BREAKFAST TIMING AND FREQUENCY AS A PREDICTOR OF INCIDENT CORONARY ARTERY DISEASE IN OLDER ADULTS: THE CARDIOVASCULAR HEALTH STUDY

by

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Dalhousie University is located in Mi'kma'ki, the
ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

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Abstract

Coronary artery disease (CAD) is a leading cause of disease burden worldwide, particularly in older adults. Previous studies indicate that the timing and frequency of meals, particularly breakfast, may have metabolic consequences leading to risk of CAD.

This thesis project characterized a sample of 5,888 American men and women aged 65 years and older (Cardiovascular Health Study 1987-2015) based on their breakfast timing and frequency. Fine-Grey subdistribution hazard ratio models were used to quantify the risk of myocardial infarction (MI) and CAD based on participants' breakfast timing and frequency while accounting for the competing risks and relevant covariables.

Breakfast timing and frequency may be markers for a pattern of demographic and lifestyle risk factors for CAD in older adults. Overall, breakfast timing was not associated with risk of incident MI/CAD in this cohort. However, in men only, eating breakfast daily was associated with a modest increase in MI/CAD risk.

List of Abbreviations Used

aSHR	Adjusted Subdistribution Hazard Ratio
AHA	American Heart Association
BMI	Body Mass Index
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Graph
CHS	Cardiovascular Health Study
CI	Confidence Interval
CVD	Cardiovascular Disease
FVI	Fruit and Vegetable Intake
HDL	High Density Lipoprotein
HR	Hazard Ratio
IF	Intermittent Fasting
LDL	Low-Density Lipoprotein
MetS	Metabolic Syndrome
MI	Myocardial Infarction
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
RCT	Randomized Controlled Trial
RR	Risk Ratio
SES	Socioeconomic Status
SHR	Subdistribution Hazard Ratio
UNICEF	United Nations International Children's Emergency Fund

US	United States
WHO	World Health Organization

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Chapter 1: Introduction

Advancements made in medicine, lower birth rates, and improvements in survival have resulted in a rapidly ageing world population. The global population of adults age 60 years and over is expected to rise to 2.1 billion by 2050 (1). An ageing population has created a demand for more research that promotes optimal health in older adults by preventing diseases whose prevalence increases with age, like coronary artery disease (CAD) and metabolic syndrome (MetS).

This thesis aimed to characterize the relationship between breakfast timing and frequency and risk of CAD in older adults. CAD results in the obstruction of blood flow to the heart and has many risk factors, including the components of MetS: obesity, hypertension, elevated triglycerides, low levels of high-density lipoprotein ('good cholesterol'), and insulin resistance (2,3). Nutrition is a modifiable risk factor for the prevention of both MetS and CAD. A person's diet can be broken down into two categories: diet quality ("what they eat") and meal timing and frequency ("when they eat"). Diet quality, the focus of most nutritional studies, has been shown to be inversely associated with adverse health outcomes (4,5). Meal timing and frequency studies, although limited, show that irregular timing of meals has metabolic consequences that result in an increased risk for CAD and MetS (6,7). Nutritional studies that have examined meal timing and frequency, especially breakfast consumption, as a risk factor for CAD are limited, and none have been conducted specifically in older adults. Studies have shown contradicting evidence for the importance of breakfast consumption for cardiometabolic health. A few studies that have longitudinally examined the association between breakfast consumption and cardiovascular disease (CVD), inclusive of CAD, have found that skipping breakfast increases the risk for CVD (7–10). Likewise, observational

studies have shown that skipping breakfast is associated with an increased odds for MetS, a major cardiometabolic risk factor (11–15). None of these studies were conducted specifically in older adults, a population that is at increased risk for both CAD and MetS.

This present thesis begins with a review of the literature on CAD and MetS and describes the research to date on breakfast timing and frequency as a risk factor for cardiometabolic disease (chapter 2). Chapter 2 also details potential mechanisms, like disruptions of circadian rhythms, stress and hormones, and inflammation, that may explain how breakfast timing and frequency could result in adverse health outcomes. This chapter concludes by identifying the knowledge gap, rationale, and hypothesis for this thesis. The characteristics of older adults who skip breakfast or have late breakfast times are unknown. In addition, until the present thesis, there have been no prospective studies that directly look at the relationship between breakfast timing/frequency and CAD risk specifically in older adults. This present study was conducted to fill these gaps in the literature and add to existing studies to assist in providing evidence to inform dietary recommendations for eating timing and frequency.

Chapter 3 describes the objectives and methods used in this longitudinal cohort study, including the rationale and descriptions of the exposure variables, outcome variables, and covariables. This study utilizes data from the Cardiovascular Health Study, which began in 1987, and includes 5,888 men and women were 65 years and older at baseline. This chapter also provides an overview of the statistical models and relationships that were studied between breakfast timing and frequency and CAD.

Chapter 4 consists of the results of the analyses in written and tabular formats. Chapter 5 highlights the results of the study and how they relate to existing literature. Chapter 5 also

discusses the strengths and limitations of the study, its potential implications, and how future research can build on the results of this study.

Chapter 2: Background

2.1 Coronary Artery Disease

Coronary artery disease (CAD), also referred to as ischemic heart disease or coronary heart disease, is defined as the narrowing or blockage of the coronary arteries, which obstructs the flow of oxygen-rich blood to the heart. This obstruction of the coronary arteries often results in CAD-related events like myocardial infarction (MI, also known as a heart attack) or angina, which is chest pain/discomfort resulting from the narrowing or blockage of the coronary arteries (2). CAD is one of the leading causes of chronic disease worldwide, accounting for 30% of all deaths globally (16). In Canada, CAD is the 2nd leading cause of death and approximately 2.4 million Canadians over the age of 20 live with diagnosed CAD (17). Overall in North America, CAD is the leading cause of death attributed to cardiovascular disease (CVD) (2,18).

Lifestyle risk factors for CAD include smoking, physical inactivity, poor diet, and excess alcohol intake (2). An individual's sex gender, age, ethnicity, socioeconomic status, underlying psychological factors, and genetic predisposition for CAD are also risk factors for CAD (2,19). There are notable differences in risk of CAD depending on age and sex. Specifically, men are more likely to experience incident CAD and CAD-related death than women (20,21). However, the association between sex and CAD attenuates in older adults as the risk for incident CAD is much higher among older adults than their younger counterparts, and life expectancy can differ by sex (22). Lastly, metabolic risk factors for CAD include hypertension, obesity, high levels of cholesterol in the blood (hypercholesterolemia), and insulin insensitivity (2).

Due to its high prevalence and impact on health, the economic burden on health care systems from treating CAD and its related conditions is high (23). This burden results from direct costs, such as hospitalizations, rehabilitations, and drugs, and indirect costs such as loss of productivity and disability. In 2019, the American Heart Association (AHA) estimated that the United States (US) spent approximately $351.2 billion on direct and indirect costs of CVD, of which $218.7 billion was related to heart disease (24). In Canada, patients who were admitted to the hospital due to heart failure alone accounted for $482 million of healthcare costs in 2013 and by 2030 that figure is expected to rise to $720 million (25). In addition to the economic burden of CAD, there is emotional/psychological distress that can come to patients who have experienced or become disabled from a CAD event (26). Psychological distress, such as depression and anxiety, can have a negative impact on health-related quality of life, which is a measure of a person's perceived well-being in the physical, emotional, and social domains of their life (27,28). These psychosocial factors are important predictors of primary outcomes, such as subsequent cardiovascular events and mortality, in patients who have suffered from a CAD event (27,29). The economic burden in addition to the morbidity and loss of quality of life that is associated with CAD remains high, emphasizing the importance of preventing events and creating better approaches for improving disease management.

For this study, CAD was defined through two separate outcomes: 1) fatal and non-fatal MI and 2) non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty and/or death due to atherosclerotic CAD. A CABG procedure is conducted on patients with CAD and is used to improve blood flow to the heart by creating a new passage for oxygen-rich blood to bypass the blocked coronary artery and

reach the heart (30). An angioplasty is a procedure that widens clogged arteries by inserting a balloon catheter into the blocked blood vessels improving blood flow to the heart (31). CABG and angioplasty are treatment options for patients with CAD whose disease progression cannot be managed through medication and lifestyle modifications alone (32). Therefore, these two procedures are important to capture CAD in participants who are at a high risk for experiencing CAD-related events.

2.2 The Metabolic Syndrome

The metabolic syndrome (MetS) is defined as a cluster of risk factors that increases the risk for cardiovascular disease, including CAD, by 3-fold (33–36). In 2014, 15.2% of Canadian adults were found to have MetS, with older adults having a higher chance of being diagnosed than younger adults or children (37,38). Diagnosis of MetS is dependent on the presence of at least three of the following risk factors: abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol, hypertension, and insulin insensitivity (33,39,40). There are three widely accepted clinical definitions of MetS, from World Health Organization (WHO), National Cholesterol Education Program third-Adult Treatment Panel III (NCEP: ATPIII) and International Diabetes Federation (IDF), which make it harder to accurately assess the global prevalence of the disease (33,41,42). Despite this limitation, there is a consensus that the prevalence of MetS has increased worldwide with an estimated one billion people now affected by the disease (33,43).

In 2009, members of several major health organizations (The IDF Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, AHA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study

of Obesity) came together to harmonize the criteria used for clinically diagnosing MetS (3). This harmonized definition encompasses important aspects of each of the definitions highlighted previously and was used to define MetS for this study (3). For a diagnosis of MetS, an individual must meet a minimum of three of the following criteria:

- Abdominal Obesity via waist circumference measurements (population and country-specific thresholds recommended for North America)
    - Men: ≥ 102 cm
    - Women: ≥ 88 cm
- Elevated Triglycerides
    - ≥ 150 mg/dl (1.7 mmol/L)
- Low High-Density Lipoprotein
    - Males: < 40 mg/dl (1.0 mmol/L)
    - Females: < 50 mg/dl (1.3 mmol/L)
- Hypertension
    - Systolic ≥ 130 mmHg and/or Diastolic ≥ 85 mmHg or antihypertensive therapy
- Elevated fasting glucose
    - ≥ 100 mg/dl (6.11 mmol/L) or drug treatment for increased glucose

2.2.1 MetS Risk Factors

Abdominal obesity or visceral obesity results from an increase of adipose tissue that surrounds the intra-abdominal organs (44). In MetS, this is measured by waist circumference; cut-off values differ depending on sex and ethnicity. Visceral adipose tissue is hormonally active and releases a variety of active molecules like cytokines and hormones which in excess has been associated with other risk factors for cardiovascular disease, including CAD, insulin resistance, elevated triglycerides, hypertension, and low high-density lipoprotein (HDL) cholesterol (44–47).

Triglycerides are lipids found in the blood that the body stores and uses as an energy source between meals. High triglycerides, or hypertriglyceridemia, is characteristic of MetS and can be measured through blood tests (45). Excess triglycerides in the blood can lead to the hardening or thickening of arteries leading to an increased risk of CAD (48,49).

HDL, often referred to as "good" cholesterol, is a complex of proteins whose function is to transport excess cholesterol (lipids) back to the liver from other parts of the body (50). Having low HDL in the body means that lipids are not transported from the blood as they should be leading to a build-up of cholesterol in the blood. This cholesterol build-up can result in the hardening of the arteries leading to an increased risk for CAD (51,52). Generally, women have higher HDL levels than men, but this advantage diminishes after the onset of menopause (53).

Hypertension is elevated arterial blood pressure and is often caused by artery constriction or narrowing making it harder for the heart to pump blood (54). There are two measures of blood pressure, systolic and diastolic. Systolic pressure is the measure of pressure in the arteries when the heart muscles contract whereas diastolic pressure is the measure of pressure in the arteries when the heart is relaxed in between beats. Blood pressure is usually measured using a sphygmomanometer, which consists of a cuff, a pressure meter, and a stethoscope (55). A consistent blood pressure reading of over 140 mmHg systolic and/or over 90 mmHg diastolic in a clinic or a home blood pressure measurement of over 135 mmHg systolic and/or over 85 mmHg is considered to be high (56). Hypertension can cause damage to the arterial walls and if left untreated can lead to CAD (54).

Insulin is a hormone secreted by the pancreas whose function is to maintain normal glucose levels by signaling cells to uptake glucose from the blood (57). Insulin also has a role in lipid and protein metabolism. Insulin resistance or insensitivity is a condition in which cells do not respond to insulin properly. In response, the pancreas releases more insulin and over time if the cells become increasingly insulin resistant there will be excess glucose and insulin in the bloodstream resulting in a damaged pancreas and/or type 2 diabetes. Type 2 diabetes is a known risk factor for CVD, including CAD (58,59). Additionally, insulin resistance has been associated with atherosclerosis which is also a risk factor for CVD (60).

The components of MetS are intertwined with one another. For example, abdominal obesity can contribute to low HDL, insulin resistance, hypertension, and high triglycerides (44–46). Excess triglycerides can result in low HDL and insulin resistance and vice versa (45,61). Furthermore, low HDL can cause a plaque build-up in the arteries leading to hypertension, coupling the two risk factors (50,62,63).

Over the years, the prevalence of MetS has increased exponentially; however, it remains unclear whether the prevalence of MetS is currently higher in men or women as studies show varying statistics (33,64–68). This discrepancy could be because of the way each component of MetS differentially affects men and women (66,69). Prevalence of MetS also increases with age (70–72). MetS can be managed at its individual components; medications can be used to treat insulin resistance, hypertension, elevated triglycerides, and low HDL (73). Additionally, diet and lifestyle changes are also encouraged to manage these components, especially for abdominal obesity (74).

2.3 The Role of Nutrition in MetS and CAD

Nutrition is an established modifiable risk factor for many chronic conditions, including CAD and MetS. Diet modifications are recommended as a part of disease education or treatment programs for many of the risk factors for CAD and MetS, including abdominal obesity, increased cholesterol, or low HDL. An individual's diet can be assessed for both diet quality ('what' they eat) and meal timing and frequency ('when' they eat).

2.3.1 Diet Quality

In the field of nutrition, diet quality is a term used to describe the content of an individual's food intake in relation to the quality of foods and the amount of nutrients required to maintain health (75). Diet quality can be measured using indices developed based on national nutrition recommendations and/or country-specific dietary guidelines (76). Indices have been constructed to either examine nutrient intake or food groups or a combination of both (75,77).

Several diet quality indices have been created over the years, each constructed using different matrices of food and nutrient variables (78). The food and nutrient variables that should be included in diet quality indices have been widely debated. Further, some indices include food and nutrient variables that are not often measured in large studies. Although there is no leading diet quality index that has consistently performed the strongest in multiple populations, the existing diet quality indices do consistently include fruit and vegetable intake, and daily fruit and vegetable intake has been proven to be a consistent marker of diet quality (79,80). Fruits and vegetables are a top dietary source of vitamins, minerals, fluids, fiber, and healthy microorganisms (79) without including many controversial or negative

nutrients. Dietary assessments almost always include fruit and vegetable intake, making it a valuable marker of diet quality to be used as a covariable in analyses.

Having a higher diet quality is inversely associated with adverse health outcomes. For example, increased intake of vitamins and minerals is associated with a lower risk for chronic diseases like CAD and MetS (4,5). These associations have been fairly well established as nutrition research has mainly centered around nutrient intake. Comparatively, there are fewer studies that highlight meal timing and frequency and its association with health outcomes (81).

2.3.2 Meal Timing and Frequency

The concept of meal timing and frequency encompasses the idea that the timing of food intake, as opposed to or regardless of what the meal consists of, has an impact on health outcomes. Meal timing and frequency has been studied in less detail than diet quality, but it is a timely topic in relation to heart health. Notably, the AHA released a scientific statement encouraging future research into meal timing and frequency and the implications for CVD prevention (7).

The most popular and 'trendiest' topic in this area is intermittent fasting (IF) (82). IF is an umbrella term for various eating patterns that involve cycles of eating and fasting. IF has been shown to reduce cardiometabolic risk factors such as weight, low-density lipoprotein (LDL) cholesterol, hypertension, and insulin resistance in some cases (7). Comparatively, some studies also found that there were no significant changes to the lipid profile in participants who fasted (83–85). As IF studies conducted on human participants are short

term and adherence to the fasting regimen is variable, it is unclear if the benefits from fasting can be maintained long term (86,87).

Studies have also shown that the irregular timing and frequency of meals are associated with adverse health outcomes (6,7). Specifically, late-night eating and skipping breakfast have been associated with CAD and other cardiometabolic risk factors (6–8,88). The results of these studies have been debated since there are limited longitudinal studies that highlight the long-term effects of irregular meal timing. As of now, due to a lack of research, official, evidence-based recommendations do not exist for how often and at what time of day an adult should have meals, snacks, and drinks other than water.

2.3.3 Dietary Patterns in Older Adults over Time

The world population is rapidly ageing, and many older adults suffer from chronic diseases whose prevalence increases with age, like CAD and other cardiometabolic conditions. Nutrition is a major determinant of successful ageing and nutrition therapy is an effective tool for disease management and prevention of chronic diseases (89). However, many older adults face challenges that affect their nutritional status such as physiological changes, living arrangements, finances, disability, and transportation issues (89). These challenges may affect the dietary patterns of older adults, including their diet quality and their meal timing and frequency.

The consistency of dietary patterns in older adults, has rarely been studied long term. One longitudinal study, conducted in Australian men and women who were 55 years and older, found that over a 4-year period, dietary intake patterns, assessed using diet quality, remained relatively stable in men and women (90). There are insufficient studies that describe the

stability, or lack thereof, of dietary intake in older adults, and as such it is impossible to state whether older adults tend to maintain their eating patterns over longer periods of time. Factors such as education level, socioeconomic status, sex/gender, race/ethnicity, medical history, chronic illness, marital status, and mental health have been shown to affect eating patterns in older adults (90–95), and some of these variables can change or develop in older adulthood. For example, studies have reported that married participants were more likely to consume two or meals a day compared to participants who were single, divorced, or widowed, while female and college-educated participants were the most likely to improve their diet over time or practice healthy eating compared to male participants and participants who did not have a higher education (90–92).

2.4 Impact of Breakfast Consumption on Health

One aspect of meal timing and frequency that has been heavily debated in popular media is breakfast consumption. Breakfast is commonly touted as the most important meal of the day; however, North American food guides do not provide any recommendations about eating breakfast but rather focus on overall nutrient intake (96,97). Approximately 20% of adults skip breakfast, which is a substantial population-level impact if breakfast skipping is either harmful or beneficial (7,98–100). Unfortunately, nutritional guidelines that highlight the importance of eating breakfast are geared towards children and although information or advice is abundant and readily available for adults on the internet, these recommendations are not evidence-based and so are potentially dangerous.

