THE SENSE OF SMELL AND CARDIOVASCULAR HEALTH IN OLDER ADULTS

By

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ABSTRACT

Background and objectives: Poor olfaction is common but underrecognized in older adults. This sensory deficit has broader health implications beyond being a prodromal symptom of neurodegeneration. Although biologically plausible, its cardiovascular health implications are unclear. Therefore, we aimed to investigate the associations of poor olfaction with incident stroke, coronary heart disease (CHD), and heart failure (HF), as well as subclinical cardiac biomarkers, by using two well-established community-dwelling cohorts of older adults in the US.

Methods: In the Health Aging, and Body Composition (Health ABC) Study, we analysed data of 2,537 participants (aged 75.6±2.8 years) who completed a 12-item Brief-Smell Identification Test in 1999-2000. We defined good olfaction as a test score of 11-12, moderate olfaction as 9-10, and poor olfaction as ≤8. We followed at-risk participants from baseline until the date of the first cardiovascular outcome of interest, death, last contact, or the end of the 12-year follow-up, whichever occured first. We used the cause-specific Cox regression to estimate the associations of olfaction with incident stroke, CHD, and HF, respectively. Further, we leveraged data from the Atherosclerosis Risk in Community (ARIC) Study which was designed for cardiovascular health research to independently investigate the associations of olfaction with risks of stroke, CHD, and HF. Olfaction was assessed using the 12-item Sniffin' Sticks odor identification test in 2011-2013 and defined categorically the same as in the Health ABC Study. We followed at-risk participants to the date of the first cardiovascular event of interest, death, last contact, or December 31, 2020, whichever came first. We used the discrete-time sub-distribution hazard model to estimate the marginal absolute risk of each outcome of interest across olfactory statuses and adjusted risk ratios (aRRs), accounting for competing risk of death and covariates. The cross-sectional associations of olfaction with subclinical HF markers were estimated using the quantile regression for N-terminal

pro-B-type natriuretic peptides (NT-proBNP) and high-sensitive cardiac troponin T (hs-cTnT) and using the logistic regression for electrocardiography-defined structural heart disease.

Results: In the Health ABC Study, we identified 353 incident CHD, 258 strokes, and 477 HF events during up to 12 years of follow-up. Poor olfaction was significantly associated with HF, but not with CHD or stroke. In the ARIC Study, among 5,799 participants who were free of stroke at baseline, we identified 332 incident stroke events (256 ischemic) during up to 9.6 years of follow-up. Compared with good olfaction, poor olfaction was robustly associated with higher stroke risk throughout the follow-up, albeit the association was modestly attenuated after 6 years. Among 5,142 participants free of CHD at baseline, we identified 280 incident CHD events during up to 9.6 years of follow-up. Poor olfaction was associated with a higher CHD risk during the first 6 years of follow-up, but not beyond. Among 5,217 participants without clinical HF at baseline, we identified 622 incident HF hospitalizations during up to 9.6 years of follow-up, including 212 HF with reduced ejection fraction (HFrEF), 250 HF with preserved EF, and 160 with unknown left ventricular EF. Compared with good olfaction, poor olfaction was associated with a modestly higher risk of HF for 8 years. The association was largely limited to HFrEF. Participants with poor olfaction had higher median levels of NT-proBNP and hs-cTnT, and higher odds of structural heart disease than those with good olfaction.

Conclusions: Among community-based older adults in the US, we found preliminary evidence that poor olfaction assessed by a single smell test is associated with the risk of major adverse cardiovascular outcomes. The data from both cohorts are consistent for HF, supported by subclinical HF biomarkers. However, associations of olfaction with stroke and CHD were observed only in the ARIC Study. We suggest future studies be conducted to confirm our findings and investigate the underlying mechanisms.

To my family ─ especially my parents ─ for believing in my potential and supporting me unconditionally

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

3MS: Modified Mini-Mental State examination

APOE: Apolipoprotein E

ARIC Study: The Atherosclerosis Risk in Community Study

BMI: body mass index

B-SIT: Brief-Smell Identification Test

CHD: coronary heart disease

CHF: congestive heart failure

CIF: cumulative incidence function

CI: confidence interval

CVD: cardiovascular disease

DAG: directed acyclic graph

ECG: electrocardiogram

eGFR: estimated glomerular filtration rate

Health ABC Study: The Health Aging, and Body Composition Study

HDL-C: high-density lipoprotein-cholesterol

HF: heart failure

HFmrEF: heart failure with mildly reduced ejection fraction

HFpEF: heart failure with preserved ejection fraction

HR: hazard ratio

HFrEF: heart failure with reduced ejection fraction

hs-cTnT: high-sensitive cardiac troponin T

ICD-CM: International Classification of Disease Clinical Modification

IPW: inverse probability weighting

LV: left ventricular

LVEF: left ventricular ejection fraction

MI: myocardial infraction

NT-proBNP: N-terminal pro-B-type natriuretic peptides

OR: odds ratio

RD: risk difference

RR: risk ratio

SS: Sniffin’ Sticks

CHAPTER 1: INTRODUCTION

1.1 Dissertation Overview

Poor olfaction is common but often goes unnoticed in older adults. This sensory deficit is one of the most important prodromal symptoms of neurodegenerative diseases. Interestingly, emerging evidence has shown that poor olfaction robustly predicts all-cause mortality in older adults, but only a small portion of excess deaths related to poor olfaction can be attributed to dementia or Parkinson's disease, suggesting that poor olfaction may have profound health implications beyond neurodegeneration. Cardiovascular disease, a group of heterogeneous adverse health conditions, represents a substantial public health burden and ranks as the leading cause of death. Given the potential structural and functional connections between olfaction and the cardiovascular system, poor olfaction may signify future adverse cardiovascular outcomes. On the one hand, poor olfaction in late life may be a sensitive marker of impaired cardiovascular health, like the "canary in the coal mine". On the other hand, poor olfaction may contribute to the deterioration of cardiovascular health. Either as an early marker or a contributor, poor olfaction may signify future adverse cardiovascular events in the older population. However, empirical evidence on whether olfaction signifies cardiovascular health in older adults so far has been sparse.

Leveraging two well-established community-based cohorts of older adults in the US, the overall objective of this project was to evaluate the associations of olfactory status with incident stroke, coronary heart disease (CHD), and heart failure (HF), as well as with established subclinical cardiac biomarkers.

This project will provide empirical evidence on the under-investigated links between olfaction and incident major adverse cardiovascular outcomes in the context of aging, filling a critical knowledge gap. Further, it will potentially identify a novel and easy-to-assess biomarker

to monitor impaired cardiovascular health in older adults, potentially promoting early prevention and reducing cardiovascular-related morbidity and mortality. In addition, this work may inspire new research areas to study cardiovascular health through this sensory loss, eventually deepening our understanding and advancing geriatric care in cardiovascular health. Given that both poor olfaction and cardiovascular outcomes are common among older adults, the findings may potentially have significant public health implications.

1.2 Dissertation Organization

This dissertation has been organized into eight chapters. Chapter 1 provides an overview of this dissertation project. Chapter 2 describes the background of poor olfaction, the three types of major adverse cardiovascular outcomes (including stroke, CHD, and HF), and their potential biological connections. Chapter 3 presents the overall methodology. Chapter 4 focuses on the first publication[1], regarding the association of poor olfaction with incident stroke, CHD, and congestive heart failure (CHF) in the Health Aging, and Body Composition (Health ABC) Study. Chapter 5-7 each represents a separate manuscript, focusing on poor olfaction in relation to risk of incident stroke, coronary heart disease, and heart failure, respectively, using data from the Atherosclerosis Risk in Community (ARIC) Study. Chapter 8 summarizes this project's overall findings, limitations, future directions, and conclusions.

CHAPTER 2: BACKGROUND

Poor olfaction affects over a quarter of older adults and its prevalence rapidly increases with age[2,3]. This sensory loss is best known as an early symptom of neurodegenerative diseases[4]. Accumulating empirical data have shown that poor olfaction is robustly associated with higher all-cause mortality in older adults[5]. Major cardiovascular disease is the leading cause of mortality, morbidity, and disability in older adults[6]. Despite wide speculations of the connections between olfaction and cardiovascular health, there is limited empirical evidence regarding cardiovascular health implications of poor olfaction in older adults. In this chapter, we will introduce each of these health phenotypes and discuss the biological plausibility of their connections and existing evidence regarding olfaction and cardiovascular health in older adults.

2.1 Olfaction

Olfaction, also known as sense of smell, is an old sense in evolution. Human being has the comparable olfactory neuron number to rodents[7] and can distinguish around one trillion different odor combinations[8]. The sense of smell may play a crucial role in the human well-being, supported by an increasing body of literature. In this section, we will detail our current understanding of olfaction by structuring this sub-chapter into the following 5 parts: Olfactory system; Olfactory dysfunction; Assessment techniques; Epidemiology; and Causes and health implications.

2.1.1 Olfactory System

The olfactory system has sophisticated structures to support odor detection, signal processing, and smell-related cognitive functions. Peripheral olfactory structures start from the back of the nasal cavity with odorant-binding mucus covering the olfactory epithelium[9]. The olfactory epithelium consists of olfactory receptor cells, sustentacular (supporting) cells, basal cells (multipotent stem cells), and duct cells of the Bowman's glands[10]. Bundles of olfactory receptor axons constitute

Cranial Nerve I, projecting to the olfactory bulb located on the cribriform plate. The interneurons in the olfactory bulb further project to the anterior olfactory nucleus connecting to ventral tenia tecta, anterior hippocampal continuation, and indusium griseum[11]. Neurons in the pathway further rapidly projects to olfactory tubercle, piriform cortices, amygdaloid nuclei, and entorhinal cortex. The olfactory bulb is also indirectly linked to orbitofrontal cortex and other cortices via the olfactory-related feedback from entorhinal cortex[12,13]. The hippocampus, amygdala, and orbitofrontal cortex controls one's memory, emotion, and personality & behavior respectively[14–16]. As a result, olfactory function is anatomically and functionally related to higher-order brain functions.

Other supportive systems, such as the circulatory system, are also crucial for normal olfactory function. The epithelium of the nasal cavity has rich capillaries that warm and humidify the incoming air while providing protection against various pathogens[9]. The blood supply of the olfactory epithelium and the olfactory bulb comes from the olfactory artery and the accessory olfactory artery[17]. The olfactory artery, which may have up to three terminal branches, originates directly from the anterior cerebral artery, a branch of the internal carotid artery. The accessory olfactory artery is also called the posterior ethmoidal artery, which converges with the anterior ethmoidal artery on the cribriform plate. All these arteries are the end vessels and do not anastomose with other vascular territories, thus these arteries' narrowing and occlusion may lead to abnormality of olfactory function. The anterior and middle cerebral arteries supply blood to the orbitofrontal cortex and hippocampus[18], while the anterior choroidal artery, branching from internal carotid artery, supplies blood to the amygdala[19]. The impaired blood perfusion in any structure along the olfactory pathway may lead to a decline or loss in olfactory function.

2.1.2 Olfactory Dysfunction

Olfactory dysfunction can be defined using different criteria[20]. Based on whether the olfactory abnormality involves the strength or the quality of the odor, it can be classified as quantitative or qualitative olfactory dysfunction. Olfactory dysfunction can also be categorized according to its pathological location, for example, whether the abnormal function is attributed to blockage of an airway, or to the impairment of neuroepithelium or central neural loci. Although the potential causes of olfactory dysfunction are various and largely unknown, it is not uncommon to classify olfactory dysfunction according to the underlying etiology. **Table 2.1** lists the detailed categories of olfactory dysfunction following different classification criteria.

Table 2.1 Types of olfactory dysfunction based on different criteria

Terminology	**Definitions**
Dysfunction type	
Hyposmia	Quantitatively declined smell ability
Anosmia	Quantitatively complete loss of smell
Hyperosmia	Quantitatively increased smell ability
Parosmia	Distorted perception of the odor
Phantosmia	Perceiving an odor in the absence of a stimulus
Pathological location	
Conductive dysfunction	Blockage of the airway to inhibiting the transmission of the odors
Sensorineural dysfunction	Damage of olfactory epithelium or olfactory nerve
Central dysfunction	Damage of the key processing central nervous regions
Etiology	
Olfactory dysfunction due to sinonasal disease	Some sinonasal diseases, like chronic rhinosinusitis, trigger one or more underlying pathogenesis[21].
Post-infectious olfactory dysfunction	Pathogens, especially viruses (e.g., common cold, influenza, COVID-19), result in transient or prolonged smell dysfunction.
Posttraumatic olfactory dysfunction	Traumatic head injury may cause instant or delayed smell loss[22]. This is a major cause of permanent smell loss.
Olfactory dysfunction due to neurodegeneration	Smell loss due to neurodegenerative pathologies in the peripheral and/or central olfactory system.[4]
Olfactory dysfunction related to aging	Largely unknown, may be related to age-related physiological or pathological changes
Others	olfactory dysfunction due to toxins or medications; congenital olfactory dysfunction; idiopathic olfactory dysfunction

2.1.3 Assessment Techniques

Olfactory assessments can be divided into 4 categories[20]. The first category is subjective assessment. While self-reported sense of smell is an important measure in determining the impact of the smell impairment in one's daily life, people often do not recognize this sensory deficit[2,23,24]. The second type of assessment is the psychophysical olfactory measurement, most frequently used in large population and clinical settings. Psychophysical smell tests primarily assess three olfactory modalities, separately or combined[25]. The first is the odor threshold which measures the lowest concentration of an odor that can be detected. This smell ability is usually affected by conductive dysfunction. Odor discrimination refers to one's nonverbal ability to distinguish different odors. Last, odor identification indicates one's ability to detect and match odors to verbal or visual clues that describe the smell. The latter two olfactory modalities also require the normal functioning of the central olfactory structures[26,27]. These psychophysical tests all have the weakness that they cannot determine the location of pathology, therefore more sophisticated examinations are required.

Imaging techniques provide ways to pinpoint the underlying pathologies. For example, magnetic resonance imaging can measure olfactory bulb volume and olfactory sulcus depth. However, advanced imaging techniques are expensive and require special equipment and expertise, thus it is not widely used beyond lab research settings[25]. Electrophysiological techniques can test cellular ionic currents and the ion channels, thus recording the sequential processing at the neuron level[28]. However, this technique has been limited in its use due to the cost and logistic issues[29].

2.1.4 Epidemiology

The epidemiology of olfactory dysfunction is primarily from studies using objective

psychophysical smell tests, because compared to smell identification test results, self-reported olfactory function has relatively low sensitivity (~20-30%)[24]. A recent Meta analysis reported that the pooled prevalence of olfactory dysfunction among populations aged from 18 to 97 years was 22%[30]. It was estimated that nearly 32 million (27.5%) of American adults aged 50 years and older were affected by olfactory dysfunction. While the prevalence of olfactory dysfunction is affected by study populations and smell test types and cut-offs, it has been consistently found to increase with age. For example, Murphy *et al.* used an 8-item San Diego Odor Identification Test and reported 6% of olfactory impairment among adults in their 50s, increasing to over 60% when adults were older than 80[2]. While a few studies focused on Eastern Asia, most studies were conducted in the US and Europe[30]. Multiple studies have identified racial and gender difference in olfactory function among the US adult population with olfactory dysfunction being more prevalent among Black individuals compared to White individuals, and more common in males than females[23,31,32].

While longitudinal investigations are limited, the existing empirical data have consistently shown that the rate of olfactory decline increases with age[3,33–36]. For example, among adults aged 57-85 years from the National Social Life, Health, and Aging Project, Pinto *et al.* found that the 5-year decline in odor identification score was 0.25 score higher with every 10-year age increase[3]. Other demographics' associations with the rate of olfactory decline were not consistent across studies.

2.1.5 Causes and Health Implications

Olfactory dysfunction can be caused by infection. As the olfactory system is directly exposed to various pathogens, upper respiratory tract infections which lead to nasal local inflammation and swelling will block the airflow, disturbing olfactory function. Luckily, such olfactory dysfunction is in general temporary and will recover once the inflammation is relieved. Influenza-like infection

may also cause smell abnormality without concurrent stuffy nose[37]. Interestingly, the smell loss without stuffy nose has also been found prevalent among patients with SARS-CoV-2 infection[38].This type of olfactory dysfunction may be related to the downregulation of odor detection pathways[39]. Despite the existence of long-term smell loss in COVID-19 patients, over 85% recovered their sense of smell within 2 months[40].

Sinonasal diseases, including chronic and acute rhinosinusitis, are also a primary cause of olfactory dysfunction[20]. The mechanisms of smell loss with sinonasal disease can be complex. It may be caused by the mechanical obstruction of odor transmission due to edema with or without nasal polyps, the inflammation-mediated odorant binding dysfunction, or neuroepithelium/ olfactory bulb remodeling[20,41,42]. Depending on the mechanisms involved, olfactory dysfunction can be transient or chronic, usually paralleling the progress of sinonasal diseases.

As olfactory modalities, especially those involving high-order functions, rely on both peripheral and central neural structures, any damage throughout the neural pathways may also affect olfactory function[43]. For example, traumatic head injury may distort nasal structure, shear the olfactory fila, or even lead to brain hemorrhage, causing olfactory impairment. Head-trauma related olfactory dysfunction mostly recovers quickly within months, while in some rare cases, the olfactory dysfunction may last over 5 years[44].

Olfactory dysfunction is also a common symptom of neurodegeneration[45,46]. Importantly, this sensory deficit often occurs in the early stages of neurodegenerative progression. Braak *et al.* first proposed the staging of Alzheimer's disease and Parkinson's disease based on the neuropathology in post-mortem samples[47,48]. Specifically, this theory posits that Alzheimer's disease and Parkinson's disease initiates in the olfactory structures years before the overt cardinal symptoms and signs of neurodegeneration. It sheds light on opportunities to pinpoint high-risk

populations in the early stage of neurodegeneration and prevent the disease from continuously progressing to clinical manifestations[49]. Notably, poor olfaction identified by a single smell test has been found associated with a 2- to 3- fold higher risk of dementia[50–52] and a 4- to 5- fold higher risk of Parkinson's disease during up to a decade of follow-up[53].

Despite the specific causes of olfactory dysfunction covered above, most cases with smell loss have unknown causes. Olfactory dysfunction may be the consequence of long-term exposure to environmental hazards, the manifestation of biological aging, or a mixture of the two. Olfactory epithelium is an interface of connecting interior and exterior body environments, and thus constantly exposed to diverse environmental insults. As a result of being located at such an unprotected position, olfactory system has a remarkable regenerating ability to recover from countless environmental insults[54]. However, neurogenesis in the olfactory system may slow down or become exhausted due to prolonged exposure to environmental hazards and the natural aging process[55]. As the first line of defense against external hazards, the olfactory system may exhibit early abnormalities before other symptoms become apparent.

Olfactory dysfunction has been increasingly found to have broader health implications beyond its links to neurodegenerative diseases[5,56]. Emerging evidence has found that impaired olfaction is a strong predictor of all-cause mortality[5], supporting that olfactory loss may provide insights into survival beyond chronological age and existing comorbidities in older adults. Interestingly, using data from the Health ABC Study, Liu *et al.* found that only 22% of excess mortality associated with poor olfaction could be explained by dementia and Parkinson's disease in older adults[57]. This longitudinal mediation study provided empirical evidence regarding the potential health implications of poor olfaction in older adults beyond what is currently known. However, evidence on other health implications of olfactory dysfunction remains limited.

2.2 Major Adverse Cardiovascular Outcomes

Cardiovascular disease (CVD) is a group of heterogeneous disorders related to the heart and circulatory system which represent a substantial disease burden. Globally, major CVDs are the leading cause of mortality, with a combined age-standardized death rate of 196.1 per 100,000 in 2021[6]. In the US, CVDs account for a quarter of deaths and affect over 28.6 million (10% of) adults aged 20 years or older in 2020[58,59]. Based on pooled data from 7 US cohorts, the lifetime risk of developing CVDs at age 55 ranged from 15.3% to 38.6% for females and from 21.5% to 47.8% for males, depending on diabetic status[60]. Therefore, primary prevention of CVDs remains critical in public health.

CVDs share some underlying mechanisms, such as atherosclerosis and inflammation[61], and have some common risk factors, for example, hypertension, diabetes, obesity, and hyperlipidemia[62–64]. Despite these similarities, each major CVD has its own distinct pathological features and progression trajectories. For example, the hallmark of CHD pathophysiology is the development of atherosclerotic plaque in the coronary artery[65]. While CHD is one of the most common causes of HF, clinical HF represents an advanced stage with unrecoverable functional and/or structural heart anomaly due to any cardiac pathologies, such as valvular disease and cardiomyopathy[66]. Like CHD, stroke occurs primarily due to obstructed blood arteries, but its pathology happens in the cerebral arteries with more complicated etiology, adding complexity to stroke prevention[67]. Given the distinctions across major CVDs, it is hereby crucial to investigate each individual CVD.

