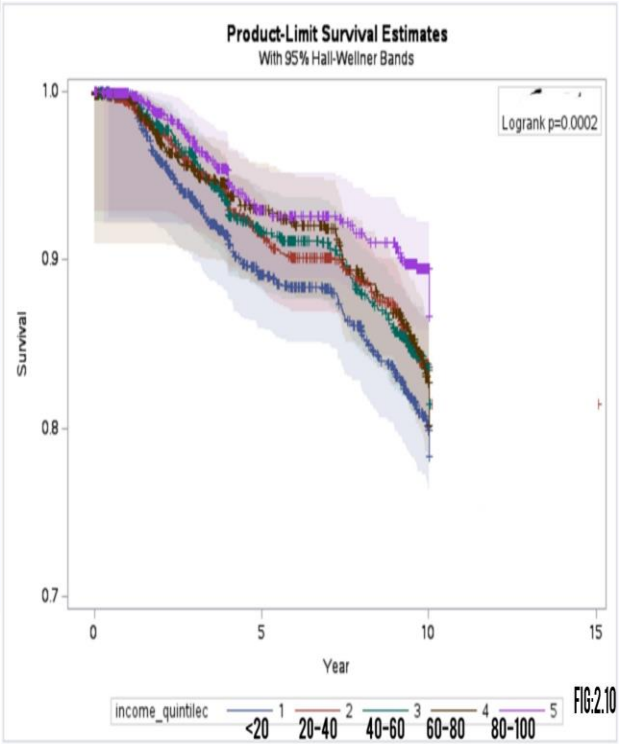
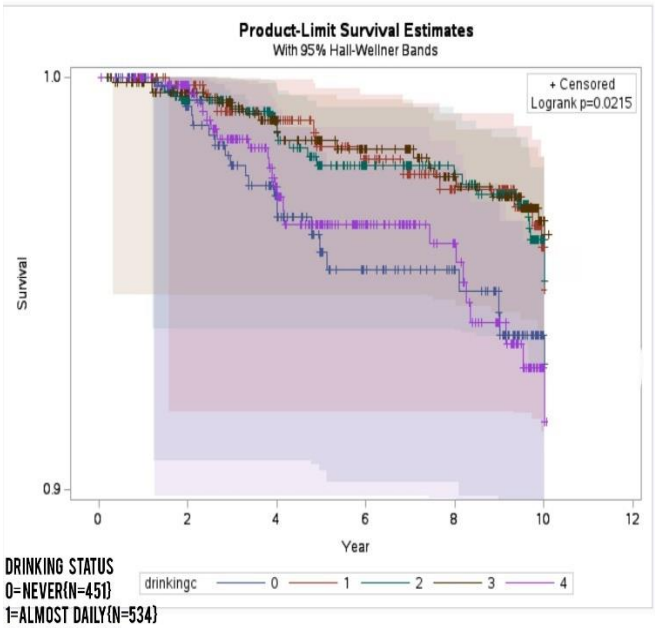


FIG:2.10

Subgroup analyses

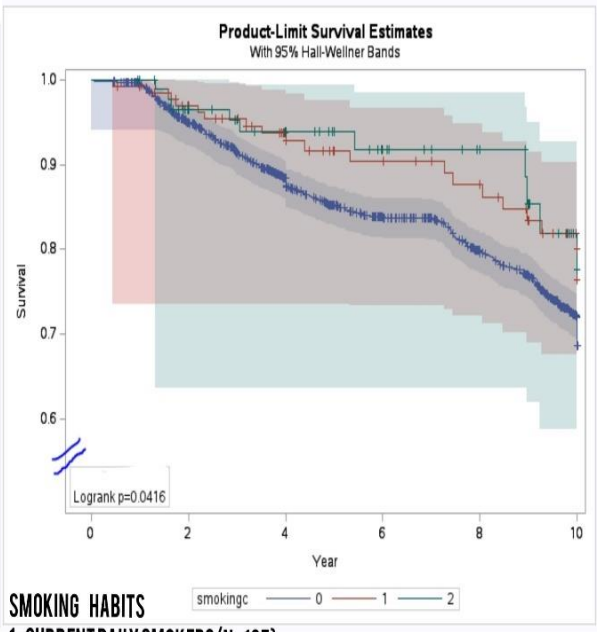
KAPLAN MEIER CURVE FOR DRINKING ONLY ON MALE POPULATION



DRINKING STATUS
0=NEVER(N=451)
1=ALMOST DAILY(N=534)
2=WEEKLY(N=918)
3=MONTHLY(N=835)
4=RECENTLY NOT DRINKING(N=539)

FIG:2.11

KAPLAN MEIER CURVE FOR SMOKING ONLY ON FEMALE POPULATION



SMOKING HABITS
1=CURRENT DAILY SMOKERS(N=135)
2-OCCASIONAL SMOKERS(N=90)
0-NON-SMOKERS(N=3220)

FIG:2.12

4.2.2 Univariate Cox model

These initial univariate models confirmed that advanced age over 70 years (HR=1.451, 95% CI=1.198–1.756, p=<0.0001) and female sex (HR=6.83, 95% CI: 5.56–8.38, p=0.001) were strongly and positively associated with osteoporosis risk (Table 2). Lower educational attainment [elementary and middle school graduates (grades 1–9) (HR=0.75, 95% CI=0.60–0.94, p=0.012)] and lower household income (HR=0.80, 95% CI: 0.66–0.97, p =0.027) were also significantly associated with a heightened risk.

Individuals with hyperlipidemia (HR=1.44, 95% CI=1.261.66, p=<0.0001) were at higher risk of osteoporosis than were those who were not diagnosed with hyperlipidemia, whereas having private pension or insurance coverage demonstrated that they have a better survival from osteoporosis.

Interestingly, smoking and alcohol consumption both exhibited inverse relationships with osteoporosis risk. Patients who smoke and consumed alcohol had a lower risk of developing osteoporosis than that of their counterparts. Baseline BMI, marital status, ability to perform physical activities, hyperthyroidism, hypertension, CVD, acute pancreatic disease, and weight change in the last two years were not significantly associated with osteoporosis.

Table 3 : Univariate Cox hazards regression model for time to osteoporosis

Covariate	Hazard Ratio (95% C.I)	p-value
Sex		
Male	1	
Female	6.831(5.563-8.389)	<.0001
Age (continuous)	1.020(1.012-1.028)	<.0001
Age (50-60)	1	
Age (60-70)	1.452(1.232-1.712)	<.0001
Age (70+)	1.451(1.198-1.756)	<.0001
BMI (continuous)	0.977(0.954-1.000)	**0.0538**
BMI (< 18.5)	1	
BMI (18.5 - 25)	0.931(0.673-1.289)	0.6676
BMI (25-30)	0.786(0.557-1.111)	0.1726
BMI (>=30)	0.807(0.431-1.511)	0.5023
Marital Status		
Never Married	1	
Married	0.721(0.299-1.740)	0.4671
Separated	1.154(0.475-2.800)	0.7521
Education		
No Education	1	
Elementary & Middle	0.757(0.609-0.941)	0.0121
High School	0.472(0.365-0.610)	<.0001
University	0.302(0.211-0.431)	<.0001

Covariate	Hazard Ratio (95% C.I)	p-value
Income Quintile		
<20	1	
20-40	0.806(0.665-0.977)	0.0279
40-60	0.806(0.659-0.985)	0.0354
60-80	0.802(0.644-0.998)	0.0476
80-100	0.564(0.441-0.720)	<.0001
Smoking Habit		
Never Smoker	1	
Previous Smoker	0.215(0.163-0.284)	<.0001
Current Smoker	0.199(0.153-0.259)	<.0001
Drinking Habit		
Non-Drinker	1	
Daily Drinker	0.248(0.164-0.374)	<.0001
2-3 times/week	0.277(0.196-0.392)	<.0001
Once in a week	0.574(0.410-0.803)	0.0012
Monthly Drinker	0.834(0.716-0.970)	0.0188
Ability to do Physical Activity		
No Physical Activity	1	
No problem to do Physical Activity	0.712(0.229-2.215)	0.5573
Little problem to do Physical Activity	1.059(0.339-3.310)	0.9216
Private Pension/Life insurance		
Nothing	1	
Private Pension	0.488(0.262-0.911)	0.0243
Life insurance	0.727(0.553-0.956)	0.0227
Both	0.377(0.121-1.172)	0.0920
Hyperthyroidism		
NO	1	
YES	1.222(0.721-2.073)	0.4565
Hypertension		
NO	1	
YES	1.000(0.868-1.152)	1.0000
Hyperlipidemia		
NO	1	
YES	1.449(1.260-1.666)	<.0001
CVD		
NO	1	
YES	1.111(0.930-1.327)	0.2473
Acute Pancreatic disease		
NO	1	
YES	1.392(0.768-2.522)	0.2760
Weight Change		
Almost No change	1	
5 kg above gain	0.698(0.384-1.266)	0.2366

Covariate	Hazard Ratio (95% C.I)	p-value
5kg above loss	0.871(0.574-1.321)	0.5162

*P-value based on log-rank test/Wilcoxon test

4.2.2 Multivariable Cox hazards regression model

All variables achieving significance at the 10% level in the univariate models were included in the multivariable Cox model [98]. After adjusting for multiple risk factors simultaneously, the final Cox model identified five variables that remained significant independent predictors: sex, age category, smoking status, and presence of hyperlipidemia and hypertension (Table 3). Although education, income, and pension/insurance status were significant in unadjusted models, they no longer maintained significance after multivariable adjustment. Notably, hypertension emerged as a significant predictor in the multivariable model despite lacking significance in univariate testing. Diabetes status did not attain significance in either the univariate or multivariable models. A significant interaction was detected between age category and sex, indicating that osteoporosis risk was the highest for females in the older age groups.

Cox hazards regression models was further utilized to derive estimates of the HR for osteoporosis among diabetes patients compared to their normoglycemic counterpart. Relative to the reference group of ages 50–60 years, the HR for the age group 60–70 years was 4.81 (95% CI=1.56–14.78), indicating a nearly five-fold higher risk. Similarly, the HR for ages 70 years and above was 10.33 (95% CI=3.25–32.80), signifying over a ten-fold higher risk. On comparing women with men, the HR was 9.05 (95% CI=5.32–15.40), underscoring the substantially elevated risk for women.

Other significant risk factors included hyperlipidemia, which has a HR of 1.339 (95% CI=1.153–1.555). This indicates that individuals with hyperlipidemia have a higher risk of experiencing

osteoporotic events compared to that of patients without this condition and are normotensive, which had an HR of 0.839 (95% CI=0.718–0.981) indicative of a protective effect. This implies that individuals with hypertension have a reduced likelihood of having osteoporotic events compared to the risk in those without hypertension.

Current daily smokers have a HR of 0.71 (95% CI=0.520–0.992), indicating a lower risk of osteoporotic events. This means that individuals who currently smoke daily have a reduced likelihood of experiencing osteoporotic events compared to that in non-smokers.

Furthermore, previous smokers have a HR of 0.68 (95% CI=0.48–0.96), suggesting a lower risk of osteoporotic events. This means that individuals who used to smoke in the past have a reduced likelihood of experiencing osteoporotic events compared to that in non-smokers.

Regarding diabetes, the HR for osteoporotic events is 0.87 (95% CI=0.73–1.04), indicating that it is not a significant risk factor in this model. This means that diabetes does not have a substantial impact on the likelihood of experiencing osteoporotic events.

There was a significant interaction between age and sex in the final multivariate model (Table 3).