2.4.1 The Breakfast Controversy

For years now breakfast frequency has been a topic of controversy as researchers have found contradicting evidence for the importance of breakfast eating and its potential role in maintaining good health (101). Some studies show that eating breakfast is beneficial for higher cognitive performance, increased intake of macro and micronutrients, weight control, and a lower risk for cardiometabolic risk factors (7,100–103). Conversely, there are studies that show that skipping breakfast is protective against obesity, insulin resistance, hypertension, and other common CAD disease risk factors (101,102,104,105). However, due to the limited and inconsistent results from research, how breakfast timing and frequency impact the risk of CAD and MetS remains poorly understood in adults (106–109). To date, there are no prospective studies that directly look at the relationship between breakfast timing/frequency and CAD risk specifically in older adults.

The lack of a uniform definition of breakfast consumption is a major factor that impedes establishing consistent conclusions on the association between breakfast frequency and cardiometabolic risk factors (110). Generally, breakfast eating and skipping definitions are based on frequency or time of day but researchers may sometimes choose to include specific macronutrients or calorie levels in their study-specific definitions (110). There is currently no validated definition for breakfast timing or frequency.

2.4.2 Breakfast Consumption and Race/Ethnicity

Studies that examine race/ethnicity and breakfast consumption specifically in older adults are limited. A comparative study, conducted in 1998 within a population of 248 older adults that were 60 years and above, found that white Americans were more likely to eat breakfast

regularly compared to the Black American participants (111). Similarly, a US study that included a population of adults 19 years and older found that compared to Black Americans and Hispanics, a higher percentage of white Americans were observed to be breakfast consumers (112). In contrast, a systematic review of studies conducted on this topic in a population of young adults, found that in three of four studies included in their review, Caucasian participants were more likely to skip breakfast compared to Asians and Black American participants, and one study found no association between ethnicity and breakfast consumption (113). A similar finding was observed in a population of Canadian adults (18 years and older) where, although there were no significant ethnic differences between breakfast consumers versus non-consumers, a higher percentage of immigrants consumed breakfast compared to participants who were born in Canada (114).

2.4.3 Breakfast Timing

Breakfast timing refers to the time or hour a person eats to break their overnight fast. Studies that look at breakfast timing are very limited. A review on eating times, published in 2019 by Lopez-Minguez et al., reported that breakfast timing is metabolically important as it is related to the body's fasting state at night (89). They proposed that having breakfast too early could be harmful if melatonin levels within the body are high leading to the modification of the body's normal metabolism. They also cautioned against eating breakfast too late, essentially skipping breakfast, due to some evidence of its association with obesity. Breakfast timing has rarely been specifically studied; however, many studies that review meal timing and frequency advocate for eating times that are in harmony with the body's circadian rhythm. Timing meals to the body's internal clock could reduce harmful metabolic disruptions that

could have resulted in an increased risk for chronic conditions like CAD, type 2 diabetes, and MetS.

2.4.4 Breakfast Frequency and CAD

To date, only two prospective cohort studies have directly examined the association between breakfast frequency and CAD risk in adults. The first study, published in 2013 by Cahill et al., examined the association between breakfast eating and CAD on 26,902 American male health professionals. They defined breakfast eating as a positive response to any of the following eating times: before breakfast, breakfast, and between breakfast and lunch. CAD was defined as fatal or non-fatal heart attacks diagnosed based on WHO criteria. The participants in their study were between the ages of 45 to 82 and the duration of follow-up was 16 years. They reported that those who did not eat breakfast were more likely to be younger, full-time workers, smokers, less physically active, unmarried and to drink more alcohol. After adjusting for age and other relevant diet and lifestyle factors, they found that men who skipped breakfast were at a 27% higher risk for CAD compared to men who were breakfast eaters (RR = 1.27, 95% CI [1.06,1.53]). The study concluded that eating breakfast was associated with a lower risk of CAD among mostly white male health professionals. To our knowledge, a comparable study in women or a more diverse population has not been published, and it is unknown whether the results are generalizable to a more representative sample of adults (8).

In 2016, a similar study was conducted among 82,772 Japanese men and women between the ages of 45 and 74 years. Kubota et al. classified breakfast eaters into four groups: those who ate breakfast 0-2, 3-4, 5-6, or 7 times a week. The outcome of interest in their study was

stroke and incident CAD (including heart attacks). Participants who ate breakfast less frequently were younger, drank more alcohol, smoked, lived alone, and had a higher BMI. After 12.7 years of follow-up, Kubota et al. observed no association between breakfast frequency and incident CAD. The authors attributed this finding to the low rate of CAD within the Japanese population. Importantly, they did find that consuming breakfast only 0-2 times/week was associated with other important vascular conditions including a 14% increased risk for CVD (HR = 1.14 [1.01,1.27]) and 18% increased risk in stroke (HR= 1.18 [1.04,1.34]) (115).

In 2021, a retrospective cohort study was conducted in Japan analyzing the association between eating behaviors and CVD (10). This study involved almost 2 million Japanese men and women who were 20 years and older and did not have a history of CVD events. The median age for participants in the study was 45 years and the median follow up was 978 days. Information about eating habits were obtained through questionnaires that were administered during required annual health-checkups. Regarding breakfast consumption, skipping breakfast less than 3 times a week was considered as optimal eating behaviour. Participants who had non-optimal eating behaviours had a higher prevalence of cardiometabolic risk factors including obesity, high waist circumference, dyslipidemia, and smoking. Prevalence of hypertension and type 2 diabetes was found to be higher in participants with optimal eating behaviours. In this study, Kaneko et al., found that skipping breakfast was associated with a 12% (HR = 1.12 [1.02, 1.24]) increased risk for MI, 10% (HR = 1.10 [1.04, 1.16]) increased risk for stroke, and 9% (HR = 1.09 [1.05, 1.13]) increased risk for heart failure.

A systematic review and meta-analysis examining the association between skipping breakfast and risk of CVD-related morbidity and mortality was conducted in 2019. Four prospective cohort studies were included in the review, specifically two US cohorts and two Japanese cohorts with an age range from 40 to 82 years. The review reported the pooled results from a random-effects meta-analysis, which indicated that adults who skipped breakfast were at a 21% increased risk for incident CVD, (inclusive of CAD), and CVD-related mortality (HR = 1.21 [1.08,1.35]) (109). There were not enough studies of CAD alone as an outcome for the meta-analysis. Other limitations of their review include errors resulting from residual confounding as not all the studies adjusted for the same confounders. Likewise, misclassification errors could also have been introduced as breakfast frequency was only measured at baseline for these studies and a uniform definition to measure breakfast frequency was not used. The authors of the review conclude that skipping breakfast may be associated with an increased risk for CVD morbidity and mortality but call for more large prospective studies to be conducted to provide more evidence for the observation. There are no other systematic reviews that examine the association between breakfast timing and frequency and risk for CAD in adults.

There are no clinical intervention studies that look at the relationship between breakfast timing and frequency and CAD risk in adults. This is potentially due to the ethical issues that would arise from requiring participants to skip a meal for an extended period of time. Additionally, the economic burden of providing balanced uniform meals to a control group every day would limit the study feasibility. For these reasons, epidemiological cohort studies examining the association between breakfast timing and frequency and CAD risk are necessary, especially in older adult populations who are at increased risk for the disease.

2.4.5 Breakfast Frequency and MetS

Prospective cohort studies in adults examining the relationship between breakfast frequency and MetS, rather than its individual components, are limited. In 2013, a study published by Odegaard et al. examined the association between breakfast intake frequency and metabolic health in adults who were 18 to 30 years old at the beginning of the study. Breakfast intake frequency was assessed using the CARDIA diet history questionnaire and was categorized as infrequent breakfast intake (0-3 days/week), frequent breakfast intake (4-6 days/week), and daily breakfast intake (7 days/week). Over the 18-year follow-up period, the researchers found that compared to infrequent breakfast intake, those who ate breakfast daily had a significantly lower risk for incident MetS (HR = 0.82 [0.69,0.98]), after adjusting for age, sex, race, and other important lifestyle factors. They conclude that eating breakfast daily is associated with better metabolic health in young adults (15). This is the only prospective cohort study that has examined this association in adults. There are currently no prospective cohort studies that have examined the relationship between breakfast timing and frequency and MetS, specifically in older adults.

There are currently no systematic reviews that focus on breakfast timing and frequency and MetS in adults or older adults. However, there are two reviews and meta-analyses that look at the association between breakfast skipping and risk for type 2 diabetes, which is a risk factor for CAD and a condition that people with MetS are at five times more risk for. In 2015, Bi et al. concluded in their review that included four cohort studies, one case-control study, and three cross-sectional studies that breakfast skipping was associated with an increased risk for type 2 diabetes (RR = 1.15 [1.04,1.27]) (116). In 2019, Ballon et al. found the same association in a meta-analysis that included six prospective cohort studies (117). After

adjustment for BMI in their analysis, which they concluded partially mediates the relationship between breakfast skipping and type 2 diabetes, they found that participants who skipped breakfast were at a 22% higher risk for type 2 diabetes than those that did not skip breakfast (RR = 1.22 [1.12,1.34])[1] (117). The authors of this review also conducted a non-linear dose-response meta-analysis which found that the risk for type 2 diabetes increased with every additional day of skipping breakfast until it plateaued at 4-5 days per week. They found that skipping breakfast 4-5 days per week was associated with a 55% increased risk for type 2 diabetes (RR = 1.55 [1.41,1.71]) (117). A few of the limitations that these reviews were faced with was the possibility of residual confounding, lack of a uniform definition of breakfast consumption, and lack of generalizability since most of their included studies were from the US and Asia (116,117).

Cross-sectional studies that have examined the association between breakfast frequency and MetS have reported contradictory results. Cross-sectional studies using survey data from the National Health and Nutrition Examination Survey (NHANES) in the US and Korea, found that breakfast consumption was associated with a lower odds for cardiometabolic risk factors, including MetS, in adults (11–14). Additionally, another cross-sectional study in Korean adults found that compared to no morning meal, eating in the morning was associated with a lower prevalence for MetS (118). In contrast, a Japanese study examining the association between late-night dinner eating and breakfast skipping with MetS found that alone neither of these meal patterns were associated with MetS but together they were associated with

[1]This risk was calculated using only four out of the six studies used in the meta-analysis as only four studies presented the results before and after adjusting for BMI.

MetS (107). There are also no cross-sectional studies that have examined this association specifically in older adults.

There are no clinical intervention studies that directly look at the relationship between breakfast timing and frequency and MetS. A systematic review and meta-analysis, published in 2020, analyzed randomized controlled trials (RCTs) that examined the effect of skipping breakfast on cardiometabolic risk factors, that include the components of MetS, over a short period of time (4 to 16 weeks) (119). The findings of the review showed that breakfast skippers experienced a modest weight loss but an increased level of LDL cholesterol, a major risk factor for atherosclerosis.[2] There were no significant differences in the other MetS components, blood pressure, triglycerides, HDL levels, and insulin, between breakfast eaters and skippers (119). These findings are in alignment with a previous meta-analysis of RCTs, by Sievert et al., which also showed that participants who skipped breakfast experienced modest weight loss but there were no significant changes in their other body composition measurements (105). The studies included in this review were of low quality with a high risk of bias and as such the results of this analysis should be cautiously interpreted (105). They were also further limited by the short duration of the studies included in their analysis which makes it difficult to draw conclusions about changes in body composition. Both reviews agree that future studies with longer durations are needed to fully understand how breakfast timing and frequency can impact the development of MetS and affect cardiometabolic health.

[2] The reviewers caution interpreting the increase in LDL cholesterol as only three out of seven trials included reported on this outcome.

2.5 Proposed Mechanism Linking Breakfast Timing and Frequency to MetS and CAD

The mechanisms through which breakfast eating or skipping can lead to a potential increased risk for MetS and CAD are not very well understood. These mechanisms can be complex and overlapping, involving multiple genetic, environmental, and social factors. The following section highlights three potential pathways linking breakfast timing and frequency and MetS and CAD: circadian rhythms, stress and hormones, and inflammation.

2.5.1 Circadian Rhythms

The most common mechanism researchers cite to link infrequent breakfast timing and frequency to MetS and CAD is through disruption of the human biological circadian clock. Chrononutrition is the novel discipline that examines the association between nutrition and circadian rhythms (100,101). Most meal timing and frequency reviews implicate circadian mechanisms as a potential cause of effect between meal timing and adverse health outcomes (63,77,89,102,103). This is because meal timing is an important factor for metabolic regulation as there is a strong interaction between the circadian clock and metabolism (120).

The central circadian clock, located in the suprachiasmatic nucleus of the hypothalamus in the brain, and peripheral clocks, located in the peripheral organs, regulate circadian rhythms (121). The central clock acts as a "conductor" for the peripheral clocks. While the central clocks guide the peripheral clocks through light-cues, the peripheral clocks themselves entrain feeding/fasting cycles, controlling physiological processes such as hormonal secretion, lipid and glucose homeostasis, and the immune and digestive systems (122).

Modern lifestyle has disrupted the human circadian rhythms through shift work, prolonged exposure to artificial light, and irregular eating timing (81). Eating that is not in harmony

with the circadian clock or fasting may lead to disruptions within the internal cellular and tissue metabolic processes (123). These disruptions can lead to hormone dysregulations such as reduced leptin (which promotes satiety), increased ghrelin (which increases appetite and promotes fat storage), and increased insulin leading to insulin insensitivity (6,120,123,124). The influence of eating timing on the circadian clock leads to metabolic disturbances that increase the risk for chronic diseases like diabetes, metabolic syndrome, and CVD (120,123,124).

On the other hand, time-restricted feeding (fasting) has been shown to be effective in reducing cardiometabolic risk factors such as abdominal obesity and isulin insensitivity. These benefits are potentially from the metabolic switch that the body undergoes during fasting which results in switching from glucose as the source of fuel to fatty acids and ketone bodies (which are broken down from triglycerides) (82). Ketone bodies are also powerful signalling molecules which influence cellular pathways and have effects on metabolism (82), which may be the reason that short-term fasting studies done in humans show an improvement in the cardiometabolic profile of participants who intermittently fasted.

2.5.2 Stress Hormones

Another possible explanation for a potential association between breakfast skipping and CAD and MetS is the stress on the body created by prolonged fasting (125). During the fasting state, blood sugar levels drop and in response, the body decreases insulin production and secretes glucagon (126). Glucagon is a hormone responsible for breaking down stored glycogen in the liver to raise the concentration of glucose in the blood (127). Glucagon can also stimulate the release of other stress hormones such as cortisol and epinephrine from the

adrenal glands (128). Cortisol prevents cells from responding to insulin essentially promoting insulin resistance during the body's fasting state. Prolonged chronic exposure to cortisol, from meal skipping, could impair metabolism and insulin action leading to hyperglycemia (129). Hyperglycemia is a leading risk factor for diseases such as diabetes, MetS, and CVD (61). These stress hormones are also related to mood disorders such as depression and irritability, which are related to poor health choices such as meal skipping and increase the risk for MetS and CAD (130). Experiencing prolonged physiological stress also disrupts the body's homeostasis, which in turn can lead to erratic eating patterns that increase the risk for obesity (131). Overall, meal skipping has the potential to induce physiological stress responses which over time may disrupt normal metabolic processes increasing the risk for chronic diseases.

Alternatively, intermittent fasting has been associated with stress resistance in animal models. Cells in animals on intermittent fasting regimens show improved function and resistane to various types of stress, including metabolic and oxidative stress, through increased antioxidant defenses, increased autophagy and DNA repair, and increased minctochindiral stress resistance (82). This increase in stress resistance reduces markers for oxidative stress that are associated with CAD (82).Therefore, fasting, which may involve breakfast skipping, may potentially reduce the risk for CAD.

2.5.3 Inflammation

Breakfast skipping has been associated with low diet quality resulting in inadequate intake of essential nutrients (12,13,101,132–134). Undernutrition, as a result of infrequent eating, is a form of malnutrition which has been linked to chronic inflammation (135,136). Longer

fasting times as a result of breakfast skipping have also been associated with increased inflammation (125,137). This form of immune dysfunction results in an increased risk for non-infectious diseases like type 2 diabetes, MetS, and CVD (136,138,139). Malnutrition and low diet quality can also lead to changes in the gut microbiome which could result in intestinal inflammation, a disruption in metabolic processes, and an increased risk for diseases (140). Comparatively, eating too often can lead to another form of malnutrition, called overnutrition, which has also been linked to chronic inflammation (136). Eating timing and frequency influence metabolic processes, human and bacterial, and disruptions of these processes can lead to unwanted inflammation resulting in an increased risk for chronic diseases.

2.6 Predictors of CAD and MetS

There are multiple genetic, social, environmental, and lifestyle factors that could predict CAD and MetS in older adults. These include age, sex, diet quality, smoking status, alcohol intake, physical activity, socioeconomic status, sleep, stress, emotional disorders, race/ethnicity, and medical history. As discussed previously, men are at a higher risk for CAD than women and there is a discrepancy in the prevalence of MetS in men and women. Older adults are at a higher risk for both CAD and MetS compared to younger adults. Having low diet quality leads to common risk factors for these diseases like obesity, hypertension, hyperglycemia, and hypotriglyceridemia. Other lifestyle factors such as smoking, excess alcohol intake, and low physical activity can increase the risk for CAD or MetS. Nicotine and carbon monoxide released from cigarette smoking affects the lining of blood vessels, increases blood fats, specifically LDL cholesterol, and affect clotting which all lead to atherosclerosis over time (141). Excessive alcohol intake has been associated with

hypertension, in a dose-dependent manner, stemming from impaired cellular activities that lead to plaque build-up and hormone imbalances (142). Low physical activity levels can lead to a build-up of fatty deposits in the arteries leading to heart attacks (143). Exercise can strengthen the heart to withstand the normal stress that it undergoes when pumping blood throughout the body (143). Among older adults, light to moderate physical activity, such as walking, was shown to be inversely associated with incident CAD (144).

Socioeconomic status (SES), measured through individual factors such as education, income, and occupation, has been associated with CVD risk (125). People of low SES are likely to benefit less from medical advancements and have less access to quality care as compared to people of higher SES, which increases their risk for CAD-related morbidity and mortality (125,126). Additionally, low SES has been associated with other CAD risk factors, stemming from lifestyle choices, such as smoking, obesity, poor diet quality, and low physical activity (126–128). SES has also been linked to stress and emotional disorders due to its impact on an individual's self-esteem and self-efficacy (126). However, these factors also independently impact the risk for CAD (129). Emotional disorders, such as anxiety and depression, are components of psychological stress (130). Together, psychological risk factors for CAD can have direct effects through hormone dysregulations and/or heart palpitations associated with anxiety and hypertension (131). Indirect effects of emotional disorders stem from poor lifestyle factors such as smoking, excessive drinking, and nutrition (131,132).