2.2.1 Stroke

Stroke, a type of cerebrovascular disease, can be classified into two categories: over 80% in the US are ischemic, while the remaining cases are hemorrhagic[68,69]. Ischemic stroke occurs due to

artery blockage, while hemorrhagic stroke is caused by bleeding from a ruptured blood vessel[67]. Ischemic stroke can be classified into different subtypes based on clinical features, brain imaging, and other imaging or laboratory assessments, according to the TOAST classification[70]. Stroke due to large artery atherosclerosis requires either greater than 50% stenosis or occlusion of a major intracranial or extracranial artery on vascular imaging with clinical symptoms of cerebral cortical impairment, brains stem or cerebellar dysfunction. This type stroke accounts for ~13% of ischemic strokes[68]. Cardio-embolism is brain arterial occlusions due to an embolus happening in the heart, so the diagnosis of cardioembolic stroke requires at least one cardiac source identified for an embolus[70]. Its clinical features and brain imaging may resemble those of large artery atherosclerosis, making differential diagnosis between the two subtypes critical. Cardioembolic stroke explains ~27% of ischemic strokes[68]. The third subtype is lacunar stroke mainly due to small vessel occlusion in the brain's deep structures. Unlike the first two subtypes, this type of stroke is characterized by typical lacunar syndromes rather than cerebral cortical syndromes, along with imaging evidence that supports subcortical lesions smaller than 1.5 cm and rules out large artery and cardioembolic strokes[70]. Lacunar stroke accounts for 23% of ischemic strokes[68]. Less than 3% of ischemic strokes are those with other determined etiology, such as hematologic disorders, nonatherosclerotic vasculopathies, and hypercoagulable states[67]. The last category of ischemic stroke is cryptogenic stroke, which accounts for around 35% of ischemic strokes[69]. This subtype is non-lacunar stroke confirmed by imaging but without an identified cause[67].

The incidence of stroke has declined significantly over the years. From 1990 to 2019, worldwide incidence of stroke decreased by 17%[71]. The age-standardized incidence of stroke was estimated as 151 per 100,000 people in 2019. In the US, the ARIC Study has found a reduction in stroke incidence over the last three decades in males and females as well as in White and Black

individuals[72]. Nevertheless, stroke has still been associated with substantial disease burden, especially as populations age. It is the second leading cause of death and the third leading cause of death and disability combined across the world[71]. In 2019 alone, it caused 6.55 million deaths worldwide, accounting for 11.6% of total deaths. In the US, stroke ranks the fifth leading cause of death, accounting for 4.8% of total deaths[58]. Further, stroke is also closely related to subsequent cognitive decline and dementia. One study found that stroke brought forward the onset of dementia by 4 years in people who have had minor strokes or by 25 years in those who have had severe strokes[73]. Given the great disease burden related to stroke, it is imperative to identify the at-risk population early and prevent stroke events.

2.2.2 Coronary Heart Disease

CHD has also been referred to as coronary artery disease and ischemic heart disease. While CHD often first presents as an acute event, its genesis requires chronic buildup of pathologies. Cascades of inflammatory reactions triggered by various risk factors are linked to the accumulation of atherosclerosis in the endothelium of coronary arteries[65]. As the plaque progresses, the artery may calcify and become stenotic or even occluded. As arterial remodeling leads to decline in the blood supply to the heart, it may cause chest pain, and other chronic symptoms of angina pectoris[74]. Without proper intervention of the progression, the rupture of plaques potentially provokes acute coronary thrombosis, leading to acute myocardial infarction (MI)[65]. The acute MI is often fatal and among survivors result in reduced heart function, further affecting the normal functioning of the cardiovascular system as well as potentially compromising other organs and systems.

CHD has been once one of the most common fatal conditions since the 1930s[75]. In the US, the mortality of CHD continued to increase until the 1960s[76]. This rise is probably attributed to the upward trend of smoking, changes in dietary choices, increased sedentary behaviors, and the

increasing identification of CHD with the assistance of electrocardiography[75]. In 1978, the expert panel in the famous 1978 Conference on the Decline in CHD in Bethesda, US, acknowledged the decline in CHD mortality since mid-1960s[76]. While the causes of the decline have been debated, the decline was likely to be owing to the improvements in different levels of CHD prevention, including the decline in CHD incidence due to public health initiatives and the improved survival among CHD patients due to advancements in medical care[77,78]. Despite the decline in CHD mortality since the late 1960's, CHD still ranks as the top cause of death worldwide and in the US[6,79]. CHD affects more than 20 million adults in the US, with its prevalence increasing with age and being higher in men than in women across all age groups[58]. Notably, it is estimated that an individual in the US experiences an MI every 40 seconds. Therefore, CHD is still an important public health issue, requiring comprehensive systems of care designed to treat acute coronary events as well as continued public health efforts to control risk factors such as smoking, hypertension, and diabetes.

2.2.3 Heart Failure

HF is a complex heart syndrome resulting from any functional or structural impairment of ventricular filling or ejection of blood[66]. Given that the progression to symptomatic HF is gradual and chronic, the American College of Cardiology and American Heart Association have developed a staging system for HF to highlight the importance of stage-specific preventive and prognostic interventions[66]. The most severe stage, stage D, is also called the advanced HF stage. In this stage, even with the use of medical therapy, HF signs and symptoms still interfere with daily life and often result in recurrent hospitalizations. Stage C is symptomatic HF which requires current or previous HF manifestations. In stage C and D, HF management seeks to control symptoms and increase overall survival. In contrast, patients in stage B which is also called the pre-HF stage do

not have HF symptoms but show the presence of structural or functional changes in the heart that portend clinical disease. Specifically, these changes can be identified by cardiac structural changes, increased filling pressure, or elevated levels of cardiac biomarkers indicating myocardial stretch or injury. N-terminal pro-B-type natriuretic peptides (NT-proBNP) and high-sensitive cardiac troponin T (hs-cTnT) are well-established HF biomarkers and widely used in clinical practices to assist the prevention, diagnosis, and prognosis of HF[80]. Individuals in stage A are those at risk of developing HF but without symptoms, structural heart disease or abnormal cardiac biomarkers. People classified as stage A include those with atherosclerotic CVDs, hypertension, diabetes, metabolic syndrome, obesity, genetic susceptibility of cardiomyopathy, or exposure to cardiotoxic agents. Among adults age 67-91 years in the ARIC Study, over half of them had Stage A HF, followed by 30% with Stage B HF, 13% with clinical HF, and only 5% without any HF-related risk factors and abnormalities[81].

Left ventricular ejection fraction (LVEF), a measurement of left ventricular systolic function, is defined as the fraction of the blood volume ejected in systole over the blood volume in the ventricle at the end of diastole[82]. This measure is related to disease severity and prognosis[66]. Based on LVEF, patients with HF events can be classified into three groups: HF with reduced ejection fraction (HFrEF) defined as LVEF ≤40%, HF with preserved ejection fraction (HFpEF) defined as LVEF ≥50%, and HF with mildly reduced ejection fraction (HFmrEF) defined as 40%< LVEF <50%. HFmrEF may be more similar to HFrEF than HFpEF, as the former two HF types are more likely attributed to CHD[83,84].

HF affected more than 64 million people worldwide in 2017[85]. While the incidence of HF has been stable at the level of 1-20 per 1,000 person-years over the last two decades, the prevalence of HF keeps rising owing to the aging population, better survival from CHD, and the elongated

life expectancy of HF patients[86]. The US is seeing an increase in HF from a prevalence of 2.4% in 2012 to an estimated 3% in 2030[58]. The incidence of HF rises with age, reaching 6.0-7.9 per 1000 person-years after age 45 and approximately 21 per 1000 person-years among those over 65 years[87]. Survival rates of HF have improved over time thanks to evidence-based treatments for HFrEF, including pharmacotherapies, coronary revascularization, cardioverter defibrillators, and cardiac resynchronization therapies[88]. However, the economic burden related to HF is substantial. In the US, it is expected to have over 8 million HF patients by 2030 with an annual cost of $30,000 per patient[89]. Given the significant disease burden associated with HF, it is crucial to assess HF risk early during preclinical stages, to prevent the progression to clinical HF events, and to protect Stage A HF from developing in the first place.

2.3 Biological Plausibility of Olfaction with Cardiovascular Health

There are several reasons why olfaction could have a biologically plausible relationship with the development of major cardiovascular outcomes in older adults. First, olfactory dysfunction may be an early marker of the compromised cardiovascular health before clinical symptoms show up. Olfactory identification involves high-order cognitive functions and thus requires intact structures and functions of the peripheral and central olfactory systems. As sufficient blood perfusion is critical to the normal functioning of the olfactory system, olfactory function may be sensitive to compromised cardiovascular health. For example, empirical evidence found that some subclinical carotid atherosclerotic biomarkers, such as carotid intima media thickness and the number of sites in carotid artery with plaques, were associated with olfactory loss[90,91]. Interestingly, the main arteries of blood supply to the olfactory epithelium, the olfactory bulb, and certain central loci derive from the internal carotid artery[17]. In addition, patients with idiopathic intracranial hypertension, an established risk factor for stroke[92], were also found to have olfactory

dysfunction[93,94]. Therefore, olfactory dysfunction may be sensitive to disturbed blood supply and serve as an early unspecific symptom of compromised cardiovascular health.

Further, olfactory dysfunction may contribute to impaired cardiovascular health in older adults by jeopardizing one's eating behaviors. This sense assists our decision making about food. Retro-nasal olfaction interacting with sense of taste contributes to our perception of food and drinks[95]. Smell perception may also entangle with the state of metabolism and food choices, affecting our dietary behaviors and nutritional status[96,97]. While the role of sense of smell in nutritional status can be complex, limited empirical evidence suggests that olfactory dysfunction may be adversely associated with one's appetite, dietary intake, and diet quality[98–101]. Since dietary patterns and calorie intake are crucial for maintaining cardiovascular health, poor olfaction may elevate the risk of cardiovascular disease morbidity by affecting nutritional intake[102,103].

Finally, olfaction may signify future cardiovascular health as a general marker of accelerated aging. Although the direct evidence is limited, empirical data has consistently found that poor olfaction is associated with faster decline in cognitive and physical function[104,105] and higher risk of developing depressive symptoms[106]. These cognitive, physical, and mental downturns emerge with advanced age and are closely related to mortality and morbidity in older adults[107,108]. In support, accumulating empirical evidence has found that cognitive impairment, depression, and reduced physical function are associated with higher risk of future CVD[109–111]. Therefore, poor olfaction may be associated with incident CVD as a marker indicating accelerated aging.

Frailty is a geriatric syndrome featured by a multi-dimensional systematic decrease in physiological reserve[108]. This syndrome is prevalent and associated with substantial mortality and disability among older adults[112]. A growing body of literature has recently shown the connections

between frailty and incident cardiovascular outcomes among older adults[113,114]. Frailty may elevate one's vulnerability to internal or external insults in late adulthood or share the similar pathologies with adverse cardiovascular outcomes and accelerated aging[115,116]. Given the growing empirical evidence connecting poor olfaction with frailty in older adults[117], research on frailty and cardiovascular health should consider exploring the relationship among poor olfaction, frailty, and CVD.

However, empirical evidence regarding olfaction and cardiovascular health is limited. In detail, a few studies have reported the cross-sectional connections between olfactory status and cardiovascular disease in older adults[2,35,118–124]. Such snapshot investigations cannot elucidate the temporal order and have limited empirical implications. Several longitudinal studies mainly focused on the metabolic and cardiovascular origin of olfactory dysfunction[35,36,125,126], which is different from our study goals. To our knowledge, only one longitudinal study investigated the association of olfactory function with incident heart disease in the National Social Life, Health, and Aging Project[127]. Specifically, Siegel *et al.* reported that five-year olfactory decline was marginally associated with higher odds of incident heart diseases (odds ratio [OR]: 1.75, 95% CI: 0.93-3.31). However, their diagnosis of heart diseases was self-reported only once in their year-10 survey and heart diseases were analyzed only as the secondary outcome of interest. **Appendix 1** lists the detailed information on all the related population studies.

This current project will focus on associations of olfaction with future major cardiovascular outcomes and overcome previous limitations by leveraging two independent well-established longitudinal cohorts with long-term follow-up, and detailed outcome surveillance and adjudications.

CHAPTER 3: METHODOLOGY

We used two well-established cohorts of older adults in the US to investigate our aims. The Health ABC Study served as the preliminary investigation to examine the association of olfactory status with incident stroke, CHD, and CHF in older adults (**Chapter 4**). In the ARIC Study, we conducted a more detailed investigation of each major cardiovascular outcome of interest, including stroke (**Chapter 5**), CHD (**Chapter 6**), and HF (**Chapter 7**). This chapter focuses on the overall methodology and related methodological considerations.

3.1 Study Populations

The Health ABC Study was established in 1997-1998, aiming to study the interrelationships across behavioral factors, age-related conditions, and comorbidities in the context of aging[128,129]. In brief, the study recruited 3,075 well-functioning older adults aged 70 to 79 years (48.8% men and 41.6% Black participants) in Memphis, Tennessee, and Pittsburgh, Pennsylvania. White participants were randomly sampled from Medicare beneficiaries and Black participants of eligible age were identified in specified zip code areas. The eligibility criteria included no difficulty walking a quarter mile or climbing up ten steps, no active life-threatening cancer in the last 3 years, and no plan to move outside the study areas in the next 3 years. The study conducted clinic visits annually since enrollment (Year 1) through Year 6, then in Year 8, 10, 11, and 16. Participants were contacted through phone calls semiannually until Year 15, and then quarterly through Year 17. Year-3 clinic visit in 1999-2000, including a smell test, was considered the baseline of our analysis.

The ARIC Study, established in 1987-1989, was designed to investigate atherosclerosis and its cardiovascular sequelae[130,131]. Briefly, the ARIC Study recruited 15,792 community-dwelling adults aged 45-64 years selected from four communities (Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County,

Maryland). Specifically, age-eligible participants from each community were selected by probability random sampling based on a predefined list of households or individuals. Since enrollment, participants underwent periodic in-person clinical examinations and annual phone interviews (semiannually since 2012) to update their health status. The fifth clinical examination (Visit 5) in 2011-2013 including a smell testing was considered as our study baseline.

Overall, the two studies included both males and females, and white and Black participants. They had comparable average age, similar study designs, and data collection strategies. However, they were entirely independent and had differences in eligibility criteria of enrollment, calendar periods of the follow-up, and original cohort objectives.

3.2 Smell Testing

Both studies used a 12-item brief smell identification test. The Health ABC Study used the "scratch and sniff" Brief-Smell Identification Test (B-SIT) at Year-3 clinic visit[132]. The ARIC Study used the "felt-tip pen" Sniffin' Sticks (SS) test at Visit 5[133]. Both tests are reliable (test-retest reliability: 0.73-0.78) and have been widely used in large population and clinical settings[134–139]. Both tests required participants to smell 12 common odors, one at a time, and select the right odorant from 4 possible choices in a forced multiple-choice format. One correct answer was given one score, so the test score ranged from 0 to 12. As the two tests in the two cohorts had a very similar score distribution, we defined good olfaction as a score of 11-12, moderate olfaction as 9-10, and poor olfaction as 8 or lower, corresponding to the tertile of the score distribution among study participants from either cohort. Using these cut-offs, previous studies have identified the associations of olfactory status with risks of Parkinson's disease, dementia, and all-cause mortality[52,53,57].

3.3 Outcomes

Both studies closely monitored the health and survival of study participants via clinic visits, telephone calls, and cohort-wide surveillance of hospitalizations and deaths[140–142]. Major cardiovascular adverse events and deaths were identified through cohort-wise surveillance or annual/semi-annual follow-ups. However, the specific identification and adjudication procedures varied between the two cohorts. In the Health ABC Study, local adjudicators extracted and reviewed inpatient/outpatient medical records according to a standardized study protocol and a central expert committee adjudicated the cause of death for fatal events. In the ARIC Study, possible CVD events were first identified through International Classification of Disease (ICD) codes and keywords in the discharge summary and related medical records were extracted. The possible events of CHD and stroke were first classified by the computer-based algorithm and confirmed by a physician in the ARIC Morbidity and Mortality Classification Committee. The HF hospitalizations were independently adjudicated by physicians in the ARIC Study. **Table 3.1** presents the definition of each major cardiovascular outcome in the two studies.

Table 3.1 The definition of major cardiovascular outcomes in the two cohorts

	Health ABC Study	**ARIC Study**
CHD	**MI:** evolving/diagnostic ECG pattern + abnormal cardiac enzymes; ischemic symptoms + [either an evolving ST-T pattern or an obscure ECG pattern] [143,144] **Angina pectoris** **Death with CHD as the underlying cause**	**MI:** evolving/diagnostic ECG pattern + abnormal cardiac enzymes; ischemic symptoms + [either an evolving ST-T pattern or an obscure ECG pattern] + abnormal cardiac enzymes[144,145] **Death with CHD as the underlying cause**

Table 3.1 (cont'd)

Stroke	**Stroke (probable or possible):** with evidence of sudden or rapid onset of neurological symptoms lasting for over 24 hours or leading to death in the absence of evidence for a non-stroke cause[143,146] **Death with stroke as the underlying cause**	**Stroke (definite or probable):** stroke is categorized into thrombotic and cardioembolic brain infarction, subarachnoid and intracerebral hemorrhage[147]. The detailed definition of each subtype refers to the ARIC Stroke Cohort Surveillance Procedures, Manual of Operations[146] **Death with stroke as the underlying cause**
HF	**CHF**: the first overnight hospitalization with CHF as the primary inpatient reason or a concurrent event [143]	**HF**: the first overnight hospitalization with HF. HF is categorized into ADHF, chronic stable heart failure and heart failure unlikely or unclassifiable[148,149]. HF is further categorized into HFrEF(EF<50%) and HFpEF (EF≥50%)[150]

Abbreviations: CHD: coronary heart disease; MI: myocardial infarction; ECG: electrocardiogram; CHF: congestive heart failure; HF: heart failure; ADHF: acute decompensated heart failure; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; EF: ejection fraction.

Notably, the ARIC Study was among the first of several large cohorts specifically designed to study CVD etiology and risk factors, substantially contributing to our knowledge about cardiovascular health over the past three decades. Accordingly, compared to the Health ABC Study, the ARIC Study presumably had more stringent event identification and adjudication protocols, along with more detailed information on CVD events. Further details on each study outcome are provided in the following chapters.

3.4 Covariates

We consider a range of covariates mostly collected at each study baseline. Although the covariate list varied between studies and across outcomes of interest, we primarily considered three types of covariates in our analyses. The first type of covariates were basic demographics, including age, sex, race, study site, and education. The second type of covariates were established risk factors for adverse cardiovascular outcomes, such as smoking, body mass index

(BMI), hypertension, diabetes, blood cholesterol, and other prevalent major cardiovascular outcomes. The third type included potential predictors for adverse cardiovascular outcomes, for example, renal function and frailty. The lists and definitions of covariates are described in the Method of the following chapters (**Chapter 4-7**).

3.5 Statistical Considerations and Analyses

In this project, our target population is older adults with an average baseline age of 75.5 years at risk of developing stroke, coronary heart disease, or heart failure in the US. Therefore, taking the issue of competing risk of death into statistical consideration is crucial. In the descriptive analysis, instead of using the Kaplan-Meier curve, we used the cumulative incidence function[151,152], as the Kaplan-Meier survival curve $S(t) = \Pr(T > t)$ (where $\Pr(T > t)$ denotes the distribution of event times) assumes that the event of interest would occur for all subjects, which is impossible in the presence of the competing event of death. As a result, using the Kaplan-Meier curve will overestimate the incidence. In contrast, the cumulative incidence function (CIF), defined as $CIF_k(t) = \Pr(T \leq t, D = k)$ (where D denotes the type of event that occurred), will not necessarily approach unity as time becomes large, because this estimator considers that the occurrence of the competing event will preclude the occurrence of the event of interest. The non-parametric maximum likelihood estimator of the CIF of cause *k* is

$$F_k(t) = \sum_{T_l \leq t} \frac{d_{kl}}{Y_l} S(t_{l-1}),$$

Where $k \geq 2$ is the type of event, $t_1 < t_2 < t_3 \ldots < t_l$ are the distinct uncensored times, Y_l is the number of subjects at risk at t_l, d_{kl} is the number of events that occurred at t_l, $S(t_l)$ is the Kaplan-Meier estimator that would have been obtained by assuming that all failure causes are of the same type.

In the presence of competing events of death, **Figure 2.1** shows the conceptual relationship

among poor olfaction, major cardiovascular outcomes, and deaths before cardiovascular outcomes in the form of the directed acyclic graph (DAG). In the presence of competing risk of death, the association of olfaction with cardiovascular outcomes arises through two pathways: the first pathway is the direct association between olfaction and cardiovascular outcomes (Path 1 in **Figure 2.1**), and the other pathway is the indirect association through competing event of death (Path 2 in **Figure 2.1**). Notably, in our case, the existence of an indirect association pathway would attenuate the total association between olfaction and cardiovascular outcomes (i.e. Path 1 + Path 2), because poor olfaction is strongly associated with higher mortality and death is an absorbing status (i.e., nullifying the "risk" for the cardiovascular outcomes). Therefore, it is important to articulate which association is estimated in the presence of competing risk of death.