Table 4 : Multivariate Cox hazards regression model (time to Osteoporosis)

Parameter	Parameter Estimate	Standard Error	P-value	Hazard Ratio	95% Confidence Limits
Sex					
Male	1			1	
Female	2.20301	0.27122	**<.0001**	9.052	5.320-15.404
Age					
Age (50-60)	1			1	
Age(60-70)	1.57003	0.57312	**0.0062**	4.807	1.563-14.781
Age (70+)	2.33499	0.58959	**<.0001**	10.329	3.252-32.805

Parameter	Parameter Estimate	Standard Error	P-value	Hazard Ratio	95% Confidence Limits
Hyperlipidemia No Yes	 1 0.29169	 0.07636	 **0.0001**	 1 1.339	 1.153-1.555
Hypertension No Yes	 1 -0.17525	 0.07944	 **0.0274**	 1 0.839	 0.718-0.981
Diabetes No Yes	 1 -0.13005	 0.08787	 0.1389	 1 0.878	 0.739-1.043
Smoking Habit Never Smoker Previous Smoker Current Smoker	 1 -0.37388 -0.33125	 0.17492 0.16503	 **0.0326** **0.0447**	 1 0.688 0.718	 0.488-0.969 0.520-0.992
Age *sex Age (60-70)*sex Age (70+) *sex	 -0.55071 -0.93980	 0.29683 0.30722	 0.0636 **0.0022**	 0.577 0.391	 0.322-1.032 0.214-0.713

Interaction terms analysis was conducted between covariates and statistical significance was examined. Results revealed that the most significant interaction was between age and sex. Examination of interaction terms revealed that women had significantly higher HRs than those of men across both older age groups.

Results showed that those belonging to age group 60–70 years and female sex [**Age (60–70) *female**] have approximately 5.2 times higher hazards compared to those of individuals in the same age group and the male population (**Age (60-70) *male**):

Equation 1: [Age (60–70) *Female] / [Age (60–70) * Male]

$$\mathbf{HR = e^{(1.570+2.20+(-0.550)(1*1)} / e^{(1.570+0+(-0.550)(1*0)}}$$

$= e^{3.22} / e^{1.570} = e^{(3.22–1.570)}$

$= e^{1.65} = 5.20$

Moreover, individuals belonging to age group (70+) and female sex (**Age (70+) *female**) have about 3.52 times higher hazards compared to those of the same age group and male population (**Age (70+) *male**):

Equation 2: [Age (70+) *Female] / [Age (70+) * Male]

$HR = e^{(2.33+2.20+(-0.939)(1*1)} / e^{(2.33+0+(-0.939)(1*0)}$

$= e^{3.591} / e^{2.33} = e^{(3.591–2.33)}$

$= e^{1.261} = 3.52$

The significant age-sex interaction indicated that osteoporosis risk for females was amplified within the older age groups. Specifically, women aged 60–70 years had 5.2 times higher hazard compared to those of their male counterparts. Similarly, women over 70 years had 3.5 times higher hazard than those of their age-matched male counterparts.

This interaction demonstrated that female sex compounded the risks associated with aging. Older women faced particularly disproportionate burdens compared to those experienced by older men. This finding reveals that preventive interventions should be targeted most aggressively towards older women to curb the steep risks they face.

In summary, the survival analyses provided insights into the demographic and clinical risk profiles for osteoporosis among adults with diabetes. The results can guide screening and prevention strategies for those most vulnerable, particularly aging women.

4.2.3 Summary of Cox hazards regression models

The Cox regression analyses determined that advanced age, female sex, presence of hyperlipidemia, and absence of hypertension were the strongest independent demographic and clinical risk factors for osteoporosis onset within the sample of adults with diabetes. Although socioeconomic variables such as education and income exhibited univariate associations, they were likely confounded by the demographic and clinical factors revealed in multivariable modeling. Smoking and alcohol consumption demonstrated unexpected inverse associations that may reflect residual confounding. Overall, diabetes status did not independently predict osteoporosis risk after accounting for the demographic and clinical risk factors.

4.3 Model selection

The Cox PH model was selected using likelihood ratio tests to compare model fit. The AIC provided further guidance for model selection, with lower values indicative of improved fit. The final model contained six predictors along with the age-sex interaction term and had the lowest AIC value (AIC=12631.064) compared to those of alternative candidate models. PH assumptions were checked and satisfied based on log-log plots and martingale residuals. Overall goodness-of-fit was assessed using the log-likelihood test.

In summary, the PH regression effectively modeled the risk relationships and quantified the HR for the demographic and clinical predictors of osteoporosis risk between the middle-aged and older adult with diabetes population. The results underscored the substantially elevated risks conferred by older age and female sex in particular. These findings can inform targeted screening and prevention strategies for those at highest risk. The lack of significance for diabetes status after

adjusting for confounders suggests that optimal diabetes care may help mitigate excess osteoporosis risk among patients with diabetes.

4.4 Goodness of Fit

In this section, we assessed the suitability of the Cox multivariate multiplicative hazards model by utilizing martingale residuals, deviance residuals, and a Cox-Snell plot.

4.4.1 Martingale residual plot:

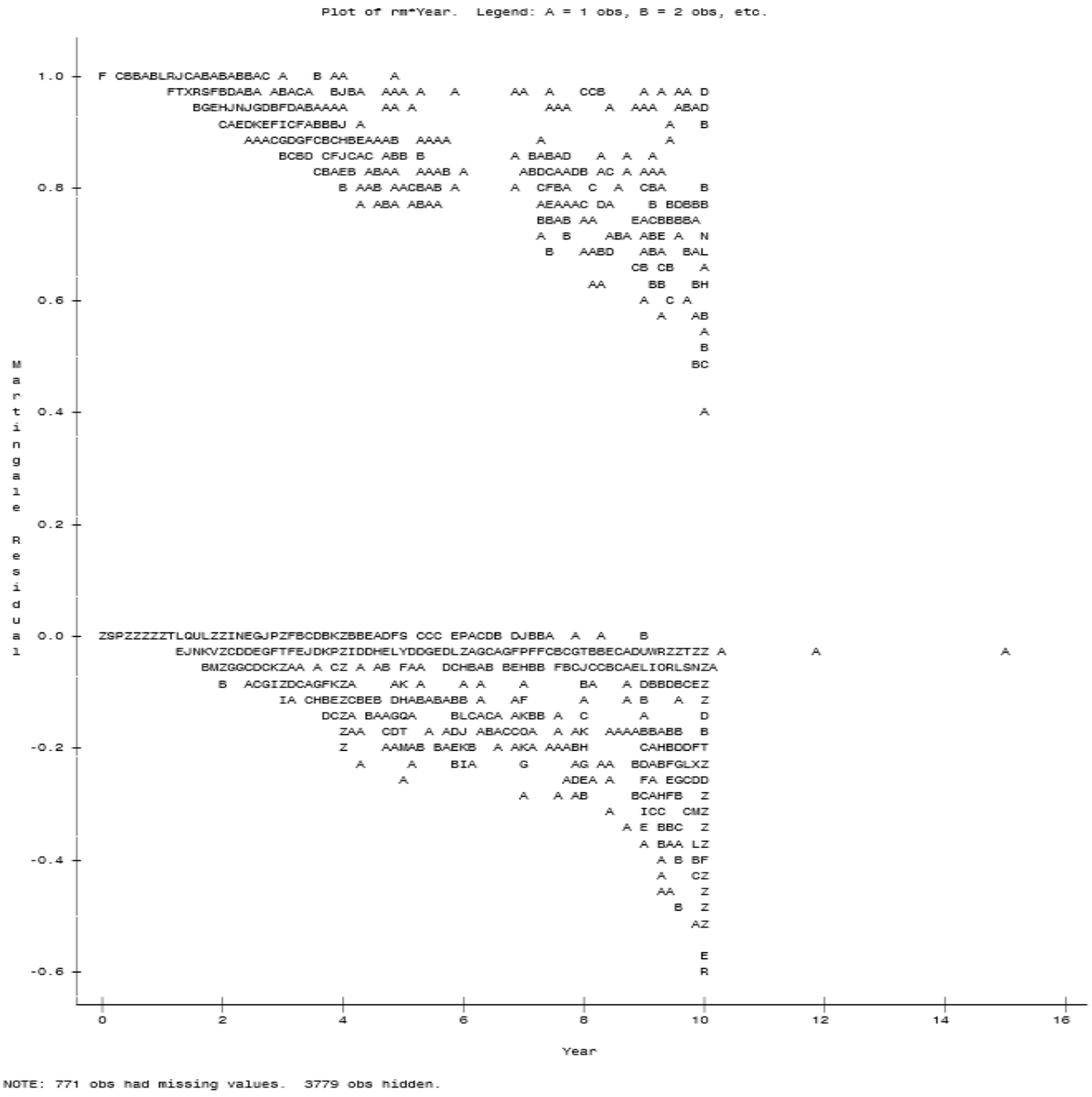


Figure 3 : Martingale residual plot

The martingale residual plot shows the residuals versus time. The points exhibit a random scattering around zero residual throughout the entire period. There are no clear trends or curvature evident, suggesting that the functional form of the model is appropriate, and the PH assumption holds well over time. The symmetrical random scatter also indicates censoring has been properly

accounted for in the model fitting. There is no accumulation of residuals at the censoring points. A few potential outliers are visible at large positive or negative residuals. These may be influential observations warranting further investigation.

4.4.1 Deviance residual plot:

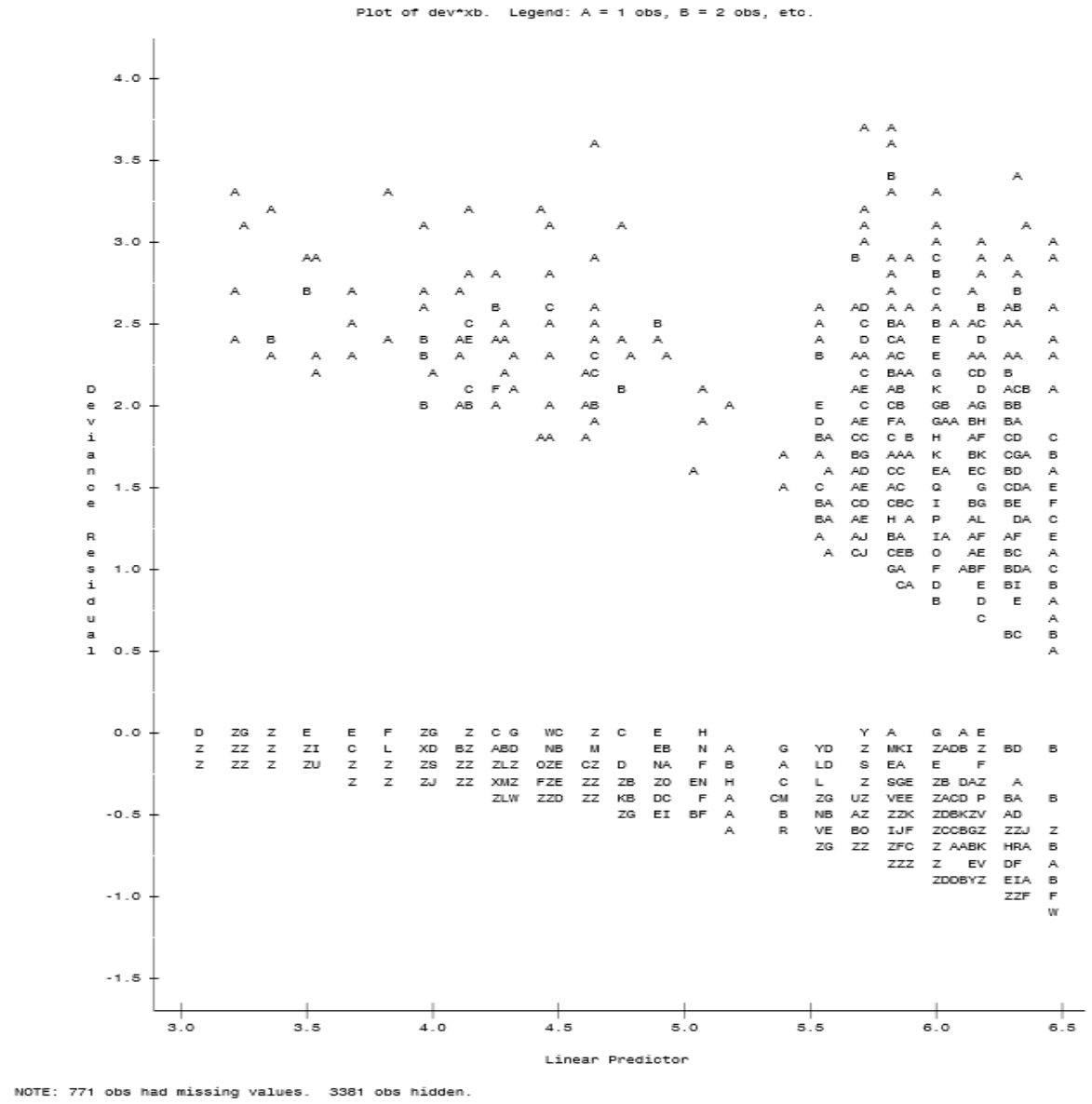


Figure 4: Deviance residual plot

The deviance residual plot shows the residuals versus the linear predictor values from the fitted Cox PH model. Overall, the points follow a relatively random scatter around zero residual with no

apparent curvature or systematic patterns. This suggests the PH assumption holds reasonably well with the covariates having a multiplicative effect on the hazard.