Ethnic or racial disparities also contribute to the risk of CAD-related morbidity and mortality (145). In the United States, Black Americans are at a higher risk for incident CAD and overall CVD-related mortality than white Americans (145). The reason for these disparities is

not well understood and can be a result of a combination of social and environmental factors. However, independent of SES and traditional risk factors, race has been established as a risk factor for CAD (146). In comparison, the prevalence of MetS, in 2012, appears to be lower in Black Americans than whites and highest in Hispanic Americans (147). However, each component of MetS can differentially affect the risk for the disease based on ethnicity/race (148).

Medical history, including a family history of diseases, current health status, and previous CVD events are also independent predictors of CAD and MetS. A family history of CAD, from parents and siblings, has been associated with a higher risk for CAD (137,138). Likewise, the components of MetS have also been shown to be clustered within families (139). Parental history of CVD has also been shown to be associated with MetS in the offspring (140). Current health status, which includes a diagnosis of other chronic illnesses can predict CAD or MetS. MetS is often present in people diagnosed with CVD or type 2 diabetes (27). Individuals with diabetes have a 2 to 4-fold higher risk for CAD than those without type 2 diabetes (141,142). Additionally, experiencing a CVD event, such as a heart attack, can predict risk for secondary events (143).

2.7 Rationale, Hypothesis, and Knowledge Gap

Current literature provides some evidence that breakfast timing and frequency is a modifiable risk factor for CAD and MetS, through complex metabolic pathways that remain to be fully understood. However, with a limited number of studies and studies showing contradictory results, the true relationship between these factors has yet to be determined, most especially in older adults who are at higher risk for these chronic conditions.

Longitudinal datasets that have measured meal timing and frequency, particularly breakfast, are rare and as such examining a potential relationship between breakfast timing and frequency and risk for CAD must be done from existing observational datasets. There are currently no longitudinal studies that assess breakfast timing and frequency as a predictor for CAD in older adults. This study aims to fill that gap in the literature and add to existing studies about breakfast timing and frequency and adverse health outcomes to help determine the relationship between these factors.

Skipping breakfast may be a marker for a pattern of lifestyle behaviors (109,117). Characteristics of older adults who are breakfast skippers versus breakfast eaters are not known. Having that information may be useful in creating targeted educational and health promotional policies to potentially reduce the risk of CAD stemming from breakfast consumption patterns. Another purpose of this study is to gain an understanding of the characteristics of older adults that skip breakfast versus those who eat breakfast and those who eat breakfast earlier versus those who eat breakfast later as this is also a major gap in the literature. Within these two aims, I also examined MetS as a characteristic and a potential effect modifier in the relationship between breakfast timing and frequency and risk of CAD. This is the first study to do so. Before conducting my analysis, I hypothesized that skipping breakfast and eating breakfast later are risk factors for CAD in older adults.

Chapter 3: Methods

3.1 Objectives

Objective 1: To characterize a sample of older adults based on their breakfast timing and frequency.

Objective 2: To analyze the relationship between breakfast timing and frequency and risk for MI (non-fatal and fatal) and CAD (non-fatal and fatal MI, angina, CABG, angioplasty, and/or death due to atherosclerotic CAD) in older adults.

3.2 Data and Participants

Data for this study were from the Cardiovascular Health Study (CHS) conducted by the National Heart, Lung, and Blood Institute. The CHS is a population-based longitudinal study with the purpose of identifying risk factors for the onset of CAD and stroke in older adults, as previously reported (149). Starting in 1987, the CHS recruited participants who were 65 years or older from the American communities of Forsyth County in North Carolina, Sacramento County in California, Washington County in Maryland, and Pittsburgh in Pennsylvania. There were 5,888 participants enrolled in the study, 3,393 of whom were women and 2,495 were men. These participants were divided into two cohorts. Cohort one consisted of 5,201 predominately white Americans and three years later the second cohort of 687 African American participants was recruited.

Participants were eligible to participate in the CHS if they were 65 years and older, not institutionalized, able to give informed consent without a proxy at baseline, and were planning to remain in their respective areas for the next three years (145). Participants who were wheelchair-bound at home at baseline, receiving hospice care, or receiving cancer

therapy (radiation or chemotherapy) were excluded. Eligible and consenting participants underwent baseline examinations which consisted of a home interview and clinical exams. Participants are still contacted by phone every six months. For this present thesis analysis, the follow-up time for cohort one was 26 years and the follow-up time for cohort two was 23 years, until the end date of 2015.

3.3 Exclusion Criteria

Participants with missing data for breakfast timing and frequency were excluded from the present analysis. Participants were also excluded if they had cancer within the last 5 years from the study start date (except for those with non-melanoma skin cancer) (8,150,151). Participants with prevalent CAD at baseline were also excluded from the analysis.

3.4 Ethics

Ethics approval for the use of the CHS data was granted to supervisor Dr. Leah Cahill. My name was subsequently added to the Data and Materials Distribution Agreement form for use of the data for this project. Nova Scotia Health Authority Research Ethics Board (NSHA-REB) approval was granted on October 23, 2018 (ROMEO file #1023829).

3.5 Exposure Variables

The exposure variables of interest in this study are breakfast timing and frequency. CHS participants' responses to the question “How often do you eat breakfast?” from the dietary questionnaire was used to assess their breakfast frequency (Table 1). Participants had the option to choose the following responses: never, every day, some days, rarely, and weekends only. Breakfast frequency refers to how often participants ate breakfast throughout the week. For this study, breakfast frequency was categorized as whether participants ate breakfast

everyday (yes/no). Frequent breakfast consumers (categorized as yes) are all individuals who responded, “every day” to the question noted above. Likewise, the category of non-frequent breakfast consumers (referred to as “breakfast consumers: no” for this analysis), was created by combining participant responses originally categorized as some days, never, rarely, and weekends only.

Breakfast timing refers to the first clock time (hour, minute, and am or pm) participants ate or drank something after waking. For this exposure, the median of the participants’ breakfast eating times was taken and used to describe breakfast timing as either earlier than the median or later than the median. This method of dichotomizing participants based on their breakfast timing was adapted from a recent novel study that dichotomized their participants based on the midpoint of their meal intake (breakfast, lunch, and dinner) (152). The distribuition of participants based on their breakfast time can be found in Appendix B. Breakfast timing and frequency were only measured at baseline for both cohorts. The diet questionnaire can be found in Appendix C.

3.6 Outcome Variables

The outcome variables of interest for objective 2 are incident MI and incident CAD (Table 2). Incident MI has been pre-defined as fatal and non-fatal MI. Incident CAD is a broader variable that includes MI (fatal and non-fatal), angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD (153–155). Study criteria for characterizing cardiac events can be found in Appendix D. Incident MI and CAD events were adjudicated by the Cardiac Subgroup of the CHS Events Subcommittee based on the satisfaction of CHS appropriate algorithms for classification (155).

3.7 Covariate Assessment

Variable selection for this study was guided by background and literature research as well as through the application of the Broaden Framework: a context-based approach to nutritional risk in community-dwelling older adults by Emily Rosta, a past Community Health and Epidemiology master's student (Figure 1) (156). The Broaden framework combines two already existing frameworks, Solar and Irwin's framework for the Social Determinants of Health and the maternal and child malnutrition framework from the United Nations International Children's Emergency Fund (UNICEF). This framework encompasses socio-economic and political context as well as structural and intermediary determinants of nutritional risk (Appendix A). Using this framework allows for the consideration of the multifactorial role nutritional risk plays as a determinant and dimension of health (156).

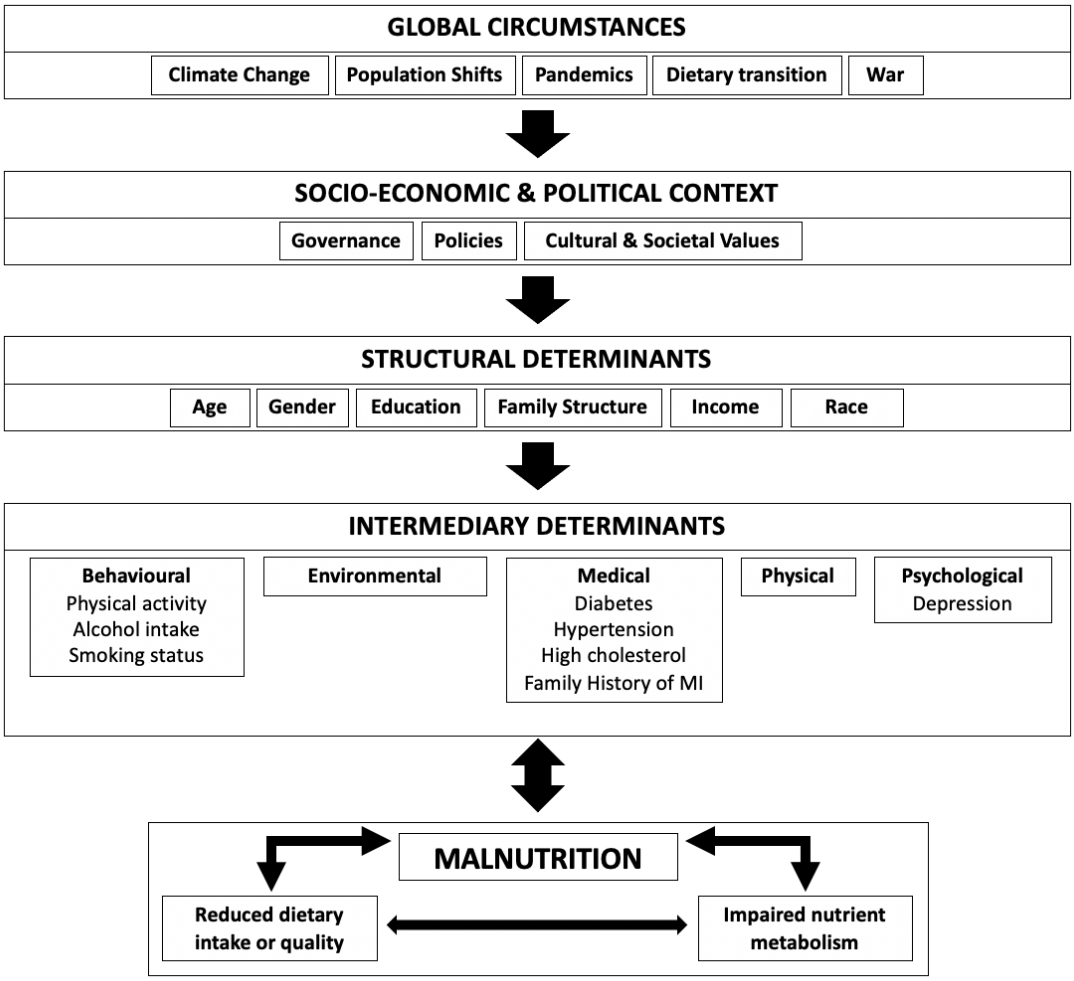

Figure 1: Modified Broaden Framework that includes the relationships between variables that was used in the analysis for breakfast timing and frequency as a predictor of CAD.

The covariates selected for this study include age, sex, ethnicity/race, marital status, physical activity, smoking status, alcohol intake, BMI, waist circumference, education, income level, fruit and vegetable intake, meal and after-dinner snacking frequency, hypertension, hypercholesteremia, depression, and family history of heart attacks. For the analysis, only baseline data for the covariates were used. That is, time-varying covariates were not updated. This was done because the exposure variables were only measured at baseline and updating

time-varying covariates would result in the updated measurements having more weight in the statistical model than the exposure. The covariates and how they were coded and their criteria for categorization can be found in Table 3.

MetS in participants was determined by using baseline anthropometric measurements in accordance with the harmonized definition for the clinical diagnosis of MetS (27). Each component of MetS was categorized as a binary variable (yes/no) based on if they met the criteria for clinical diagnosis. The thresholds for the criteria are as follows: a waist circumference of 102 cm or more for men and 88 cm or more for women, a triglyceride measurement of 150 mg/dl and more, an HDL measurement of less than 40 mg/dl in men and less than 50 mg/d in women, a systolic blood pressure of 130 mmHg and higher and/or diastolic blood pressure of 85 mmHg or higher or receiving antihypertensive therapy, and an elevated fasting glucose measurement of 100 mg/dl or more or receiving drug treatment for increased blood glucose levels. MetS was then be categorized as yes if the sum of participants' components is 3 or more and no if less than 3.

3.8 Power Calculation

3.8.1 Objective 2

Given the sample size for this study, power was calculated a priori for the association between breakfast timing and frequency and MI and CAD. According to CHS, from baseline to December 31, 2010, out of 5,888 participants, 1,007 (17.1%) experienced an MI event and 1,754 (29.8%) experienced a CAD event. In a two-sided test (alpha=0.05), with a probability of a MI event being 17.1% and the proportion of breakfast-skippers being 20% we had at least 85.92% power to identify a statistically significant hazard ratio of 1.27 (from Cahill et

al. (8)) or greater. In a two-sided test (alpha=0.05), with a probability of a CAD event being 29.8% and the proportion of breakfast-skippers being 20%, we had at least 97.97% power to identify a statistically significant hazard ratio of 1.27 (from Cahill et al .(8)) or greater.

3.9 Statistical Analysis Plan

All analysis was conducted using STATA IC software version 16.1.

3.9.1 Objective 1

Descriptive statistics were used to categorize the sample of older adults based on their breakfast timing and frequency. Additionally, univariate logistic regression models, with 95% confidence intervals, were used to examine the associations between breakfast timing and frequency and each covariate. Based on statistical significance, these associations were used to inform variable selection for the adjusted model in objective 2. Complete case analysis was utilized for variables with less than 1% missing data. For the variable 'Family History of MI', a missing category was created to represent the participants with missing data for this variable. For the variable income, complete case analysis was chosen over multiple imputation as education was the only variable appropriate to impute missing values from which, if done, may have resulted in bias. A sensitivity analysis was conducted with the missing data for income categorized as missing and no differences in subdistribution hazard ratio (SHR) was observed (Appendix E). Assumptions for logistic regression (independence of observations and errors, linearity of continous variables, absence of multicolliniearity, and lack of influential outliers) were checked prior to conducting analyses.

3.9.2 Objective 2

Fine-Grey subdistribution hazard regression models with 95% confidence intervals were used to ascertain the risk of experiencing an MI and CAD event depending on participants' breakfast timing and frequency. The Fine-Grey subdistribution hazard model accounts for competing risks and is used to the report relative change in the instantaneous rate of the event of interest in participants who are event-free or who have experienced a competing event (157). This model was chosen over the cause-specific hazard model because it is more appropriate for predicting the probability of the occurrence of the outcome over time (157). Competing risks that were accounted for in this study are non-CAD related death and stroke. Non-CAD related death was accounted for as a competing risk because if a participant has died prior to experiencing an incident MI/CAD event then they can no longer be at risk for these events. Similarly, as incident ('new event') MI/CAD are the outcomes of interest for this study, participants who have had a stroke are no longer free of vascular disease and are at a greater risk for experiencing another CVD event. Competing risks was chosen as the method to account for stroke over establishing an exclusion criteria because participants would still be at risk of experiencing an incident MI/CAD event up until they had experienced a competing event (i.e. stroke). The proportional hazard assumption was checked using Schoenfeld residual methods.

Covariates, except for waist circumference, BMI, and age, used in the final model were chosen based on their significant relationship to the exposure variables calculated through univariate logistic regression in objective 1. Waist circumference and BMI were found to be correlated with prevalent MetS and were removed from the final model (correlation factor (BMI) = 0.42, correlation factor (waist circumference) = 0.44). Meal frequency was

correlated with breakfast frequency and so removed from the models where breakfast frequency was the exposure of interest (correlation factor = -0.44). Survival time for analysis was set according to age. Age is a risk factor for CAD, and as each participant enrolled in the study at a different age their exposure to the outcome of interest would have started at different times. Left truncation, by setting the survival time according to age, accounts for this discrepancy. Additionally, because the survival time was set according to age, all interpretations of the Fine-Grey models follow the assumption that the risk for MI/CAD based on participants' breakfast timing and frequency is present only if the participant has survived to 65 years.

Three variables were created to set the survival time according to age: date of birth, study entry date, and study exit date. As date of birth was not available for the study, it was calculated as the baseline age of participants minus the year of enrollment for each cohort (1989 for cohort 1 and 1992 for cohort 2). This calculated the year of birth for each participant and the month was set to January 1 for all participants. Study entry was dated as January 1st, 1989 and January 1st, 1992, for cohort 1 and 2 respectfully. Study exit date was calculated as study entry date plus the recorded time to events (MI or CAD). The time to event variables were coded as the number of days from baseline till participant experienced an event or were censored because they didn't experience an event or experienced another event of interest for CHS.

As highlighted in chapter 2, it is possible that the effect of breakfast timing and frequency on the risk for CAD in older adults could differ based on participants sex, race, and prevalent MetS status, all of which are established risk factors for CAD. Therefore, interaction terms

for these factors were included in the multivariable models to test for effect modification. Only the interaction term for sex was found to be significant in the model where breakfast frequency was the exposure of interest and CAD was the outcome of interest. However, as decided a priori, final models for breakfast frequency were stratified by sex for both outcomes, incident MI and CAD.

3.10 Tables

Table 1. Breakfast timing and frequency and how they were defined and coded for use in analyses

Exposure Variable	Question and Response Options on the CHS Nutrition Form	Exposure Variable Coding
Frequent Breakfast Consumption (Objective 1 and 2)	Question: How often do you eat breakfast? Response options: never, every day, some days, rarely, weekends only	0= No (combined responses for somedays, never, rarely and weekends only) 1= Yes (combined responses for every day)
Breakfast Timing (Objective 1 and 2)	Question: On Monday to Friday about what time do you usually first eat or drink something after waking up? Response: hour, minute, am/pm	0= Earlier than median 1= Later than median

Table 2. Incident myocardial infarction and coronary artery disease, defined by the Cardiovascular Health Study, and how they were coded for use in analyses

	Coding of Outcome Variables	Notes
Incident Myocardial Infarction (Objective 2)	0= No 1= Yes	Incident MI defined by CHS as a fatal or non-fatal heart attack (153). Study criteria for characterizing cardiac events can be found in Appendix D.
Incident Coronary Artery Disease (Objective 2)	0= No 1= Yes	Incident CAD defined by CHS as MI, angina, whether the patient has received a coronary artery bypass graft (CABG) angioplasty, and/or death due to atherosclerotic CAD (153). Study criteria for characterizing cardiac events can be found in Appendix D.