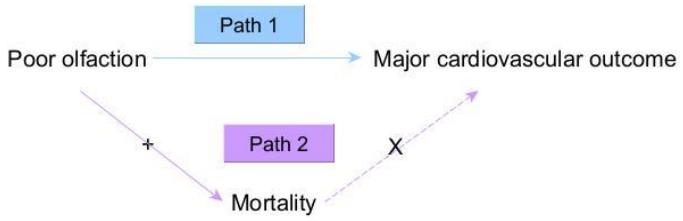


Figure 2.1 Partial* directed acyclic graph of differential survival during the follow-up. * Other variables are omitted to avoid clutter

In the survival analysis, hazard and risk are commonly used to quantify the association. Hazard is defined as the instantaneous rate of the event of interest among the at-risk population. Risk is the cumulative risk of the event among the at-risk population during a fixed equal exposure period. In other words, hazard is a velocity measure of event occurrence while risk is a cumulative measure over time. Hazard can be used to calculate the cumulative risk.

In the presence of competing risk of death, there are two types of hazards[151,153]. One type is cause-specific hazard defined as

$$\lambda_k^{cs}(t) = \lim_{\Delta t \to 0} \frac{Prob(t \leq T < t+\Delta t, D=k | T \geq t)}{\Delta t},$$

where T is the time from baseline until the occurrence of the event of interest, D is the type of event of interest.

It represents the instantaneous risk of having k^{th} event among participants who do not yet have any types of events. The cause-specific hazard ratio (HR) can be directly estimated from the cause-specific Cox regression and estimates the **direct association** in the scale of HR. However, HR is less preferable than risk ratio (RR). First, HR is not an effect measure. Because hazard is conditional on individuals who have not had the outcome or competing events, and thus it is impossible to compare the hazard of the outcome of interest among the "same" individuals with different exposure levels[154]. Further, there are criticisms that this method considers death events the same as loss to follow-up, even though loss to follow-up is fundamentally different from death events. Censoring due to loss to follow-up is possible to be avoided in a study by implementing more flexible data collection strategies and improving participants' awareness of the project; however, deaths are impossible to be eliminated, especially in an older population. As such, in the presence of competing risk of death, another way is to estimate absolute risk using the Fine-Gray sub-distribution hazard[153]. Sub-distribution hazard is defined as

$$\lambda_k^{sd}(t) = \lim_{\Delta t \to 0} \frac{Prob(t \leq T < t+\Delta t, D=k | T \geq t \cup (T < t \cap K \neq k))}{\Delta t},$$

where T is the time from baseline until the occurrence of the event of interest, D is the type of event of interest.

In other words, it refers to the instantaneous risk from the k^{th} event in participants not yet having the event of k. This hazard measure can be used to predict the cumulative risk of the k^{th} event in the presence of competing risk of death. The RR and risk difference (RD) can be calculated subsequently. As the calculated absolute risk accounts for the competing risk of death, the risk-related association measures quantify the **total association**[155]. While this association measure is

affected by both direct and indirect pathways, it has a causal interpretation and is thus preferred in medical studies. Further, with more assumptions, it is also possible to estimate the direct association in the scale of risk-based association measures (i.e., RR and RD)[155].

Appendix 2 lists the commonly used regression models in the presence of competing risk of death. The Cox proportional hazards model has been widely used in survival analysis. However, the semiparametric nature of Cox regression requires the proportional hazard assumption during the whole follow-up, and it cannot correct the selection bias when loss to follow-up does not occur completely at random. To overcome these limitations, investigators from the Framingham Study first proposed to use the pooled logistic regression which showed decent performance when compared to the Cox proportional hazards model[156]. Because this modeling can easily incorporate time-varying covariates, time-varying coefficients, and inverse probability weighting (IPW), it has been increasingly used in the causal inference field[157]. Under the framework proposed by Young *et al.*[155], we used pooled logistic regression to estimate sub-distribution hazard in the discrete-time scale, calculating marginalized absolute risk across olfactory statuses and estimating the total association in the scale of the RR.

In the Health ABC Study, we used cause-specific Cox regression to estimate the direct associations of poor olfaction with incident major cardiovascular outcomes (**Chapter 4**). In the ARIC Study, we estimated both the total association in the RR scale and the direct association in the scale of the cause-specific HR to demonstrate the potential influence of competing risk of death in our results (**Chapter 5-7**). Methodological details are presented in the corresponding chapters.

3.6 Institutional Review Board Approval

The work conducted for this dissertation was reviewed and approved by the Michigan State University Institutional Review Board (STUDY00009824). To obtain the data from the Health

ABC Study, investigators should submit an analytical proposal online at https://healthabc.nia.nih.gov/ancillary-biospecimen-proposals, which will be reviewed and approved by the Health ABC Study. To access the data from the ARIC Study, investigators should submit an analytical proposal which will be reviewed and approved by the ARIC Study. For both studies, Data Use Agreements need to be developed and signed.

CHAPTER 4: OLFACTORY STATUS IN RELATION TO MAJOR ADVERSE CARDIO-VASCULAR OUTCOMES IN THE HEALTH ABC STUDY

This study has been already published in the *Journal of the American Heart Association*[1].

4.1 Introduction

The human sense of smell declines with age in older adults. Prevalence of poor olfaction, assessed by smell-identification screening, quickly increases from ~6% in age 50s to over 60% in 80s[2]. This age-dependent olfactory decline has been confirmed in multiple community-based studies[3,23]. Despite the high prevalence of poor olfaction in older adults, our understanding of its health implications has been largely limited to its role as a prodromal symptom of neurodegeneration and its robust association with mortality[20]. Interestingly, our recent findings[57] indicated that only 22% of the excess mortality associated with poor olfaction could be explained by dementia and Parkinson's disease, suggesting that poor olfaction may have more profound health implications than what is known to date. Further, this association with higher mortality was limited to participants who self-reported good-to-excellent health at baseline[57], raising the possibility that poor olfaction may be a marker of deteriorating health that precedes the emergence of more traditionally recognized signs and symptoms of health decline.

Beyond neurodegenerative diseases and mortality, the health implications of poor olfaction have been subject to wide speculation, with limited empirical evidence. Recent data suggest that poor olfaction is associated with carotid intima-media thickness and artery plaques[90,91], suggesting that smell loss may be a marker of atherosclerosis – the underlying pathogenesis of cardiovascular disease. Further, poor olfaction may gradually degrade one's food choices, adversely affecting dietary quality and nutrition[98,100], which may contribute to cardiovascular disease over time. Therefore, as a nonspecific subclinical marker and/or a potential contributor, poor olfaction may

be related to cardiovascular risk. Because poor olfaction is prevalent among older adults and cardiovascular disease is the leading cause of death and disability, this potential association should be investigated further.

To the best of our knowledge, only one study[127] has prospectively examined the association between olfaction and heart diseases, and reported an elevated but statistically non-significant association with heart attack and/or heart disease. We hereby comprehensively examined olfactory status in relation to the risk of three major adverse cardiovascular conditions − CHD, stroke, and CHF among community-dwelling older adult participants in the Health ABC Study.

4.2 Methods

4.2.1 Study population

The Health ABC Study aims to investigate the interrelationships among aging-related conditions, social and behavioral factors, and physiological and functional changes in older adults[128]. Briefly, in 1997 and 1998, this study recruited 3,075 well-functioning, community-dwelling older adults (51.5% women and 41.7% blacks) aged 70-79 years in the designated zip code areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Eligibility criteria included no reported difficulty in walking 1/3 mile or climbing up 10 steps, no active fatal cancers, and no plans to move in 3 years. Study participants were followed with annual clinic visits through Year 6, and then in Year 8, 10, 11, and 16. Phone interviews were conducted to update health status every 6 months until Year 15 and then quarterly through Year 17. In the current analysis, we used the Year-3 clinic visit (1999-2000) as the baseline which was when the olfaction test was conducted. The primary analysis was limited to 2,537 participants after excluding those who missed Year-3 clinic visit (n=154) and did not take the smell test (n=384). In the analysis of each cardiovascular outcome, we excluded prevalent cases of that outcome at baseline, respectively. As

case adjudications for major health outcomes (except death) were conducted through August 14, 2012, we followed at-risk participants from baseline until the first cardiovascular outcome, death, last contact (attrition rate < 2%), or the end of the 12-year follow-up, whichever came first. The Health ABC Study protocol was approved by all relevant institutional review boards, and all participants provided written informed consent at enrollment.

4.2.2 The Brief-Smell Identification Test

Olfaction was tested at the Year-3 clinic visit, using the 12-item cross-cultural B-SIT. This test is a shortened version of the 40-item University of Pennsylvania Smell Identification Test and has been widely used in large populations[132]. The 12-item test is brief, convenient, and well-suited to field settings in large epidemiological studies and quick clinical screening[139,158]. Participants were instructed to smell each of the 12 odorants, one at a time, and then to identify the odorant from 4 possible answers in a forced multiple-choice format. One point was given for each correct answer with a total score ranging from 0 to 12. We defined poor olfaction as a B-SIT score ≤8, moderate as 9-10, and good as 11-12, approximately corresponding to the tertile distribution of the B-SIT testing score in the study population. Using these cut-points, we have reported strong associations of poor olfaction with Parkinson's disease, dementia, total mortality, and pneumonia hospitalization in this cohort[53,52,105,159].

4.2.3 Major adverse cardiovascular outcomes

The Health ABC Study closely monitored the health and survival of study participants via study clinic visits, semiannual phone updates, and surveillance of hospitalization and death. As detailed previously [160–163], major adverse cardiovascular outcomes were first identified via the cohort's routine follow-ups and health surveillance and then adjudicated according to a standard protocol. Briefly, at each clinic visit and semi-annual telephone interview, participants or their proxies were

asked directed questions about cardiovascular disease events diagnosed by a physician, overnight hospitalizations, and outpatient cardiovascular procedures such as angioplasty since the last interview. Once an event was reported, local medical event adjudicators collected and reviewed related medical records according to a standardized study protocol[143]. For each death event, study investigators had an exit interview with a knowledgeable proxy who provided detailed information on the death event and the participant's physical functioning before death. The immediate and underlying causes were adjudicated centrally by an expert committee after reviewing hospital records, death certificates, autopsy findings, and informant interviews.

In this study, we defined incident CHD as the first event of myocardial infarction, angina pectoris, or death with CHD as the underlying cause. According to the protocol[143], MI adjudication accounted for evolving diagnostic ECG pattern; diagnostic ECG pattern and abnormal cardiac enzymes; or ischemic symptoms and either an evolving ST-T pattern or an obscure ECG pattern. The adjudication of angina pectoris considered symptoms such as chest pain, chest tightness, shortness of breath, and a diagnosis from a physician, as well as medical treatment including nitroglycerin, beta-blocker, or calcium channel blocker. We defined stroke as the first event of stroke or death with cerebrovascular diseases as the underlying cause, considering evidence of a rapid onset of neurologic deficit attributed to obstruction or rupture of the arterial system and new CT/MRI lesion consistent with clinical presentation of stroke without evidence of alternative causes (e.g., tumor or infection). We defined CHF as the first admission of overnight hospitalization with CHF adjudicated as the primary inpatient reason or a concurrent event. The adjudication considered physician diagnosis, and medical treatments for CHF including both a diuretic and digitalis or a vasodilator, or the presence of cardiomegaly and pulmonary edema on chest X-ray, or evidence of a dilated ventricle and global/ segmental wall motion abnormalities

with deceased systolic function either by ECG or contrast ventriculography.

4.2.4 Covariates

As few risk factors have been established for olfactory loss in older adults except for age, sex, and race, we mainly considered cardiovascular risk factors/predictors as covariates in the analyses. The adjustment of these covariates may help control for potential confounding and improve statistical efficiency[164]. With a few exceptions, we used covariate data from the Year-3 clinic visit when the smell testing was conducted. Age, sex, race, study site, education level, smoking status, minutes of brisk walking per week, and general health status were self-reported. BMI was calculated by dividing weight by height-squared (kg/m^2) and systolic blood pressure by averaging two measures in the sitting position. The use of antihypertensive medication was assessed using the medication inventory method coded with the Iowa Drug Information System Drug Vocabulary and Thesaurus[165]. We defined comorbidities according to published protocols, in brief, 1) diabetes as self-reported diagnosis by a physician, the use of anti-diabetic drugs, a fasting blood glucose level of ≥126 mg/dL, or an oral glucose tolerance test of ≥200mg/dL[166]; 2) dementia as the score of the Modified Mini-Mental State examination (3MS) at the Year-1 clinic visit less than 80, a decline in 3MS score from Year 1 through Year 3 at least 1.5 race-stratified standard deviations, an adjudicated diagnosis of dementia based on hospitalization, or documented medication uses for dementia[57]; 3) Parkinson's disease as adjudicated by two movement disorder specialists by consensus after review of self-reported diagnosis by a physician, medication uses, hospitalization records, and adjudicated cause of death[53]. Depressive symptoms were defined as a score of ≥10 on the Center for Epidemiologic Studies Depression Scale Short form[167]. When covariate data are not available for the Year-3 clinic visit, we used data from previous years. Resting heart rate was measured at Year 1. Left ventricular hypertrophy was diagnosed using Year-1 ECG according to

the Minnesota code criteria[161]. Abnormal lung function was defined as the forced expiratory volume in the 1st second measured at Year 1 below the lower limit of the age-, sex- and race-specific normalized reference values of the National Health and Nutrition Examination Survey III equations[168]. Plasma total cholesterol and high-density lipoprotein-cholesterol (HDL-C) were measured using fasting EDTA plasma collected at Year 2 and Year 1, respectively[169]. Serum albumin was measured using samples collected at Year 1[170], interleukin 6 using samples collected at Year 2[171], and cystatin C and creatinine using samples collected at Year 3[172]. All these biomarkers have been widely analyzed in the Health ABC Study with details reported previously. We estimated eGFR mainly using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation; for 9.6% of the sample with missing creatinine data, we estimated eGFR using the CKD-EPI cystatin C equation[173]. Among those with creatinine measures, these two eGFR estimates were highly correlated with a Spearman coefficient of 0.82. As the proportions of missingness in other covariates were <5%, we used simple imputation by the mode for discrete variables and the median for continuous variables.

4.2.5 Statistical analysis

In descriptive analyses, we used linear regressions for continuous variables and logistic or multinomial regressions for categorical variables to estimate their age-adjusted marginal means/percentages in each olfaction group. We then calculated the CIF of each type of cardiovascular outcome and its corresponding competing risk of death, and tested the equality of CIF across baseline olfactory status using the Gray's test[174]. In multivariable analyses, we used the Cox cause-specific hazard model with the robust sandwich standard error estimate[175] to account for the competing risk of death and reported cause-specific HR and 95% CI for each type of cardiovascular event. This approach quantifies the direct association between olfactory status and

each outcome of interest, not affected by the association of olfaction with death, fitting our analytical goal[153]. In the analyses, we first controlled for age, sex, race, education, and study site (model 1), and then further adjusted for key lifestyle cardiovascular risk factors in model 2[63,110], including smoking status, brisk walking, BMI, self-reported general health status, antihypertensive medication use, diabetes, depressive symptoms, systolic blood pressure, total cholesterol, and HDL-C. As prevalent atherosclerotic diseases could be an important risk factor for CHF[176], we also included prevalent CHD or stroke as a covariate in model 2 of the CHF analysis. Finally, we constructed model 3 for CHF by further adjusting for previously identified markers of CHF in the cohort[161–163], including left ventricular hypertrophy, abnormal lung function, heart rate, serum albumin, interleukin 6, and eGFR. In all regression analyses, we applied the Supremum Test to check the proportional hazard assumption and, when applicable, stratified the covariates that did not satisfy the assumption in the regression model[177]. Finally, given the strong association of olfaction with dementia and Parkinson's disease, we conducted a sensitivity analysis by excluding participants with prevalent dementia or Parkinson's disease at baseline.

For outcomes that showed a significant association with olfaction in the primary analysis, we conducted secondary subgroup analyses by age, sex, race, self-reported health status, and history of other major cardiovascular diseases at baseline. These analyses were pre-planned because the prevalence of poor olfaction is age-dependent and substantially higher in men than in women and in blacks than in whites, and our prior analysis showed that the association of poor olfaction with higher mortality was limited to people with self-reported good-to-excellent health at baseline[57]. Interestingly, for CHF, we found that the association was evident mostly among individuals who self-reported very-good-to-excellent health. We therefore conducted two post hoc exploratory analyses in this subgroup. First, we reestimated the full model in this subgroup. Next,

we further modeled the B-SIT score on a continuous scale, the non-linearity form of which was regressed by using the quadratic term. We used the SAS software (version 9.4; SAS Institute, Cary, NC) for all the analyses with a two-sided α of 0.05.

4.3 Results

At baseline, participants were, on average, 75.6±2.8 years old, with 51.6% female and 38.5% Black. In the overall study sample, compared with participants with good olfaction, those with poor olfaction were more likely to be older, men, Black, smokers, and from Memphis (**Table 4.1**). They were also more likely to report a high-school education level or less and fair-to-poor general health status, and to have diabetes, abnormal or missing lung function, lower BMI, TC, HDL-C, and eGFR. As age is the most important risk factor for olfactory loss in older adults, we also presented age-adjusted covariates by olfaction in **Table A3.1.** Once age was adjusted, the imbalances of prevalent diabetes, lung function, BMI, and cholesterol level across olfaction groups disappeared.

Table 4.1 Population characteristics by baseline olfactory status (n=2,537) [a]

	Olfactory status		
Variable	**Good (n = 845)**	**Moderate (n = 867)**	**Poor (n = 825)**
Age in years, median (IQR)	75.0 (4.0)	75.0 (5.0)	76.0 (4.0)
<75 years	391 (46.3)	370 (42.7)	279 (33.8)
≥75 years	454 (53.7)	497 (57.3)	546 (66.2)
Male sex, n (%)	324 (38.3)	418 (48.2)	485 (58.8)
Black race, n (%)	265 (31.4)	331 (38.2)	380 (46.1)
Study site, n (%)			
Memphis	377 (44.6)	432 (49.8)	428 (51.9)
Pittsburgh	468 (55.4)	435 (50.2)	397 (48.1)
Education, n (%)[b]			
≤high school	414 (49.0)	490 (56.5)	510 (61.8)
>high school	431 (51.0)	377 (43.5)	315 (38.2)
Body mass index, n (%)[b]			
<25 kg/m^2	273 (32.3)	270 (31.1)	313 (37.9)
25-30 kg/m^2	366 (43.3)	363 (41.9)	338 (41.0)
>30 kg/m^2	206 (24.4)	234 (27.0)	174 (21.1)
Smoking status, n (%)[b]			

Table 4.1 (cont'd)

Never	429 (50.8)	390 (45.0)	351 (42.5)
Former & <30 pack-years	235 (27.8)	217 (25.0)	215 (26.1)
Current or ≥30 pack-years	181 (21.4)	260 (30.0)	259 (31.4)
Brisk walking, n (%) [b]			
<90 min/wk	744 (88.0)	786 (90.7)	754 (91.4)
≥90 min/wk	101 (12.0)	81 (9.3)	71 (8.6)
General health status, n (%)[b]			
Very good to excellent	423 (50.1)	384 (44.3)	325 (39.4)
Good	292 (34.6)	351 (40.5)	312 (37.8)
Fair to poor	130 (15.4)	132 (15.2)	188 (22.8)
Systolic blood pressure in mmHg, median (IQR)	134 (26)	134 (24)	134 (28)
Antihypertensive drug use, n (%)[b]	497 (58.8)	533 (61.5)	483 (58.5)
Diabetes, n (%)	181 (21.4)	214 (24.7)	220 (26.7)
Depressive symptoms, n (%)[b]	86 (10.2)	108 (12.5)	115 (13.9)
Heart rate in beats per minute, median (IQR) [b]	63 (14)	63 (14)	65 (16)
LVH, n (%)	98 (11.6)	97 (11.2)	96 (11.6)
Abnormal lung function, n (%)			
No	689 (81.5)	682 (78.7)	610 (73.9)
Yes	75 (8.9)	104 (12.0)	104 (12.6)
Missing	81 (9.6)	81 (9.3)	111 (13.5)
Total cholesterol in mg/dL, median (IQR) [b]	206.0 (51.0)	204.0 (49.0)	202.0 (51.0)
HDL-C in mg/dL, median (IQR) [b]	52.0 (19.0)	51.0 (21.0)	51.0 (20.0)
Albumin in g/dL, median (IQR) [b]	4.0 (0.4)	4.0 (0.4)	4.0 (0.5)
Interleukin 6 in pg/mL, median (IQR) [b]	2.27 (2.15)	2.33 (2.49)	2.33 (2.24)
eGFR in mL/min/1.73m^2, median (IQR) [b]	81.1 (24.3)	81.3 (24.5)	77.3 (26.6)
Prevalent major cardiovascular diseases			
Prevalent CHD, n (%)	199 (23.6)	207 (23.9)	207 (25.1)
Prevalent stroke, n (%)	69 (8.2)	73 (8.4)	65 (7.9)
Prevalent CHF, n (%)	37 (4.4)	44 (5.1)	35 (4.2)