However, there is some minor fanning out of the residuals at higher predictor values. This implies the proportionality assumption may be weakly violated for some covariates, with their hazard effects changing slightly over time, rather than remaining proportional. Nonetheless, the fanning is fairly minor, indicating only a small departure from proportionality for those variables.

A few potential outliers are visible at residuals greater than ±2. These observations may have high leverage and influence on the model fitting. Further investigation is required to assess their impact and whether exclusion is warranted.

In summary, the general random scatter indicates an adequate model fit. The slight fanning suggests minor non-proportionality issues for some covariates and outliers need to be examined further. Overall, there are no major evident deficiencies.

4.4.2 Cox-Snell plot

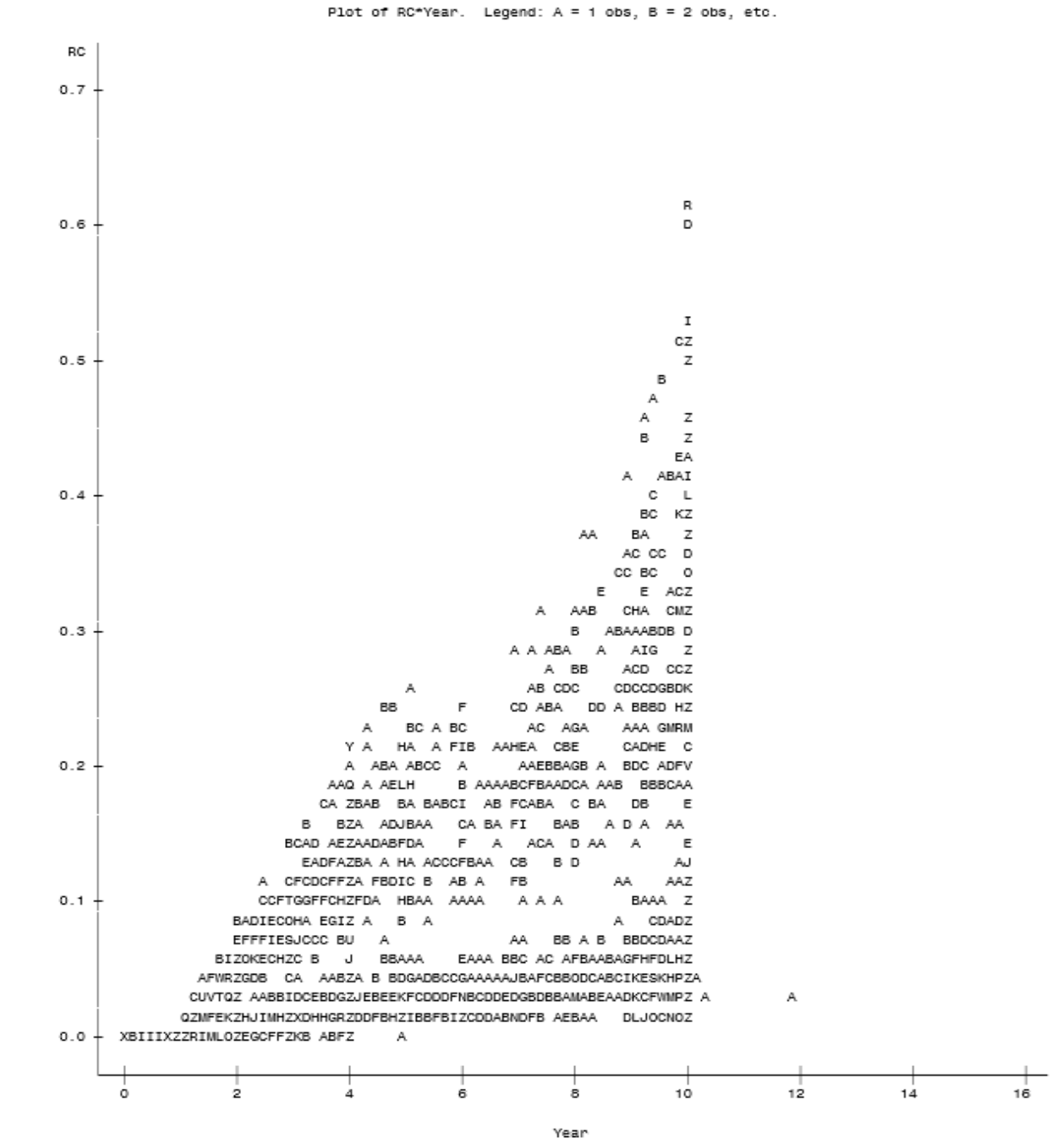


Figure 5: Cox-Snell plot

The Cox-Snell residual plot shows the cumulative hazard function for the fitted Cox PH model versus the cumulative hazard for the hypothetical population. Overall, the fitted cumulative hazard closely follows the ideal 45-degree line, indicating a good fit of the model to the data.

The curve initially closely follows the 45-degree line but then drops below it slightly for higher cumulative hazard values. This suggests the model may underestimate the hazard at larger values, implying some non-proportionality in hazards for certain covariates. However, the deviation is minor, indicating this is a relatively small effect.

The close following of the ideal line for most of the curve indicates that overall, the PH assumption holds reasonably well. The fitted cumulative hazard remarkably closely approximates the population cumulative hazard.

There are no obvious outliers or concerning deviations from the 45-degree line. Overall, the Cox-Snell plot suggests an adequate model fit with only minor potential violations of the PH assumption. It provides general confidence in the appropriateness of the fitted Cox model for these data.

Overall, the martingale residual plot indicates a good model fit with no obvious deficiencies. The deviance plot shows only a minor departure from PH for some covariates. The presence of outliers requires further examination. However, in general, the random scatter suggests goodness-of-fit with the chosen Cox model. There are no issues with respect to censoring or PH overtime.

4.5 Summary

The objective of this study was three-fold: 1) To compare osteoporotic event probability in individuals with and without diabetes using Korean national data; 2) To determine if diabetes represents an independent osteoporosis risk factor; and 3) To compare osteoporosis probability between males and females.

For the objective 1, Kaplan-Meier analysis showed no significant difference in osteoporosis-free survival between diabetes and non-diabetes groups (Figure 2.6). For the objective 2, Univariate Cox models (Table 3), and multivariate Cox regression (Table 4) models demonstrated that diabetes status was not a significant independent predictor of osteoporosis after adjustment for confounders like age and sex. For objective 3, Chi-square descriptive analysis (Table 1), Kaplan-Meier curves (Figure 2.2), univariate Cox models (Table 3), and multivariate Cox regression (Table 4) all illustrated substantially and significantly higher risks and hazards for developing osteoporosis among females compared to males.

Key findings were that advanced age, female gender, hyperlipidemia, and lack of hypertension had the strongest associations with osteoporosis onset in this cohort of older Korean adults with and without diabetes. Descriptive analyses revealed greater comorbidities among diabetes patients at baseline. Kaplan-Meier curves showed significantly higher risks among women, seniors, and those with less education or income. Notably, diabetes itself did not independently predict osteoporosis probability after accounting for demographic and clinical factors in multivariate Cox models. This indicates optimal diabetes management may mitigate excess skeletal risks, although further study is warranted. Overall, these results help characterize

osteoporosis risk profiles in older adults with diabetes to guide screening and prevention approaches, emphasizing the substantially increased risks for women and older individuals.

Chapter 5 Discussion

Our large population-based cohort study of over 7,000 Koreans aged 50 years, with an 11-year follow-up period aimed to elucidate the risk factors for developing osteoporosis, a debilitating disease that predisposes to fragility fractures. The key findings were that age, sex, and comorbidities such as hyperlipidemia significantly influenced osteoporosis risk, while diabetes itself was not a significant predictor. Specifically, older age, female sex, and hyperlipidemia significantly predicted increased osteoporosis risk, whereas smoking and hypertension had a protective effect. Diabetes itself did not independently associate with osteoporosis development after controlling for some demographic and clinical factors. In this data, types of diabetes (type 1 and type 2 diabetes) are not available. In general, diabetes of older adults is type 2 and we used age group more than 50 years and older for this analysis. So, we can assume most of our diabetic participants are type 2.

Our results have important clinical and public health implications for identifying high-risk patients with diabetes who may benefit from proactive osteoporosis screening and preventive interventions. Older women with diabetes and concurrent hyperlipidemia appear to be a particularly vulnerable group warranting monitoring, lifestyle counseling, and pharmacological management if indicated. Timely risk modification in such patients could substantially reduce the personal, societal, and economic burdens associated with osteoporotic fractures.

Diabetes measured at baseline or over time was not significantly associated with osteoporosis risk in our multivariate Cox model. This indicates that diabetes may not directly impact osteoporosis development in this population when accounting for other factors.

Conversely, the lack of association between diabetes and low bone density suggests osteoporosis development is multifactorial, and diabetes alone does not necessarily predispose to accelerate skeletal deterioration. This highlights the need for a nuanced, individualized approach in assessing osteoporosis risk rather than blanket screening of all diabetics. Moreover, the results indicate that optimal diabetes care and prevention of complications may mitigate any detrimental effects of diabetes on bone health.

The significantly increased osteoporosis hazard across older age groups and in women mirrors extensive epidemiological data showing age- and sex-related differences in peak bone mass, bone loss trajectories, and fracture risk.

Specifically, the HRs showed a pronounced increase in osteoporosis risk with advancing age, especially in the 60–70 and over 70 years age groups [99-102]. This aligns with a previous study that identified age as a major risk factor, due to the natural decline in bone density over time. By early adulthood, typically by 30 years of age, our bones have reached their peak density and strength. Once that point has been reached, bone mass gradually diminishes over time [103,104].

In comparison to men, women had a substantially higher osteoporosis risk across all age groups. Previous studies have shown that women have a higher risk of the disease. The peak bone mass of women is typically lower than that of men. This is consistent with the prior evidence of lower peak bone mass and accelerated postmenopausal bone loss in women compared to the slower age-related bone loss in men [105]. The accelerated postmenopausal bone loss in women likely explains the pronounced female predisposition to osteoporosis, especially during the early postmenopausal period between ages 60–70 years. Hormonal changes and gradual testosterone reduction in men are less abruptly pronounced than the estrogen withdrawal in women is,

contributing to lower osteoporosis incidence in men [105]. Structural and geometric bone differences as well as hormonal factors may further amplify this sexual dimorphism in fracture risk [104-106].

The association between smoking and osteoporosis conflicts with several studies demonstrating bone-damaging effects of smoking [67,73]. However, smoking behavior is complex, dynamic, and challenging to accurately capture over long periods [72]. The quantity, duration, cumulative exposure, and timing of smoking may exhibit nonlinear effects on skeletal health. Furthermore, the constituents of cigarette smoke, such as nicotine and cadmium, are thought to impair bone, but it can vary widely between cigarette brands [72]. Thus, the weak link observed here should not supersede the wealth of mechanistic and epidemiological data suggesting smoking cessation benefits bone health. However, in our study, current and past smoking were not major contributors to osteoporosis in this cohort. This diverges from previous evidence suggesting smoking is an important risk factor [67,73].

In another study, smoking and central obesity were positively associated. Current smokers were a higher risk of obesity in their lower abdomen [107]. According to some Chinese studies, being obese appeared to protect against osteoporosis [108,109]. Thus, a correlation may exist between smoking and osteoporosis in Asian setting, and central obesity or higher BMI is the intermediate connection between smoking and osteoporosis, indicating that BMI act as an effect modifier. Figure 6 shows the direct and indirect effects among smoking, obesity, and osteoporosis.