Table 3. Covariates, chosen through the application of the Broaden Framework, and how they were named and categorized for use in analyses

Covariate	**Categorization of Variable**	**Notes**
Age	Continuous	Measured in years
Sex	0= Male 1= Female [Ref]	
Majority Ethnic Group	0= Yes [Ref] 1= No	Defined as yes if participant represents the majority ethnic group which in this sample was white
Marital Status	0= Currently Married [Ref] 1= Not Currently Married	
Family history of MI	0= No Family History of MI [Ref] 1= Yes Family History of MI	Categorized by CHS
Education	0= Less than High School 1= High School Graduate/GED [Ref] 2= More than High School	
Depression Score	0= Low (< 10) [Ref] 1= High (≥ 10)	Categorized by CHS based on Center for Epidemiologic Studies Depression Scale
Combined Family Income	0= < $25,000 1= $25,000-$49,999 [Ref] 2= ≥ $50,000	Household income before taxes for the past 12 months
Physical Activity	0= No/Low Exercise [Ref] 1= High/Moderate Exercise	Defined via exercise intensity measures by combining participant responses to physical activity like walking, mowing, tennis, cycling, gardening etc.
Smoking Status	0= Non-Smoker [Ref] 1= Current Smoker 2= Former Smoker	
Alcohol Intake	0= 0 – 7 Drinks per Week [Ref] 1= ≥7 Drinks per Week	Categorized as number of drinks per week based on the 2015-2020 US Dietary Guidelines for Americans (97)
Fruit and Vegetable Intake	0= No [Ref] 1= Yes	Categorized based on whether or not participants are consumed 3 or more servings of fruits and vegetables per day (158,159)

Covariate	Categorization of Variable	Notes
Meal Frequency	0= 0-2 Meals per Day [Ref] 1= ≥ 3 Meals per Day	
Snacks After Dinner	0= Yes [Ref] 1= No	Categorized as yes if participants reported having 1 or more snacks after dinner
BMI	0= <18.5 kg/m^2 1= 18.5 kg/m^2< BMI< 25 kg/m^2[Ref] 2= 25 kg/m^2≤ BMI< 30 kg/m^2 3= BMI ≥30 kg/m^2	Categorized based on CDC definition of Obesity (160)
Waist Circumference	Continuous	Measured in cm
Cholesterol	0= Desirable (< 200 mg/dl) [Ref] 1= Borderline High (200-239 mg/dl) 2= High (> 240 mg/dl)	Categorized by CHS according to NCEP guidelines
Hypertension/ Antihypertensive Medication Use	0= No [Ref] 1= Yes	Categorized as yes if seated blood pressure average of systolic blood pressure ≥140 and average diastolic pressure of ≥ 90 and/or the if participant is on anti-hypertensive medication
Prevalent Diabetes	0= No [Ref] 1= Yes	Categorized by CHS based on ADA guidelines (161)

Chapter 4: Results

4.1 Participants Eligible for Analyses

The initial sample of CHS participants included 5,888 men and women in cohort 1 and cohort 2 combined. 1,154 (19.6%) participants were excluded due to prevalent CAD and 156 (2.6%) were excluded due to a five-year history of cancer (except non-melanoma cancer). Participants were also excluded if they had missing data for the exposure variables of interest, breakfast time (n=21(0.4%)) and breakfast frequency (n=1 (<0.1%)). Participants with missing data for the variables: marital status, smoking, exercise intensity, waist circumference, meal frequency, snacks after dinner, education, depression score, alcohol intake, fruit and vegetable intake, BMI, cholesterol, hypertension, prevalent diabetes, and prevalent MetS had less than 1% missing data. Participants with missing information for the variable income were also dropped (n=300 (5.1%)). After these exclusions, a sample size of 4,058 participants remained for analyses for objectives 1 and 2. A flow diagram detailing the number of participants excluded is shown in Figure 2.

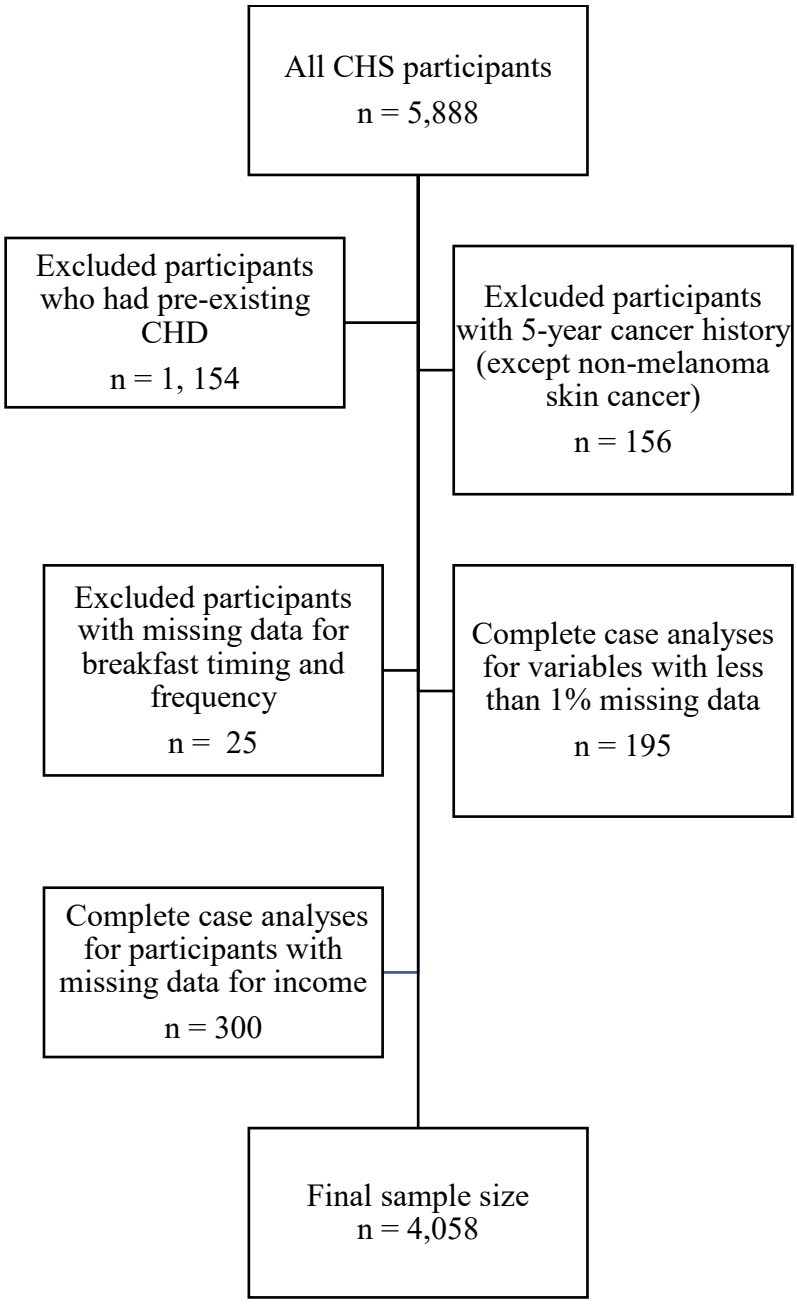

Figure 2: Flow chart of the number of participants from the Cardiovasculr Health Study excluded from analyses for objective 1 and 2

4.2 Objective 1

4.2.1 Breakfast Frequency

Results for objective 1, with breakfast frequency as exposure of interest, are presented in Table 4. Participants' baseline characteristics are described according to whether they reported everyday breakfast consumption or not. Out of 4,058 older adults, 3,467 (85.4%) reported eating breakfast every day and 591 (14.6%) reported eating breakfast some days, rarely, never, or weekends only. Among participants who reported eating breakfast every day, the average age was 72.79 ± 5.54 years, 58.84% were women, 13.47% were a part of a minority ethnic group, 32.97% were not married, and 27.40% had a family history of MI. Among participants who reported not having breakfast every day, the average age was 70.85 ± 4.60 years, 65.14% were women, 28.60% were part of a minority ethnic group, 42.13% were not married, and 25.72% had a family history of MI.

Univariate logistic regression was conducted to analyse the relationship between breakfast frequency and each covariate. The assumptions for logistic regression were met for both exposure variables and all potential covariates. Breakfast frequency was significantly associated ($p<0.01$) with age, sex, race, marital status, education, income, smoking, fruit and vegetable intake, BMI, waist circumference, cholesterol, and prevalent MetS. Participants who reported not eating breakfast every day had significantly higher odds of being female (OR=1.31 [1.09, 1.57]), being a part of a minority ethnic group (OR=2.57 [2.10, 3.15]), unmarried (OR=1.48 [1.23, 1.77]), have a household income of less than $25,000 a year (OR=1.57 [1.26, 1.95]), be a current smoker (OR=2.56 [2.01, 3.25]), be obese (OR=1.95 [1.55, 2.46]), have high cholesterol (OR=1.31 [1.04, 1.64]), and have prevalent MetS (OR=1.29 [1.08, 1.53]) compared to participants who reported eating breakfast every day.

They also had significantly lower odds of having more than a high school education (OR=0.75 [0.61, 0.93]) and of consuming 3 or more servings of fruits and vegetables a day (OR=0.56 [0.43, 0.73]) compared to participants who reported eating breakfast every day (Table 4).

4.2.2 Breakfast Timing

Results for objective 1, with breakfast timing as the exposure of interest, are presented in Table 5. Participants' baseline characteristics are described according to whether they ate breakfast earlier or later than the median time (8:00 am). Participants who reported eating at the median time were included in the group with participants who reported eating earlier than the median. A sensitivity analysis showed no difference in the SHR when participants who ate at the median time was included in the group with participants who ate later than the median (Appendix F). In this sample of 4,058 older adults, 2,815 (69.4%) reported eating breakfast earlier than or at 8:00 am and 1,243 (30.6%) reported eating breakfast later than 8:00 am. Among participants who reported eating breakfast earlier than the median, the average age was 72.39 ± 5.34 years, 58.37% were female, 11.26% were part of the minority ethnic group, 31.76% were not married, and 28.60% had a family history of MI. Among participants who reported eating breakfast later than the median, the average age was 72.78 ± 5.71, 62.91% were female, 25.66% were part of the minority ethnic group, 40.06% were not married, and 23.89% had a family history of MI.

Breakfast timing was significantly associated ($p<0.01$) with age, sex, race, family history of MI, marital status, depression score, income, smoking, meal frequency, snacks after dinner, exercise intensity, cholesterol, BMI, waist circumference, prevalent diabetes, and prevalent

MetS. Participants who reported eating later than the median had a significantly higher odds of being female (OR=1.21 [1.05, 1.39]), be a part of the minority ethnic group (OR=2.72 [2.29, 3.23]), unmarried (OR=1.44 [1.25, 1.65]), be depressed (OR=1.43 [1.17, 1.75]), have a household income of less than $25,000 a year (OR=1.25 [1.07, 1.46]), be a current smoker (OR=1.40 [1.15, 1.73]), have no snacks after dinner (OR=1.38 [1.20, 1.59]), be underweight (OR=1.63 [1.02, 2.62]) or obese (OR=1.95 [1.55, 2.46]), have high cholesterol (OR=1.32 [1.11, 1.58]), have prevalent diabetes (OR=1.30 [1.08, 1.57]), and have prevalent MetS (OR=1.29 [1.08, 1.53]) compared to participants who reported eating breakfast at the median time or earlier than the median. Participants who reported eating later than the median also had significantly lower odds for having a family history of MI (OR=0.89 [0.80, 0.99]), for having moderate to high physical activity levels (OR=0.84 [0.73, 0.96]), eating 3 or more servings of fruits and vegetables a day (OR=0.56 [0.43, 0.73]), and for eating 3 or more meals a day (OR=0.39 [0.34, 0.45]) (Table 5).

4.3 Objective 2

In the 26- and 23-year follow-up time for cohort 1 and cohort 2 respectively, a total of 708 (17.4%) participants experienced an MI event and a total of 1,471 (36.2%) participants experienced a CAD event. During this follow-up time, 3,004 (74.0%) participants experienced a competing event (non-CAD-related death or stroke) when the outcome of interest was MI, and 2,283 (56.3%) participants experienced a competing event when the outcome of interest was CAD.

Covariates included in the multivariable model when the exposure of interest was breakfast frequency include sex, race, marital status, education, income, smoking, cholesterol, and

prevalent MetS. Covariates included in the multivariable model when the exposure of interest was breakfast timing include sex, race, family history of MI, marital status, income, smoking, meal frequency, snacks after dinner, depression score, cholesterol, prevalent diabetes, and prevalent MetS. Sensitivity analyses were conducted with BMI and waist circumference variables in the models and no difference in the subdistribution hazard ratios was observed (results not shown). Proportional hazards assumptions were met for the exposure variables and each of the covariates included in the multivariable models.

4.3.1 Breakfast Frequency

Results for the association between breakfast frequency and incident MI and CAD are presented in Table 6. In the presence of competing risks, compared to participants who ate breakfast every day, participants who did not eat breakfast every day had an aSHR of 0.89 [0.71, 1.11] for experiencing an MI event and an aSHR of 0.88 [0.75, 1.03] for experiencing a CAD event. In these multivariable models, breakfast frequency was not found to be significantly associated with an increase or decrease in the risk for incident MI or CAD in older adults.

4.3.3 Breakfast Timing

Results for the association between breakfast timing and incident MI and CAD are presented in Table 7. In the presence of competing risks, compared to participants who ate breakfast earlier than the median, participants who ate breakfast later than the median had an aSHR of 0.95 [0.80, 1.13] for experiencing an MI event and an aSHR of 1.05 [0.93, 1.18] for experiencing a CAD event. Breakfast timing was not found to be significantly associated with an increase or decrease in the risk for incident MI or CAD in our sample.

4.3.2 Testing for Effect Modification

Interaction terms for prevalent MetS, race, and sex were included in multivariable models to test for effect modification. The interaction term between prevalent MetS and breakfast timing and frequency was non-signficant for both outcomes (MI/CAD) ([prevalent MetS and breakfast frequency: p-val. (MI)=0.71, p-val. (CAD)=0.71], [prevalent MetS and breakfast timing: p-val. (MI) =0.82, p-val. (CAD)=0.92], and the interaction coefficient was close to 1 ([prevalent MetS and breakfast frequency: SHR (MI)=1.08, SHR (CAD)=0.95], [prevalent MetS and breakfast timing: SHR (MI) =0.96, SHR (CAD)=1.01] suggesting that the effects of the interaction between prevalent MetS and breakfast timing and frequency did not increase the risk for CAD compared to the baseline model (model that did not consist of an interaction term). Similiarly, the interaction term between breakfast timing and frequency and race was also non-significant in all models [race and breakfast frequency: p-val. (MI)=0.92, p-val. (CAD)=0.88], [race and breakfast timing: p-val. (MI)=0.84, p-val. (CAD)=0.54]). The interaction coefficient for race and breakfast timing and frequency is also close to 1 [race and breakfast frequency: SHR (MI)=0.97, SHR (CAD)=0.97], [race and breakfast timing: SHR (MI)=1.05, SHR (CAD)=0.91]) indicating that the effects of the interaction between these variables does not increase the risk for CAD compared to the base model. The interaction term for sex was significant only when breakfast frequency was the exposure of interest and CAD was the outcome of interest (p-val.=0.036, SHR(CAD) = 1.40). The interaction term between breakfast frequency and sex when the outcome of interest was MI was non-significant (p-val.=0.058, SHR(CAD) = 1.50) but the coefficient was similar to when CAD was the outcome of interest suggesting that the combined effect of breakfast frequency and sex may be comparable for both outcomes. Additionally, as incident

MI is a component of the incident CAD variable and stratification for both outcomes was decided on a priori, analyses were stratified by sex for both MI and CAD.

Multivariable models examining the association between breakfast frequency and incident MI and CAD stratified by sex can be found in Tables 8 and 9. In the presence of competing risks, compared to male participants who ate breakfast every day, male participants who did not eat breakfast every day had a 31% lower risk (aSHR=0.69 [0.48, 0.98]) for experiencing an MI event and a 29% lower risk (aSHR=0.71 [0.55, 0.93]) for experiencing a CAD event. In the presence of competing risks, compared to female participants who ate breakfast every day, female participants who did not eat breakfast every day have an aSHR of 1.11 [0.84, 1.47] for experiencing an MI event and an aSHR of 1.04 [0.86, 1.26] for experiencing a CAD event. In these stratified models, not eating breakfast every day was associated with a decreased risk for incident MI and CAD in older men only. In older females, breakfast frequency was not found to be significantly associated with an increase or decrease in the risk for incident MI or CAD.