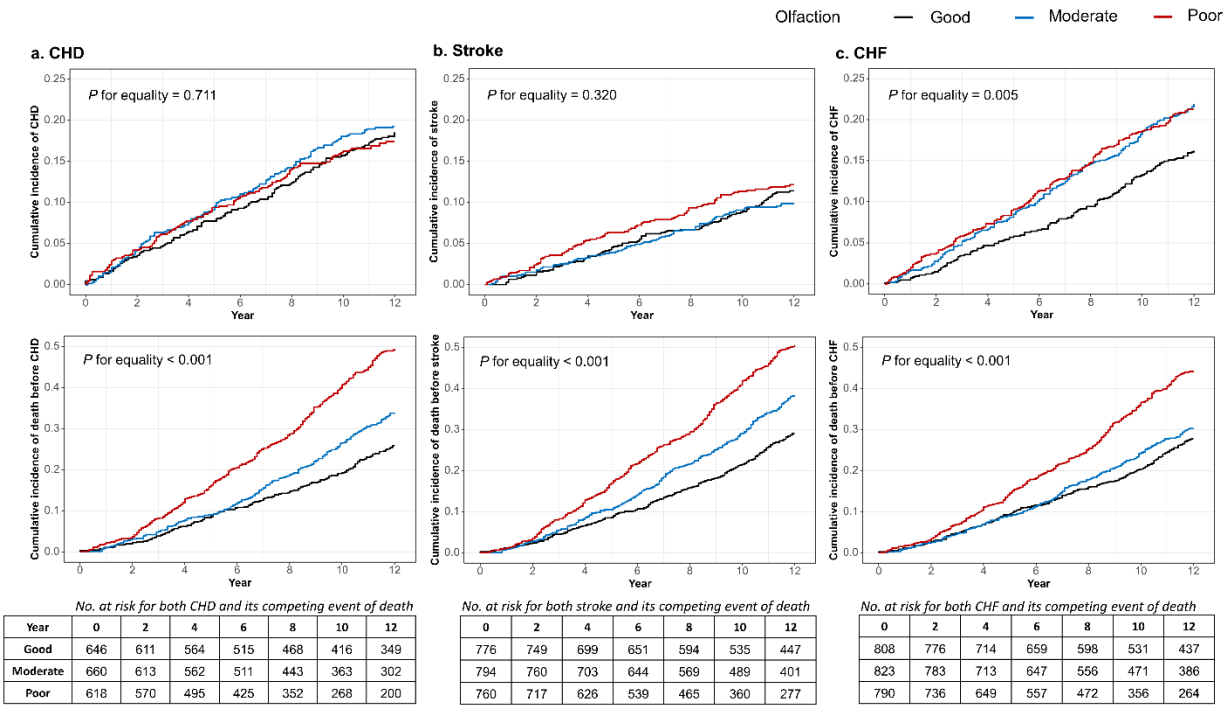
Table 4.1 (cont'd)

Abbreviations: IQR: inter-quartile range; HDL-C: high-density lipoprotein-cholesterol; LVH: left ventricular hypertrophy; eGFR: estimated glomerular filtration rate; CHD: coronary heart diseases; CHF: congestive heart failure.

[a] Prevalent case of outcomes of interest are included in this table. Please see Supplementary Materials for tables for each outcome of interest without corresponding prevalent cases.

[b] Missing values (<5%) were singly imputed. Specifically, the numbers of missningness in covariates are as follows: eudaction: n=7 (0.28%), body mass index: n=2 (0.08%), smoking status: n=33 (1.3%), brisk walking: n=1 (0.04%), general health status: n=3 (0.12%), antihypertensive medication: n=1(0.04%), depressive symptoms: n=2 (0.08%), heart rate: n=1 (0.04%), total cholesterol: n=13 (0.51%), HDL-C: n=85 (3.35%), albumin: n=24 (0.95%), eGFR: n=71 (2.8%), and interleukin 6: n=104 (4.10%).

After excluding prevalent cases at baseline, 1,924 participants were at risk for incident CHD, 2,330 for stroke, and 2,421 for CHF. During 12 years of follow-up, 353 individuals (18.3%) had an incident CHD event, 258 (11.1%) experienced an incident stroke, and 477 (19.7%) had an incident CHF hospitalization. In the descriptive analysis (**Figure 4.1**), baseline olfactory status was not statistically significantly associated with the cumulative incidence of CHD or stroke using the Gray's test. However, this test showed a statistically significant difference for the cumulative incidence of CHF across olfaction groups. In all analyses, poor olfaction was associated with a higher competing risk of death, consistent with our previous findings on the association between olfaction and all-cause mortality using the same data source[57].



No. at risk for both CHD and its competing event of death

Year	0	2	4	6	8	10	12
Good	646	611	564	515	468	416	349
Moderate	660	613	562	511	443	363	302
Poor	618	570	495	425	352	268	200

No. at risk for both stroke and its competing event of death

0	2	4	6	8	10	12
776	749	699	651	594	535	447
794	760	703	644	569	489	401
760	717	626	539	465	360	277

No. at risk for both CHF and its competing event of death

0	2	4	6	8	10	12
808	776	714	659	598	531	437
823	783	713	647	556	471	386
790	736	649	557	472	356	264

Figure 4.1 Cumulative incidence function by baseline olfactory status (good, moderate, poor) of a) coronary heart diseases (CHD) and its competing event of death (n=1,924); b) stroke and its competing event of death (n=2,330); c) congestive heart failure (CHF) and its competing event of death (n=2,421)

Multivariable models confirmed the unadjusted findings (**Table 4.2**). After adjusting for demographics, compared to participants with good olfaction, the cause-specific HR of CHF during a median 10.8 years of follow-up was 1.35 (95% CI: 1.08,1.70) for those with moderate olfaction and 1.39 (95% CI: 1.10, 1.75) for those with poor olfaction. The associations were barely changed with further adjustment for lifestyle risk factors and prevalent CHD/stroke, and were only modestly attenuated after further adjusting for ECG-based, spirometry-based, and blood-based biomarkers for CHF. In the fully adjusted model, the HR became 1.32 (95% CI: 1.05, 1.66) for moderate vs. good olfaction and 1.28 (95%CI: 1.01, 1.64) for poor vs. good olfaction. As in the descriptive analyses, neither CHD nor stroke outcome was statistically significantly associated with baseline olfactory status. For example, the cause-specific HR comparing poor with good olfaction were 0.97 (95% CI: 0.73, 1.28) for CHD and 1.12 (95 % CI: 0.82, 1.52) for stroke. After

removing prevalent cases of dementia or PD at baseline, the results were consistent with our primary findings (**Table A3.2**).

Table 4.2 The association of baseline olfactory status with incident coronary heart diseases (CHD), stroke, and congestive heart failure (CHF) for up to 12 years of follow-up [a]

Olfactory function	No. of Event	Person-years	Incidence (per 1,000 person-year)	Model 1 [b]		Model 2 [c]		Model 3 [d]	
				HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
CHD (n=1,924)									
Good	119	6124	19.4	Reference		Reference			
Moderate	127	5939	21.4	1.06 (0.83,1.37)	0.636	1.01 (0.78,1.31)	0.937		
Poor	107	5018	21.3	1.01 (0.77,1.33)	0.920	0.97 (0.73,1.28)	0.815		
Stroke (n=2,330)									
Good	88	7665	11.5	Reference		Reference [e]			
Moderate	78	7514	10.4	0.86 (0.63,1.17)	0.334	0.85 (0.62,1.16)	0.298		
Poor	92	6428	14.3	1.13 (0.84,1.53)	0.429	1.12 (0.82,1.52)	0.476		
CHF (n=2,421)									
Good	130	7792	16.7	Reference		Reference		Reference [f]	
Moderate	180	7533	23.9	1.35 (1.08,1.70)	0.009	1.31 (1.05,1.65)	0.019	1.32 (1.05,1.66)	0.017
Poor	167	6561	25.5	1.39 (1.10,1.75)	0.006	1.37 (1.08,1.74)	0.010	1.28 (1.01,1.64)	0.043

Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval

[a] Associations were estimated from Cox cause-specific models with the robust sandwich standard error estimate to account for the competing risk of death.

[b] Model 1 included age, sex, race, education, and study site as covariates.

[c] Model 2 further included smoking status, brisk walking, body mass index, self-reported general health status, systolic blood pressure, use of antihypertensive medications, diabetes, depressive symptoms, total cholesterol, and high-density lipoprotein-cholesterol as covariates. For CHF, Model 2 further included prevalent CHD/stroke in addition to the above covariates.

[d] Model 3 (only for CHF) further included heart rate, left ventricular hypertrophy, abnormal lung function, albumin, interleukin 6, and estimated glomerular filtration rate.

[e] Brisk walking and antihypertensive medication use were stratified in the Cox model.

[f] Tertile of interleukin 6 was stratified in the Cox model.

The associations of olfaction with CHF were robust across subgroups of age, sex, race, and baseline history of CHD and stroke (**Figure 4.2**). Although we did not observe a statistically significant interaction, the association between olfaction and CHF appears to be more evident and

monotonic among participants with very-good-to-excellent health at baseline. In contrast, the estimated associations were close to null among participants who self-reported fair-to-poor health. For example, compared with participants with good olfaction, the cause-specific HR of CHF for poor olfaction was 1.76 (95%CI: 1.20, 2.58) among participants with self-reported very good-to-excellent health, versus 0.92 (95%CI: 0.58, 1.47) among those with fair-to-poor health.

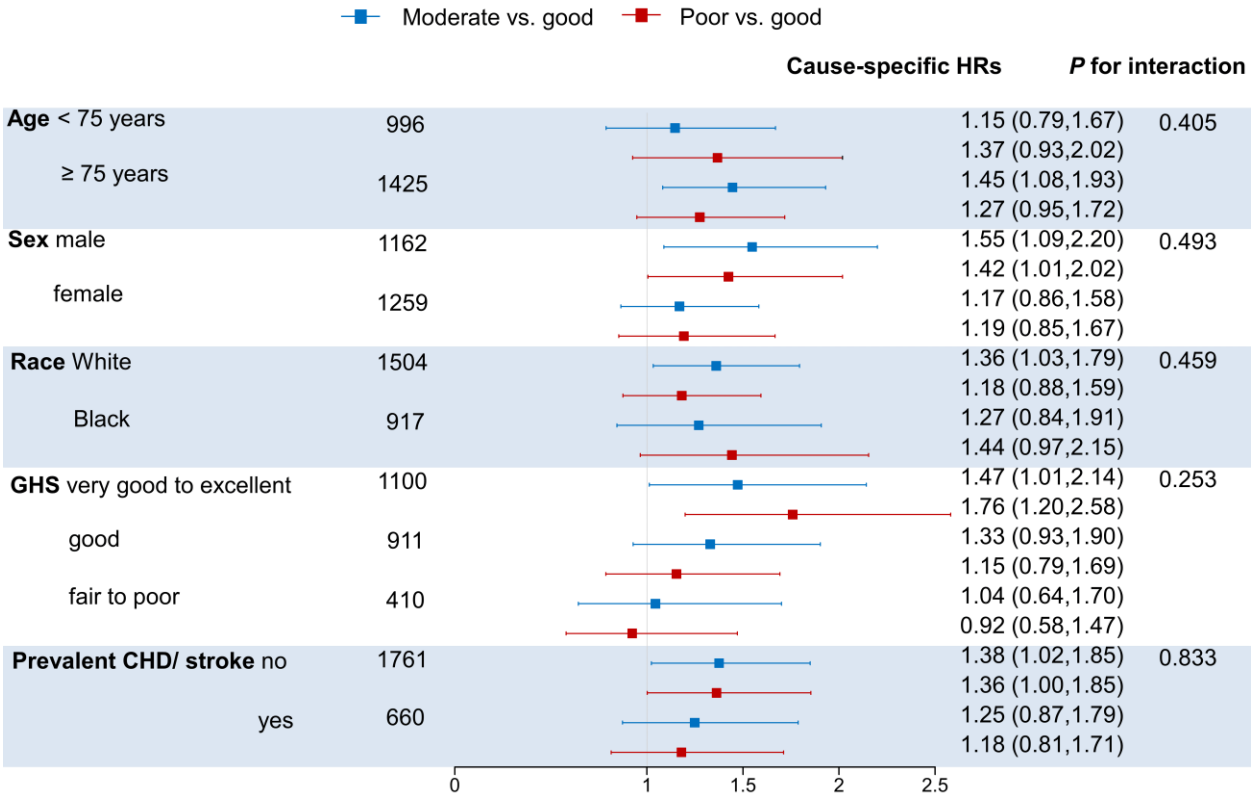
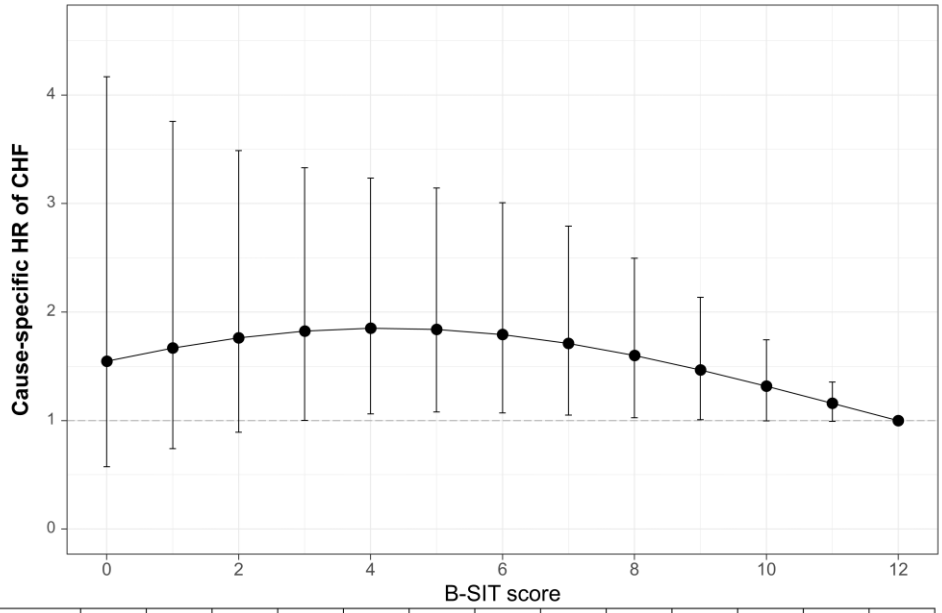


Figure 4.2 Cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs) of olfaction in relation to congestive heart failure with up to 12 years of follow-up in subgroup analyses (n=2,421). Each model was adjusted for the interaction between baseline olfactory status and the subgroup factor of interest, plus covariates of age, sex, race, education, study site, smoking status, brisk walking, body mass index, self-reported general health status (GHS), systolic blood pressure, use of antihypertensive medications, diabetes, depressive symptoms, total cholesterol, high-density lipoprotein-cholesterol, prevalent coronary heart diseases (CHD)/stroke, heart rate, left ventricular hypertrophy, abnormal lung function, albumin and estimated glomerular filtration rate, stratified by the tertile of interleukin 6

We, therefore, further explored details of this relationship among participants who self-reported a very-good-to-excellent health at baseline. When we analyzed the B-SIT score as a continuous variable using the perfect score of 12 as the reference, the cause-specific HR of CHF

ascended as the olfaction performance decreased until the B-SIT score of 4, after which the HRs were slightly attenuated (**Figure 4.3**).



B-SIT	0	1	2	3	4	5	6	7	8	9	10	11	12
HR	1.55	1.67	1.76	1.83	1.85	1.84	1.79	1.71	1.6	1.47	1.32	1.16	1

Figure 4.3 Cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for congestive heart failure (CHF) by continuous olfaction score among participants who self-reported very-good-to-excellent health (n=1,100). Olfaction was measured by the Brief-Smell Identification test (B-SIT), the perfect score of which as 12 was used to be the reference. The model was adjusted for age, sex, race, education, study site, smoking status, brisk walking, body mass index, use of antihypertensive medications, diabetes, depressive symptoms, total cholesterol, high-density lipoprotein-cholesterol, prevalent coronary heart disease/stroke, heart rate, left ventricular hypertrophy, abnormal lung function, albumin, interleukin 6 and estimated glomerular filtration rate, stratified by groups of systolic blood pressure (140mmHg as the cut-off)

4.4 Discussion

To our knowledge, this is the first study that aims to examine the association of olfaction with major cardiovascular diseases among older adults. Such an investigation is important because poor olfaction is prevalent in older adults, cardiovascular disease is the leading cause of death, and their connections are biologically plausible. In this large community-dwelling cohort, we found that a single test of olfactory status was associated with the risk of developing CHF for up to 12 years of

follow-up. This association was robust across subgroups of age, sex, race, and prevalent CHD/stroke, but appeared to be more evident among participants who reported very-good-to-excellent health at baseline. However, olfactory status was not statistically significantly associated with the risk of developing CHD or stroke. Taken together, this study provides interesting preliminary evidence that poor olfaction may be associated with long-term CHF risk in older adults, particularly among those who consider their general health as very good or excellent.

Cardiovascular disease is the leading causes of death, and its incidence increases with age[178]. While cardiovascular risk factors are among the best characterized[62], as people age, known associations with cardiovascular diseases may attenuate, possibly due to aging and resilience to existing risk factors among survivors[179]. There remains a critical need to identify novel factors associated with adverse cardiovascular outcomes in older adults to further inform risk prediction and intervention. In contrast to known cardiovascular risk factors, including hypertension, obesity, and smoking, even health-conscious individuals rarely pay attention to their sense of smell[2,23,24].

In older adults, poor olfaction is age-dependent[2,3,23] and robustly predicts age-related neurodegenerative diseases and all-cause mortality[180,181]. Emerging evidence further suggests that poor olfaction is associated with a broad range of age-related adverse health conditions beyond neurodegenerative diseases, including cardiovascular diseases[2,127,123,118,122,35], diabetes[182,183], cirrhosis[184], kidney dysfunction[185], frailty[186], pneumonia[159], depression[106], physical functioning decline[105], and loss of body lean mass[187]. Some of the evidence comes from well-designed longitudinal cohorts[105,106,127,159,185,187]. These intriguing findings, together with well-documented associations of poor olfaction with neurodegenerative diseases and mortality, raise the possibility that poor olfaction may be a marker of accelerated biological aging across multiple systems. As olfaction identification tests are simple, fast, and non-invasive, future studies should investigate

this hypothesis and explore how it may help promote healthy aging by identifying potential health issues in older adults early.

Although our findings are preliminary and need confirmation, we speculated that, in older adults, poor olfaction may be related to cardiovascular health either as a subclinical marker or a potential risk factor. As vascular remodeling develops and progresses, insufficient blood supply may gradually impair the health of nasal epithelium and structures in the olfactory signal pathway, limiting normal olfactory functioning[9]. Supporting this viewpoint, preliminary evidence suggests that carotid intima-media thickness and artery plaques, two subclinical markers of atherosclerosis, have been associated with the olfactory decline in older adults[90,91]. On the other hand, it is also biologically plausible that poor olfaction may adversely affect cardiovascular health. It has been speculated that impaired olfaction may alter ones' diet and food choices, which could negatively impact their nutritional status and overall health over time[98–100]. Further, impaired olfaction may contribute to a depressed mood, social isolation, and physical inactivity[188,189]. All these may potentially increase one's vulnerability to endogenous and exogenous stressors, contributing to or exacerbating cardiovascular disease risk. However, to date, the role of olfaction in cardiovascular health remains speculative with limited evidence.

To the best of our knowledge, only one prospective study has explored the association of poor olfaction with the risk of cardiovascular diseases. In the National Social Life, Health, and Aging Project, Siegel et al reported that olfactory decline during the first 5 years was associated with marginally significantly greater odds of reporting a diagnosis of heart disease (odds ratio: 1.75, 95% CI: 0.93–3.31)[127]. Notably, in this study, the diagnosis of heart disease was self-reported only once at the year-10 follow-up survey and was analyzed as a secondary outcome. The current study is large, community-based, and specifically designed to examine olfaction in relation to the

risk of adjudicated incident CHD, stroke, and CHF. In the analyses, we carefully accounted for the competing risk of death and relevant covariates. We found that a single smell test was not statistically significantly associated with incident CHD or stroke events. However, compared to participants with good olfaction, those with moderate or poor olfaction had a robust, albeit modest, increase in CHF risk for up to 12 years of follow-up. In contrast to CHD and ischemic stroke where arterio- and/or atherosclerosis are major mechanisms[190,191], CHF is etiologically more complex. The latter is a multiorgan syndrome with a net outcome of a failing heart, characterized by a reduced cardiac output and increased venous pressure[192]. Coronary arteriosclerosis contributes to CHF, but any sustained myocardial stress such as increased cardiac pressure and volume overload may lead to myocardial hypertrophic response and cardiac remodeling, eventually resulting in CHF[176]. Although speculative, the differential results of CHF from CHD/stroke support the possibility that poor olfaction may signal or elevate one's vulnerability to myocardial stressors. Future studies are warranted to confirm our observations and to investigate potential mechanisms, which may lead to interventional opportunities with poor olfaction either as a red flag or a potential target of intervention, for example through olfactory training, dietary manipulation, and exercise[193–195].