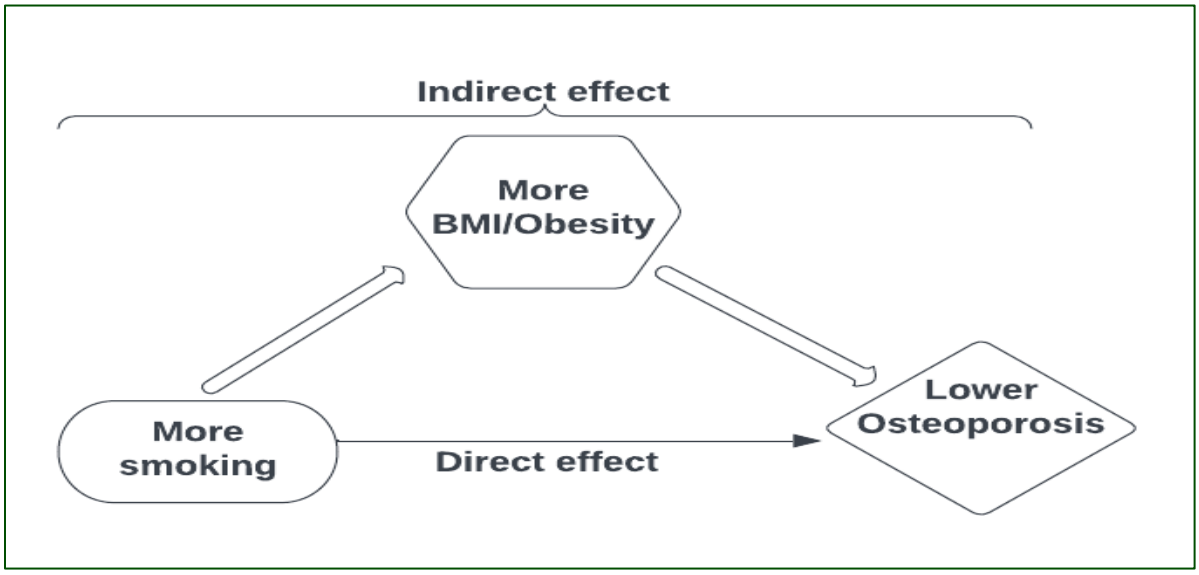


Figure 6 : Direct and indirect effects among smoking, obesity, and osteoporosis

Research has found that obese women have higher BMD than that of non-obese women, although obesity is commonly seen as a risk factor for various health problems. Osteoporosis appears to be prevented by obesity [108,109]. According to the findings, obese Qatari women have higher spine and femur BMD [109]. Therefore, obese women in this study had stronger bones than those of non-obese women. This result corroborates another Chinese study that observed a negative correlation between obesity and osteoporosis among older women [109].

Similarly, the positive association between hyperlipidemia and low bone density aligns with proposed biological mechanisms whereby lipid accumulation impairs osteoblast function and disrupts bone remodeling [84]. Moreover, some earlier studies have linked hyperlipidemia with increased osteoporosis risk [84], providing support to this finding. Routine screening and

management of glycemic and lipid profiles as part of comprehensive diabetes care may therefore have ancillary benefits in terms of osteoporosis prevention.

In contrast, the lower osteoporosis hazard with hypertension diverges from the results of some studies, showing increased fracture risks in hypertensive cohorts [110]. While speculative, this protective effect could potentially arise from enhanced perfusion and mechanical loading on bone tissue induced by elevated blood pressure [83]. This discrepancy may arise from sample characteristics, survivorship bias if hypertensive patients had higher mortality, or confounding from co-prescribed anti-hypertensive drugs that influence bone density. The ubiquity of multi-drug regimens for managing chronic conditions highlights the need to disentangle the effects of individual agents on osteoporosis risk. However, the mechanisms linking hypertension with bone metabolism likely involve a complex interplay of systemic factors that require further elucidation [83].

Moreover, hypertension increases the risk of osteoporotic fractures [82], and a significant association exists between hypertension and osteoporosis risk [83], which aligns with our findings. According to some Chinese studies we found that obesity also increases the risk of hypertension [111][112]and researchers also found that being obese appeared to protect against osteoporosis [108][109]. So, obesity can influence both exposure and outcome as a confounder. Figure 7 shows the direct and indirect effects among hypertension, obesity, and osteoporosis.

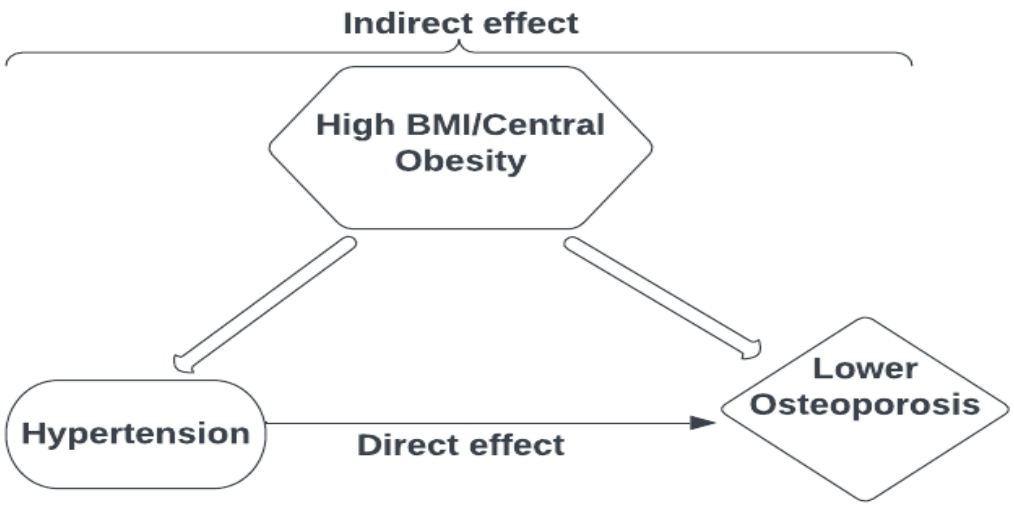


Figure 7 : Direct and indirect effects among hypertension, obesity, and osteoporosis

The lack of association between diabetes and long-term osteoporosis development aligns with several recent longitudinal studies after controlling for comorbidities and potential demographic confounders [113,114]. Their findings imply that despite short-term impacts, diabetes may not represent an independent causal risk factor for osteoporosis onset in many populations.

The lack of association between diabetes and osteoporosis risk contradicts previous studies showing diabetes as a risk factor [110,115,116]. However, other recent evidence found no significant link between diabetes and low bone density [113,114,117]. Diabetes has also been associated with an increase in bone density, indicating that diabetes has protective effect against osteoporosis [118,119]. The inconsistency in this relationship warrants further investigation through longitudinal studies.

Study strengths

This study possessed several major strengths that bolstered the validity and reliability of its findings. The nationwide, population-based cohort design was a key asset, enhancing generalizability of the results compared to localized cohorts. The robust sample size of over 7,000 participants provided ample statistical power to detect clinically meaningful effects across this large yet homogeneous South Korean population. Standardized clinical diagnosis codes were utilized as objective outcome measures of osteoporosis, as described in the methods section. Given that the physicians documenting participant records were blinded to the specific study hypotheses, the risk of biased outcome ascertainment or classification was reduced. The extensive collection of data on demographics, socioeconomic factors, clinical history, and health behaviors allowed adjustment for possible confounders using rigorous multivariate proportional hazards regression techniques. The focus on an Asian population helps address knowledge gaps regarding region-specific osteoporosis epidemiology. The multivariate PH regression approach adjusted for potential confounders to isolate independent effects. Lastly, participants served as their own controls longitudinally when quantifying diabetes associations. The time-varying Cox model accounts for complex temporal relationships between chronic disease states.

Study limitations

Some limitations should be considered when interpreting the results of this study. First, no direct BMD data were available to confirm osteoporosis classification, and thus diagnostic misclassification may exist without direct BMD measurements to confirm osteoporosis. However, fracture history data helped identify severe osteoporosis cases. Second, the generalizability of the study findings to non-Korean populations is uncertain given potential ethnic differences in bone

geometry, density, and metabolism. As this study was based exclusively in Korea, extrapolation to other ethnicities should be made with caution. Third, the median follow-up duration of 11 years may potentially have underestimated any markedly long-term diabetes-osteoporosis relationships. Lastly, details were lacking regarding anti-diabetic medications, vitamin D, calcium intake, or supplement use. Given the modest diabetes-osteoporosis association, the findings require replication in larger multi-country cohorts with extended follow-up periods. Residual confounding from unmeasured variables may have affected the magnitudes of estimated relationships bias.

In summary, the lack of diabetes-osteoporosis association in Korean older adults warrants confirmation but adds to growing evidence that properly managed diabetes may not independently jeopardize long-term bone health. Although requiring prudent verification, this could help avoid over-diagnosis and over-treatment in certain populations based on the assumption that diabetes equates to elevated osteoporosis risk. However, identifying and controlling modifiable risks such as hyperlipidemia appears valuable for mitigating hazards. Given the complex multifactorial etiology of osteoporosis, large prospective studies with detailed treatment data, fracture outcomes, bone density measures, and widened ethnic representation may help further disentangle the relative contributions of diabetes, age, sex, medications, and lifestyle habits to fracture susceptibility.

Future research

Future research can build upon these analyses by exploring longitudinal impacts. Additional large-scale, multi-country studies with radiographic osteoporosis confirmation could help validate the generalizability of our findings globally. Incorporating detailed medication, dietary, biochemical, and lifestyle data would also clarify the mechanisms linking hyperlipidemia and hypertension to osteoporosis risks. Prospective studies tracking BMD changes before and after diabetes onset will help disentangle this complex association. Robust survival modeling with expanded risk factors and repeated measures will offer further insights into the evolution of risk over time. Cost-effectiveness analyses can also help guide efficient allocation of limited resources based on the hazards identified.

In summary, our survival models of time to osteoporosis event provide a foundation; however, further complex analytic approaches are needed to disentangle the web of risks facing susceptible populations. There are also opportunities to integrate molecular markers and genetic factors. A multifaceted understanding of osteoporosis hazard will enable clinicians to deliver personalized risk stratification and interventions. Further, modeling bone density changes from diabetes onset until late-life fracture can precisely elucidate how diabetes impacts skeletal health over time.

Chapter 6 Conclusion

This longitudinal cohort study found no evidence supporting time-dependent diabetes diagnosis increased the risk of developing osteoporosis among community-dwelling Korean adults over a median follow-up of 11 years. Multivariate PH regression showed that diabetes status, whether measured at baseline or as a time-varying covariate, exhibited no significant association with altered hazards for osteoporosis events after adjustment for confounders.

However, female sex, older age (70+ years), presence of hyperlipidemia and lower education level were all strongly associated with heightened osteoporosis hazards. Interestingly, hypertension and smoking history also emerged as modest protective factors associated with reduced hazards. Significant age-by-sex interactions indicated that within a high-risk group of postmenopausal women, those in their 60s faced the highest hazard of osteoporosis onset compared to that of women over 70 years.

These findings contribute to a complex body of literature regarding potential relationships between dysglycemia and bone health. While microvascular changes, inflammation, and oxidative stress associated with diabetes may adversely impact bone integrity, results remain inconsistent regarding diabetes as an independent contributor to long-term osteoporosis development versus a marker of generalized metabolic dysregulation. Controlling blood sugars and preventing diabetes complications appear to mitigate detrimental effects on bone. The lack of association after adjustment underscores that routinely managing all adults with diabetes as high-risk for osteoporosis may result in unnecessary testing and treatment. Alternatively, identifying and addressing modifiable lifestyle and clinical risks may prove more impactful for prevention. Considering ethnic differences is also prudent, given divergent effects between the Korean cohort

and predominantly Caucasian populations. Additional prospective studies with larger samples, fracture outcomes, BMD data, and diverse ethnicities could help further clarify to whom and when bone density screening should be selectively targeted.

In summary, diabetes does not independently increase osteoporosis hazards among Korean adults, whereas female sex, aging, and hyperlipidemia heightened risks significantly. Our findings can help inform clinical practice and future studies on determining selective, targeted approaches for optimizing osteoporosis screening and prevention in Asia.