4.4 Tables

Table 4. Baseline characteristics of participants from the Cardiovascular Health Study based on their breakfast frequency and the odds ratios from unadjusted logistic regression models of the relationship between each characteristic and breakfast frequency

Characteristics	Everyday Breakfast Consumption		Unadjusted odds of reporting non-daily breakfast consumption
	Yes (n=3,467)	No (n=591)	
	Mean/SD or N/%	Mean/SD or N/%	Odds Ratio [95% CI]
Age	72.79 ± 5.54	70.85 ± 4.60	**0.93** [0.91, 0.94]
Female Sex	2040 (58.84)	385 (65.14)	**1.31** [1.09, 1.57]
Minority Ethnic Group[1]	467 (13.47)	169 (28.60)	**2.57** [2.10, 3.15]
Not Currently Married	1143 (32.97)	249 (42.13)	**1.48** [1.23, 1.77]
Family History of MI[2]	950 (27.40)	152 (25.72)	1.12 [0.99, 1.28]
Education			
Less than High School	960 (27.69)	194 (32.83)	1.08 [0.87, 1.35]
High School/GED	952 (27.46)	178 (30.12)	1.00 [Ref]
More than High School	1555 (44.85)	219 (37.06)	**0.75** [0.61, 0.93]
High Depression Score (≥10)	397 (11.45)	83 (14.04)	1.26 [0.98, 1.63]
Combined Family Income			
<$25,000	2032 (58.58)	404 (68.36)	**1.57** [1.26, 1.95]
$25,000-$49,999	946 (27.29)	120 (20.30)	1.00 [Ref]
≥$50,000	490 (14.13)	67 (11.34)	1.08 [0.78, 1.48]
Moderate-High Physical Activity	1558 (44.94)	243 (41.12)	0.86 [0.72, 1.02]

	Mean/SD or N/%	Mean/SD or N/%	Odds Ratio [95% CI]
Smoking Status			
Non-Smoker	1684 (48.57)	235 (39.76)	1.00 [Ref]
Current Smoker	375 (10.82)	134 (22.67)	**2.56** [2.01, 3.25]
Former Smoker	1408 (40.61)	222 (37.56)	1.13 [0.93, 1.38]
≥ 7 Alcoholic Drinks per Week	485 (13.99)	88 (14.89)	1.08 [0.84, 1.38]
≥ 3 Fruit &Vegetable Servings per Day	654 (18.86)	68 (11.51)	**0.56** [0.43, 0.73]
≥ 3 Meals per Day	2674 (77.13)	110 (18.61)	0.07 [0.05, 0.08]
No Snacks After Dinner	2119 (61.12)	384 (64.97)	1.18 [0.98, 1.42]
BMI (kg/m^2)			
BMI <18.5	66 (1.90)	12 (2.03)	1.31 [0.70, 2.47]
18.5≤BMI<25	1321 (38.10)	183 (30.96)	1.00 [Ref]
25≤ BMI< 30	1459 (42.08)	228 (38.58)	1.13 [0.92, 1.39]
BMI ≥30	621 (17.91)	168 (28.43)	**1.95** [1.55, 2.46]
Waist Circumference	93.58 ± 12.94	96.52 ± 14.51	**1.02** [1.01, 1.02]
Cholesterol (mg/dl)			
Desirable (< 200)	1404 (40.50)	221 (37.39)	1.00 [Ref]
Borderline High (200-239)	1353 (39.03)	224 (37.90)	1.05 [0.86, 1.28]
High (≥ 240)	710 (20.48)	146 (24.70)	**1.31** [1.04, 1.64]
Hypertension/ Antihypertensive Medication Use	1974 (56.94)	341 (57.70)	1.03 [0.86, 1.23]
Prevalent Diabetes	486 (14.02)	78 (13.20)	0.93 [0.72, 1.20]
Prevalent MetS	1365 (39.37)	269 (45.52)	**1.29** [1.08, 1.53]

BMI = Body Mass Index, CI = Confidence Interval, GED = General Education Development, MetS = Metabolic Syndrome, MI = Myocardial Infarction, N= Number, SD = Standard Deviation

[1] Not in majority ethnic group, which in this sample was white

[2] Missing category for Family History of MI: breakfast frequency (yes) = 293 participants & breakfast frequency (no) =70 participants

Table 5. Baseline characteristics from the Cardiovascular Health Study based on their breakfast timing and the odds ratios from unadjusted logistic regression models of the relationship between each characteristic and breakfast timing

	Breakfast Timing[1]		
Characteristics	**Earlier**(n=2815)**	**Later**(n=1243)**	**Unadjusted odds of being a later breakfast eater**
	Mean/SD or N/%	**Mean/SD or N/%**	**Odds Ratio [95% CI]**
Age	72.39 ± 5.34	72.78 ± 5.71	**1.01** [1.00, 1.03]
Female Sex	1643 (58.37)	782 (62.91)	**1.21** [1.05, 1.39]
Minority Ethnic Group[2]	319 (11.26)	319 (25.66)	**2.72** [2.29, 3.23]
Not Currently Married	894 (31.76)	498 (40.06)	**1.44** [1.25, 1.65]
Family History of MI[3]	805 (28.60)	297 (23.89)	**0.89** [0.80, 0.99]
Education			
Less than High School	779 (27.67)	375 (30.17)	1.08 [0.91, 1.30]
High School/GED	783 (27.82)	347 (27.92)	1.00 [Ref]
More than High School	1253 (44.51)	521 (41.91)	0.94 [0.80, 1.10]
High Depression Score (≥10)	299 (10.62)	181 (14.56)	**1.43** [1.17, 1.75]
Combined Family Income			
<$25,000	1631 (57.94)	804 (64.68)	**1.25** [1.07, 1.46]
$25,000-$49,999	764 (27.14)	302 (24.30)	1.00 [Ref]
≥ $50,000	420 (14.92)	137 (11.02)	0.83 [0.65, 1.04]
Moderate-High Physical Activity	1286 (45.68)	515 (41.43)	**0.84** [0.73, 0.96]
Smoking Status			
Non-Smoker	1359 (48.28)	560 (45.05)	1.00 [Ref]
Current Smoker	322 (11.44)	187 (15.04)	**1.40** [1.15, 1.73]
Former Smoker	1134 (40.28)	496 (39.90)	1.06 [0.92, 1.23]

	Mean/SD or N/%	Mean/SD or N/%	Odds Ratio [95% CI]
≥ 7 Alcoholic Drinks per Week	403 (14.32)	170 (13.68)	0.95 [0.78, 1.15]
≥ 3 Fruit &Vegetable Servings per Day	556 (19.75)	166 (13.35)	**0.63** [0.52, 0.76]
≥ 3 Meals per Day	2111 (74.99)	673 (54.14)	**0.39** [0.34, 0.45]
No Snacks After Dinner	1672 (59.40)	831 (66.85)	**1.38** [1.20, 1.59]
BMI (kg/m^2)			
BMI <18.5	48 (1.71)	30 (2.41)	**1.63** [1.02, 2.62]
18.5≤BMI<25	1088 (38.65)	416 (33.47)	1.00 [Ref]
25≤ BMI< 30	1171 (41.60)	516 (41.51)	1.15 [0.99, 1.34]
BMI ≥30	508 (18.05)	281 (22.61)	**1.45** [1.20, 1.74]
Waist Circumference	93.54 ± 13.21	95.05 ± 13.19	**1.01** [1.00, 1.01]
Cholesterol (mg/dl)			
Desirable (<200)	1157 (41.10)	468 (37.65)	1.00 [Ref]
Borderline High (200-239)	1100 (39.08)	477 (38.37)	1.07 [0.92, 1.25]
High (≥240)	558 (19.82)	298 (23.97)	**1.32** [1.11, 1.58]
Hypertension/ Antihypertensive Medication Use	1581 (56.16)	734 (59.05)	1.13 [0.98, 1.29]
Prevalent Diabetes	363 (12.90)	201 (16.17)	**1.30** [1.08, 1.57]
Prevalent MetS	1071 (38.05)	563 (45.29)	**1.35** [1.18, 1.54]

BMI = Body Mass Index, CI = Confidence Interval, GED = General Education Development, MetS = Metabolic Syndrome, MI = Myocardial Infarction, N= Number, SD = Standard Deviation

[1] Breakfast timing was defined as earlier than or later than the median based on the median time that all CHS participants reported eating in the morning

[2] Not in majority ethnic group, which in this sample was white

[3] Missing category for Family History of MI: breakfast time (earlier) = 252 participants & breakfast time (later) =111 participants

*Breakfast time is the time that a participant first 'breaks fast' in the day and so participants who skip breakfast are still included because they did still eat ('break fast'); they are in the 'later' group

**As compared to the median time

Table 6. Multivariable model[1] for the association between breakfast frequency and incident myocardial infarction and coronary artery disease among participants from the Cardiovascular Health Study

	Myocardial Infarction		Coronary Artery Disease[2]	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	**P-Value**	**Subdistribution Hazard Ratio (aSHR) [95% CI]**	**P-Value**
Non-Daily Breakfast Eaters	0.89 [0.71, 1.11]	0.29	0.88 [0.75, 1.03]	0.10
Female Sex	0.56 [0.48, 0.67]	< 0.0001	0.63 [0.56, 0.72]	< 0.0001
Minority Ethnic Group	0.78 [0.62, 0.99]	0.04	0.97 [0.83, 1.13]	0.66
Not Currently Married	1.28 [1.07, 1.54]	0.01	1.15 [1.01, 1.30]	0.03
Education				0.14
Less than High School	1.23 [1.00, 1.52]	0.05	1.12 [0.97, 1.29]	
High School/GED	1.00 [Ref]		1.00 [Ref]	0.81
More than High School	1.14 [0.93, 1.38]	0.20	1.02 [0.89, 1.16]	
Income				
<$25,000	1.01 [0.82, 1.24]	0.94	1.07 [0.93, 1.23]	0.33
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.12 [0.88, 1.42]	0.36	1.04 [0.88, 1.24]	0.63
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.86 [0.67, 1.11]	0.24	0.83 [0.70, 0.99]	0.04
Former Smoker	1.01 [0.86, 1.20]	0.86	1.00 [0.89, 1.12]	0.94
≥ 3 Fruit &Vegetable Servings per Day	0.88 [0.72, 1.07]	0.20	0.98 [0.85, 1.12]	0.73
Cholesterol (mg/dl)				
Desirable (<200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.07 [0.91, 1.27]	0.41	1.03 [0.91, 1.16]	0.63
High (≥240)	1.08 [0.87, 1.33]	0.48	1.11 [0.96, 1.29]	0.15

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent MetS	1.25 [1.07, 1.46]	0.004	1.34 [1.21, 1.50]	< 0.0001

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction,

[1]Model is adjusted for sex, race, marital status, education, income, smoking, fruit and vegetable intake, cholesterol levels, and prevalent MetS status at baseline

[2]CAD composes of non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD

Table 7. Multivariable model[1] for the association between breakfast timing[2] and incident myocardial infarction and coronary artery disease among participants from the Cardiovascular Health Study

	Myocardial Infarction		Coronary Artery Disease[3]	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	**P-Value**	**Subdistribution Hazard Ratio (aSHR) [95% CI]**	**P-Value**
Later than Median Breakfast Eaters	0.95 [0.80, 1.13]	0.57	1.05 [0.93, 1.18]	0.45
Female Sex	0.56 [0.48, 0.67]	< 0.0001	0.63 [0.56, 0.71]	< 0.0001
Minority Ethnic Group	0.81 [0.63, 1.02]	0.08	0.96 [0.82, 1.12]	0.59
Family History of MI	1.01 [0.90, 1.13]	0.85	1.08 [1.00, 1.17]	0.05
Not Currently Married	1.30 [1.08, 1.54]	0.01	1.14 [1.00, 1.29]	0.05
High Depression Score (≥10)	0.86 [0.67, 1.12]	0.28	1.05 [0.88, 1.24]	0.60
Income				
<$25,000	1.03 [0.85, 1.25]	0.74	1.09 [0.96, 1.25]	0.19
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.13 [0.89, 1.43]	0.32	1.04 [0.87, 1.24]	0.67
Moderate-High Physical Activity	0.99 [0.84, 1.15]	0.89	0,99 [0.89, 1.11]	0.87
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.88 [0.68, 1.12]	0.30	0.83 [0.69, 0.99]	0.04
Former Smoker	1.02 [0.87, 1.20]	0.81	0.99 [0.88, 1.11]	0.87
≥ 3 Fruit &Vegetable Servings per Day	0.86 [0.71, 1.05]	0.15	0.96 [0.84, 1.11]	0.59
≥ 3 Meals per Day	1.13 [0.95, 1.34]	0.18	1.11 [0.98, 1.26]	0.09
No Snacks After Dinner	0.94 [0.81, 1.10]	0.47	0.98 [0.88, 1.10]	0.73
Cholesterol (mg/dl)				
Desirable (<200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.10 [0.92, 1.30]	0.29	1.05 [0.93, 1.19]	0.44
High (≥240)	1.10 [0.89, 1.35]	0.39	1.13 [0.97, 1.30]	0.11
Prevalent Diabetes	1.28 [1.03, 1.60]	0.03	1.29 [1.10, 1.52]	0.001

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent MetS	1.20 [1.01, 1.41]	0.03	1.27 [1.14, 1.43]	< 0.0001

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction

[1]Model is adjusted for sex, race, family history of MI, marital status, depression score, physical activity, smoking status, fruit and vegetable intake, meal frequency, snacking after dinner, cholesterol levels, and prevalent diabetes and MetS status at baseline

[2] Breakfast timing was defined as earlier than or later than the median based on the median time that all CHS participants reported eating in the morning

[3] CAD composes of non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD

Table 8. Multivariable model[1] for the association between breakfast frequency and incident myocardial infarction stratified by sex among participants from the Cardiovascular Health Study

	Myocardial Infarction			
	Male		Female	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	**P-Value**	**Subdistribution Hazard Ratio (aSHR) [95% CI]**	**P-Value**
Non-Daily Breakfast Eaters	0.69 [0.48, 0.98]	0.04	1.11 [0.84, 1.47]	0.47
Minority Ethnic Group	0.82 [0.59, 1.15]	0.25	0.76 [0.55, 1.04]	0.09
Not Currently Married	1.23 [0.91, 1.67]	0.17	1.30 [1.04, 1.64]	0.02
Education				
Less than High School	1.09 [0.80, 1.48]	0.58	1.36 [1.02, 1.81]	0.03
High School/GED	1.00 [Ref]		1.00 [Ref]	
More than High School	1.01 [0.76, 1.34]	0.94	1.27 [0.97, 1.66]	0.09
Income				
<$25,000	1.10 [0.83, 1.46]	0.51	0.91 [0.68, 1.21]	0.49
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.30 [0.95, 1.78]	0.10	0.90 [0.62, 1.30]	0.56
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.84 [0.58, 1.23]	0.37	0.85 [0.61, 1.19]	0.34
Former Smoker	1.00 [0.79, 1.26]	0.99	1.03 [0.81, 1.30]	0.83
≥ 3 Fruit &Vegetable Servings per Day	0.78 [0.57, 1.08]	0.14	0.98 [0.75, 1.28]	0.87
Cholesterol (mg/dl)				
Desirable (<200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.08 [0.86, 1.36]	0.49	1.07 [0.82, 1.38]	0.62
High (≥240)	0.94 [0.66, 1.35]	0.75	1.14 [0.87, 1.51]	0.33

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent MetS	1.15 [0.92, 1.44]	0.21	1.38 [1.12, 1.71]	0.003

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction

[1]Model is adjusted for sex, race, marital status, education, income, smoking, fruit and vegetable intake, cholesterol levels, and prevalent MetS status at baseline

P-value = 0.058

Table 9. Multivariable model[1] for the association between breakfast frequency and incident coronary artery disease stratified by sex among participants from the Cardiovascular Health Study

	Coronary Artery Disease[2]			
	Male		Female	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	**P-Value**	**Subdistribution Hazard Ratio (aSHR) [95% CI]**	**P-Value**
Non-Daily Breakfast Eaters	0.71 [0.55, 0.93]	0.01	1.04 [0.86, 1.26]	0.70
Minority Ethnic Group	0.96 [0.76, 1.22]	0.76	0.96 [0.78, 1.18]	0.69
Not Currently Married	1.18 [0.95, 1.47]	0.13	1.13 [0.96, 1.32]	0.14
Education				
Less than High School	1.08 [0.86, 1.35]	0.52	1.15 [0.95, 1.38]	0.16
High School/GED	1.00 [Ref]		1.00 [Ref]	
More than High School	0.96 [0.77, 1.18]	0.67	1.08 [0.91, 1.28]	0.40
Income				
<$25,000	1.10 [0.90, 1.34]	0.37	1.04 [0.86, 1.26]	0.69
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.13 [0.89, 1.44]	0.33	0.94 [0.73, 1.21]	0.64
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.87 [0.66, 1.14]	0.31	0.79 [0.62, 1.00]	0.05
Former Smoker	1.01 [0.84, 1.20]	0.96	0.98 [0.84, 1.15]	0.85
≥ 3 Fruit &Vegetable Servings per Day	0.84 [0.67, 1.06]	0.14	1.10 [0.92, 1.31]	0.30
Cholesterol (mg/dl)				
Desirable (<200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.02 [0.86, 1.21]	0.81	1.04 [0.87, 1.24]	0.66
High (≥240)	1.05 [0.81, 1.37]	0.72	1.15 [0.96, 1.38]	0.14

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent MetS	1.25 [1.06, 1.48]	0.01	1.44 [1.25, 1.67]	< 0.0001

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction

[1]Model is adjusted for sex, race, family history of MI, marital status, depression score, physical activity, smoking status, fruit and vegetable intake, meal frequency, snacking after dinner, cholesterol levels, and prevalent diabetes and MetS status at baseline

[2] CAD composes of non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD

P-value = 0.036

Chapter 5: Discussion

5.1 Overview of Results

This study was the first to characterize a sample of older adults based on their breakfast timing and frequency. In univariate models of baseline data, breakfast timing and frequency were associated with a variety of demographic and lifestyle factors that are established risk factors for MI/CAD. These factors include 1) demographic factors: age, sex, race, marital status, family history of MI, SES, 2) lifestyle factors: physical activity levels, smoking, diet quality, meal frequency, snacking after dinner, and 3) health factors and conditions: BMI, waist circumference, cholesterol level, prevalent diabetes, and prevalent MetS.

This study was also the first to examine the relationship between breakfast timing and frequency and risk for CAD in older adults. The multivariable model showed that breakfast timing was not statistically significantly associated with an increased or decreased risk for incident MI or CAD in older adults. However, among the sub-set of 1,633 male participants, those who did not eat breakfast every day had a 31% (aSHR=0.69 [0.48, 0.98]) and 29% (aSHR=0.71 [0.55, 0.93]) lower risk for experiencing an MI event and CAD event, respectively, compared to men who ate breakfast every day. This association was not observed in women in our sample, despite women making up the majority of the participants.

These findings did not support the hypothesis that eating breakfast later than the median or eating breakfast irregularly would increase the risk for MI/CAD. However, they do provide preliminary evidence that non-daily breakfast eating patterns are potentially associated with decreased risk of MI/CAD in men, but not women.

5.2 Demographic Characteristics Associated with Breakfast Timing and Frequency in Older Adults

The factors associated with breakfast timing and frequency appear to be multifactorial, including biological, socioeconomic, and social factors. For example, older adults in the present study who did not eat breakfast every day or ate breakfast later than the median were more likely to be part of a minority group and have low SES (measured through income and/or education). The relationship between race/ethnicity, SES, and breakfast timing/frequency has not been well studied. Racial/ethnic disparities are associated with differences in SES and residential environments (minority races are more likely to be poor and more likely to live in poorer communities) (162), which have been associated with food insecurity and behaviours that include breakfast skipping (163,164). The association between SES and lifestyle behaviours is not isolated to minority groups (165). Older adults who skip breakfast may be doing so because they cannot afford a morning meal. Lack of food security means lack of access to nutritious food which increases the risk for poor health (166). Skipping breakfast as a consequence of food insecurity has also been associated with depressive symptoms, a finding consistent with this sample of older adults who ate breakfast later than the median (167). Food insecurity is an important public health issue, and SES, specifically income, is an important determinant of food security (168).