Although the results were not statistically significant across subgroups of self-reported health status, the association of poor olfaction with incident CHF appeared to be more evident among participants who self-reported very-good-to-excellent health status at baseline, similar to our finding on the association of poor olfaction with mortality[57]. In contrast, the association was close to null among individuals who self-evaluated their overall health as fair or poor. Self-reported health is a subjective perception that one may integrate their biological, social, mental, and functional health perspectives with their personal and cultural beliefs and their attitudes towards

health[196]. While the report is subject to individual interpretation, it has been commonly used in health research to assess one's general health status and it robustly predicts the risk of mortality in older adults[197]. We speculated individuals who rated their health as fair or poor might already have multiple comorbidities or risk factors that play a detrimental role in their myocardial health, outweighing that from poor olfaction. In contrast, among those who reported very-good-to-excellent health, poor olfaction may serve as an early signal for deteriorating myocardial health in the absence of other clinical signals for increased CHF risk. Notably, in this subgroup, the association estimate of poor olfaction with CHF was modestly higher than that of known leading causes of CHF such as prevalent cardiovascular disease and habitual smoking (**Table A3.3**). Taken together, we speculate poor olfaction is likely an early indicator for deteriorating myocardial health in apparently healthy older adults, awaiting independent confirmation and investigation of underlying mechanisms.

Strengths of this study include the relatively large number of community-based participants, more than a decade of follow-up, meticulous health surveillance and outcome assessments, careful covariate identification, and statistical analyses. Our study also has several notable limitations. First, study participants were all older than 70 at enrollment but were relatively high-functioning. Therefore, study findings may not be readily generalizable to younger populations or populations with different demographics or health status. Second, olfaction was only assessed once. As olfactory function declines fast with age in older adults, participants' olfaction may continuously decline over follow-up, which was not captured in the current study. We therefore might have underestimated the role of olfaction in signifying or maintaining cardiovascular health in older adults. Future longitudinal studies with relatively younger participants and repeated assessments of olfaction may better characterize the role of olfaction in

cardiovascular health in the context of aging. Third, as the B-SIT was designed to screen for smell identification deficit in large populations, our study did not address the association of other olfactory modalities (e.g., detection and discrimination) with the risk of major cardiovascular outcomes. Fourth, while our study findings were robust as evidenced in multiple sensitivity analyses, as in any observational study, we could not exclude the possibilities of chance finding or residual confounding. Finally, while our study suggests that both poor and moderate olfaction are associated with the future risk of experiencing a CHF event, it provides little clue to the underlying mechanisms.

In conclusion, in this well-established community-based study of older adults, we found that poor olfaction was statistically significantly associated with risk for CHF for up to twelve years, but not with risk for CHD or stroke. Future studies should confirm this observation and investigate underlying mechanisms.

CHAPTER 5: OLFACTORY STATUS IN RELATION TO STROKE IN THE ARIC STUDY

5.1 Introduction

Stroke occurs in about 800,000 adults annually in the US and is the fifth leading cause of death[58]. While over 80% of stroke events can be categorized as ischemic, the pathologies and causes of stroke are heterogenous, even among ischemic strokes[67]. Less than half of ischemic strokes can be attributed to large artery atherothrombosis or cardiac-origin emboli[68]. Conventional risk factors may not sufficiently stratify stroke risk, especially for strokes with atypical or complex pathologies, such as those due to cerebral small vessel disease[198]. In addition, known risk factors may have attenuated associations with incident stroke in the elderly[179]. It is hereby imperative to identify novel markers to facilitate the risk stratification of stroke in older adults.

Olfactory dysfunction is common in older adults, affecting over a quarter of those aged 65 years and older[2]. This sensory deficit can be simply tested with a non-invasive smell identification test[199,200]. Smell identification involves odor sensation and cognition, and thus requires intact functions of both the peripheral and central olfactory structures[43]. Cerebral hemodynamic abnormalities related to the olfactory system may compromise normal olfactory functioning. In support of this, major risk factors for stroke, such as subclinical intracranial atherosclerosis[191] and disturbed intracranial fluid dynamics[92], are found to be associated with olfactory dysfunction[90,91,93,94]. Moreover, olfactory dysfunction may adversely affect one's diet and lifestyle[99,100] which may in turn increase future risk of stroke[201]. Therefore, either as a marker or a contributor, poor olfaction may signify higher risk of stroke in older adults.

Despite the intriguing biological plausibility of an association between olfaction and stroke, empirical evidence is scant. In a hospital-based magnetic resonance imaging study, stroke

patients were found to have smaller peripheral and central olfactory areas than control patients[124]. In contrast, we did not observe a statistically significant association between poor olfaction and risk of stroke in the Health ABC Study[1]. Therefore, we further investigated whether poor olfaction is related to future stroke risk in a large community-dwelling US cohort of older adults from the ARIC Study.

5.2 Methods

5.2.1 Study Population

The ARIC Study is a community-based prospective cohort that aimed to investigate the etiology of atherosclerosis and its clinical sequelae in the US[130,131]. Briefly, between 1987-1989, this study recruited 15,792 participants aged 45-64 years from four U.S. communities (Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland)[130,131]. Since enrollment, this study conducted periodic comprehensive in-person clinical examinations and annual or semi-annual (since 2012) phone calls to update participant's health. Meanwhile, the study has closely monitored the health and survival of participants via the cohort-wide hospitalization and death surveillance. Over the past three decades, the ARIC study has provided invaluable information in the cardiovascular field and demonstrated the importance of population-based research in the understanding of cardiovascular health[131].

The ARIC's fifth clinical examination (Visit 5) in 2011-2013 included a brief smell identification test and was thus considered as the baseline for the current analysis. Of 6,515 who attended Visit 5 in-person and provided their written informed consent, we excluded 18 participants with race other than Black or White, 24 Black participants from Minneapolis and Washinton County due to small numbers, 437 with missing olfactory score, and 237 with history

of stroke. We therefore followed 5,799 at-risk participants until the date of first stroke event, death, last contact, or December 31, 2020, whichever came first. The ARIC study protocol was approved by all participating institutions' institutional review boards. This specific analysis was approved by the institutional review board of Michigan State University.

5.2.2 Olfactory Status

Olfactory status was assessed using the 12-item SS odor identification test[133]. Briefly, participants were asked to smell 12 common odors in felt-tip pens, one at a time, and then to select the odor from four possible answers in a multiple-forced-choice format. This test is reliable and easy to administer[133]. It has been commonly used in clinical and epidemiological settings[202–205]. The test score ranges from 0 to 12, as each correct answer is given one point. We defined poor olfaction as a smell score ≤8, moderate as 9-10, and good as 11-12, which correspond to the tertile of the test score distribution in the study population. In the sensitivity analysis, we further categorized poor olfaction into anosmia (score≤6) and hyposmia (7-8), consistent with previous published studies[22,206].

5.2.3 Stroke Events

The fatal and non-fatal hospitalized strokes were identified by annual or semi-annual phone interviews and record review for hospitalizations[146,147,207,208]. Throughout the follow-up, hospitalizations with possible stroke-related discharge diagnosis codes were identified for ARIC participants. Specifically, the ARIC Study considered the ICD -9-Clinical Modification (CM) codes of 430-438 before 1997 as possible stroke-related hospitalizations, followed by ICD-9-CM codes 430-436 and ICD-10 codes G45, I60-I67 until 2019, and ICD-10 codes G45, I60-I64 afterward. The stroke-related deaths were identified through linkage to the vital statistics department for each death or else the National Death Index[146,207]. All the events were classified

independently by the computerized stroke algorithm and a physician reviewer from the Stroke-Mortality and Morbidity Classification Committee[147]. Disagreement between the two sources led to adjudication by another physician. In this study, we considered definite or probable incident fatal and non-fatal strokes as the primary outcome. As detailed before[146,147], strokes were categorized into 1 of 4 primary types based on the standardized protocol, including subarachnoid hemorrhage, intracerebral hemorrhage, thrombotic brain infarction, and embolic brain infarction. Given that most strokes in the US are ischemic, in one sensitivity analysis, we restricted the outcome of interest to ischemic stroke which includes thrombotic and embolic brain infarction.

5.2.4 Covariates

We considered a range of covariates at Visit 5 when olfaction was assessed. Date of birth, sex, race, and education level were self-reported at Visit 1 and smoking status at Visit 5. As Black participants were predominantly from Jackson, we further categorized race based on the study center as is commonly done in the analysis of ARIC data[209]. We defined education as less than high school, high school or equivalent, and at least some college. Apolipoprotein E (APOE) genotype was measured using TaqMan system and dichotomized to APOE4 carrier (≥1 ε4 alleles) and noncarrier (no ε4 alleles)[210]. BMI was calculated by dividing weight by height-squared (kg/m^2) and the systolic blood pressure by averaging 2 measurements in the sitting position. The uses of lipid-lowering and antihypertensive medications were collected by asking participants to bring prescription and nonprescription drugs they had used in the last 4 weeks[211,212]. We defined comorbidities based on published protocols: 1) diabetes as a fasting glucose level ≥ 126 mg/dL, a non-fasting glucose level ≥200 mg/dL, HbA_{1C} ≥6.5%, a self-reported physician diagnosis, or self-reported use of antidiabetic medications[150]; 2) CHD as a combination of self-reported CHD at Visit 1 and adjudicated events between Visit 1 and Visit 5[213]; 3) HF ascertained from adjudicated heart

failure hospitalization since 2005, self-reported HF at Visit 3-5, or hospitalization with ICD-9-CM code of 428 before 2005[81]; 4) atrial fibrillation identified from the electrocardiogram or hospitalization discharge diagnosis[214]; 5) dementia adjudicated through in-person neuropsychological evaluations, or identified through telephone interview for cognitive status score, informant rating, or hospitalization[215]; 6) Parkinson's disease adjudicated by experts' review of self-reported diagnosis, medication uses, hospitalization discharges, or death certificate, along with additional diagnostic information from patients and their treating physicians[216]; 7) depressive symptoms defined as ≥ 9 out of 11 items on the Center for Epidemiologic Studies Depression questionnaire at Visit 5[217]. We assessed frailty using the Fried Frailty phenotype and combined prefrailty and frailty as having ≥1 of the five phenotypes, including weight loss, exhaustion, slow walking speed, low physical activity, and low grip strength[218]. Total cholesterol and HDL-C were measured in fasting plasma following standard procedures[219]. Plasma creatinine and cystatin C were used in the CKD-EPI creatinine-cystatin equation for eGFR[173,220].

5.2.5 Statistical Analyses

In descriptive analyses, we calculated the crude CIF of stroke along with its competing risk of death, and tested the equality of CIF across olfactory statuses at baseline using the Gray's test[174]. In the multivariable analyses, we used the discrete-time Fine-Gray sub-distribution model to estimate the association of olfactory status with risk of stroke, accounting for covariates and competing events of death[155,156]. In brief, we used the pooled logistic regression with 1-month interval to estimate the sub-distribution hazard of developing stroke at each month. To investigate the potential time-varying association of olfactory status with the outcome of interest during the follow-up, we added interaction terms between olfactory statuses and follow-up time in the pooled logistic regression. For covariates, we used the Kolmogorov-Smirnov test and the Cramer von

Mises test to check the proportional sub-distribution hazard assumption[221]. If either test showed a statistically significant time-varying association of a covariate with the outcome, we added an interaction term between the covariate and time. We selected the cubic spline with the degree of freedom of 4 (one inner knot at 52 month) as the functional form of time, because it has the least prediction error[222] at most of the follow-up years by using 100-fold cross-validation, compared with cubic splines with other degrees of freedom and the non-parametric step function. We calculated the counterfactual cumulative risk of stroke ($\Pr[Y_t^a]$) at each follow-up month for all the study participants given their covariates under the hypothetical conditions of different olfactory statuses[155]. We used the following equation

$$\Pr[Y_t^a] = \sum_z E[Y_t^a | a, Z = z] \Pr[Z = z]$$

$$= \sum_z \left\{ \sum_{j=1}^{t} h_j^{sb}(a|z) \prod_{k=0}^{j-1} \left[1 - h_k^{sb}(a|z)\right] \right\} \Pr[Z = z]$$

at time t ($t = 1, \ldots, T$), where $h_t^{sb}(a|z)$ is the conditional sub-distribution hazard at time t when the olfactory status is a. Specifically, the sub-distribution hazard function is defined as $h_t^{sub}(a|z) = \Pr[Y_t^a = 1 | Y_{t-1}^a = 0, z]$ under the discrete time scale. Finally, we compared the absolute risk across olfactory statuses based on the baseline covariate distribution of the entire sample and then estimated the period-specific RD and RR with good olfaction as the reference.

We presented three sets of models with sequentially increasing numbers of covariates adjusted. Model 1 was adjusted for basic demographics of age, sex, race–center, and education. Model 2 aimed to assess the association of olfaction with risk of stroke independent of important vascular and cardioembolic risk factors[223,63,62,67], including APOE4 carrier, smoking status, BMI, total cholesterol, HDL-C, lipid-lowering medication use, diabetes, systolic blood pressure, antihypertensive medication use, prevalent atrial fibrillation, CHD, heart failure, and eGFR.

Finally, as frailty is common in older adults and associated with both poor olfaction[224–226] and incident stroke[114,227], we further adjusted for frailty in Model 3. To further demonstrate the robustness of study findings to analytical approaches, we used the cause-specific Cox regression to estimate the period-specific cause-specific hazard ratio for olfactory status.

Further, we conducted multiple subgroup analyses by age groups (<75 vs. ≥ 75 years), sex (male vs. female), race (White vs. Black), and history of major cardiovascular events including CHD and heart failure (no vs. yes). In addition, we conducted the following sensitivity analyses to check the robustness of study findings: 1) we classified poor olfaction into hyposmia and anosmia to further examine the dose-response pattern of the olfaction-stroke relationship; 2) to minimize the potential impact of dementia on olfactory testing, we redid the analysis by excluding participants with dementia at baseline; 3) we analyzed ischemic stroke as the outcome of interest; 4) we conducted multiple imputation for the 7.9% missing values of frailty and repeated the primary analysis, as detailed in **Appendix 4**. Finally, to demonstrate the strength of olfaction–stroke association in the context of other known major risk factors for stroke, we additionally presented the associations of for CHD, as a proxy of systemic atherosclerosis, and atrial fibrillation, as a risk factor for cardioembolic stroke, with stroke risk, using the same analytical approach as described above. We used SAS (version 9.4; SAS Institute Inc. Cary, NC, USA) for description and cause-specific hazard modeling, and R (version 4.1.3) for all the other analyses with a two-sided α of 0.05.

5.3 Results

Eligible study participants included 3,423 women and 2,376 men, with an average age at baseline of 75.5±5.1 years old and 22.2% Black. Compared with participants with good olfaction, those with poor olfaction were more likely to be older, male, Black, APOE4 carriers, and current/former

smokers, and to report lower education level (**Table 5.1**). They were also more likely to use antihypertensive and lipid-lowering medications, and to have diabetes, atrial fibrillation, CHD, heart failure, prefrailty/frailty, dementia, Parkinson's disease, depressive symptoms, and lower levels of total cholesterol, HDL-C, and eGFR.

Table 5.1 Population characteristics by baseline olfactory status (n=5,799), the ARIC Study 2011-2013

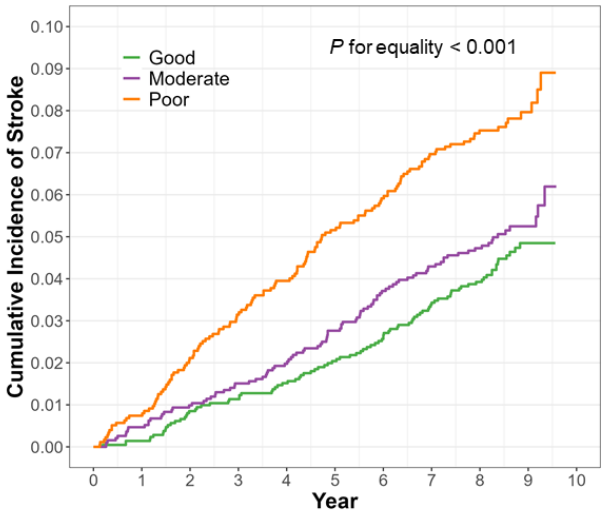
Variables [a]	Olfactory status		
	Good (n=2,121)	Moderate (n=1,924)	Poor (n=1,754)
Age in year	74 (71, 78)	75 (71, 79)	77 (72, 81)
Sex Male	721 (34)	797 (41.4)	858 (48.9)
Race Black	231 (10.9)	420 (21.8)	637 (36.3)
Center			
Forsyth county	532 (25.1)	423 (22)	338 (19.3)
Jackson	208 (9.8)	382 (19.9)	608 (34.7)
Minneapolis suburbs	739 (34.8)	567 (29.5)	377 (21.5)
Washington County	642 (30.3)	552 (28.7)	431 (24.6)
Race–center			
White in Forsyth County	509 (24)	385 (20)	309 (17.6)
White in Minneapolis suburbs	739 (34.8)	567 (29.5)	377 (21.5)
White in Washington County	642 (30.3)	552 (28.7)	431 (24.6)
Black in Forsyth County	23 (1.1)	38 (2)	29 (1.7)
Black in Jackson	208 (9.8)	382 (19.9)	608 (21.8)
Education			
Less than high school	176 (8.3)	259 (13.5)	382 (21.8)
High school or equivalent	894 (42.1)	823 (42.8)	702 (40)
At least some college	1051 (49.6)	842 (43.8)	670 (38.2)
APOE4 carrier	481 (22.7)	501 (26)	557 (31.8)
Smoking status			
Never smoker	944 (44.5)	785 (40.8)	701 (40)
Former smoker	1077 (50.8)	1017 (52.9)	947 (54)
Current smoker	100 (4.7)	122 (6.3)	106 (6)
Body mass index in kg/m^2			
<25.0	550 (25.9)	445 (23.1)	437 (24.9)
25.0 - <30	851 (40.1)	790 (41.1)	752 (42.9)
≥30.0	720 (33.9)	689 (35.8)	565 (32.2)
Total cholesterol in mmol/L	4.68 (4.03, 5.46)	4.63 (3.96, 5.40)	4.53 (3.83, 5.20)
HDL-C in mmol/L	1.34 (1.11, 1.58)	1.29 (1.09, 1.55)	1.28 (1.06, 1.50)
Use of lipid lowering agents	1143 (53.9)	1074 (55.8)	1016 (57.9)

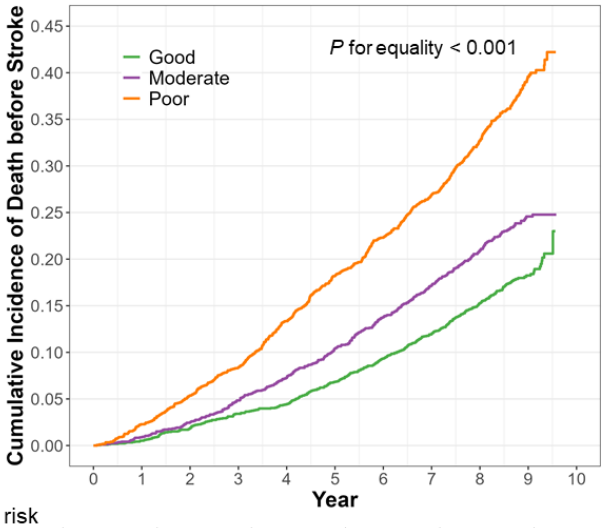
Table 5.1 (cont'd)

Diabetes	601 (28.3)	641 (33.3)	675 (38.5)
Systolic pressure in mmHg	128.5 (118, 140.5)	128.5 (117.5, 140.5)	129 (118, 141.5)
Antihypertensive use	1503 (70.9)	1459 (75.8)	1390 (79.2)
eGFR in mL/min/1.73m^2	67.7 (55.9, 79.9)	66.7 (54.2, 79.2)	64.2 (50.6, 76.3)
Atrial fibrillation	109 (5.1)	135 (7)	153 (8.7)
CHD	258 (12.2)	259 (13.5)	296 (16.9)
Heart failure	187 (8.8)	223 (11.6)	306 (17.4)
Fried Frailty phenotype			
Robust	1077 (50.8)	838 (43.6)	568 (32.4)
Prefrail or frail	940 (44.3)	955 (49.6)	960 (54.7)
Missing	104 (4.9)	131 (6.8)	226 (12.9)
Dementia	8 (0.4)	23 (1.2)	182 (10.4)
Parkinson's disease	3 (0.1)	5 (0.3)	30 (1.7)
Depressive symptoms	102 (4.8)	142 (7.4)	140 (8.0)

Abbreviations: ARIC: Atherosclerosis Risk in Communities; HDL-C: high-density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate; CHD: coronary heart diseases.
[a] Continuous variables are presented as median (25th, 75th percentile), and categorical variables as number (column %)

During up to 9.6 years (median 8.3 years) of follow-up, 332 individuals had an incident stroke event, of which 256 were classified as ischemic stroke. The number of incident stroke events was 95 among participants with good olfaction, 100 among those with moderate olfaction, and 137 among those with poor olfaction. **Figure 5.1** shows the crude association of olfactory status with incident stroke along with the competing event of death. For both outcomes, participants with poor olfaction had a higher cumulative incidence than those with better olfactory statuses during the follow-up.