Chapter 7 Reference

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Chapter 8 Appendix A SAS codes

8.1 Baseline characteristics

```
Data thesis_step_01;
set Thesis_spss_data_03Feb2022;
if ou3 in (2309) or ou4 in (2309) or ou5 in (2309) or cd1 in (2309)
or cd2 in (2309)
or in25 in(23091) or md3 in (2309) then osteoporosis =1;
else osteoporosis = 0;
sex= c3;
rename c3=sex2;
run;



PROC IMPORT OUT= WORK.Thesis_data_20Nov2022
            DATAFILE= "C:\Users\Tanmoy Das\OneDrive\Desktop\SAS
workshop\KHP_2008_2018_yr_ver8_18Nov.csv"
            DBMS=csv REPLACE;

RUN;

proc contents; run;

proc print data = Thesis_data_20Nov2022(obs = 10); run;


/*THIS CODE IS FOR MAKING THE AGE TABLE*/
data Thesis_data_20Nov2022step1;
TITLE "THIS CODE IS FOR MAKING THE AGE TABLE";
     set Thesis_data_20Nov2022;
     if bthd>0 then age = base_year - bthd;
     else age = .;
run;

/*THIS CODE IS FOR CHECKING THE AGE TABLE (TOTAL 29142)*/
proc freq data = Thesis_data_20Nov2022step1;
TITLE "CHECKING THE AGE TABLE (TOTAL 29142)";
     table age;
run;

/*MULTIPLE WORK HAS BEEN DONE IN THIS CODE,ONE SIDE WE ARE
RESTRICTING THE AGE IN 50 AND THE OTHERSIDE
 WE ARE DELETING ALL THE PARTICIPANTS WHO HAVE ALREADY SUFFERING
WITH OSTEOPOROSIS in the baseline
2008 and 2014 where new patients are entered into the study*/
 data Thesis_data_20Nov2022step2;
```

```
     set Thesis_data_20Nov2022step1;
     if age>=50;
     if osteo_8 = 1 then delete;
     if osteo_14 = 1 then delete;
run;

/*THIS CODE IS FOR CHECKING THE AGE TABLE (TOTAL 9077)*/
proc freq data = Thesis_data_20Nov2022step2;
     table age;
run;


/*here in this code we are try to obtain the osteoporosis case
at baseline
and we get 743 new osteoporsis case*/

proc freq data = Thesis_data_20Nov2022step2;
TITLE "obtain the osteoporosis case
and we get 794 new osteoporsis case";
     table osteo_;
     *where base_year = 2010 or base_year = 2016;
      where osteo_ = 1;
run;

/*
MAKING THE DIABETES VARIABLE*/

data Thesis_data_20Nov2022step3;
     set Thesis_data_20Nov2022step2;
     TITLE "MAKING THE DIABETES VARIABLE";
     if type2_=1 or type1_=1 then Diabetes = 1;
    if type2_=0 and type1_=0 then Diabetes = 0;
run;
/*CHEKING THE DIABETES VARIABLE*/
proc freq data = Thesis_data_20Nov2022step3;
TITLE "CHEKING THE DIABETES VARIABLE";
     table diabetes;
run;
/*the type2
number differnce */

proc freq data = Thesis_data_20Nov2022step3;
TITLE "CHEKING THE DIABETES VARIABLE  type2";
     table type2_;
     WHERE age>=50 and diabetes=1;
run;
/*
```

```
Here in this code we try to obtain those patient who have
diabetes in the baseline
and they develop osteoporosis at the first CASE
*/
PROC freq Data=Thesis_data_20Nov2022step3;
TITLE "FREQ OF GROUP DIABETES AND OSTEOPOROSIS ";
table diabetes*osteo_/chisq missing;
     *where base_year = 2008 or base_year = 2014;
      where diabetes = 1;
RUN;




/*HERE WE WILL Categorize ALL variableS THAT WILL NEED LATER FOR
ANALYSIS*/
ods listing close;
ods rtf file='C:\Users\Tanmoy Das\OneDrive\Desktop\Thesis
work/Thesis_data_12june2022_part2.rtf';


/*HERE WE ARE TRY TO Categorize AGE variable(DONT RUN THIS CODE
WHEN YOU ARE )*/
data Thesis_data_20Nov2022step4;
set Thesis_data_20Nov2022step3;
if age >= 50 and age <= 64 then agec = 1;
if age >= 65 then agec=2;
run;
/*HERE WE ARE TRY TO Categorize AGE variable in for different
new categories*/
data Thesis_data_20Nov2022step4;
set Thesis_data_20Nov2022step3;
if age >= 50 and age <= 59 then agec = 1;
if age >= 60 and age <= 69 then agec = 2;
if age >= 70 and age <= 79 then agec = 3;
if age >= 80 then agec=4;
run;

PROC MEANS Data=Thesis_data_20Nov2022step4 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF GROUP DIABETES AND AGE";
VAR Age;
CLASS agec diabetes;

RUN;
```

```
/*MEAN OF BMI as an continuous variable";
VAR bmi; */
PROC MEANS Data=Thesis_data_20Nov2022step5 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF BMI as an continuous variable";
VAR bmi;
CLASS bmi diabetes ;
RUN;
PROC MEANS Data=Thesis_data_20Nov2022step5 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF BMI as an continuous variable";
VAR bmi;
CLASS bmi diabetes ;
RUN;

data Thesis_data_20Nov2022step5;
set Thesis_data_20Nov2022step4;
if bmi < 18.5 then bmic = 1;
if bmi >= 18.5 and bmi < 24.9 then bmic = 2;
if bmi >= 25 and bmi < 29.9 then bmic=3;
if bmi >= 30 then bmic=4;
run;
PROC MEANS Data=Thesis_data_20Nov2022step5 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF BMI";
VAR bmi;
CLASS bmic diabetes ;
RUN;

/*
present/past smoking amount   Are you currently smoking?    S2
                (1) current daily smoking  Y   CURRENT SMOKERS
                (2) occasionally smoking   Y
                (3) smoked but not smoking now  P   PREVIOUS
                (4) Never                       N
                (-9) unknown/no respond
                (-1) NA
*/
data Thesis_data_20Nov2022step6;
set Thesis_data_20Nov2022step5;
if smk_cur= 1 or smk_cur= 2 then smokingc = 1;

if smk_cur= 3 then smokingc= 2;
if smk_cur= 4 then smokingc= 0;
if smk_cur= -9 or smk_cur= -1 then smokingc=.;
run;
```

```
proc phreg data = Thesis_data_20Nov2022step6;
title "UNIVARIATE COX REGRESSION of variable drinkingc where the
outcome is osteoporosis ";
CLASS  smokingc(ref="0")/PARAM=REF;
model Year*osteo_(0)= smokingc /covb risklimits;
run;


PROC freq Data=Thesis_data_20Nov2022step6;
TITLE "MEAN OF GROUP DIABETES AND current smokers";
table smokingc*diabetes/chisq missing;
RUN;


/*drinking status   How often have you been drinking in the last
year?     S17
            (1) Never                          Non 0
               (2) recently  non-drink           N   0
               (3) less than once per month      MODERATE
               (4) once a month                  M        4
               (5) 2-3 times per month           M
               (6) once a week                        3
               (7) 2-3 times per week                 2
               (8) almost daily                  H    1
               (-9) unknown/no respond
*/

data Thesis_data_20Nov2022step7;
set Thesis_data_20Nov2022step6;
if drink_1yr= 1 then drinkingc = 0;
if drink_1yr= 8 then drinkingc=1;
if drink_1yr= 7 or drink_1yr= 6 then drinkingc=2;
if drink_1yr= 3 or drink_1yr= 4 or drink_1yr= 5  then
drinkingc=3;
if drink_1yr= 2 then drinkingc=4;

if drink_1yr= -9 then drinkingc=.;
run;


proc phreg data = Thesis_data_20Nov2022step7;
title "UNIVARIATE COX REGRESSION of variable drinkingc where the
outcome is osteoporosis ";
CLASS  drinkingc(ref="0")/PARAM=REF;
```

```
model Year*osteo_(0)= drinkingc /covb risklimits;
run;

PROC freq Data=Thesis_data_20Nov2022step7;

table drinkingc*diabetes/chisq missing;

RUN;

/*Ability to exercise    What do you think of your athletic
ability?  SJ1
            (1) no problem with walking
               (2)  some problem with walking
               (3)  always lay down
               (-1) NA
               (-9)  no response/refusing response

*/

data Thesis_data_20Nov2022step8;
set Thesis_data_20Nov2022step7;
if PYSICAL= 1 then PYSICALC=1;
if PYSICAL= 2 then PYSICALC=2;
if PYSICAL= 3 then PYSICALC=3;
if PYSICAL= -9 or PYSICAL= -1 then PYSICALC=.;
run;
PROC freq Data=Thesis_data_20Nov2022step8;
table PYSICALC*diabetes/chisq missing;

RUN;

/*marriage status   What is your OOO (household members name)
marriage status
C7           (1) marriage (including putative marriage)  YES 1
               (2) separate (Divorce premise)              NO
               (3) widow or disappearance                  N
2
               (4) divorce                                 N
               (5) none
               3
               (-1)NA
               (-6) not surveyed
*/
data Thesis_data_20Nov2022step9;
set Thesis_data_20Nov2022step8;
if marital= 1 then maritalc = 1;
if marital= 2 or marital= 3 or marital= 4 then maritalc= 2;
```

```
if marital= 5 then maritalc= 3;
if marital= -1 or marital= -6 then maritalc=.;
run;


PROC freq Data=Thesis_data_20Nov2022step9;

table maritalc*diabetes/chisq missing;

RUN;
/*JUST CHECKING THE FREQUENCY OF EDU*/
PROC freq Data=Thesis_data_20Nov2022step9;
table edu;

RUN;

/*education    How far did you OOO (household members name)
go to school, or are you attending?     C8
             (1) preschool(under 7 years old)
                (2) no education (Illiteracy)            NONE
                (3) no education but literacy            NO
                (11) ~ (16) 1~ 6 elementary school       CAT 1
                (21) ~ (23) 1~3 middle school            C 1
                (31) ~ (33) 1~3 high school              C2
                (41) ~ (46) 1~6 university               C3
                (51) master in graduate school           C3
                (52) PhD in graduate school              C3
*/
data Thesis_data_20Nov2022step10;
set Thesis_data_20Nov2022step9;

if edu= 2 or edu= 3
then educ = 0;

if edu= 1 or edu= 4 or edu= 5 or edu= 6 or edu= 7 or edu= 8 or
edu= 9 or edu= 10 or edu= 11 or edu= 12 or
edu= 13 or edu= 14 or edu= 15 or edu= 16 or
edu= 17 or edu= 18 or edu= 19 or edu= 20 or
edu= 21 or edu= 22 or edu= 23
then educ=1;

if edu= 31 or edu= 32 or edu= 33
then educ = 2;

if edu= 34 or edu= 35 or edu= 36 or edu= 37 or edu= 38 or
edu= 39 or edu= 40 or edu= 41 or edu= 42 or
edu= 43 or edu= 44 or edu= 45 or edu= 46 or
```

```
edu= 47 or edu= 48 or edu= 49 or edu= 50 or
edu= 51 or edu= 52
then educ = 3;
run;


PROC freq Data=Thesis_data_20Nov2022step10;

table educ*diabetes/chisq missing;

RUN;

/*Hyperlipidemia*/


data Thesis_data_20Nov2022step11;
set Thesis_data_20Nov2022step10;
if Hyperlipidemia_= 1 then Hyperlipidemiac_ = 1;
if Hyperlipidemia_= 0 then Hyperlipidemiac_=0;
run;


PROC freq Data=Thesis_data_20Nov2022step11;

table Hyperlipidemiac_*diabetes/chisq missing;

RUN;



/*hyperthyroidism
PROC freq Data=thesis_data_new_step_04;
TITLE "freq OF GROUP of people with
 DIABETES & have the hyperthyroidism";
table hyperthyroidism;
WHERE Base_Year = 2008;
where type2=1 & hyperthyroidism=1;
RUN;*/


data Thesis_data_20Nov2022step12;
set Thesis_data_20Nov2022step11;
if Hyperthyroidism_= 1 then hyperthyroidismc_ = 1;
if hyperthyroidism_= 0 then hyperthyroidismc_=0;
run;
```

```
PROC freq Data=Thesis_data_20Nov2022step12;

table hyperthyroidismc_*diabetes/chisq missing;

RUN;


/*CATEGORIZATION OF THE HYPERTENSION VARIABLE*/
data Thesis_data_20Nov2022step14;
set Thesis_data_20Nov2022step12;
if hypertension_= 1 then hypertensionc_ = 1;
if hypertension_= 0 then hypertensionc_=0;
run;


PROC freq data=Thesis_data_20Nov2022step14;

table hypertensionc_*diabetes/chisq missing;

RUN;

/*calculating the income_quintile=1 or income_quintile=2 or
income_quintile=3
or income_quintile=4 or income_quintile=5
total householdincome 5%tile (weight applied)
     W_TOTAL_Q5
               (1) 1st quintile
               (2) 2nd quintile
               (3) 3rd quintile
               (4) 4th quintile
               (5) 5th quintile
               (-9) unknown

*/
data Thesis_data_20Nov2022step15;
set Thesis_data_20Nov2022step14;
if income1=1 then income_quintilec=1;
if income1=2 then income_quintilec=2;
if income1=3 then income_quintilec=3;
if income1=4 then income_quintilec=4;
if income1=5 then income_quintilec=5;
if income1=-9 then income_quintilec=.;
run;


PROC freq Data=Thesis_data_20Nov2022step15;
```

```
table income_quintilec*diabetes/chisq missing;

RUN;

/*Private Pension / Life Insurance join
Have you (household members names) joined private company's
(banks, insurers and asset managers and securities) private
pension or life insurance ?
C18
(1) Only Private Pension   join
(2) only Life Insurance join
(3) both  join
(4) both  Not included
(-9)  not know*/

PROC freq Data=Thesis_data_20Nov2022step15;
table life_insur;

RUN;
data Thesis_data_20Nov2022step16;
set Thesis_data_20Nov2022step15;
if life_insur=1 then life_insurc=1;
if life_insur=2 then life_insurc=2;
if life_insur=3 then life_insurc=3;
if life_insur=4 then life_insurc=4;
if life_insur=-9 then income_quintilec=.;

run;
PROC freq Data=Thesis_data_20Nov2022step16;

table life_insurc*diabetes/chisq missing;

RUN;


/*CVD_
0 NO
1 YES*/

PROC freq Data=Thesis_data_20Nov2022step15;
table CVD_;

RUN;
data Thesis_data_20Nov2022step17;
set Thesis_data_20Nov2022step16;
if cvd_=1 then cvd_c=1;
if cvd_=0 then cvd_c=0;
```

```
run;
PROC freq Data=Thesis_data_20Nov2022step17;

table cvd_c*diabetes/chisq missing;

RUN;

/*weight change     Have you gained or lost more than 5kg in the
last two years?
(except for changes in weight due to pregnancy)        S34_1
(1) 5kg above gain
(2) 5kg above lose
(3) almost no change
(4) 5kg above , change but now similar to the previous
(-9) unknown/no respond
*/
PROC freq Data=Thesis_data_20Nov2022step15;
table wgt_change_5;

RUN;

data Thesis_data_20Nov2022step18;
set Thesis_data_20Nov2022step17;
if wgt_change_5=1 then wgt_change_5c=1;
if wgt_change_5=2 then wgt_change_5c=2;
if wgt_change_5=3 then wgt_change_5c=3;

if wgt_change_5=4 or wgt_change_5=-9 then wgt_change_5c=.;
run;

PROC freq Data=Thesis_data_20Nov2022step18;

table wgt_change_5c*diabetes/chisq missing;

RUN;
/*Acute pancreatic Disease
0 no
1 yes
K85*/
PROC freq Data=Thesis_data_20Nov2022step15;
table pancrease_;
RUN;

data Thesis_data_20Nov2022step19;
set Thesis_data_20Nov2022step18;
if pancrease_= 1 then pancrease_c = 1;
```

```
if pancrease_= 0 then pancrease_c=0;
run;
PROC freq Data=Thesis_data_20Nov2022step19;

table pancrease_c*diabetes/chisq missing;

RUN;



data Thesis_data_20Nov2022step20;
set Thesis_data_20Nov2022step19;
if sex= 1 and diabetes= 1 then sex_diabetes = 1;
if sex= 2 and diabetes= 1 then sex_diabetes = 2;
if sex= 1 and diabetes= 0 then sex_diabetes = 3;
if sex= 2 and diabetes= 0 then sex_diabetes = 4;
run;

proc freq data=Thesis_data_20Nov2022step20;
table sex diabetes sex_diabetes;
run;

ods rtf close;
ods listing;
/*NOW WE WILL CHECK THOSE PARTICIPANTS WHO ARE FROM NO DIABETES
GROUP AT FIRST BUT DURING THE TIMEPERIOD
SOME OF THEM DEVELOP DIABETES AND FROM THAT FOLLOW UP GROUP SOME
OF THEM MAY DEVOLOP OSTEOPOROSIS
MY TARGET AUDIENCE IS THEY*/
PROC freq Data=Thesis_data_20Nov2022step20;
table No_DB____DB;
RUN;



ods listing close;
ods rtf file='C:\Users\Tanmoy Das\OneDrive\Desktop\Thesis
work/Thesis_data_17Nov2022_baseline table 1.rtf';


PROC MEANS Data=Thesis_data_20Nov2022step4 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF GROUP DIABETES AND AGE";
VAR Age;
CLASS agec diabetes;
RUN;
```

```
PROC MEANS Data=Thesis_data_20Nov2022step4 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF GROUP DIABETES AND AGE as an cOntinuous
variable";
VAR Age;
CLASS diabetes;
RUN;

PROC freq Data=Thesis_data_20Nov2022step4;
TITLE "FREQ OF GROUP DIABETES AND AGE";
table AGEC*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step5;
TITLE "FREQ OF GROUP DIABETES AND BMI as an continuous
variable";
table sex*diabetes/chisq missing;
RUN;

PROC MEANS Data=Thesis_data_20Nov2022step5 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF sex";
VAR sex;
CLASS diabetes ;
RUN;
PROC MEANS Data=Thesis_data_20Nov2022step5 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF BMI";
VAR bmi;
CLASS diabetes ;
RUN;
PROC MEANS Data=Thesis_data_20Nov2022step5 N Mean Median std
MaxDec = 2;
TITLE "MEAN OF BMI as an continuous variable";
VAR bmi;
CLASS bmic diabetes ;
RUN;

PROC MEANS Data=Thesis_data_20Nov2022step5 N Mean Median std
MaxDec = 2;;
TITLE "MEAN OF sex";
VAR sex;
CLASS sex diabetes ;
RUN;

PROC freq Data=Thesis_data_20Nov2022step4;
```

```
TITLE "FREQ OF GROUP DIABETES AND AGE as an cntinuous variable";
table AGEc*diabetes/chisq missing;
RUN;


PROC freq Data=Thesis_data_20Nov2022step5;
TITLE "FREQ OF GROUP DIABETES AND BMIC";
table BMIC*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step5;
TITLE "FREQ OF GROUP DIABETES AND sex";
table sex*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step6;
TITLE "MEAN OF GROUP DIABETES AND current smokers";
table smokingc*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step7;
 TITLE "freq OF GROUP DIABETES AND drinking";
table drinkingc*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step8;
TITLE "freq OF GROUP DIABETES AND ph activity";
table PYSICALC*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step9;
TITLE "freq OF GROUP DIABETES AND marital status";
table maritalc*diabetes/chisq missing;
RUN;

pROC freq Data=Thesis_data_20Nov2022step10;
TITLE "freq OF GROUP DIABETES AND Educational level";
table educ*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step11;
TITLE  "freq OF GROUP DIABETES AND hyperlipidemia";
table Hyperlipidemiac_*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step12;
TITLE "freq OF GROUP DIABETES AND hyperthroidism";
```

```
table hyperthyroidismc_*diabetes/chisq missing;
RUN;

PROC freq data=Thesis_data_20Nov2022step14;
TITLE "freq OF GROUP DIABETES AND hypertension";
table hypertensionc_*diabetes/chisq missing;
RUN;

PROC freq Data=Thesis_data_20Nov2022step15;
TITLE "freq OF GROUP DIABETES AND income quintile";
table income_quintilec*diabetes/chisq missing;
RUN;
```