Another demographic factor that was associated with non-daily breakfast consumption and late breakfast timing was marital status. Older adults who live alone are vulnerable to poor nutrition as they tend to consume fewer meals (169). A study conducted in a population of US adults age 50 years and older found that living arrangements, specifically living alone or with someone other than a spouse, was associated with poor diet quality compared to living

with a spouse (170). Malnutrition in older adults can be a result of many factors. Living alone can lead to skipping meals, specifically breakfast, if the older adult is physically impaired, isolated, depressed, using heavy medication, frail, or is experiencing food insecurity because of lower income status post retirement (94). As a vulnerable population, breakfast timing and frequency in older adults needs to be more thoroughly researched to understand how racial, financial, and social inequalities, both separate and intertwined, may play a role in the relationship between breakfast timing and frequency and CAD.

5.3 Breakfast Timing and Frequency as a Predictor of a Pattern of Lifestyle Behaviours

Breakfast frequency has previously been found to be positively correlated with conscientiousness, well-being, age, and general health (171). In the present study, older adults who did not eat breakfast every day and ate breakfast later than the median were more likely to be current smokers and have poor diet quality. Additionally, older adults who ate breakfast later than the median were also more likely to have low physical activity levels. Similar to this present study, the first in older adults, previous studies of younger adults also report that breakfast consumption may be a proxy variable or a marker for a healthy lifestyle (7–9,171–173).

Smoking, diet quality, and physical activity levels are known cardiometabolic risk factors. Studies that have characterized younger adult participants who skip breakfast also found that they were more likely to be current smokers, have poor diet quality, and low physical activity levels (8,172,174–176). Lifestyle behaviours of older adults who skip breakfast are likely intertwined. For example, participants who were current smokers likely had a lower appetite, a side effect of nicotine use, and so were less likely to be hungry in the morning (177). Not

eating a morning meal may result in a lack of mental or physical energy to engage in physical activity, especially older adults, who move less due to their age (178,179). Additionally, several studies have shown that individuals who skip breakfast have lower than recommended intakes of important nutrients, such as fibre, iron, calcium, folate, and riboflavin, compared to those who eat breakfast regularly (114,180–183). This is a potential contributor to the poorer diet quality in older adults, some of whom are already at risk for poor nutrition due to changes in gastric absorption, a decline in oral health, and/or reduced ability to swallow, observed among late breakfast eaters in this study (178). Late breakfast eaters in this present study also had 63% (OR = 1.63 [1.02, 2.62]) increased odds of being underweight. Malnutrition in older adults can increase the risk for chronic diseases, infections, results in longer hospital stays, and is associated with increased mortality (184,185). Interventions to reduce the frequency of breakfast skipping in malnourished older adults may help to improve their nutrition status (184,186).

5.4 Association Between Breakfast Timing and Frequency with Prevalent MetS

This study found that older adults who did not eat breakfast every day and ate breakfast later than the median breakfast time had an increased odds of having MetS and its related factors: obesity and high cholesterol. Approximately 40% of older adults in this sample had MetS at baseline (187). Older adults in this sample who ate later than the median were also more likely to have prevalent type 2 diabetes, a chronic illness that people with MetS are 5 times higher risk for (188). The few observational studies that have been conducted show that eating a morning meal is associated with a lower risk for MetS (11–15,106). In addition, a Korean study conducted in middle-aged adults, 47 to 59 years, found that individuals who prefer later times for daily activities like waking, eating, and sleeping, had a 74% (OR = 1.74

[1.05, 2.87]) increased odds for MetS compared to participants who preferred morning activities (189). The findings of previous studies were evident after adjustment for confounders, whereas in our study we only investigated the univariable associations. Future longitudinal studies that can evaluate how breakfast eating behaviours change after a MetS diagnosis may help to further elucidate the relationship between breakfast eating and MetS. The cross-sectional nature of our analysis limited the conclusions we can draw since it is possible that people changed their eating behaviours with age, or with a diagnosis of MetS or other chronic conditions.

Both BMI and cholesterol levels are factors that are closely related to MetS. The results of this study show that breakfast timing and frequency were associated with obesity and high cholesterol cross-sectionally in older adults. This finding is not surprising as previous meal timing and breakfast frequency studies have shown similar results in younger adults, where longer fasting times and unusual eating patterns were associated with an increased risk of obesity and elevated cholesterol levels. The findings of this present study are in contrast with intermittent fasting studies which have shown that participants who fast, which involved skipping breakfast or having later breakfast times, experience modest weight loss and have lower total cholesterol levels (7,105,119,190–192). Conversely, fasting studies also show varying results in how cholesterol levels and body weight are affected by fasting and reduction in cholesterol seem to be related to baseline cholesterol levels and the amount of weight participant loses (7). As intermittent fasting is a relatively new diet trend, it is unlikely that this sample of older adults, whose meal timing and frequency were assessed in 1989 and 1992, would be participating in intermittent fasting limiting the ability to compare the results of these studies with the present study. However, the relationship between

breakfast timing and frequency with MetS factors observed in this study can be used to direct future research in older adults who are metabolically different than children and younger adults, the main population of interest for these studies so far.

5.5 Association Between Breakfast Frequency and MI/CAD

The findings of this study are partially in agreement with two longitudinal studies. A prospective cohort study, by Kubota et al., found that in their sample of Japanese men and women, breakfast skipping was not associated with incident CAD (115). However, Kubota et al. did find that participants who ate breakfast less frequently (0-2 times/week) had a 14% (HR = 1.14 [1.01, 1.27]) increased risk for CVD, which is inclusive of CAD (115). Similarly, a prospective cohort study, by Rong et al., found that skipping breakfast was associated with a 134% (HR = 2.34 [1.44, 3.80]) increased risk for heart disease-specific death in models adjusted for age, sex, and race/ethnicity (172). However, in the fully adjusted model, breakfast skipping was not significantly associated with heart disease-specific mortality (172). In our study of older adults, there was no significant association between not eating breakfast every day and incident MI or CAD, which included mortality associated with MI and CAD. A possible explanation for this finding could be that as breakfast frequency is associated with a cluster of risk factors for CAD in older adults, like age, smoking, poor diet quality, obesity, high cholesterol and MetS, independent of these factors breakfast frequency does not increase the risk for CAD. Survival bias offers another explanation for these findings. It is possible that older adults who survived to participate in this study were already in good health regardless of their exposure status. This would result in an attenuation of the association between breakfast frequency and CAD. Additionally, accounting for stroke as competing risk was a conservative method that could have resulted in the statistical non-

significance observed in the association between breakfast frequency and CAD risk. However, as highlighted in chapter 3, the outcome of interest in this study was new vascular disease (MI/CAD). A participant who experienced a stroke, a vascular disease, is at a higher risk for other CVD events. Applying an exclusion criterion based on incident stroke would have also resulted in bias as these participants are at risk for incident MI/CAD up until they experience a stroke. Therefore, choosing to address stroke as a competing risk, although a conservative method, was more appropriate for adjusting for the event.

Our findings also suggest that men, who do not eat breakfast every day have a lower risk for experiencing a CAD event. Notably, the findings of this present study contrast that of Yokoyama et al. and Cahill et al. who found that in men skipping breakfast was associated with an increased risk for CAD and death from circulatory disease, respectively (193). However, in the study conducted by Cahill et al., they found that skipping breakfast was not associated with CAD risk among men in their sample who were over the age of 60. This finding could be attributed to the low proportion of older men in their study who skipped breakfast (8). Like this present study, Yokoyama et al. found that there was no significant association between breakfast skipping and death from circulatory disease in women (193). This study by Yokoyama et al. was not conducted specifically in older adults. Perhaps in older men, non-daily breakfast consumption leads to overall lower energy intakes which prevents obesity, a cardiometabolic risk factor. This would result in non-daily breakfast consumption having a protective effect against CAD risk as observed in this present study but not in that of Cahill et al. and Yokoyama et al.

A potential explanation for the protective effect against MI/CAD in men who do not eat breakfast every day, but not in women, observed in this study, could be a result of different metabolic and hormonal changes, that accompanies ageing, between men and women. As mentioned previously, non-daily breakfast consumption may be protective against obesity in older men. Some studies show that older women have a healthier diet than older men (194,195); however, over time they still gain more weight than men (195), potentially due to hormonal changes, like menopause, and metabolic differences between men and women (196,197). This could explain why not eating breakfast every day was protective against CAD in men only. In addition, stratified analyses can result in limitations in power to assess a significant result. In this study, there were more women than men; however, the event rate for incident MI and CAD is higher in men than women by 7%. The lack of statistical significance observed between breakfast frequency and MI/CAD risk in women is unlikely to be due to a lack of power but not entirely impossible due to the differences in event rate.

In the present study, baseline MetS was not found to be an effect modifier in the relationship between breakfast timing and frequency and CAD. Breakfast timing and frequency are associated with many factors, like obesity and cholesterol, that are components of MetS (7), which together increase the risk for CVD by 3-fold. Therefore, it is possible that rather than being a modifier, MetS is a mediator in the relationship between breakfast timing and frequency and CAD as biologically it could be on a causal pathway between eating timing/frequency and risk of CAD. In the present study, MetS was adjusted for as a confounder due to its relationship to both breakfast timing and frequency, established in this study. If MetS is on the causal pathway between breakfast timing and frequency and CAD, adjusting for MetS as a confounder may have attenuated the relationship between breakfast

timing and frequency and CAD. More longitudinal studies, with mediation analyses, must be conducted to draw conclusions about how developing MetS influences the relationship between breakfast timing and frequency and long-term risk of CAD.

5.6 Association between Breakfast Timing and MI/CAD

There are no studies that have examined the association between breakfast timing and CAD. In this study, breakfast timing was not associated with an increased or decreased risk for incident MI or CAD in older adults. As highlighted previously, skipping breakfast or irregular mealtimes, have been associated with cardiometabolic risk factors and CAD. It is possible that since the definition of breakfast timing used in this study was not validated that it does not accurately measure the exposure attenuating the association between breakfast timing and CAD. The definition of breakfast timing used in this study was one adapted from a study conducted by Dashti et al., who examined the association between late eating and cardiometabolic risk factors (152). In their study, they divided their participants by the midpoint of their meal intakes, the time between breakfast and dinner, and classified them as early or later eaters. However, Dashti et al. do not clarify how they classified their participants who ate at the median time. In this sample of older adults, 1,184 (29.2%) participants ate breakfast at the median time of 8:00 am, which is within the normal window of a morning meal, and these participants were classified as early eaters. Participants who ate at the median time could have been categorized with the later than the median group or as a separate category altogether. A sensitivity analyses conducted showed that classifying these participants as late breakfast eaters did not change the results (Appendix F). A separate category for participants who ate at the median time was not created because of the requirements of logistic regression to have a binary outcome, and ease of interpretation and

continuity between the logistic regression and Fine-Grey models. Survival bias is, again, another explanation for why the association between breakfast timing and CAD was non-significant. A validated definition for breakfast timing along with more studies examining this association is needed to understand the role breakfast timing plays in its potential relationship with CAD.

5.7 Limitations and Strengths

There are several limitations of this study that warrant further discussion. Firstly, this study is susceptible to survivor bias. Older adults who were eligible for this study may inherently be healthier than participants who may have had CAD or had CAD at baseline but died or were excluded before they could contribute to the analyses. This introduces a potential bias associated with exposed participants regardless of their outcome. Older adults with cardiometabolic risk factors at baseline may have changed their eating timing and frequency upon learning that they had the cardiometabolic risk factors. The cross-sectional nature of some of our analyses would not be able to account for this change in eating habits and it would distort the true relationship between the exposure and outcome. Next, there is no validated definition of breakfast timing and frequency that could have been utilized to accurately classify participants' exposure status increasing the likelihood for misclassification bias. Eating habits were self-reported, introducing errors from recall bias or misclassification errors from potential incorrect interpretations of the questions. The quality of the breakfast eaten could also not be determined which could have affected the relationship between breakfast timing and frequency and risk for CAD. Additionally, because daytime snacking was not assessed by CHS, the total number of eating times per day could not be adjusted for in the analysis. Similarly, because participants' total daily energy intake

was not measured at baseline, it could not be adjusted for in the models and participants could not be excluded based on implausible energy intakes. Participant eating timing and frequency patterns were only assessed at baseline which could have increased the potential for misclassification errors since their eating patterns may have changed over the course of the follow-up time. As a result, time-varying covariates were also not updated, and baseline measurements were used to correlate with exposure measurements. Cancer could not be accounted for as a competing risk, as incident cancer data for participants were not available. This study was also susceptible to confounding through unmeasured factors such as circadian rhythms, stress, inflammation, and sleep patterns. Likewise, the generalizability of the study findings has limitations given that the participants were from small US communities with a low percentage of non-white participants. The results of the present thesis also cannot be generalized to older adults who are experiencing more severe health issues, such as malnutrition.

Despite these limitations, there are several important strengths of this study. The study is novel for its contribution of knowledge of the characteristics, inclusive of prevalent MetS status, of a sample of older adults, based on their breakfast timing and frequency patterns as well as the association between breakfast timing and frequency and risk for CAD in older adults. The CHS dataset includes a large sample size of 5,888 older adults with a long follow-up time of 23 and 26 years for cohorts one and two respectively. The prospective design of objective 2 allowed for the assessment of risk between breakfast timing and frequency and CAD in the presence of competing outcomes, stroke and non-CAD related death. Additionally, we were able to control for a variety of demographic, lifestyle, dietary, and economic variables in our models.

5.8 Study Implications

Skipping breakfast has been repeatedly shown to be associated with various demographic variables, like age, sex, race/ethnicity, marital status, and SES in younger adults, but has not been thoroughly investigated in older adults. The results of this present study show that older adults who do not consume breakfast regularly or who have late breakfast eating times were more likely to be female, identify as a minority, be unmarried, and have low income or low education levels. The results of this study also show that not eating breakfast every day and having later breakfast eating times are associated with lifestyle behaviours and biological factors such as having MetS that are risk factors for CAD. This clustering of cardiometabolic risk factors may have resulted in the non-significant association between breakfast timing and frequency and MI/CAD observed in this sample of older adults. Alone breakfast timing and frequency may not increase the risk for CAD; however, addressing breakfast consumption in older adults may improve other established cardiometabolic risk factors such as malnutrition or poor diet quality, low physical activity levels, and the components of MetS. The demographic characteristics of older adults, identified in this study, could be used to create targeted health promotion treatment or education programs that could encourage participants to adopt healthy lifestyle practices and reduce the risk for CAD.

Overall, the findings of this study indicate the importance of more longitudinal studies that examine breakfast timing and frequency in various populations and sub-populations. The results of the multivariable models show that more studies are needed to be conducted in older adults to understand why breakfast frequency was associated with a lower risk for CAD in men only. Since breakfast timing studies are extremely limited, the results of this study

could be used as a stepping-stone for other studies to examine the association between meal timing and adverse health outcomes.

5.9 Future Research Directions

Several studies have shown that skipping breakfast is a risk factor for CAD; however, as the present study demonstrates, this relationship is still poorly understood within various populations. Breakfast timing and frequency were observed in this study to be associated with other cardiometabolic risk factors in older adults. However, due to the cross-sectional nature of this analyses it's unclear whether breakfast timing and frequency lead to those lifestyle risk factors or vice versa. Future longitudinal studies that examine the relationship between breakfast timing and frequency and cardiometabolic risk factors are needed to elucidate the relationship between these factors. Additionally, key demographic factors like race and SES were found to be associated with breakfast timing and frequency in older adults in this study. These factors may be intertwined with each other, and future studies may consider recruiting participants of various races/ethnicities and SES in rural and urban communities to understand how the relationship between breakfast timing and frequency and CAD risk may vary in marginalized communities.

In older men in this study, non-daily breakfast consumption was associated with a lower risk for MI and CAD. This finding was not found to be the same in older women in this sample. Future studies that examine the association between breakfast frequency and CAD should investigate further how the relationship is modified by sex and gender (a factor unavailable for the present study but certainly a relevant social factor). Furthermore, as the relationship between breakfast timing and frequency with CAD risk was not found to be modified by

MetS, future research might consider it as a mediating factor to understand where MetS may lie on the potential pathway between breakfast consumption and CAD.

More prospective cohort studies analyzing the relationship between breakfast timing and frequency and chronic illnesses, like CAD and MetS, must be conducted to understand how they impact health in older adults. These studies should include repeated measurements for breakfast timing and frequency to control for the change in diet patterns over time. With the rise of popular diet trends, which may involve skipping breakfast, future studies should take into account participants participating in these diets for weight loss or reduction of cardiometabolic risk factors to avoid bias.

5.10 Conclusion

In this prospective cohort study of older adults, non-daily breakfast consumption and late breakfast times were cross-sectionally associated with a cluster of demographic, lifestyle, and metabolic risk factors for CAD. These factors together may increase the risk for CAD or may be mediators in the relationship between breakfast timing and frequency and risk for CAD. The present study did not observe an association between breakfast timing and CAD risk; however, non-daily breakfast consumption was associated with a lower risk for MI and CAD in men only, suggesting that older men and women may be metabolically different and older men may benefit from some sort of fasting pattern. Replicating this study in older adults and other populations, especially marginalized communities, would be beneficial in understanding how potential lifestyle cardiovascular risk factors, like breakfast timing and frequency, can possibly be modified to improve health in older adults.