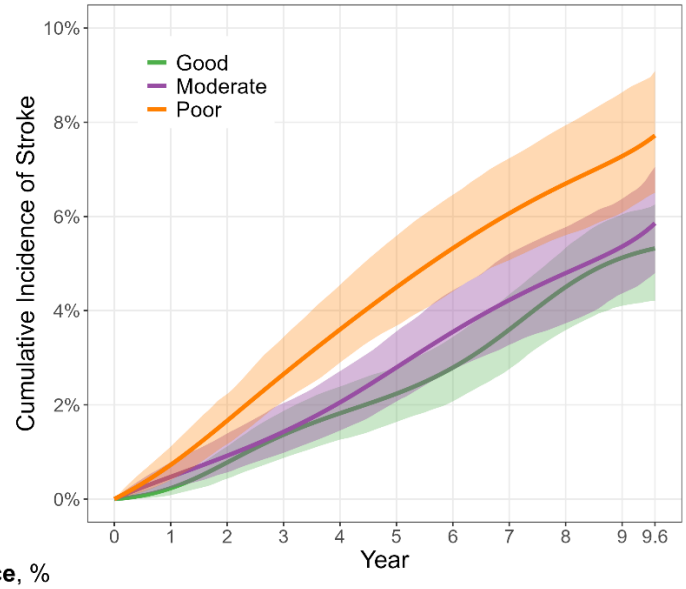
No. at risk

Year	0	2	4	6	8
Good	2121	2059	1975	1840	1508
Moderate	1924	1855	1737	1564	1235
Poor	1754	1616	1441	1231	874

Figure 5.1 Crude cumulative incidence function of stroke and its competing event of death by baseline olfactory status (n = 5,799)

Multivariable analyses confirmed the association of poor olfaction with higher risk of stroke throughout the follow-up (**Figure 5.2 and Table 5.2**). At year 9.6, the marginal cumulative incidence of stroke was 5.3% (95% CI: 4.2-6.3%) for good olfaction group, 5.9% (95% CI: 4.8-7.1%) for moderate olfaction, and 7.7% (95% CI: 6.5-9.1%) for poor olfaction. We however also found that the association appeared to be more evident during the first 6 years of follow-up and

was modestly attenuated afterwards. For example, the fully adjusted RR for poor vs. good olfaction was 2.14 (95% CI: 1.22, 3.94) at year 2, 1.98 (95% CI: 1.43, 3.02) at year 4, 1.91 (95% CI: 1.43, 2.77) at year 6, 1.49 (95% CI: 1.17, 2.00) at year 8, and 1.45 (95% CI: 1.16, 1.95) at year 9.6 (**Table 5.2**). Correspondingly, the RD between poor and good olfaction groups increased fast during the first 6 years, and then stabilized with extended follow-up (**Figure 5.2**). The findings were consistent in the alternative analysis using cause-specific hazard models (**Table A4.1**). In both analyses, we did not observe a statistically significant difference in risk or cause-specific hazard of stroke between moderate and good olfaction.



Risk difference, %

Olfactory status	Follow-up years				
	2-year	4-year	6-year	8-year	9.6-year
Moderate vs. good	0.1 (-0.4,0.7)	0.2 (-0.6,1.1)	0.8 (-0.4,1.9)	0.3 (-1.1,1.8)	0.5 (-0.9,2.5)
Poor vs. good	0.9 (0.2,1.6)	1.8 (0.9,2.8)	2.5 (1.4,4.0)	2.2 (1.0,3.8)	2.4 (1.0,4.2)

Figure 5.2 Marginal adjusted cumulative incidence function of stroke by olfactory status and the risk difference comparing moderate and poor vs. good olfaction. The cumulative incidence was estimated by the discrete-time sub-distribution hazard model, adjusting for covariates in Model 3

Table 5.2 Marginal adjusted risk ratios of stroke comparing moderate/poor with good olfaction during the follow-up (n=5,799)

	Risk ratio (95% confidence interval) [a] by follow-up years				
Olfactory status	2-Year	4-Year	6-Year	8-Year	9.6-Year
Model 1[b]					

Table 5.2 (cont'd)

Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.31 (0.69,2.49)	1.22 (0.79,1.93)	1.34 (0.94,1.98)	1.1 (0.79,1.48)	1.14 (0.89,1.56)
Poor	2.53 (1.46,4.67)	2.22 (1.6,3.36)	2.04 (1.57,2.96)	1.55 (1.22,2.06)	1.51 (1.2,2.02)
Model 2 [c]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.2 (0.62,2.31)	1.14 (0.72,1.81)	1.29 (0.9,1.9)	1.07 (0.78,1.46)	1.11 (0.86,1.52)
Poor	2.17 (1.24,3.97)	2 (1.44,3.09)	1.94 (1.47,2.84)	1.51 (1.2,2.02)	1.47 (1.18,1.97)
Model 3 [d]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.18 (0.61,2.26)	1.13 (0.71,1.8)	1.27 (0.89,1.86)	1.07 (0.77,1.45)	1.1 (0.85,1.53)
Poor	2.14 (1.22,3.94)	1.98 (1.43,3.02)	1.91 (1.43,2.77)	1.49 (1.17,2)	1.45 (1.16,1.95)

[a] Marginal adjusted risk ratio was calculated through the multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples.
[b] Model 1 includes age, sex, race-center, and education, plus interaction terms between time and olfactory status.
[c] Model 2 further includes APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, HDL-cholesterol, lipid lowering medication, atrial fibrillation, coronary heart disease, heart failure, and estimated glomerular filtration rate, plus two-way interaction terms between time and education & HDL-cholesterol.
[d] Model 3 further includes frailty.

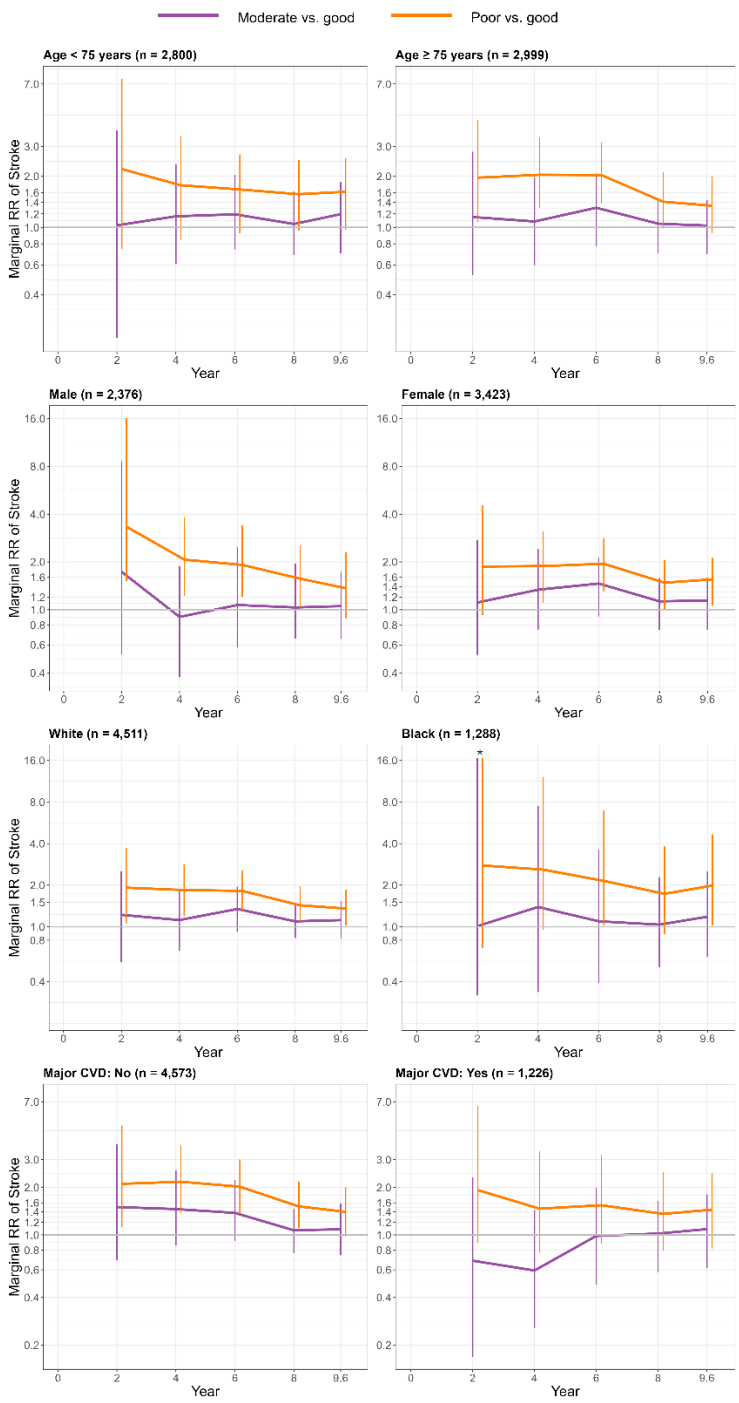


Figure 5.3 Stratified marginal adjusted risk ratios (RRs) and 95% confidence intervals (95% CIs) of stroke in the subgroup analyses by baseline age groups (<vs. ≥ 75 years), sex (male vs. female), race (White vs. Black) or history of other major cardiovascular diseases (no vs. yes). * Due to the small number of incident events, the 95% CIs for Black participants were imprecise at year 2, so we did not present the actual values in the plot scale. Specifically, the adjusted RR of stroke at year 2 was 1.01 (95% CI: 0.09, 1.2×10^{12}) for moderate olfaction and was 2.78 (95% CI: 0.71, 4.5×10^{12}) for poor olfaction

The association of poor olfaction with higher risk of stroke was consistently observed across subgroups of age, sex, race, and history of major cardiovascular events (**Figure 5.3**). In sensitivity analyses, separating poor olfaction into hyposmia and anosmia further demonstrated the dose-response relationship between olfactory statuses and risk of stroke, particularly during shorter follow-up periods (**Figure A4.1 and Table A4.2**). For example, at year 2, the adjusted RR of stroke was 1.19 for moderate olfaction group, 1.59 for hyposmia group, 2.83 for the anosmia group, whereas the corresponding RR was 1.10, 1.41, 1.50, respectively at year 9.6. Findings were also found to be robust to the sensitivity analyses of excluding baseline dementia Parkinson's disease, or depressive symptoms (**Table A4.3**), using ischemic stroke as the outcome of interest (**Table A4.4**), and using multiple imputation to address missingness on frailty (**Table A4.5**). Finally, the strength of association between poor olfaction and stroke risk was comparable to those of two well-known stroke risk factors ─ CHD and atrial fibrillation (**Table A4.6**).

5.4 Discussion

In this large community-dwelling cohort of older adults, we found that poor olfaction identified from a single smell test was robustly associated with an elevated risk of stroke for up to 9.6 years of follow-up. Our statistical analyses were comprehensive and accounted for a wide range of covariates. The results were robust to different analytical strategies, across subgroups of age, sex, race, and prior history of major cardiovascular events, and in multiple sensitivity analyses. To the best of our knowledge, this study provides the first prospective evidence that poor olfaction may be an early signal for stroke risk among older adults. Notably, the strength of this association was comparable to those of some well-established risk factors for stroke. As the smell identification test is simple, non-invasive, and can be easily administered, our findings may have clinical implications in monitoring the risk of stroke in older adults.

Stroke has a substantial public health burden, particularly in the older population[58,228]. While there are many well-documented risk factors for stroke, they may not be as strong and as clinically useful for stroke risk stratification in older adults for the following reasons. First, the disease is heterogeneous in etiology and pathogenesis. While the majority of strokes can be categorized as ischemic, over half of ischemic stroke events cannot be attributed to cardioembolic emboli or large artery stenosis[67]. For example, cerebral small vessel disease is the most common cause of lacunar stroke, accounting for a quarter of ischemic strokes[67]. Several studies recently found that conventional risk factors, such as obesity, hypertension, diabetes, and history of cardiovascular disease, could not explain majority variance in white matter hyperintensities, a key magnetic resonance imaging marker of small vessel disease[198,229]. Further, the association strengths of well-established risk factors with stroke may diminish with advanced age[179,230]. For example, the REasons for Geographic And Racial Differences in Stroke Study found that diabetes and hypertension had substantially abated associations with stroke risk among older adults, compared with their younger counterparts[179]. In addition to age-related physiological and behavior changes, people who survive to their late adulthood may also be more resilient to risk factors for stroke formed in their midlife. Therefore, there remains a need to identify novel associations for stroke risk in older adults.

Poor olfaction emerges with advanced age and becomes common in older adults, although is often unrecognized[2,23,24]. A potential connection between stroke and olfactory dysfunction was first noted in a few case reports following stroke onset[231,232]. Subsequent hospital-based case-control studies confirmed that stroke patients were more likely to have olfactory dysfunction than individuals without stroke[124,121,118]. While stroke clinical presentation is acute, its underlying pathology such as atherosclerosis[191] often take time to accumulate. It is possible that olfaction

decreases as the result of progressive vascular pathologies. Blood passes through carotid artery before flowing into the olfactory artery which is the primary blood supply for olfactory epithelium and olfactory bulb[17]. Studies found that some subclinical markers of the carotid artery atherosclerosis, such as carotid intima media thickness and plaque numbers, were associated with olfactory decline[90,91]. In addition, idiopathic intracranial hypertension (IIH), another risk factor for stroke[92], was also associated with impaired olfaction[93,94]. Interestingly, the severity of olfactory dysfunction corresponded to the clinical deterioration of IIH[93]. Taken together, these preliminary observations raise the possibility that poor olfaction may be a marker of the underlying stroke pathologies which may further developed into stroke events.

Besides being a marker of preclinical vascular pathologies in the brain, poor olfaction may also increase one's vulnerability to future stroke events in the context of aging. While empirical data is limited, normal olfaction can be critical to food choices, nutrition intake, mental health, and daily life activities of older adults[56,98–100,233,234]. A sound nutritional, physical, and mental status maintains one's resilience to interior and exterior stressors[112]. Emerging evidence has shown that poor olfaction is closely associated with frailty[224,225]— the declined physiological reserve across multiple systems[112]. Interestingly, recent studies show that frailty is associated with higher risk of future cardiovascular events, including stroke[114,227]. These observations support the possibility that elevated vulnerability may contribute to compromised cardiovascular health in late life. Poor olfaction may gradually weaken one's resilience by triggering chains of adverse behavior changes, leading to clinical strokes and other cardiovascular events.

To the best of our knowledge, prior to the current study, there was only one prospective study that examined the association between poor olfaction and future stroke risk[1]. In the Health ABC Study, we observed a modest association of poor olfaction with incident congestive heart

failure, but not with stroke. The Health ABC Study population was comparable to the ARIC Study population in multiple ways. For example, their study populations were both community-based and had average ages of 75.5 years at baseline. However, the Health ABC Study primarily enrolled well-functioning older adults in their 70s with the aim to investigate changes in body composition and physical functioning in the context of aging[128]. In comparison, the ARIC Study randomly selected a sample of community-dwelling residents during their midlife specifically to study atherosclerosis and cardiovascular health[130]. As a result, the ARIC Study in Visit 5 (the baseline of the current study) included more general older participants with a wider age range. More importantly, the ARIC Study has continuously monitored cardiovascular events, including strokes, for more than 3 decades with rigorous outcome adjudication criteria and processes[72,208]. Therefore, the ARIC Study may have more valid and thorough data on stroke history and event assessments than the Health ABC Study. Admittedly, these explanations are speculative, and our findings warrant confirmation from future large prospective studies with rigorous outcome assessment.

While we identified an evident association between poor olfaction and stroke risk, the results require cautious interpretation. The overall risk of stroke in the older population is relatively low and the risk difference between poor and good olfaction groups was modest. Future studies should confirm and quantify the association in diverse populations to better explore the clinical and public health implication of this finding. Second, we found the association was modestly attenuated after 6 years of follow-up. This might be related to the increasing resilience of survivors to stroke with extended follow-up or the olfactory decline in this older adult population over time.

The notable strengths of our study include the broad coverage of community-based US older populations and high-quality data of cardiovascular outcomes over three decades from the ARIC Study. Leveraging these strengths, we performed comprehensive statistical analysis

accounting for an extensive list of covariates and competing risk of death. In addition, we conducted various subgroup and sensitivity analyses, demonstrating the robustness of the association between poor olfaction and risk of stroke.

Our study also has several limitations. First, this study included surviving US older participants with an average age of 75.5 years at the time of smell test. Therefore, our findings may not be readily generalizable to younger populations, populations with different demographics, or populations from other countries. Second, our analyses were based on data from a single smell test. Given that olfaction decreases with age quickly in older adults[3], future studies should investigate how repeated testing of olfaction may relate to stroke risk. Third, as with any observational study, our results are subject to residual confounding. However, these concerns are somewhat alleviated by the list of covariates we have adjusted for and the strength of the association we identified. Last, while the speculated explanations are biologically plausible, empirical and mechanistic evidence are still sparse largely due to lack of awareness and research on this common sensory deficit in older adults.

In conclusion, in this large community-dwelling cohort of US older adults, we found that poor olfaction assessed by a single smell identification test was robustly associated with the higher risk of stroke for up to a decade. Future study should confirm this observation and investigate the potential mechanisms.

CHAPTER 6: OLFACTORY STATUS IN RELATION TO CORONARY HEART DISEASE IN THE ARIC STUDY

6.1 Introduction

Poor olfaction affects over a quarter of US older adults, but only 30% of those affected recognize this deficit[2,23,24]. This neglected sensory deficit may have profound health implications in older adults. It is one of the most important prodromal symptoms of neurodegeneration. For example, poor olfaction identified from a single smell test signifies a 2 to 3 fold higher risk of dementia[52] and a 4 to 5 fold higher risk of Parkinson's disease over a decade of follow-up[53]. Further, poor olfaction robustly predicts all-cause mortality in older adults[5,57,235]. Interestingly, only a small portion of the excess all-cause mortality related to poor olfaction could be explained by neurodegeneration[57], suggesting that poor olfaction may have health implications beyond our current knowledge.

CHD is one of the most common CVDs and the top leading cause of death worldwide[6]. In the US, the incidence of fatal and non-fatal CHD steadily increases with age[58]. As the associations of conventional risk factors with CVD may attenuate in older adults[230], novel markers are needed for timely risk stratification in this population. Atherogenesis in the coronary artery is a fundamental pathophysiology of CHD[65]. Given the shared risk factors and genetic predisposition, coronary artery atherosclerosis is highly correlated with carotid artery atherosclerosis[236]. As such, subclinical carotid atherosclerotic markers robustly predict future risk of CHD[237,238]. Interestingly, recent studies have found that intima media thickness and the number of sites with atherosclerotic plaques, two subclinical atherosclerotic measures of carotid artery, may be associated with olfactory function[90,91]. Emerging data raise an intriguing possibility that poor olfaction may be an early symptom of atherosclerosis, and clinical CHD risk. On the other hand, poor olfaction in older

adults may contribute to suboptimal dietary behaviors[99,100], impairing their cardiovascular health over time[239]. Taken together, poor olfaction, either as an early marker or a contributor, may signify the future risk of CHD in older adults. Empirical evidence on this topic is however sparse and inconsistent[1,127]. Hereby, we further investigated olfaction in relation to risk of CHD in the ARIC Study, a well-established cohort for cardiovascular health research.

6.2 Methods

6.2.1 Study Population

The ARIC Study aims to investigate the etiology of subclinical atherosclerosis and its sequalae[130,131]. Between 1987-1989, this study enrolled 15,792 community-dwelling individuals aged 45-64 years from four geographically distinctive communities in the US (Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland). Since enrollment, participants have been followed with periodic in-person clinical examinations, annual or semiannual (2012 and after) telephone interviews, and active surveillance hospitalizations and death.