8.2 Univariate COX regression analysis

```
proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable sex where the
outcome is osteoporosis ";
 model Year*osteo_(0)=  sex /covb risklimits;
run;
proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable sex where the
outcome is osteoporosis ";
CLASS sex(REF="1")/PARAM=REF;

model Year*osteo_(0)=  sex /covb risklimits;
run;


proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable agec where the
outcome is osteoporosis ";
model year*osteo_(0)=AGE /covb risklimits;
run;

proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable agec where the
outcome is osteoporosis ";
CLASS agec(ref="1")/PARAM=REF;

model Year*osteo_(0)=AGEC /covb risklimits;
run;


proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable bmic where the
outcome is osteoporosis ";
model Year*osteo_(0)= bmi /covb risklimits;
run;

proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable bmic where the
outcome is osteoporosis ";
CLASS bmic(ref="1")/PARAM=REF;

model Year*osteo_(0)= bmic /covb risklimits;
run;
```

```
proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable marital where the
outcome is osteoporosis ";
CLASS maritalc(ref="3")/PARAM=REF;

model Year*osteo_(0)=  maritalc /covb risklimits;
run;
proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable edu where the
outcome is osteoporosis ";
CLASS educ(ref="0")/PARAM=REF;

model Year*osteo_(0)=  educ /covb risklimits;
run;
proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable income_quintilec
where the outcome is osteoporosis ";
CLASS  income_quintilec(ref="1")/PARAM=REF;

model Year*osteo_(0) =  income_quintilec /covb risklimits;
run;


proc phreg data =mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable smoking where the
outcome is osteoporosis ";
CLASS smokingc(REF="0")/PARAM=REF;

model Year*osteo_(0) =  smokingc /covb risklimits;
run;



proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable drinkingc where the
outcome is osteoporosis ";
CLASS  drinkingc(ref="0")/PARAM=REF;

model Year*osteo_(0)= drinkingc /covb risklimits;
run;

proc phreg data =mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable pysical where the
outcome is osteoporosis ";
CLASS pysical(ref="3")/PARAM=REF;
```

```
model Year*osteo_(0)= pysical /covb risklimits;
run;



proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable life_insurc where
the outcome is osteoporosis ";
CLASS  life_insurc(ref="4")/PARAM=REF;

model Year*osteo_(0) =  life_insurc /covb risklimits;
run;



proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable hyperthyroidismc
where the outcome is osteoporosis ";
CLASS hyperthyroidismc_(ref="0")/PARAM=REF;

model Year*osteo_(0) = hyperthyroidismc_ /covb risklimits;
run;

proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable hypertension where
the outcome is osteoporosis ";
CLASS hypertension_(ref="0")/PARAM=REF;

model Year*osteo_(0) = hypertension_ /covb risklimits;
run;


proc phreg data =mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable cvd_c where the
outcome is osteoporosis ";
CLASS  cvd_c(ref="0")/PARAM=REF;

model Year*osteo_(0) =  cvd_c /covb risklimits;
run;
proc phreg data = mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable Hyperlipidemia
where the outcome is osteoporosis ";
CLASS Hyperlipidemiac_(ref="0")/PARAM=REF;

model Year*osteo_(0) =  Hyperlipidemiac_ /covb risklimits;
run;
proc phreg data =mydata.feb22_nodiabetes_142am;
```

```
title "UNIVARIATE COX REGRESSION of variable pancrease_ where
the outcome is osteoporosis ";
CLASS  pancrease_(ref="0")/PARAM=REF;

model Year*osteo_(0) =  pancrease_ /covb risklimits;
run;
proc phreg data =mydata.feb22_nodiabetes_142am;
title "UNIVARIATE COX REGRESSION of variable wgt_change_5c where
the outcome is osteoporosis ";
CLASS  wgt_change_5c(ref="3")/PARAM=REF;

model Year*osteo_(0) =  wgt_change_5c /covb risklimits;
run;
```