5.11 Knowledge Translation

This project was presented in poster format during the Department of Medicine Research Week at Dalhousie University. It was also presented as a Three-Minute Thesis at the Department of Community Health and Epidemiology's annual Research Day at Dalhousie University. A manuscript with the major findings of this study will be prepared and submitted to appropriate journals. Results of this study will also be highlighted in a tweetable pictogram

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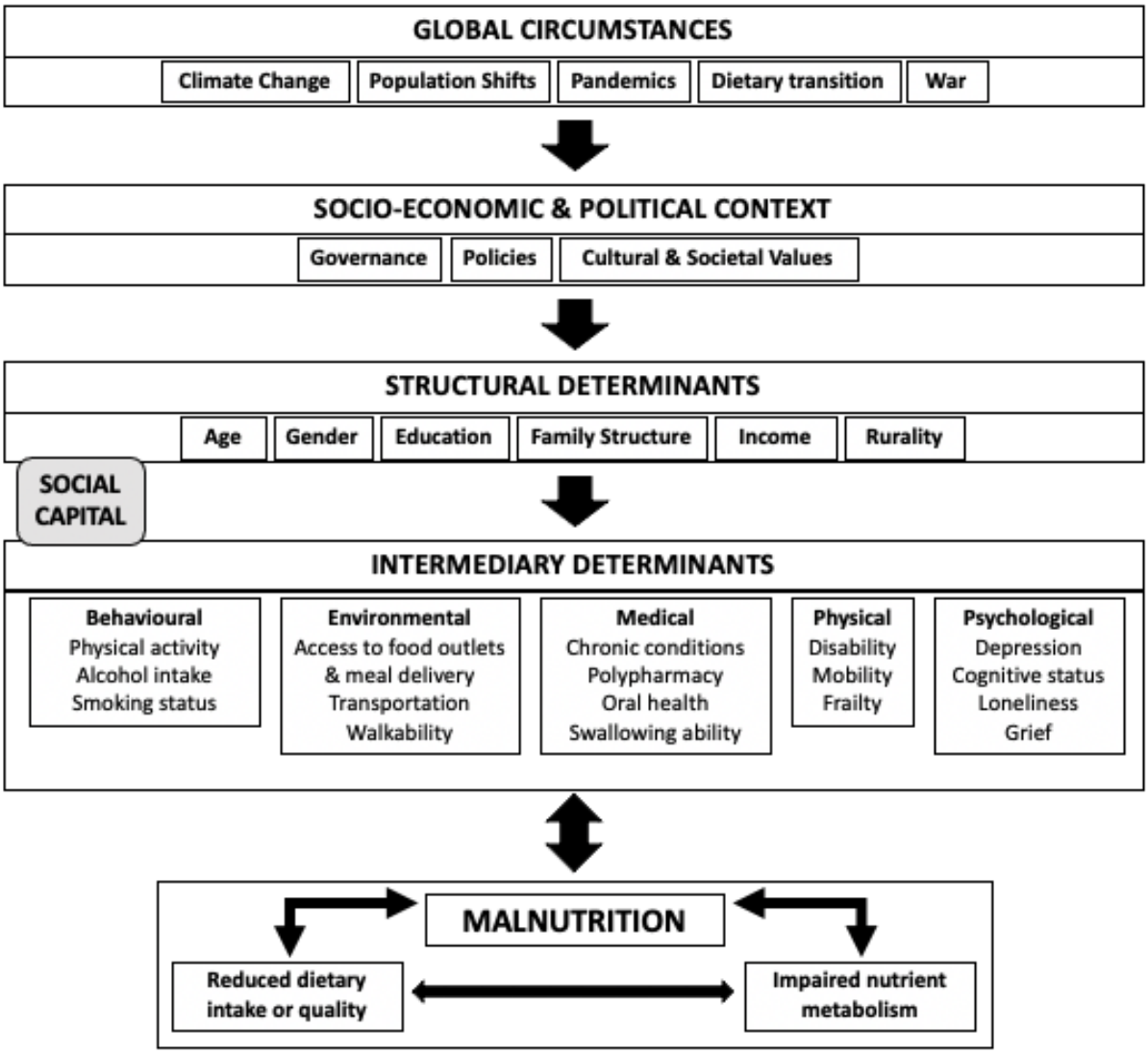
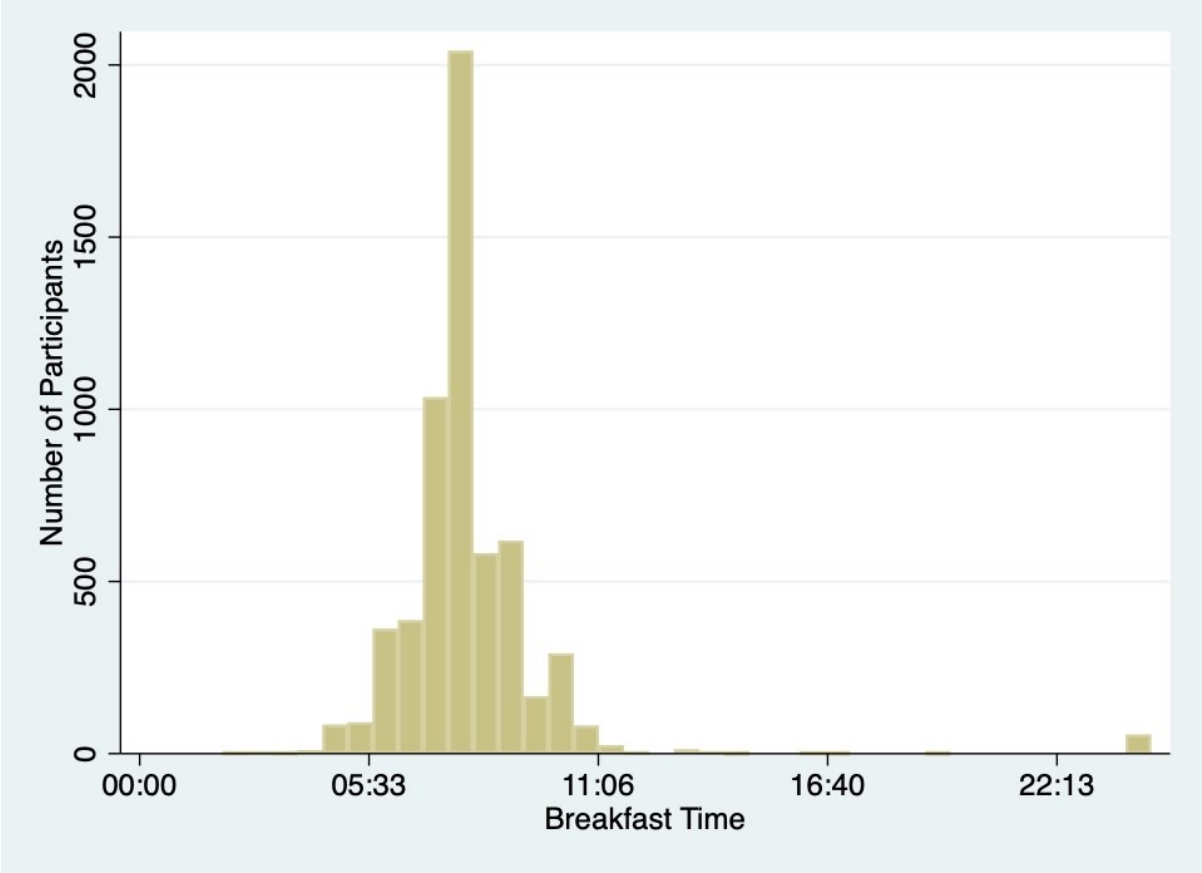
Appendix A

Unmodified Broaden Framework by Emily Rosta



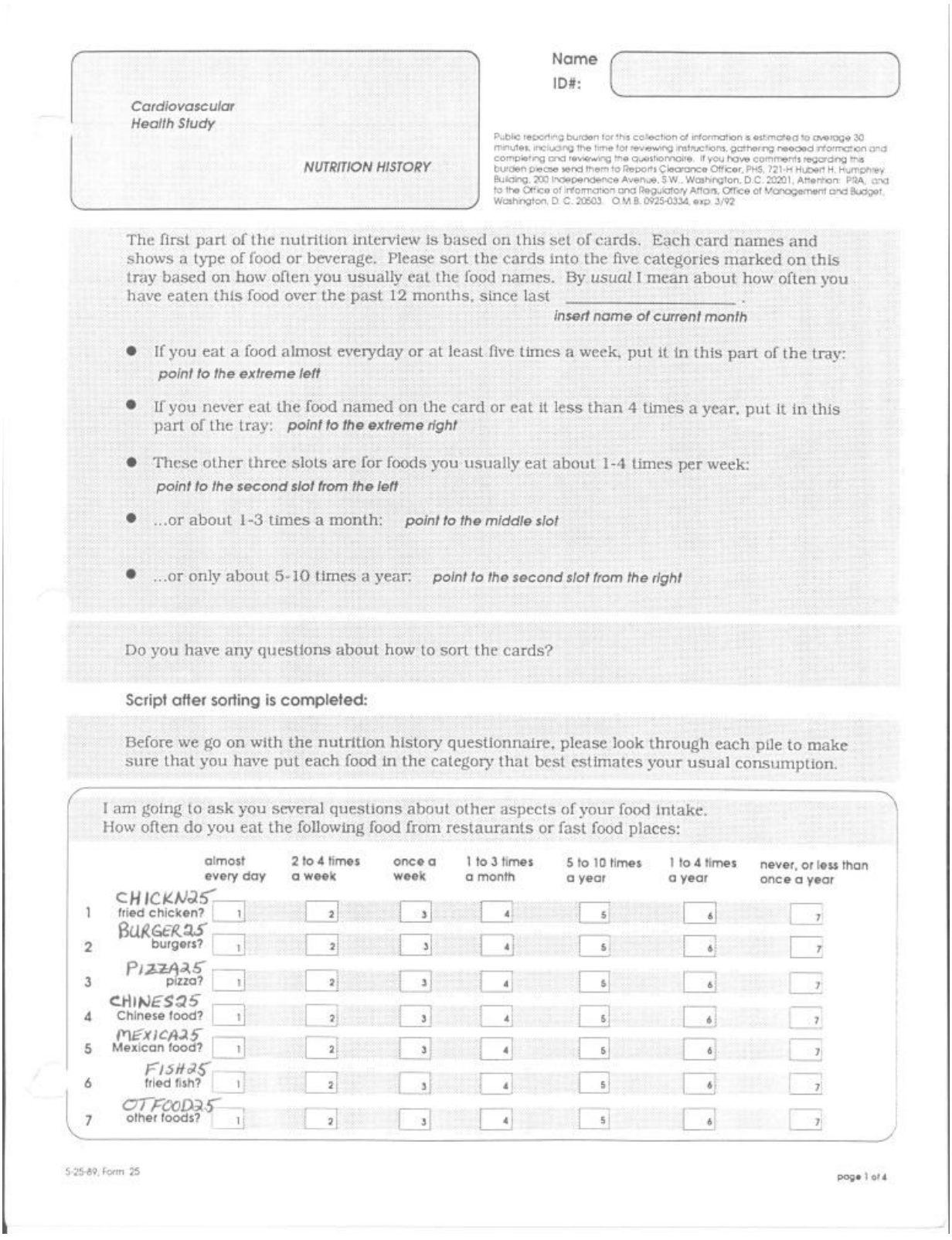
Appendix B

Distribuition of the breakfast timing variable among Cardiovascular Health Study participants prior to applying exclusion criteria and complete case analyses



Appendix C

CHS data collection form: Nutrition



Cardiovascular
Health Study

NUTRITION HISTORY

Name
ID#:

The first part of the nutrition interview is based on this set of cards. Each card names and shows a type of food or beverage. Please sort the cards into the five categories marked on this tray based on how often you usually eat the food names. By *usual* I mean about how often you have eaten this food over the past 12 months, since last _____.
insert name of current month

- If you eat a food almost everyday or at least five times a week, put it in this part of the tray: *point to the extreme left*
- If you never eat the food named on the card or eat it less than 4 times a year, put it in this part of the tray: *point to the extreme right*
- These other three slots are for foods you usually eat about 1-4 times per week: *point to the second slot from the left*
- ...or about 1-3 times a month: *point to the middle slot*
- ...or only about 5-10 times a year: *point to the second slot from the right*

Do you have any questions about how to sort the cards?

Script after sorting is completed:

Before we go on with the nutrition history questionnaire, please look through each pile to make sure that you have put each food in the category that best estimates your usual consumption.

I am going to ask you several questions about other aspects of your food intake.
How often do you eat the following food from restaurants or fast food places:

		almost every day	2 to 4 times a week	once a week	1 to 3 times a month	5 to 10 times a year	1 to 4 times a year	never, or less than once a year
1	CHICKN25 fried chicken?	1	2	3	4	5	6	7
2	BURGER25 burgers?	1	2	3	4	5	6	7
3	PIZZA25 pizza?	1	2	3	4	5	6	7
4	CHINES25 Chinese food?	1	2	3	4	5	6	7
5	MEXICA25 Mexican food?	1	2	3	4	5	6	7
6	FISH25 fried fish?	1	2	3	4	5	6	7
7	OTFOOD25 other foods?	1	2	3	4	5	6	7

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Name
ID#:

8 For about how long have you eaten the way you do now?
years: EATYRS25 if less than 1 year, # months: EATMON25

9 Are you following a special diet? DIET25 yes 1 no: 0
Is your diet: DIETW25
medically prescribed 1
self-imposed 2

10 How often do you eat the skin on chicken? SKIN25
seldom/never 1 sometimes 2 often/always 3

11 How often do you eat the fat on meat? FAT25
seldom/never 1 sometimes 2 often/always 3

How often do you use the following items in modified or specially packed form?

12 low- or reduced-sodium canned vegetables or soups: VEG25
seldom/never 1 sometimes 2 often/always 3

13 juice-pack or low-sugar canned fruits: FRUIT25
seldom/never 1 sometimes 2 often/always 3

14 low-salt bread or cereal products: BREADS25
seldom/never 1 sometimes 2 often/always 3

15 low-calorie bread: BREADC25
seldom/never 1 sometimes 2 often/always 3

16 low-calorie salad dressing: SALAD25
seldom/never 1 sometimes 2 often/always 3

17 reduced-sodium lunch meat or cold cuts: MEATR25
seldom/never 1 sometimes 2 often/always 3

18 low-fat lunch meat or cold cuts: MEATL25
seldom/never 1 sometimes 2 often/always 3

19 low-sodium or low-calorie frozen entrees or dinner: ENTREE25
seldom/never 1 sometimes 2 often/always 3

20 How often do you add salt to your food? SALT25
seldom/never 1 sometimes 2 often/always 3

21 What type of salt do you use? SLTTYP25
brand name/type: [redacted]
(sodium chloride, potassium chloride, or other salt substitutes)

Not correct - see schema

22 Is it plain or iodized salt? PLAIN25
iodized 1 not iodized 0 don't know 9

23 How often do you use fat or oil in cooking? For example, in frying eggs, meat or vegetables?
#times FATN25 per: day 1 week 2 mo 3 never 0
FATR25

24 What kind of fat or oil do you usually cook with? FATCK125 FATCK225
check 1 or 2
soft margarine 1
stick margarine 2
butter 3
liquid oil 4
lard, fatback bacon fat 5
Pam or no oil 6
don't know or don't cook 9

25 What kind of fat or oil do you usually add to vegetables, potatoes, etc.?
check 1 or 2
soft margarine 1
stick margarine 2
butter 3
half butter/half margarine 4
lard, fatback bacon fat 5
FATAD125 don't add fat 6
FATAD225 don't know 9

26 If you eat cold cereal, what kind do you eat most often? Interviewer: card 16 CEREAL25
don't eat cold cereal 000
cereal code (record code of response or of a similar cereal; other = 999):

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Name
ID#:

27 About how many servings of vegetables do you eat per day or week, not counting salad or potatoes?

#vegetables VEGF25 per: day 1 week 2 never 0

VEGT25

28 How many fruits do you usually eat per day or per week, not counting juices?

FRUITF25 # fruits: per: day 1 week 2 never 0

FRUITT25

29 How often do you eat breakfast?

every day 1 BRKAST25 rarely 3
some days 2 weekends only 4
never 0

30 On Monday through Friday about what time do you usually first eat or drink something after waking up?

EATFTH25 : EATFTM25 AMPMF25
time: am 1 pm 2

31 On Monday through Friday about what time do you usually last eat or drink something before going to bed?

EATLTH25 : EATLTM25 AMPML25
time: am 1 pm 2

32 On Monday through Friday how many meals do you usually eat per day? MEALN25

meals: don't know 9

33 On Monday through Friday how many snacks do you usually eat after dinner? SNACKN25

meals: don't know 9

The next questions are about drinking alcoholic beverages. First I will ask you separately about beer, wine and liquor:

34 Do you ever drink beer? yes 1 no 0

BEER25

35 About how often do you drink beer?

daily 1 yearly 4
weekly 2 rarely/never 9
monthly 3 BEERF25

36 How many 12 ounce cans or bottles of beer do you usually drink on one occasion?

cans or bottles: BEERN25

37 Do you ever drink wine? yes 1 no 0

WINE25

38 About how often do you drink wine?

daily 1 yearly 4
weekly 2 rarely/never 9
monthly 3 WINEF25

39 How many medium, 6 ounce, glasses of wine do you usually drink on one occasion?

servings: WINEN25

40 Do you ever drink liquor? yes 1 no 0

LIQUOR25

41 About how often do you drink liquor?

daily 1 yearly 4
weekly 2 rarely/never 9
monthly 3 LIQUOF25

42 How many drinks, equal to 1 shot of liquor, do you usually drink on one occasion?

servings:

LIQUON25

43 Have you changed your pattern of beer, wine, or liquor consumption during the past 5 years?

PATTEN25 yes 1 no 0 don't know 9

44 Was there ever a time in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day? ALC525

yes 1 no 0 don't know 9

45 How many periods of time during your life did you drink 5 or more alcoholic beverages almost every day?

ALCP525

periods: don't know 99

46 For how long altogether did these periods of time last?

#: days 1 weeks 2 months 3 years 4

ALCLN525

ALCL4525

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page 3 of 4

Name
ID#:

almost every day	1-4 times per week	1-3 times per month	5-10 times per year	never

Interview						First Edit		Second Edit			
Interviewer		month		day	year	hour	: min	month	day	hour	: min

5-25-89, Form 25

Appendix D

CHS Cardiac Events Criteria

1. Myocardial Infarction

Myocardial Infarction is defined as the death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombosis, or the rupture of a plaque. The CHS algorithm for classifying myocardial infarction includes elements of the medical history, results of the enzyme determinations, and electrocardiogram readings.

For classification as definite myocardial infarction the participant must have ONE of the following:

- An evolving diagnostic ECG pattern
- A diagnostic ECG pattern and abnormal enzymes
- Cardiac pain and abnormal enzymes and either an evolving ST-T pattern or an equivocal ECG pattern.

Definition of terms used in these criteria and the criteria for probable and suspected myocardial infarction are found in the CHS Algorithm to Classify Cardiac Enzymes and CHS Diagnostic Criteria for MI. The CHS definition of myocardial infarction includes events which occurred during surgery. The final classification of myocardial infarction is made by the Morbidity Subgroup of the Events Subcommittee based on satisfaction of the appropriate algorithm.

1a. Recurrent MI

Recurrent MIs are adjudicated if the participant was at risk for MI at enrollment into the study.

2. Angina Pectoris

Angina pectoris is defined as symptoms, such as chest pain, chest tightness, or shortness of breath, produced by myocardial ischemia that do not result in infarction. The symptoms generally last less than 20 minutes.