In 2011-2013, 6,538 ARIC participants completed the study's fifth clinical examination (Visit 5) which included a brief smell test. After excluding 23 participants who did not provide a written informed consent, 18 who self-reported as Asian or American Indian or Pacific Islander, 24 Black participants from Washington County or Minneapolis suburbs, 437 missing the smell test score data, and 894 with a history of CHD, the current analysis included 5,142 participants. We followed these at-risk individuals from Visit 5 to the date of the first CHD event, death, last contact, or administrative censoring on December 31, 2020, whichever occurred first. The ARIC Study protocol was approved by institutional review boards of all relevant institutes. This specific analysis was approved by the institutional review board of Michigan State University.

6.2.2 The Sense of Smell Test

We used the 12-item SS odor identification test to assess olfactory status[133]. This test is simple and easy-to-administer, and has been widely used in clinical and population studies[137,202,203,205]. Briefly, it requires individuals to smell 12 common odorants concealed in 12 felt-tip pens, one at a time, and then to select the odor from four possible answers in a forced multiple-choice format. Each correct answer was given one point with the final test score ranging from 0 to 12. We defined good olfaction as 11−12, moderate as 9−10, and poor as ≤8, corresponding to the tertile of the score distribution among study participants. In the sensitivity analysis, we separated poor olfaction into anosmia (≤6) and hyposmia (7−8), consistent with previous publications[22,206].

6.2.3 CHD Events

Hospitalized CHD events were identified through annual or semi-annual telephone interviews and reviews of all discharge diagnostic codes from each hospital within the community[144,145]. The study categorized CHD events into different fatal CHD categories (definite fatal MI, definite fatal CHD, possible fatal CHD, non-CHD death) and non-fatal MI categories (definite, probable, suspect, and no)[144]. For fatal CHD events that happened outside of a hospital, the committee reviewed information from death certificates, obituary notices, informant interviews and/or physician questionnaires to make an adjudication. Specifically, the criteria of definite hospitalized MI included 1) evolving diagnostic ECG pattern; 2) diagnostic ECG pattern and abnormal enzymes; or 3) cardia pain and abnormal enzymes plus evolving ST-T pattern or equivocal ECG pattern. Probable MI required 1) cardiac pain and abnormal enzymes; 2) cardia pain and equivocal enzymes plus evolving ST-T pattern or diagnostic ECG pattern; or 3) abnormal enzymes and evolving ST-T pattern. Definite fatal MI included a definite hospitalized MI within four weeks before death without known non-atherosclerotic lethal causes. Definite fatal CHD included a

history of chest pain within 72 hours before death or a clinical history of chronic ischemic heart disease without known non-atherosclerotic lethal causes. In the current study, we considered definite or probable hospitalized MI or fatal CHD as the primary outcome[145,213,240].

6.2.4 Covariates

We used a range of covariates collected at Visit 5 when smell testing was conducted except that date of birth, sex, race, and education level were self-reported at enrollment. Age at Visit 5 was calculated as a continuous variable. We categorized race together with study center as Jackson only had Black participants whereas Minneapolis suburbs and Washinton County only had White participants. We defined education attainment as less than high school, high school or equivalent, and at least some college. Smoking status was self-reported and categorized as never, former, and current smoker. We derived BMI by dividing weight in kilograms by square of height in meters and systolic blood pressure by averaging 2 measurements in the sitting position. APOE genotype was classified to APOE4 carrier and non-carrier. Medication use, including lipid-lowering and antihypertensive drugs, was collected using the medication inventory method[211,212]. Prevalent comorbidities were defined according to published definitions: 1) diabetes as a self-reported physician diagnosis, self-reported use of antidiabetic medications, a fasting glucose level ≥ 126 mg/dL, a non-fasting glucose level ≥200 mg/dL, or HbA_{1C} ≥6.5%[150]; 2) stroke as adjudicated definite or probable stroke events between Visit 1 and Visit 5[72]; 3) heart failure as a self-reported diagnosis at Visit 3-5, hospitalization with ICD-9 of 428 before 2005, or adjudicated HF hospitalization since 2005[81]; 4) atrial fibrillation as identified from the electrocardiogram or hospitalization[214]; 5) dementia as adjudicated based on in-person neuropsychological evaluations or identified from telephone cognitive assessment, informant rating, or hospitalization[215]. Plasma total cholesterol and HDL-C were measured using standardized procedures[219]. Renal function was

assessed by the estimated glomerular filtration rate using the CKD-EPI creatinine-cystatin equation[173,220]. We combined prefrailty and frailty and defined them as having one or more items of the Fried frailty items, including weight loss, exhaustion, slow walking speed, low physical activity, and low grip strength[218].

6.2.5 Statistical Analyses

We first calculated the crude CIFs of CHD and its competing events of death, and tested the equality of CIFs across olfactory statuses at baseline using the Gray's test[174]. In the multivariable analyses, we applied the discrete-time sub-distribution model to estimate the association between olfaction and risk of CHD accounting for covariates and competing risk of death, because our study goal was to evaluate the total association between olfaction and absolute risk of CHD in the existence of competing event of death[155,156]. Specifically, we used the pooled logistic regression with a 1-month interval to estimate the sub-distribution hazard of developing CHD each month. We included the interaction terms between olfactory status and time to investigate how the association with risk of CHD might change over time. We used the Kolmogorov-Smirnov test and the Cramer von Mises test to check the proportional sub-distribution hazard assumption for covariates[221]. If either test rejected the assumption, we added an interaction term between the covariate and time in the model. We chose the cubic spline with a degree of freedom of 5 (two inner knots at 34 month and 70 month) as the functional form of time, as it had the least prediction error[222] at most of the follow-up years by using 100-fold cross-validation, compared to cubic spline with 3, 4, and 6 degrees of freedom, and the step function. Using the estimated model, we calculated the absolute risk across olfactory statuses based on the baseline covariate distribution across the entire sample and estimated RRs and RDs over time (good olfaction as the reference) with the percentile-based confidence interval using bootstrapping with 300 samples.

We considered three multivariable models with sequential covariates added. Model 1 only adjusted for demographics, including age, sex, race-center, and education. Model 2 further included important cardiovascular and metabolic risk factors to examine the independence of the association between olfaction and CHD[64,63,62,241], including APOE4 carrier, smoking status, BMI, diabetes, systolic blood pressure, antihypertensive medication use, total cholesterol, HDL-cholesterol, lipid-lowering agent use, prevalent atrial fibrillation, stroke, heart failure, and renal function. Model 3 further included frailty, which is common in older adults and has been recently found associated with both poor olfaction[224,225] and incident CVD[113,114]. While the proportional hazard assumption did not hold for the whole follow-up, we additionally estimated the period-specific direct association between olfaction and incident CHD using the cause-specific Cox model to demonstrate our finding's robustness to different estimands in the existence of competing event of death.

In addition, we performed multiple sensitivity analyses: 1) we stratified the analysis by age groups (<vs. ≥ 75 years), sex (male vs. female), race (White vs. Black), and history of other CVDs (no vs. yes); 2) we separated poor olfaction into hyposmia and anosmia to further examine the dose-response pattern of the association of interest; 3) we repeated the primary analysis after excluding prevalent dementia cases at baseline. We used SAS (version 9.4; SAS Institute Inc. Cary, NC, USA) for description and cause-specific hazard modeling, and R (version 4.1.3) for all other analyses with a two-sided statistical significance of 0.05.

6.3 Results

At baseline, participants were on average 75.4 ± 5.1 years old with 62.9% female and 23.9% self-identified as Black. Compared to participants with good olfaction, those with poor olfaction were more likely to be older, male, Black, APOE4 carriers, and ever smokers, and to report having lower

education level (**Table 1**). They were also more likely to use antihypertensive medications and to have diabetes, atrial fibrillation, stroke, heart failure, and lower levels of total cholesterol, HDL-C, and renal function.

Table 6.1 Population characteristics by baseline olfactory status (n=5,142) in the ARIC Study at Visit 5

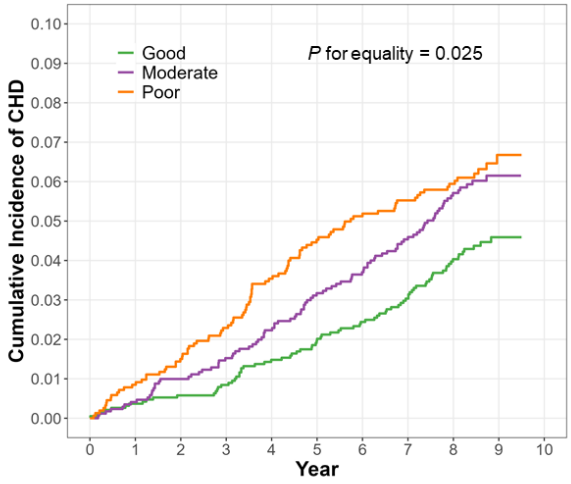
Variables [a]	Olfactory status		
	Good (n=1,901)	Moderate (n=1,708)	Poor (n=1,533)
Age in year	73 (70, 77)	74 (71, 79)	76 (72, 81)
Sex Male	578 (30.4)	639 (37.4)	689 (44.9)
Race Black	224 (11.8)	399 (23.4)	607 (39.6)
Center			
Forsyth county	475 (25)	372 (21.8)	285 (18.6)
Jackson County	203 (10.7)	365 (21.4)	580 (37.8)
Minneapolis suburbs	663 (34.9)	501 (29.3)	312 (20.4)
Washington County	560 (29.5)	470 (27.5)	356 (23.2)
Race-study center			
White in Forsyth County	454 (23.9)	338 (19.8)	258 (16.8)
White in Minneapolis suburbs	663 (34.9)	501 (29.3)	312 (20.4)
White in Washington County	560 (29.5)	470 (27.5)	356 (23.2)
Black in Forsyth County	21 (1.1)	34 (2)	27 (1.8)
Black in Jackson	203 (10.7)	365 (21.4)	580 (37.8)
Education			
Less than high school	153 (8)	220 (12.9)	336 (21.9)
High school or equivalent	801 (42.1)	724 (42.4)	613 (40)
At least some college	947 (49.8)	764 (44.7)	584 (38.1)
APOE4 carrier	434 (22.8)	453 (26.5)	489 (31.9)
Smoking status			
Never smoker	882 (46.4)	720 (42.2)	645 (42.1)
Former smoker	928 (48.8)	887 (51.9)	797 (52)
Current smoker	91 (4.8)	101 (5.9)	91 (5.9)
Body mass index in kg/m^2			
<25.0	501 (26.4)	407 (23.8)	389 (25.4)
25.0-29.9	756 (39.8)	673 (39.4)	647 (42.2)
≥30.0	644 (33.9)	628 (36.8)	497 (32.4)
Total cholesterol in mmol/L	4.8 (4.2, 5.5)	4.7 (4.1, 5.5)	4.6 (4.0, 5.3)
HDL-C in mmol/L	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.5)
Use of lipid lowering agents	944 (49.7)	887 (51.9)	816 (53.2)
Diabetes	521 (27.4)	537 (31.4)	578 (37.7)
Systolic pressure in mmHg	129 (118, 140.5)	129 (118, 140.5)	129.5 (118.5, 142)
Antihypertensive use	1286 (67.6)	1253 (73.4)	1174 (76.6)

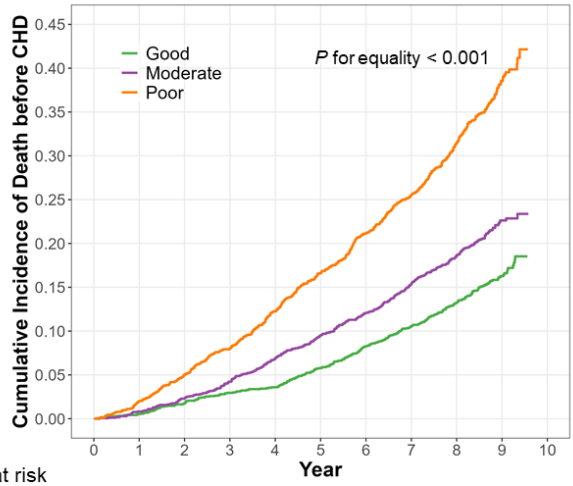
Table 6.1 (cont'd)

Renal function in mL/min/1.73m^2	68.7 (57.0, 80.4)	67.4 (54.9, 80.0)	64.8 (51.9, 76.7)
History of atrial fibrillation	80 (4.2)	107 (6.3)	111 (7.2)
Prevalent HF	104 (5.5)	142 (8.3)	185 (12.1)
Prevalent stroke	38 (2)	43 (2.5)	76 (5)
Physical frailty			
Robust	978 (51.4)	758 (44.4)	502 (32.7)
Pre-frail or frailty	830 (43.7)	831 (48.7)	833 (54.3)
Missing	93 (4.9)	119 (7)	198 (12.9)
Dementia	9 (0.5)	20 (1.2)	160 (10.4)

Abbreviations: HDL-C: high-density lipoprotein-cholesterol; HF: heart failure.
[a] Continuous variables are presented as median (25^{th}, 75^{th} percentile), and categorical variables as number (column percentage)

During up to 9.6 years (median: 8.4 years) of follow-up, 280 participants had an incident CHD event, separately 83 among individuals with good olfaction, 101 among those with moderate olfaction, and 96 among those with poor olfaction. **Figure 1** shows that participants with poor olfaction had a higher crude cumulative incidence of CHD than those with good olfaction, but the difference between the two groups appeared to decrease after 6 years of follow-up. Poor olfaction was robustly associated with higher competing risk of deaths throughout the follow-up.





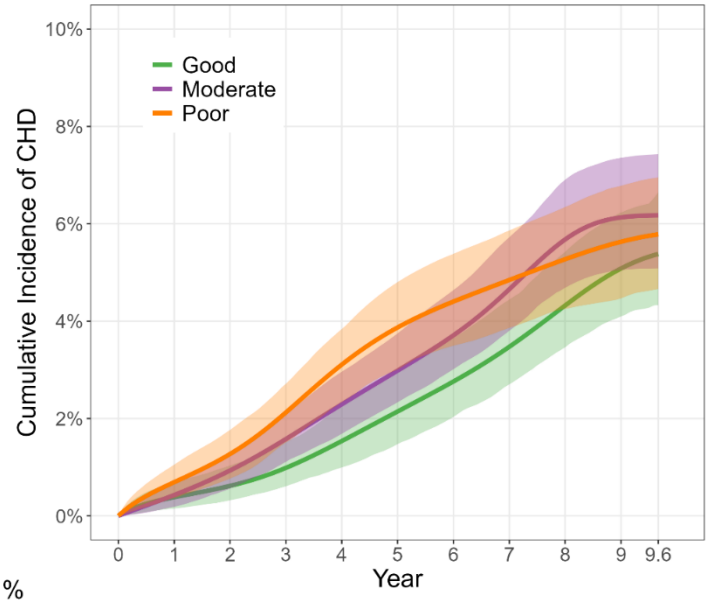
No. at risk

Year	0	2	4	6	8
Good	1901	1853	1785	1671	1383
Moderate	1708	1648	1546	1421	1113
Poor	1533	1428	1282	1106	812

Figure 6.1 Crude cumulative incidence function of coronary heart disease (CHD) and its competing event of death by baseline olfactory status (n=5,142)

Multivariable analyses confirmed the time-varying association of poor olfaction with CHD risk during the follow-up (**Figure 6.2** and **Table 6.2**). Compared with good olfaction, poor olfaction was associated with two-fold higher risk of CHD during the first 4 years of follow-up; however, the strength of the association began to attenuate afterwards and became non-significant after year 6. Specifically, the RR for poor olfaction was 2.06 (95% CI: 1.04, 4.53) at year 2, 2.02 (95% CI: 1.27, 3.29) at year 4, 1.59 (95% CI: 1.13, 2.35) at year 6, 1.22 (95% CI: 0.88, 1.70) at year 8, and 1.08 (95% CI: 0.78, 1.44) at year 9.6. Although modestly higher RRs were consistently

observed for moderate olfaction, they were not statistically significant (**Table 2**). We observed a consistent pattern of associations using the cause-specific hazard Cox model (**Table A5.1**).



Risk difference, %

Olfactory status	Risk difference by years of follow-up				
	2-year	4-year	6-year	8-year	9.6-year
Moderate vs. good	0.3 (-0.2,0.8)	0.8 (-0.1, 1.6)	0.9 (-0.2,2.1)	1.4 (-0.1,2.6)	0.8 (-0.9,2.4)
Poor vs. good	0.7 (0,1.3)	1.6 (0.5,2.6)	1.6 (0.4,2.8)	1.0 (-0.6,2.5)	0.4 (-1.4,2.2)

Figure 6.2 Marginal adjusted cumulative incidence function of coronary heart disease (CHD) and risk differences by olfactory status. The cumulative incidence was estimated by the discrete-time sub-distribution hazard model, adjusting for covariates in Model 3

Table 6.2 Olfactory status in relation to risk of coronary heart disease in the ARIC Study since Visit 5 (n=5,142)

	Risk ratio [a] (95% confidence interval) by years of follow-up				
Olfactory status	2-Year	4-Year	6-Year	8-Year	9.6-Year
Model 1[b]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.56 (0.77,3.11)	1.54 (0.99,2.47)	1.39 (0.97,2.02)	1.36 (1.01,1.75)	1.2 (0.88,1.55)
Poor	2.24 (1.11,5.03)	2.2 (1.36,3.62)	1.73 (1.20,2.54)	1.33 (0.94,1.81)	1.19 (0.84,1.58)
Model 2 [c]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.55 (0.76,3.17)	1.51 (0.97,2.39)	1.36 (0.94,1.97)	1.33 (0.98,1.73)	1.18 (0.87,1.52)

Table 6.2 (cont'd)

Poor	2.06 (1.07,4.5)	2.08 (1.29,3.38)	1.64 (1.14,2.41)	1.26 (0.89,1.74)	1.13 (0.81,1.52)
Model 3 [d]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.51 (0.75,3.01)	1.49 (0.96,2.37)	1.34 (0.94,1.93)	1.31 (0.97,1.72)	1.15 (0.85,1.49)
Poor	2.06 (1.04,4.53)	2.02 (1.27,3.29)	1.59 (1.13,2.35)	1.22 (0.88,1.70)	1.08 (0.78,1.44)

[a] Marginal adjusted risk ratio was calculated through the multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples.
[b] Model 1 includes age, sex, race-center, and education, plus interaction terms between time and olfactory status.
[c] Model 2 further includes APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein-cholesterol, lipid lowering medication, atrial fibrillation, stroke, heart failure, and renal function, plus interaction terms between time and body mass index & heart failure.
[d] Model 3 further includes frailty.

We observed similar findings across subgroups of age, sex, race, and history of CVDs, although risk estimates became less stable due to small sample size (**Figure A5.1**). With further separation of hyposmia from anosmia, we only observed an evident dose-response pattern of the association at year 2 (**Table A5.2**). Finally, results barely changed after restricting the analysis to individuals without dementia at baseline (**Table A5.3**).

6.4 Discussion

In this large community-based cohort of older US adults, we found that poor olfaction assessed by a single smell test was associated with a higher risk of CHD for up to 6 years of follow-up, albeit it attenuated afterwards. The association during the first 6 years cannot be explained by a wide range of covariates, including demographics, known cardiovascular risk factors, and frailty. Further, the association is robust in subgroup analyses and multiple sensitivity analyses.

CHD is one of the most common clinical cardiac diseases. Despite significant success in treating hypertension and hyperlipidemia and in smoking cessation, CHD remains a substantial

public health burden[242] and the leading cause of death[243]. This can be particularly concerning for the older population. While the incidence of CHD increases as people age[58], the associations of known CHD risk factors may attenuate with advanced age, making risk stratification in this population challenging[230]. One possible explanation is that some CHD risk factors (e.g., hypertension, hyperlipidemia, and obesity) often change as part of the aging process[244–247]. For example, systolic and diastolic blood pressure may decline 15 years before death in older adults, and this decline may preclude observing strong association of hypertension measured late in life with CVD as we would for hypertension measured in midlife[244]. Further, people who survive to older ages without CHD may be genetically or otherwise more resilient to the known midlife CHD risk factors. Regardless of the potential reasons, there is a need to better stratify CHD risk in the older population.

Poor olfaction affects over a quarter of older adults and shows a clear age-dependency[2,23]. While this sensory deficit is closely related to conductive abnormalities and neurodegenerative pathologies, a healthy circulatory system may also be crucial for normal olfactory functioning by providing sufficient blood perfusion to the olfactory structures[20]. Poor olfaction, may thus be a consequence of atherosclerosis, a major pathophysiology of CHD[65]. Supporting this, olfactory decline was found to be associated with subclinical atherosclerotic markers of the carotid artery, such as carotid intima media thickness and the number of sites in carotid artery with atherosclerotic plaques[90,91]. Interestingly, the carotid artery is the upstream blood vessel of the olfactory artery, providing blood to the olfactory epithelium and bulb[17]. Carotid artery atherosclerosis has been found to robustly predict future coronary heart events[237,238,248]. Therefore, poor olfaction, as a symptom of subclinical atherosclerosis, may indicate future CHD risk. On the other hand, despite limited empirical data, poor olfaction may lead to a higher risk of CHD by compromising the

nutritional, mental, and physical status of older adults[98–100,105,106,225]. For example, poor olfaction may impair one's dietary intake and cause depressed mood and physical inactivity. These unhealthy behaviors are associated with higher risk of CHD[110,249,250]. Therefore, despite limited evidence to date, it is biologically plausible that poor olfaction may be an early marker of or a contributor to future incident CHD.