8.3 Kaplan-Meier Macro

```
/*************************************************************
*/
/*          S A S   S A M P L E   L I B R A R Y
*/
/*
*/
/*    NAME: TEMPLFT
*/
/*   TITLE: PROC LIFETEST Template
*/
/* PRODUCT: STAT
*/
/*  SYSTEM: ALL
*/
/*    KEYS: graphics, ods, survival analysis, Kaplan-Meier
*/
/*   PROCS:
*/
/*    DATA:
*/
/*
*/
/* SUPPORT: saswfk                 UPDATE: July 25, 2013
*/
/*     REF: ods graphics
*/
/*    MISC:
*/
/*   NOTES: This sample provides templates for the PROC
*/
```

```
/*          LIFETEST survival plot that are modular and
*/
/*          easier to modify than the default templates.
/*https://support.sas.com/documentation/onlinedoc/stat/ex_code/1
51/templft.html*/
/************************************************************
*/
%macro ProvideSurvivalMacros;

   %global atriskopts bandopts censored censorstr classopts
           graphopts groups insetopts legendopts ntitles
stepopts tiplabel
           tips titletext0 titletext1 titletext2 xoptions
yoptions;

   %let TitleText0 = METHOD " Survival Estimate";
   %let TitleText1 = &titletext0 " for " STRATUMID;
   %let TitleText2 = &titletext0 "s";         /* plural:
Survival Estimates */
   %let nTitles    = 2;

   %let yOptions   = label="Survival Probability"
shortlabel="Survival"
                     linearopts=(viewmin=0 viewmax=1
                                 tickvaluelist=(0 .2 .4 .6 .8
1.0));

   %let xOptions   = shortlabel=XNAME offsetmin=.05
                     linearopts=(viewmax=MAXTIME
tickvaluelist=XTICKVALS

tickvaluefitpolicy=XTICKVALFITPOL);

   %let Tips       = rolename=(_tip1= ATRISK _tip2=EVENT)
                     tiplabel=(_tip1="Number at Risk"
_tip2="Observed Events")
                     tip=(x y _tip1 _tip2);
   %let TipLabel   = tiplabel=(y="Survival Probability");
   %let StepOpts   = ;

   %let Groups     = group=STRATUM index=STRATUMNUM;

   %let BandOpts   = displayTail=false &groups
modelname="Survival";

   %let InsetOpts  = autoalign=(TOPRIGHT BOTTOMLEFT TOP BOTTOM)
```

```
                    border=true
BackgroundColor=GraphWalls:Color Opaque=true;
   %let LegendOpts = title=GROUPNAME location=outside;

   %let AtRiskOpts = display=(label) valueattrs=(size=7pt);
   %let ClassOpts  = class=CLASSATRISK colorgroup=CLASSATRISK;

   %let Censored   = markerattrs=(symbol=plus);
   %let CensorStr  = "+ Censored";

   %let GraphOpts  = ;

   %macro StmtsBeginGraph; %mend;
   %macro StmtsTop;        %mend;
   %macro StmtsBottom;     %mend;

   %macro CompileSurvivalTemplates;
      %local outside;
      proc template;
         %do outside = 0 %to 1;
            define statgraph

Stat.Lifetest.Graphics.ProductLimitSurvival%scan(2,2-&outside);
               dynamic NStrata xName plotAtRisk
                  %if %nrbquote(&censored) ne %then
plotCensored;
                  plotCL plotHW plotEP labelCL labelHW labelEP
maxTime xtickVals
                  xtickValFitPol rowWeights method StratumID
classAtRisk
                  plotTest GroupName Transparency SecondTitle
TestName pValue
                  _byline_ _bytitle_ _byfootnote_;
               BeginGraph %if %nrbquote(&graphopts) ne %then /
&graphopts;;

               if (NSTRATA=1)
                  %if &ntitles %then %do;
                     if (EXISTS(STRATUMID)) entrytitle
&titletext1;
                     else                   entrytitle
&titletext0;
                     endif;
                  %end;

                  %if &ntitles gt 1 %then %do;
                     %if not &outside %then if (PLOTATRISK=1);
```

```
                        entrytitle "With Number of Subjects at
Risk" /
                                    textattrs=GRAPHVALUETEXT;
                     %if not &outside %then %do; endif; %end;
                  %end;

                  %StmtsBeginGraph
                  %AtRiskLatticeStart
                  layout overlay / xaxisopts=(&xoptions)
yaxisopts=(&yoptions);
                     %StmtsTop
                     %SingleStratum
                     %StmtsBottom
                  endlayout;
                  %AtRiskLatticeEnd

               else
                  %if &ntitles %then %do; entrytitle
&titletext2; %end;
                  %if &ntitles gt 1 %then %do;
                     if (EXISTS(SECONDTITLE))
                        entrytitle SECONDTITLE /
textattrs=GRAPHVALUETEXT;
                     endif;
                  %end;

                  %StmtsBeginGraph
                  %AtRiskLatticeStart
                  layout overlay / xaxisopts=(&xoptions)
yaxisopts=(&yoptions);
                     %StmtsTop
                     %MultipleStrata
                     %StmtsBottom
                  endlayout;
                  %AtRiskLatticeEnd(class)

               endif;

               if (_BYTITLE_) entrytitle _BYLINE_ /
textattrs=GRAPHVALUETEXT;
               else if (_BYFOOTNOTE_) entryfootnote halign=left
_BYLINE_; endif;
               endif;
               EndGraph;
            end;
         %end;
      run;
```

```
   %mend;

   %macro pValue;
      if (PVALUE < .0001)
         entry TESTNAME " p " eval (PUT(PVALUE, PVALUE6.4));
      else
         entry TESTNAME " p=" eval (PUT(PVALUE, PVALUE6.4));
      endif;
   %mend;

   %macro SingleStratum;
      if (PLOTHW=1 AND PLOTEP=0)
         bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME /
            displayTail=false modelname="Survival"
fillattrs=GRAPHCONFIDENCE
            name="HW" legendlabel=LABELHW;
      endif;
      if (PLOTHW=0 AND PLOTEP=1)
         bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME /
            displayTail=false modelname="Survival"
fillattrs=GRAPHCONFIDENCE
            name="EP" legendlabel=LABELEP;
      endif;
      if (PLOTHW=1 AND PLOTEP=1)
         bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME /
            displayTail=false modelname="Survival"
fillattrs=GRAPHDATA1
            datatransparency=.55 name="HW" legendlabel=LABELHW;
         bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME /
            displayTail=false modelname="Survival"
fillattrs=GRAPHDATA2
            datatransparency=.55 name="EP" legendlabel=LABELEP;
      endif;
      if (PLOTCL=1)
         if (PLOTHW=1 OR PLOTEP=1)
            bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL
x=TIME /
               displayTail=false modelname="Survival"
display=(outline)
               outlineattrs=GRAPHPREDICTIONLIMITS name="CL"
legendlabel=LABELCL;
         else
            bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL
x=TIME /
               displayTail=false modelname="Survival"
fillattrs=GRAPHCONFIDENCE
               name="CL" legendlabel=LABELCL;
```

```
         endif;
      endif;

      stepplot y=SURVIVAL x=TIME / name="Survival" &tips
legendlabel="Survival"
               &stepopts;

      if (PLOTCENSORED=1)
         scatterplot y=CENSORED x=TIME / &censored &tiplabel
            name="Censored" legendlabel="Censored";
      endif;

      if (PLOTCL=1 OR PLOTHW=1 OR PLOTEP=1)
         discretelegend "Censored" "CL" "HW" "EP" /
location=outside
            halign=center;
      else
         if (PLOTCENSORED=1)
            discretelegend "Censored" / location=inside
                                        autoalign=(topright
bottomleft);
         endif;
      endif;
      %if not &outside %then %do;
         if (PLOTATRISK=1)
            innermargin / align=bottom;
               axistable x=TATRISK value=ATRISK / &atriskopts;
            endinnermargin;
         endif;
      %end;
   %mend;

   %macro MultipleStrata;
     if (PLOTHW=1)
         bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME /
&bandopts
                  datatransparency=Transparency;
      endif;
      if (PLOTEP=1)
         bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME /
&bandopts
                  datatransparency=Transparency;
      endif;
      if (PLOTCL=1)
         if (PLOTHW=1 OR PLOTEP=1)
            bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL
x=TIME / &bandopts
```

```
                     display=(outline)
outlineattrs=(pattern=ShortDash);
         else
            bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL
x=TIME / &bandopts
                     datatransparency=Transparency;
         endif;
      endif;

      stepplot y=SURVIVAL x=TIME / &groups name="Survival" &tips
&stepopts;

      if (PLOTCENSORED=1)
         scatterplot y=CENSORED x=TIME / &groups &tiplabel
&censored;
      endif;

      %if not &outside %then %do;
         if (PLOTATRISK=1)
            innermargin / align=bottom;
               axistable x=TATRISK value=ATRISK / &atriskopts
&classopts;
            endinnermargin;
         endif;
      %end;

      %if %nrbquote(&legendopts) ne %then %do;
         DiscreteLegend "Survival" / &legendopts;
      %end;

      %if %nrbquote(&insetopts) ne %then %do;
         if (PLOTCENSORED=1)
            if (PLOTTEST=1)
               layout gridded / rows=2 &insetopts;
                  entry &censorstr;
                  %pValue
               endlayout;
            else
               layout gridded / rows=1 &insetopts;
                  entry &censorstr;
               endlayout;
            endif;
         else
            if (PLOTTEST=1)
               layout gridded / rows=1 &insetopts;
                  %pValue
               endlayout;
```

```
         endif;
      endif;
      %end;

%mend;

%macro SurvTabHeader(multiple);
   %if &multiple %then %do; entry ""; %end;
   entry "";
   entry "";
   entry "";
   entry &r "Median";
   entry "";
   entry "";

   %if &multiple %then %do; entry ""; %end;
   entry &r "Subjects";
   entry &r "Event";
   entry &r "Censored";
   entry &r "Survival";
   entry &r PctMedianConfid;
   entry halign=left  "CL";
%mend;

%macro SurvivalTable;
   %local fmt r i t;
   %let fmt = bestd6.;
   %let r = halign = right;
   columnheaders;
      layout overlay / pad=(top=5);
         if(NSTRATA=1)
            layout gridded / columns=6 border=TRUE;
               dynamic PctMedianConfid NObs NEvent Median
                       LowerMedian UpperMedian;
               %SurvTabHeader(0)
               entry &r NObs;
               entry &r NEvent;
               entry &r eval(NObs-NEvent);
               entry &r eval(put(Median,&fmt));
               entry &r eval(put(LowerMedian,&fmt));
               entry &r eval(put(UpperMedian,&fmt));
            endlayout;
         else
            layout gridded / columns=7 border=TRUE;
               dynamic PctMedianConfid;
               %SurvTabHeader(1)
               %do i = 1 %to 10;
```

```
                        %let t = / textattrs=GraphData&i;
                        dynamic StrVal&i NObs&i NEvent&i Median&i
                                LowerMedian&i UpperMedian&i;
                        if (&i <= nstrata)
                           entry &r StrVal&i &t;
                           entry &r NObs&i &t;
                           entry &r NEvent&i &t;
                           entry &r eval(NObs&i-NEvent&i) &t;
                           entry &r eval(put(Median&i,&fmt)) &t;
                           entry &r eval(put(LowerMedian&i,&fmt))
&t;
                           entry &r eval(put(UpperMedian&i,&fmt))
&t;
                        endif;
                     %end;
                  endlayout;
               endif;
            endlayout;
         endcolumnheaders;
      %mend;

      %macro SurvivalSummaryTable;
         %macro AtRiskLatticeStart;
            layout lattice / columndatarange=union rowgutter=10
               rows=%if &outside %then 2 rowweights=ROWWEIGHTS;
                    %else              1;;
            %if &outside %then %do; cell; %end;
         %mend;

         %macro AtRiskLatticeEnd(useclassopts);
            %if &outside %then %do;
               endcell;
               cell;
                  layout overlay / walldisplay=none
xaxisopts=(display=none);
                     axistable x=TATRISK value=ATRISK / &atriskopts
                              %if &useclassopts ne %then
&classopts;;
                  endlayout;
               endcell;
            %end;
            %SurvivalTable
            endlayout;
         %mend;
      %mend;

      %macro AtRiskLatticeStart;
```

```
      %if &outside %then %do;
         layout lattice / rows=2 rowweights=ROWWEIGHTS
                          columndatarange=union rowgutter=10;
         cell;
      %end;
   %mend;

   %macro AtRiskLatticeEnd(useclassopts);
      %if &outside %then %do;
         endcell;
         cell;
            layout overlay / walldisplay=none
xaxisopts=(display=none);
               axistable x=TATRISK value=ATRISK / &atriskopts
                         %if &useclassopts ne %then &classopts;;
            endlayout;
         endcell;
      endlayout;
      %end;
   %mend;

%CompileSurvivalTemplates
%mend;

%ProvideSurvivalMacros

%let yOptions = label="Survival"
                linearopts=(viewmin=0.7 viewmax=1
                            tickvaluelist=(0 .7 .8 .9 1.0));

%CompileSurvivalTemplates

/*Right click your file and then change the location*/
libname mylib "/home/u59196437/sasuser.v94";
data test;
set mylib.mar13_1133am;
run;


ods listing close;
ods rtf file='C:\Users\Tanmoy Das\OneDrive\Desktop\Thesis
work/km graph modified.rtf';
proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY FEMALE, MALE STATUS ";
time year*osteo_(0);
strata sex;
run;
```

```
proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY DIABETES and NO DIABETES STATUS ";
time year*osteo_(0);
strata diabetes;
run;

proc lifetest method=km plot =survival(cb=hw test);
title "KM GRAPH BY AGE GROUP AND NO MATTER DIABETES STATUS";
time year*osteo_(0);
strata agec;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY smoking STATUS ";
time year*osteo_(0);
strata smokingc;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY drinking STATUS ";
time year*osteo_(0);
strata drinkingc;
run;
proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY marital STATUS ";
time year*osteo_(0);
strata maritalc;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY edu STATUS ";
time year*osteo_(0);
strata educ;
run;
proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata income_quintilec;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata bmic;
run;
```

```
proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata pysicalc;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata life_insurancec;
run;



proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata hyperthyroidismc_;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata hypertensionc_;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata cvd_c;
run;

proc lifetest method=km plot = survival(cb=hw test);
title "KM GRAPH BY income_quintile STATUS ";
time year*osteo_(0);
strata hyperlipidemiac_;
run;



/*CREATING DUMMY VARIABLE FOR AGE */
data Thesis_data_20Nov2022step21;
set Thesis_data_20Nov2022step20;
if agec = 1
then agec_1 = 1;
else agec_1= 0;
```

```
if agec = 2
then agec_2 = 1;
else agec_2= 0;

if agec = 3
then agec_3 = 1;
else agec_3= 0;

if agec = 4
then agec_4 = 1;
else agec_4= 0;
run;

/*CREATING DUMMY VARIABLE FOR SMOKING*/
data Thesis_data_20Nov2022step22;
set Thesis_data_20Nov2022step21;
if smokingc = 1
then smokingc_1 = 1;
else smokingc_1= 0;

if smokingc = 2
then smokingc_2 = 1;
else smokingc_2= 0;

if smokingc = 0
then smokingc_0 = 1;
else smokingc_0= 0;

run;
```