CHS criteria for angina required that the participant must have ALL of the following:

- Report of symptoms, such as chest pain, chest tightness, or shortness of breath
- The diagnosis of angina from a physician, and
- Be under medical treatment for angina
- Medical treatment for angina includes a current prescription for any of the following medicines:
    - nitroglycerine (oral or sublingual), or
    - beta blocker, or
    - calcium channel blocker

In addition, any of the following criteria (adopted from the Nurses' Health Study) are sufficient but not necessary to confirm an angina pectoris diagnosis IF the participant has report symptoms such as chest pain, chest tightness or shortness of breath:

- Coronary – artery bypass graft surgery or angioplasty, or
- Coronary angiography showing more than 70% obstruction of any coronary artery, or
- ST-depression of more than 1 mm on exercise stress testing together with a positive response to the Rose questionnaire.

The final classification of angina is made by the Morbidity Subgroup of the Events Subcommittee based on the satisfaction of the appropriate algorithm.

Special Consideration for adjudication of HCFA (CMS) events:

For some evens discovered through review of HCFA (CMS) data, the only information available is the ICD9-CM codes. It was agreed at the September 1997 subcommittee meeting that the results should be as follows:

Code 414:	Not Angina
Code 411:	Probable Angina, HCFA data only
Code 413:	Probable Angina, HCFA data only

3. Congestive Heart Failure

Congestive heart failure is defined as a constellation of symptoms (such as shortness of breath, fatigue, orthopnea, and paroxysmal nocturnal dyspnea) and physical signs (such as edema, rales, tachycardia, a gallop rhythm, and a displaced PMI) that occur in a participant whose cardiac output cannot match metabolic need despite adequate filling pressure.

CHS criteria for congestive heart failure require that the participant must have BOTH of the following:

- The diagnosis of congestive heart failure from a physician, and
- Be under medical treatment for congestive heart failure.
- Medical treatment is defined as a current prescription for BOTH of the following:
    - a diuretic, and
    - digitalis or a vasodilator (e.g. nitroglycerin, apresoline, or
    - angiotensin converting enzyme [ACE] inhibitor)

In addition, any of the following criteria are sufficient but not necessary to validate a congestive heart failure diagnosis:

- The presence of cardiomegaly and pulmonary edema on chest X-ray or
- Evidence of a dilated ventricle and global or segmental wall-motion abnormalities with decreased systolic function either by echocardiography or contrast ventriculography.

The final classification of congestive heart failure is made by the Morbidity Subgroup of the Events Subcommittee based on the satisfaction of the appropriate algorithm. The Events

Subcommittee further classifies the congestive heart failure as biventricular (predominantly left or right heart failure.)

As of September 2005, CHS is also gathering information on Ejection Fraction (EF), Aortic Stenosis (AS), Aortic Regurgitation (AR) and Mitral Regurgitation (MR) , the basic goal being to minimize confounding of CHF from muscle disease with valvular CHF. Guidelines are below:

- For Ejection Fraction, the value or range from Echo data that is found in the records is recorded. If the actual value of EF is not given, the categorical value is recorded, if given. (Normal, borderline, moderately decreased, or severely decreased)
- AS, AR, and MR is classified as mild, mild to moderate, moderate, moderate to severe, or severe on the basis of Echo or other imaging study. If the Echo report describes grade 1 – it is classified as mild, grade 2 - moderate, grade 3 or 4- severe. Anything defined as 'significant' is classified as 'moderate'. Anything defined as 'trace' or 'trivial' is classified as 'mild'.
- If there is a discrepancy between the echo results and the echo dictation, the dictation conclusion is taken as the final decision.
- If Echo is not available for an incident event, data from the closest future Echo from a recurrent event may be entered for the incident event.
- If multiple Echo reports are available within a hospitalization, the Echo with the "worst" values is used. (The lowest EF, and/or the highest number values for valve regurgitation and stenosis.)
- In the event that no Echo is available, EF, AR, MR, and AS data may be captured from a Heart Catheterization or MUGA (Multiple Gated Acquisition scan) instead. If multiple reports are available, such as a Catheterization and an Echo, the Echo is the first choice for this information.

4.Claudication

Intermittent claudication is defined as leg pain, usually exertional, produced by ischemia from peripheral vascular disease. The CHS criteria for claudication rely on the history, the ratio of the ankle-arm blood pressures, and physician diagnosis.

CHS criteria for claudication require that the participant must meet the following:

- Exertional leg pain relieved by rest and ONE of the following:
    - Physician diagnosis of claudication or
    - Ankle-Arm blood pressure ratio of less than or equal to 0.8

In addition, any of the following criteria are considered sufficient but not necessary to validate a claudication diagnosis:

- Doppler-ultrasound showing an obstruction of at least 75% of the cross-sectional area of the artery or showing an ulcerated plaque, or
- Angiography showing an obstruction of 50% of the diameter or 75% of the cross-sectional area of the artery or ulcerated plaque, or
- Absence of a Doppler pulse in any major vessel, or
- Positive exercise test for claudication, or

- Bypass surgery, angioplasty, or thrombolysis for peripheral vascular disease.
- The final classification of claudication is made by the Morbidity Subgroup of the Events Subcommittee based on satisfaction of the appropriate algorithm.

Appendix E

Table A-1. Multivariable model[1] for the association between breakfast frequency and incident myocardial infarction and coronary artery disease with Cardiovascular Health Study partcipants with missing data for income was categorized as missing

	Myocardial Infarction		Coronary Artery Disease[2]	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	**P-Value**	**Subdistribution Hazard Ratio (aSHR) [95% CI]**	**P-Value**
Non-Daily Breakfast Eaters	0.89 [0.72, 1.10]	0.28	0.89 [0.76, 1.03]	0.12
Female Sex	0.55 [0.47, 0.65]	< 0.0001	0.62 [0.56, 0.70]	< 0.0001
Minority Ethnic Group	0.81 [0.65, 1.00]	0.05	0.97 [0.83, 1.12]	0.66
Not Currently Married	1.30 [1.09, 1.54]	0.003	1.18 [1.04, 1.33]	0.01
Education				
Less than High School	1.18 [0.97, 1.44]	0.11	1.10 [0.97, 1.27]	0.18
High School/GED	1.00 [Ref]		1.00 [Ref]	
More than High School	1.08 [0.90, 1.30]	0.42	1.00 [0.88, 1.14]	0.99
Income				
<$25,000	1.00 [0.82, 1.22]	0.99	1.07 [0.92, 1.22]	0.40
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.13 [0.89, 1.43]	0.32	1.05 [0.88, 1.25]	0.61
Missing	1.19 [0.87, 1.43]	0.27	0.90 [0.71, 1.15]	0.39
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.90 [0.71, 1.14]	0.37	0.86 [0.72, 1.02]	0.08
Former Smoker	1.03 [0.88, 1.21]	0.67	1.01 [0.89, 1.12]	0.87
≥ 3 Fruit &Vegetable Servings per Day	0.87 [0.72, 1.06]	0.17	0.98 [0.85, 1.12]	0.72
Cholesterol (mg/dl)				
Desirable (< 200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.07 [0.91, 1.27]	0.40	1.03 [0.92, 1.16]	0.59
High (≥ 240)	1.07 [0.88, 1.31]	0.51	1.09 [0.95, 1.26]	0.21

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent MetS	1.25 [1.08, 1.45]	0.003	1.36 [1.22, 1.50]	< 0.0001

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction,

[1]Model is adjusted for sex, race, marital status, education, income, smoking, fruit and vegetable intake, cholesterol levels, and prevalent MetS status at baseline

[2]CAD composes of non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD

Table A-2. Multivariable model[1] for the association between breakfast timing[2] and incident myocardial infarction and coronary artery disease with Cardiovascular Health Study partcipants with missing data for income was categorized as missing

	Myocardial Infarction		Coronary Artery Disease[3]	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	**P-Value**	**Subdistribution Hazard Ratio (aSHR) [95% CI]**	**P-Value**
Later than Median Breakfast Eaters	0.95 [0.80, 1.12]	0.52	1.03 [0.92, 1.16]	0.56
Female Sex	0.56 [0.47, 0.66]	< 0.0001	0.62 [0.55, 0.70]	< 0.0001
Minority Ethnic Group	0.83 [0.66, 1.04]	0.10	0.96 [0.82, 1.12]	0.61
Family History of MI	1.00 [0.90, 1.11]	0.99	1.07 [0.99, 1.16]	0.07
Not Currently Married	1.31 [1.10, 1.55]	0.003	1.16 [1.03, 1.32]	0.02
High Depression Score (≥10)	0.87 [0.68, 1.12]	0.28	1.06 [0.90, 1.26]	0.46
Income				
<$25,000	1.03 [0.85, 1.25]	0.73	1.09 [0.95, 1.24]	0.22
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.12 [0.89, 1.43]	0.33	1.04 [0.87, 1.24]	0.67
Missing	1.19 [0.88, 1.64]	0.25	0.89 [0.70, 1.14]	0.36
Moderate-High Physical Activity	1.04 [0.89, 1.20]	0.65	0.99 [0.89, 1.11]	0.97
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.92 [0.72, 1.17]	0.48	0.86 [0.72, 1.02]	0.08
Former Smoker	1.04 [0.89, 1.22]	0.63	1.00 [0.89, 1.12]	0.93
≥ 3 Fruit &Vegetable Servings per Day	0.85 [0.70, 1.04]	0.12	0.96 [0.84, 1.10]	0.56
≥ 3 Meals per Day	1.12 [0.94, 1.33]	0.20	1.11 [0.99, 1.25]	0.09
No Snacks After Dinner	0.97 [0.83, 1.13]	0.70	0.98 [0.88, 1.09]	0.74
Cholesterol (mg/dl)				
Desirable (<200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.09 [0.93, 1.29]	0.29	1.05 [0.93, 1.18]	0.41
High (≥240)	1.09 [0.89, 1.33]	0.41	1.11 [0.96, 1.28]	0.16

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent Diabetes	1.26 [1.02, 1.56]	0.03	1.28 [1.10, 1.49]	0.001
Prevalent MetS	1.20 [1.02, 1.41]	0.02	1.29 [1.15, 1.44]	< 0.0001

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction

[1]Model is adjusted for sex, race, family history of MI, marital status, depression score, physical activity, smoking status, fruit and vegetable intake, meal frequency, snacking after dinner, cholesterol levels, and prevalent diabetes and MetS status at baseline

[2] Breakfast timing was defined as earlier than or later than the median based on the median time that all CHS participants reported eating in the morning

[3] CAD composes of non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD

Table A-3. Multivariable model[1] for the association between breakfast frequency and incident myocardial infarction stratified by sex with Cardiovascular Health Study partcipants with missing data for income was categorized as missing

	Myocardial Infarction			
	Male		Female	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Non-Daily Breakfast Eaters	0.67 [0.47, 0.95]	0.03	1.11 [0.85, 1.46]	0.43
Minority Ethnic Group	0.86 [0.62, 1.18]	0.34	0.78 [0.58, 1.06]	0.11
Not Currently Married	1.20 [0.89, 1.62]	0.22	1.35 [1.08, 1.68]	0.01
Education				
Less than High School	1.06 [0.79, 1.43]	0.70	1.28 [0.98, 1.68]	0.07
High School/GED	1.00 [Ref]		1.00 [Ref]	
More than High School	1.01 [0.77, 1.33]	0.95	1.15 [0.89, 1.48]	0.30
Income				
<$25,000	1.11 [0.83, 1.46]	0.48	0.88 [0.66, 1.16]	0.36
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.30 [0.95, 1.78]	0.10	0.91 [0.63, 1.32]	0.61
Missing	1.53 [0.96, 2.44]	0.07	0.96 [0.63, 1.46]	0.85
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.88 [0.61, 1.27]	0.50	0.89 [0.64, 1.22]	0.46
Former Smoker	1.05 [0.84, 1.32]	0.65	1.01 [0.81, 1.27]	0.90
≥ 3 Fruit &Vegetable Servings per Day	0.81 [0.60, 1.10]	0.19	0.95 [0.73, 1.22]	0.67
Cholesterol (mg/dl)				
Desirable (<200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.05 [0.84, 1.31]	0.68	1.12 [0.87, 1.44]	0.37
High (≥240)	0.89 [0.63, 1.27]	0.53	1.19 [0.91, 1.55]	0.20

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent MetS	1.16 [0.94, 1.44]	0.17	1.36 [1.11, 1.66]	0.003

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction

[1]Model is adjusted for sex, race, marital status, education, income, smoking, fruit and vegetable intake, cholesterol levels, and prevalent MetS status at baseline

P-value = 0.058

Table A-4. Multivariable model[1] for the association between breakfast frequency and incident coronary artery disease stratified by sex with Cardiovascular Health Study partcipants with missing data for income was categorized as missing

	Coronary Artery Disease[2]			
	Male		Female	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Non-Daily Breakfast Eaters	0.71 [0.55, 0.92]	0.01	1.04 [0.87, 1.26]	0.65
Minority Ethnic Group	0.97 [0.77, 1.21]	0.76	0.97 [0.80, 1.18]	0.74
Not Currently Married	1.20 [0.97, 1.49]	0.10	1.17 [1.00, 1.36]	0.05
Education				
Less than High School	1.06 [0.85, 1.32]	0.61	1.13 [0.94, 1.36]	0.19
High School/GED	1.00 [Ref]		1.00 [Ref]	
More than High School	0.94 [0.77, 1.16]	0.57	1.05 [0.89, 1.25]	0.55
Income				
<$25,000	1.09 [0.90, 1.33]	0.37	1.02 [0.84, 1.23]	0.86
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.13 [0.89, 1.45]	0.31	0.94 [0.73, 1.22]	0.65
Missing	1.11 [0.76, 1.63]	0.58	0.78 [0.57, 1.07]	0.13
Smoking				
Non-Smoker	1.00 [Ref]		1.00 [Ref]	
Current Smoker	0.87 [0.66, 1.14]	0.31	0.84 [0.67, 1.05]	0.12
Former Smoker	1.03 [0.87, 1.22]	0.76	0.99 [0.85, 1.15]	0.90
≥ 3 Fruit &Vegetable Servings per Day	0.86 [0.68, 1.07]	0.18	1.09 [0.91, 1.28]	0.38
Cholesterol (mg/dl)				
Desirable (< 200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.01 [0.85, 1.19]	0.91	1.06 [0.90, 1.26]	0.47
High (≥ 240)	0.99 [0.76, 1.29]	0.95	1.16 [0.97, 1.39]	0.10

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent MetS	1.25 [1.06, 1.47]	0.01	1.45 [1.27, 1.68]	< 0.0001

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction

[1]Model is adjusted for sex, race, family history of MI, marital status, depression score, physical activity, smoking status, fruit and vegetable intake, meal frequency, snacking after dinner, cholesterol levels, and prevalent diabetes and MetS status at baseline

[2] CAD composes of non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD

P-value = 0.036

Appendix F

Table A-5. Multivariable model[1] for the association between breakfast timing[2] and incident myocardial infarction and coronary artery disease with Cardiovascular Health Study participants who ate at the median time classified as late eaters

	Myocardial Infarction		Coronary Artery Disease[3]	
	Subdistribution Hazard Ratio (aSHR) [95% CI]	**P-Value**	**Subdistribution Hazard Ratio (aSHR) [95% CI]**	**P-Value**
Later than Median Breakfast Eaters	0.92 [0.79, 1.07]	0.30	0.95 [0.87, 1.06]	0.40
Female Sex	0.56 [0.48, 0.67]	< 0.0001	0.63 [0.56, 0.72]	< 0.0001
Minority Ethnic Group	0.81 [0.63, 1.02]	0.08	0.97 [0.83, 1.14]	0.72
Family History of MI	1.01 [0.90, 1.13]	0.85	1.08 [1.00, 1.17]	0.05
Not Currently Married	1.29 [1.08, 1.55]	0.01	1.14 [1.00, 1.29]	0.05
High Depression Score (≥10)	0.87 [0.67, 1.13]	0.29	1.06 [0.89, 1.25]	0.53
Income				
<$25,000	1.03 [0.85, 1.25]	0.75	1.09 [0.96, 1.25]	0.19
$25,000-$49,999	1.00 [Ref]		1.00 [Ref]	
≥$50,000	1.13 [0.89, 1.43]	0.32	1.04 [0.87, 1.24]	0.66
Moderate-High Physical Activity	0.99 [0.84, 1.15]	0.86	0.99 [0.89, 1.11]	0.87
Smoking		0.30		
Non-Smoker	1.00 [Ref]	0.82	1.00 [Ref]	
Current Smoker	0.88 [0.68, 1.12]		0.83 [0.69, 0.99]	0.04
Former Smoker	1.02 [0.87, 1.20]		0.99 [0.88, 1.11]	0.88
≥ 3 Fruit &Vegetable Servings per Day	0.86 [0.70, 1.05]	0.14	0.96 [0.83, 1.10]	0.53
≥ 3 Meals per Day	1.12 [0.94, 1.34]	0.19	1.10 [0.97, 1.24]	0.14
No Snacks After Dinner	0.95 [0.81, 1.11]	0.50	0.98 [0.88, 1.10]	0.81
Cholesterol (mg/dl)				
Desirable (<200)	1.00 [Ref]		1.00 [Ref]	
Borderline High (200-239)	1.10 [0.92, 1.30]	0.29	1.05 [0.93, 1.19]	0.44
High (≥240)	1.09 [0.89, 1.35]	0.40	1.13 [0.97, 1.31]	0.11

	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value	Subdistribution Hazard Ratio (aSHR) [95% CI]	P-Value
Prevalent Diabetes	1.28 [1.03, 1.60]	0.03	1.29 [1.10, 1.51]	0.001
Prevalent MetS	1.20 [1.02, 1.41]	0.03	1.28 [1.14, 1.43]	< 0.0001

aSHR = Adjusted Subdistribution Hazard Ratio, CAD = Coronary Artery Disease, CI= Confidence Interval, MetS = Metabolic Syndrome, MI = Myocardial Infarction

[1]Model is adjusted for sex, race, family history of MI, marital status, depression score, physical activity, smoking status, fruit and vegetable intake, meal frequency, snacking after dinner, cholesterol levels, and prevalent diabetes and MetS status at baseline

[2] Breakfast timing was defined as earlier than or later than the median based on the median time that all CHS participants reported eating in the morning

[3] CAD composes of non-fatal and fatal MI along with CAD-related events/procedures: angina, coronary artery bypass graft (CABG), angioplasty, and/or death due to atherosclerotic CAD