8.4 Creation of Several Interaction term

```
data mydata.db_dummy_jan24_809pm;
  set mydata.db_dummy_jan20_1227pm;
 agecsex = agec*sex;
run;

data mydata.db_dummy_jan30_815pm;
  set mydata.db_dummy_jan24_809pm;
  Hyperlipidemiachypertension_ = Hyperlipidemiac_*hypertension_;
run;

data mydata.db_dummy_jan30_816pm;
  set mydata.db_dummy_jan30_815pm;
  agechypertension_ = agec*hypertension_;
run;

data mydata.db_dummy_jan30_817pm;
  set mydata.db_dummy_jan30_816pm;
  sexhypertension_ = sex*hypertension_;
run;

data mydata.db_dummy_jan30_818pm;
  set mydata.db_dummy_jan30_817pm;
  agecHyperlipidemiac_ = agec*Hyperlipidemiac_;
run;

data mydata.db_dummy_jan30_819pm;
  set mydata.db_dummy_jan30_818pm;
  sexHyperlipidemiac_ = sex*Hyperlipidemiac_;
run;

data mydata.db_dummy_jan30_820pm;
  set mydata.db_dummy_jan30_819pm;
  agecsmokingc = agec*smokingc;
run;

data mydata.db_dummy_jan30_821pm;
  set mydata.db_dummy_jan30_820pm;
  sexsmokingc = sex*smokingc;
run;


data mydata.db_dummy_jan30_822pm;
  set mydata.db_dummy_jan30_821pm;
  smokingchypertension_ = smokingc*hypertension_;
run;
```

```
data mydata.db_dummy_jan30_823pm;
  set mydata.db_dummy_jan30_822pm;
  smokingcHyperlipidemiac_ = smokingc*Hyperlipidemiac_;
run;

data mydata.feb14_753pm;
  set mydata.feb1_552pm;
Diabetessex = Diabetes*sex;
run;

data mydata.feb14_754pm;
  set mydata.feb14_753pm;
 Dialipidemiatension= Diabetes*Hyperlipidemiac_*hypertension_;
run;

data mydata.feb14_755pm;
  set mydata.feb14_754pm;
  agecDiabetes = agec*Diabetes;
run;

data mydata.feb14_756pm;
  set mydata.feb14_755pm;
  Diabeteshypertension= Diabetes*hypertension_;
run;

data mydata.feb14_757pm;
  set mydata.feb14_756pm;
  DiabetesHyperlipidemiac = Diabetes*Hyperlipidemiac_;
run;

data mydata.feb14_758pm;
  set mydata.feb14_757pm;
  agecsexDiabetes = agec*sex*Diabetes;
run;

data mydata.feb14_759pm;
  set mydata.feb14_758pm;
  Diabetessmokingc = Diabetes*smokingc;
run;

data mydata.feb14_800pm;
  set mydata.feb14_759pm;
  Diabetesdrinkingc = Diabetes*drinkingc;
run;


data mydata.feb14_801pm;
```

```
  set mydata.feb14_800pm;
  agedrinking = age*drinkingc;
run;

data mydata.feb14_802pm;
  set mydata.feb14_801pm;
  sexdrinking = sex*drinkingc;
run;
```

8.5 Multivariate Cox regression analysis

```
PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS sex(REF="1") agec(ref="1")/PARAM=REF;

model year*osteo_(0) =agec sex agecsex
 /covb risklimits;
RUN;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS Hyperlipidemiac_(REF="0") agec(ref="1")/PARAM=REF;

model year*osteo_(0) =agec Hyperlipidemiac_ agecHyperlipidemiac_
 /covb risklimits;
RUN;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS hypertension_(REF="0") agec(ref="1")/PARAM=REF;

model year*osteo_(0) =agec hypertension_ agechypertension_
 /covb risklimits;
RUN;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS smokingc(REF="0") agec(ref="1")/PARAM=REF;

model year*osteo_(0) =agec smokingc agecsmokingc
 /covb risklimits;
RUN;
```

```
PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS sex(REF="1") Hyperlipidemiac_(ref="0")/PARAM=REF;

model year*osteo_(0) =sex Hyperlipidemiac_ sexHyperlipidemiac_
 /covb risklimits;
RUN;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS sex(ref="1") hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) =sex hypertension_ sexhypertension_
 /covb risklimits;
RUN;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS sex(REF="1") smokingc(ref="0")/PARAM=REF;

model year*osteo_(0) =sex smokingc sexsmokingc
 /covb risklimits;
RUN;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS smokingc(REF="0") Hyperlipidemiac_(ref="0")/PARAM=REF;

model year*osteo_(0) =smokingc Hyperlipidemiac_
smokingcHyperlipidemiac_
 /covb risklimits;
RUN;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS smokingc(REF="0") hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) =smokingc hypertension_
smokingchypertension_
 /covb risklimits;
```

```
RUN;


PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION where the outcome is
osteoporosis ";
CLASS Hyperlipidemiac_(ref="0")
hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) =Hyperlipidemiac_ hypertension_
Hyperlipidemiachypertension_
 /covb risklimits;
RUN;


PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ agecsex
agecHyperlipidemiac_  agechypertension_  agecsmokingc
sexHyperlipidemiac_
  sexhypertension_  sexsmokingc   smokingcHyperlipidemiac_
smokingchypertension_/covb risklimits;

run;



ods rtf close;
ods listing;



ods listing close;
ods rtf file='C:\Users\Tanmoy Das\OneDrive\Desktop\Thesis
work/Thesis_data_mydata.feb4-1128_multivariate cox with one
interaction with main effect_feb4.rtf';


PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
```

```
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Hyperlipidemiachypertension_
/covb risklimits;
run;


ods rtf close;
ods listing;



PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ agecsex
/covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_
agecHyperlipidemiac_  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_
  agechypertension_  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
```

```
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_   agecsmokingc  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_   sexHyperlipidemiac_
  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_
  sexhypertension_  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_
  sexsmokingc   /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;
```

```
model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_    smokingcHyperlipidemiac_ /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_  smokingchypertension_/covb risklimits;
run;



ods rtf close;

ods listing;


ods listing close;
ods rtf file='C:\Users\Tanmoy Das\OneDrive\Desktop\Thesis
work/Diabetes in the multivariate model cox with one interaction
with main effect_feb12.rtf';


PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Diabetes
/covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="1")
/PARAM=REF;
```

```
model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Diabetes
/covb risklimits;
run;


PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_  Diabetes agecsex
/covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Diabetes
agecHyperlipidemiac_  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Diabetes
  agechypertension_  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
```

```
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Diabetes  agecsmokingc/covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_  Diabetes  sexHyperlipidemiac_
  /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_
Diabetes   sexhypertension_ /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_
 Diabetes   sexsmokingc /covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
```

```
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_  Diabetes  smokingcHyperlipidemiac_ /covb
risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Diabetes smokingchypertension_/covb risklimits;
run;

PROC phreg DATA=mydata.feb1_552pm;
title "multivariate COX REGRESSION model with interaction where
the outcome is osteoporosis ";
class sex(REF="1") agec(ref="1")smokingc(REF="0")
Hyperlipidemiac_(ref="0")hypertension_(ref="0")Diabetes(ref="0")
/PARAM=REF;

model year*osteo_(0) = agec sex smokingc Hyperlipidemiac_
hypertension_ Diabetes Hyperlipidemiachypertension_
/covb risklimits;
run;

ods rtf close;

ods listing;
```

8.6 Model Goodness of fit: Martingale and Deviance plot

```
ods listing close;
ods rtf file='C:\Users\Tanmoy Das\OneDrive\Desktop\Thesis
work/MARTINGLE AND DEVIANCE PLOT WITH FULL MODEL AND
INTERACTION.rtf';
data covset;
SET mydata.mar24_352pm;
PROC PHREG DATA= mydata.mar24_352pm;
model year*osteo_(0) = agec sex Hyperlipidemiac_ hypertension_
Diabetes agec_2sex agec_3sex agec_4sex
/covb risklimits;

output out=phout xbeta=xb resmart=rm RESMART=mart
RESDEV=dev RESSCO=sco RESSCH=sch;
proc print data=phout;
title 'Ouput of PHREG with Prostatic Cancer Eg';
run;

Data ph;
set phout;
     RC= osteo_ - RM;

PROC PLOT;
     plot RM*YEAR;
title 'Martingale Residuals of PHREG';

proc plot;
     plot RC*YEAR;
title 'Cox-Snell Residuals of PHREG';

PROC PLOT;
     plot sch*xb;

proc plot;
     plot dev*xb;
title 'Deviance Residuals of PHREG vs Risk Score';
run;

proc lifetest data=ph plots=(s, ls, 11s);
          time RC*osteo_(0);
title 'Cox-Snell for PH ';
run;
ods rtf close;
ods listing;
```

Chapter 9 Appendix B: Ethics Approval Letter

UNIVERSITY OF SASKATCHEWAN

To:	Dr. June Lim
Student:	Tanmoy Das
Date:	April 7th 2022
RE:	Exemption request, E308

Thank you for submitting your project entitled: "*To determine the risk factors of osteoporosis among Type 2 Diabetes: A population-based cohort study*". This project meets the requirements for exemption status as per **Article 2.2 of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 (2018)**, which states "Research does not require REB review when it relies exclusively on information that is:

a. publicly available through a mechanism set out by legislation or regulation and that is protected by law; or
b. in the public domain and the individuals to whom the information refers have no reasonable expectation of privacy."

It should be noted that though your project is exempt of ethics review, your project should be conducted in an ethical manner (i.e. in accordance with the information that you submitted). It should also be noted that any deviation from the original methodology and/or research question should be brought to the attention of the Behavioural Research Ethics Board for further review.

Digitally Approved on behalf of the Chair
Behavioural Research Ethics Board
University of Saskatchewan