To our knowledge, only two prospective studies have examined the association of olfaction with incident heart diseases[1,127]. In the National Social Life, Health, and Aging Project, (n=935), a 5-year olfactory decline was marginally associated with higher 5-year incidence of heart attack or heart disease (odds ratio: 1.75, 95% CI: 0.93–3.31)[127]. However, the outcome was self-reported and analyzed as a secondary interest. In the Health ABC Study (n=1,924), we did not observe an association of poor olfaction with CHD for up to 12 years of follow-up (cause-specific hazard ratio: 0.97, 95% CI: 0.73, 1.28)[1]. Compared with previous studies, the current study is substantially larger with more rigorous cardiovascular outcome assessments. Notably, the ARIC Study was designed to investigate atherosclerosis and its cardiovascular health sequela with rigid protocols of cardiovascular outcome identification and adjudication[131]. In comparison, the Health ABC Study aimed to study changes in body composition and physical functioning in the context of aging among well-functioning older adults in their 70s. Further, compared to the Health ABC Study, the ARIC study participants are more diverse in their health with a wider age range. Nevertheless, the inconsistent results between the two otherwise similar studies require further independent evaluations of the olfaction and CHD relationship in older adults.

Interestingly, the positive association of poor olfaction with CHD risk was most evident within the first 4 years of follow-up, but it decreased afterwards and became nonsignificant after 6 years. In a separate ARIC analysis, we observed that poor olfaction was associated with about

2-fold elevated risk of stroke within the first 6 years of follow-up, then the association modestly attenuated but remained statistically significant with an around 45% higher risk for poor olfaction at year 9.6 (**Chapter 5**). Although the findings are preliminary and require independent confirmation, the positive associations with both incident CHD and stroke support the idea that poor olfaction may reflect systematic atherosclerosis Further, poor olfaction appeared to have a more lasting association with risk of stroke than that of CHD. This may relate to the fact that the olfactory system is anatomically closer to the cerebrovascular system than the coronary artery system. Admittedly, these explanations are speculative. We however expect these preliminary results may generate interest in studying olfaction and cardiovascular health among older adults.

Leveraging strengths of the ARIC Study, this current study has a large sample size with diverse older populations, a lengthy follow-up for up to 9.6 years, and rigorously adjudicated CHD outcome. On top of these strengths, we performed comprehensive analyses with a careful selection of covariates and advanced statistical methodologies. Our study, however, also has some notable limitations. First, this study included US Black and White older adults with an average age of 75.4 years old, so the findings of this study may not be readily generalizable to populations with different demographics or from other countries. Second, with a single smell test in their 70s, we do not know the onset of poor olfaction of our study participants. This will be important in interpreting our findings that evidently the association of olfaction with CHD risk diminished over time. As poor olfaction starts to emerge in age 50s-60s[2], future study should repeatedly assess olfaction over time in younger populations to better understand the temporal relationship between olfaction and CHD risk. Third, despite our efforts to conduct extensive statistical analyses and adjust for a list of potential confounders, as with other observational studies, our findings could not exclude the possibility of residual confounding. Finally, while we identified an evident

association, it cannot determine the nature of this association (e.g., CHD marker or contributor) and the potential mechanisms, future studies are warranted to confirm and explain our observations.

In conclusion, in this large community-based older adult population, we found that poor olfaction assessed by one single smell test was robustly associated with higher risk of CHD for 6 years of follow-up. Future study should confirm our observations and investigate potential mechanisms.

CHAPTER 7: OLFACTORY STATUS IN RELATION TO HEART FAILURE IN THE ARIC STUDY

7.1 Introduction

HF affects around 60 million people worldwide and 6.7 million people in the US[58,251]. This health condition is characterized by the structural or functional impairment of ventricular filling or ejection of blood. It represents an advanced stage of cardiac disease, arising from various underlying pathologies, such as atherosclerosis, metabolic syndrome, cardiomyopathy, arrhythmia, and valvular defects. Given the substantial disease burden of HF on survival and healthcare costs[86], it is important to prevent its progression from preclinical stages (0, A and B) to the clinical stages (C and D)[66]. LVEF is crucial for HF classification because HF subtypes based on LVEF have distinct pathologies, etiologies, and treatments[66,252,253]. Notably, as people age, the disease progression may be entangled with frailty, a geriatric syndrome reflecting a systematic dysregulation with reduced physiological reserve[254]. In support, emerging evidence has shown that frailty is independently associated with multiple subclinical cardiac markers and with higher future risk of HF among older adults free of cardiovascular disease[116,255–258].

Poor olfaction is common in older adults[2,23] and can be easily assessed by a brief smell identification test[132,200]. While this sensory deficit is often overlooked[24], it has been found closely associated with frailty in older adults[117]. Emerging evidence from prospective studies shows that poor olfaction may foretell the development of frailty and its individual symptoms[105,187,226]. Given that frailty may accelerate or concur with the development of HF, poor olfaction, as a risk factor or indicator of frailty, may signify future HF risk. In addition, despite multifaceted causes of HF, ischemic etiology remains important for HF[252]. As such, poor olfaction may also link to future risk of HF through its connections with subclinical atherosclerosis[90,91].

Although the link between olfaction and HF is biologically plausible, empirical evidence regarding this association has been limited. Only one prospective study reported that poor olfaction was associated with higher cause-specific hazard of incident CHF in the Health ABC Study[1]. However, HF hospitalizations in this study did not include diagnostic testing for B-type natriuretic peptide levels in the HF adjudication and lacked information on LVEF[148,259]. Hereby, we leveraged data from the well-established ARIC Study (1) to estimate the prospective association of olfaction with risk of HF and its subtypes of HFrEF and HFpEF[84], and (2) to evaluate the cross-sectional association of olfaction with well-known pre-clinical HF markers, including NT-proBNP, hs-cTnT, and structural heart disease, indicating myocardial stretching stress, myocardial ischemic necrosis, and structural myocardial abnormality, respectively[80,81].

7.2 Methods

7.2.1 Study population

The ARIC Study is a prospective cohort study established to study risk factors for cardiovascular health[130,131]. Briefly, in 1987-1989, 15,792 middle-aged male and female residents were randomly selected from four communities in the US (Jackson, Mississippi, Washington County, Maryland, suburbs of Minneapolis, Minnesota, and Forsyth County, North Carolina). Since enrollment, participants have been followed with periodic in-person clinical examinations, annual (semi-annual since 2012) telephone interviews and active surveillance of hospitalization and death.

The fifth clinical examination (Visit 5) in 2011-2013 included a brief smell test and thus was considered as the baseline of the current study. The study sample included 5,217 participants following exclusion of 23 individuals without informed consent, 18 with race other than Black or White, 24 Black participants from Washington County or Minneapolis due to small numbers, 437 missing on smell score, and 819 with prevalent HF. Prevalent HF was defined as having a HF

hospitalization (ICD-9 code 428) before 2005, self-reported HF diagnosis at Visit 3-5, or adjudicated HF hospitalization from 2005 to Visit 5. At-risk participants were followed to the date of the first HF hospitalization, death, date of last contact, or December 31, 2020, whichever occurred first. The ARIC Study protocol was approved by institutional review boards of all involved institutes. The specific analysis was approved by the institutional review board of Michigan State University.

7.2.2 Olfactory status

Olfactory status was assessed by the 12-item SS smell identification test[133]. In brief, participants were asked to smell 12 common odors from felt-tip pens, one at a time, and to select the right odorant from forced multiple-choice format. This test is easy to perform and has been commonly used in large population studies and clinical screenings[137,202,203,205]. Each correct answer is given one score, so the test score ranges from 0 to 12. We defined good olfaction as a smell score of 11-12, moderate olfaction as 9-10, and poor olfaction as 8 or lower, the cut-offs of which correspond to the tertile of the test distribution among the study population. In the sensitivity analysis, we further categorized poor olfaction into anosmia (score ≤6) and hyposmia (7-8), in line with previous studies[22,206].

7.2.3 HF Hospitalization

Hospitalizations with an eligible HF ICD-10-CM or HF key word in the discharge summary were identified for all the ARIC participants as detailed previously[148,149]. Trained staff first screened hospitalizations for evidence of HF symptoms or whether HF was the in-patient reason. If evidence existed, they extracted key data from ECG, neuro-imaging reports, discharge summary, catheterization report, and chest-X ray reports, and completed the Heart Failure Abstraction form for HF confirmation. Two physicians then independently reviewed abstracted medical records

according to a standardized protocol[149] and categorized HF hospitalizations into 1 of 5 categories, including definite and possible acute decompensated HF, chronic stable HF, HF unlikely, or unclassifiable. A disagreement led to an additional adjudication by a third physician.

Our primary outcome was an incident acute decompensated HF or chronic stable HF[148]. Specifically, acute decompensated HF included evidence from symptoms, signs, imaging, or treatment of an acute exacerbation, worsening or new onset of symptom, or other decompensated circulatory state. Chronic stable HF included evidence of compensated HF symptoms or signs controlled by treatment but without evidence of augmented therapy or worsening symptom during the hospitalization. For HF hospitalizations with LVEF, we defined those with LVEF of <50% as HFrEF and those with ≥50% as HFpEF[150]. In the sensitivity analysis, we used a more restrictive event definition which only counted incident hospitalization of acute decompensated HF, as individuals with chronic stable HF might not be hospitalized at the time of diagnosis.

7.2.4 Subclinical HF markers

We considered three sub-clinical HF markers used to define HF B stage, including NT-proBNP, hs-cTnT, and ECG-defined structural heart disease measured at Visit 5[66]. NT-proBNP was measured using electro-chemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostic, Mannheim, Germany) with a measurement range of 5-35,000 pg/mL and a limit of quantitation of 35 pg/mL[260,261]. The inter-assay coefficient of variation was 6.7%. Hs-cTnT was measured using a highly sensitive assay (Elecsys Troponin T; Roche Diagnostics, Indianapolis, IN) on the same analyzer with a detection range of 3-10,000 ng/L and a limit of quantitation of 13mg/L. The inter-assay coefficient of variation was 15%. Structural heart disease was defined via ECG according to abnormal left ventricular (LV) structure and LVEF[81], if at least one of the following items was abnormal: abnormal LVEF as <57.4% in women and <59.0% in

men, left ventricular hypertrophy as >41.5 g/$m^{2.7}$ in women and >45.0 g/$m^{2.7}$ in men based on ARIC reference limits for LV mass indexed to height$^{2.7}$, moderate or greater aortic stenosis as a peak transaortic velocity of >3.0 m/sec; moderate or greater mitral regurgitation based on a mitral regurgitation get area-to-left atrial area ratio of >0.20, and moderate or greater mitral stenosis based on a mean antegrade transoral gradient of ≥5mmHg.

7.2.5 Covariates

Covariates were largely measured at Visit 5 except that date of birth, sex, race, and education was self-reported at Visit 1 and general health status was self-reported at the annual follow-up one year within the Visit 5 date. As White participants were primarily from Washington County, Minneapolis suburbs, and Forsyth County, race was categorized based on the study center. Education was classified as less than high school, high school or equivalent, and at least some college level. Age at Visit 5 was calculated as a continuous variable and BMI as weight divided by square of height (kg/m^2). We defined self-reported smoking status as never, former, and current smokers. Use of lipid-lowering medication was assessed using medication inventory method[211]. We defined prevalent comorbidities based on published criteria: 1) hypertension as an average systolic blood pressure of ≥ 140 mmHg, or an average diastolic blood pressure of ≥ 90 mmHg or use of antihypertensive medications[262]; 2) diabetes as a fasting glucose level ≥ 126 mg/dL, a non-fasting glucose level ≥200 mg/dL, HbA_{1C} ≥6.5%, self-reported physician diagnosis, or self-reported use of antidiabetic medications[150]; 3) CHD as self-reported CHD at Visit 1 or adjudicated events between Visit 1-5[213]; 4) atrial fibrillation as identified from the electrocardiogram or hospitalization[214]; 5) dementia as identified according to in-person neuropsychological evaluations, telephone cognitive assessment, informant rating, or hospitalization[215]. Prefrailty or frailty was defined as ≥1 symptoms of the Fried frailty phenotypes, including exhaustion, weight

loss, slow walking speed, low grip strength, and low physical activity[218]. Total cholesterol, HDL-C, creatinine, and cystatin were measured through standardized procedures[219,220].The latter two biomarkers were used in the CKD-EPI creatinine-cystatin equation for eGFR[173].

The HF clinical stage at baseline was used as one of our stratification factors and defined following the published protocol in the ARIC Study[81,150]. Briefly, HF Stage A required having at least one of the following HF risk factors in the absence of structural heart disease or symptoms of HF, including prevalent atherosclerotic CVD, hypertension, diabetes mellitus, obesity, metabolic syndrome, and chronic kidney disease. Stage B was defined as having structural heart disease or elevated cardiac biomarkers, including NT-proBNP of ≥125 pg/mL or hs-cTnT of >14ng/L in women and >22ng/L in men. The rest of individuals who did not at Stage A or Stage B were considered at Stage 0.

7.2.6 Statistical analysis

In the analysis of olfaction and risk of HF, we first used the Gray's test to evaluate the crude association of olfactory statuses with the CIF of HF and its competing event of death[174]. In the multivariable analyses, we used discrete-time sub-distribution model to evaluate the association of olfactory status with risk of HF accounting for covariates and competing risk of death[155,156]. The details regarding the model building were presented in previous chapters. Using the estimated model, we calculated the absolute risk across olfactory statuses conditioning on the baseline covariate distribution across the entire sample and calculated RRs and RDs with good olfaction as the reference. These risk-based assessments indicate the total association which includes both the direct association between olfaction and HF and the indirect association through competing event of death[155] (details in **Chapter 3.5**).

We considered two sets of covariates with an increasing number of covariates added.

Model 1 adjusted for basic demographics, including age, sex, race-center, and education. Model 2 further adjusted for smoking status, self-reported general health status, BMI, diabetes, hypertension, total cholesterol, HDL-C, lipid lowering medication, CHD, atrial fibrillation, and eGFR to examine the independence of the association between olfactory status and HF risk. Given the close relationships between olfaction and frailty[117] and between frailty and HF[114,255], model 3 further adjusted for frailty. We then considered HFrEF and HFpEF as the outcomes of interest, respectively. Next, we conducted stratified analyses by age (<vs. ≥ 75 years), sex (male vs. female), race (White vs. Black), HF stage (Stage 0/ Stage A vs. Stage B), self-reported general health status (excellent vs. good vs. fair to poor) and frailty (robust vs. prefrailty/frailty). Finally, we performed multiple sensitivity analyses to check the result robustness: 1) We examined the direct association between olfaction and HF risk in the scale of cause-specific HR[153]; 2) we separated poor olfaction into anosmia and hyposmia; 3) we considered acute decompensated HF only as the outcome of interest; and 4) we redid the analysis after removing prevalent dementia cases to circumvent the effect of dementia on the smell testing.

In the analysis of olfaction and HF biomarkers, the analytical sample size was 5,012 for NT-proBNP, 5,169 for hs-cTnT, and 5,217 for structural heart disease after excluding those with missing biomarker of interest. We used the quantile regression to examine the association of olfaction with the median levels of NT-proBNP and hs-cTnT, and the logistic regression for the association with structural heart disease, adjusting for the full set of covariates. We used SAS (version 9.4; SAS Institute Inc. Cary, NC, USA) for description and logistic and cause-specific Cox modeling, and R (version 4.1.3) for the rest of the analyses with a two-sided α of 0.05.

7.3 Results

Among 5,217 participants free of clinical HF in this study, the average age at baseline was 75.4±5.1

years old with 59.8% female and 20.8% Black participants. Compared with participants with good olfaction, those with poor olfaction were more likely to be older, male, Black, ever smokers, and have advanced stage HF (**Table 7.1**). They were also more likely to report having lower education levels and worse general health status, and to use lipid lowering medications, and to have prevalent diabetes, hypertension, atrial fibrillation, frailty, dementia, and lower levels of total cholesterol, HDL-C, and eGFR.

Table 7.1 Population characteristics by baseline olfaction status (n=5,217)

Variables [a]	Olfaction status		
	Good (n=1,971)	Moderate (n=1,740)	Poor (n=1,506)
Age in year	74 (71,78)	75 (71,79)	76 (72,81)
Sex Male	660 (33.5)	718 (41.3)	720 (47.8)
Race Black	206 (10.5)	363 (20.9)	515 (34.2)
Center			
Forsyth county	500 (25.4)	394 (22.6)	306 (20.3)
Jackson County	188 (9.5)	328 (18.9)	489 (32.5)
Minneapolis suburbs	692 (35.1)	522 (30)	343 (22.8)
Washington County	591 (30)	496 (28.5)	368 (24.4)
Race-center			
White in Forsyth County	482 (24.5)	359 (20.6)	280 (18.6)
White in Minneapolis suburbs	692 (35.1)	522 (30)	343 (22.8)
White in Washington County	591 (30)	496 (28.5)	368 (24.4)
Black in Forsyth County	18 (0.9)	35 (2)	26 (1.7)
Black in Jackson	188 (9.5)	328 (18.9)	489 (32.5)
Education			
Less than complete high school	147 (7.5)	215 (12.4)	293 (19.5)
High school or equivalent	832 (42.2)	741 (42.6)	607 (40.3)
At least some college level	992 (50.3)	784 (45.1)	606 (40.2)
Self-reported general health status			
Excellent	625 (31.7)	457 (26.3)	329 (21.8)
Good	1129 (57.3)	1041 (59.8)	850 (56.4)
Fair or poor	217 (11)	242 (13.9)	327 (21.7)
Smoking status			
Never smoker	893 (45.3)	711 (40.9)	612 (40.6)
Former smoker	982 (49.8)	922 (53)	799 (53.1)
Current smoker	96 (4.9)	107 (6.1)	95 (6.3)
Body mass index in kg/m^2			
<25.0	528 (26.8)	420 (24.1)	390 (25.9)
25.0-29.9	792 (40.2)	724 (41.6)	653 (43.4)

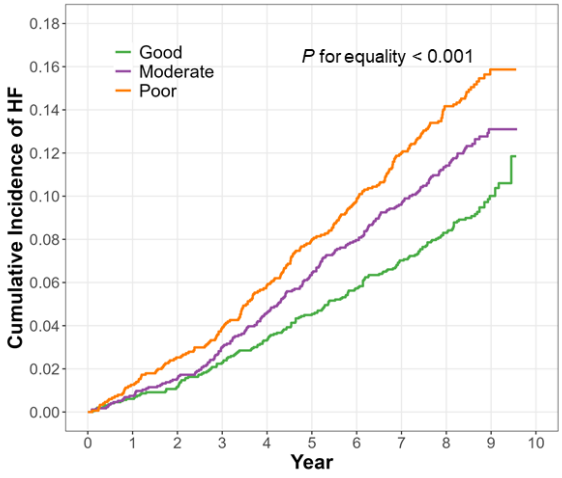
Table 7.1 (cont'd)

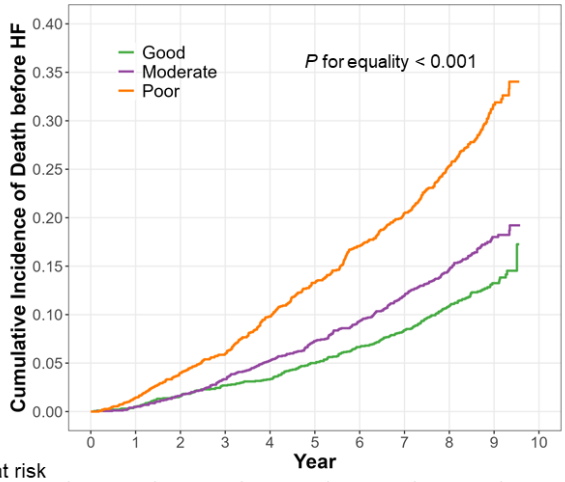
≥30.0	651 (33)	596 (34.3)	463 (30.7)
Diabetes	531 (26.9)	546 (31.4)	547 (36.3)
Hypertension	1401 (71.1)	1258 (72.3)	1135 (75.4)
Total cholesterol in mmol/L	4.7 (4.1,5.5)	4.7 (4.0,5.4)	4.6 (3.9,5.2)
HDL-C in mmol/L	1.3 (1.1,1.6)	1.3 (1.1,1.6)	1.3 (1.1,1.5)
Use of lipid lowering agents	1035 (52.5)	948 (54.5)	862 (57.2)
eGFR in mL/min/1.73m^2	68.6 (57.1,80.3)	67.5 (55.9,79.9)	65.0 (52.6,76.9)
Prevalent CHD	178 (9)	178 (10.2)	164 (10.9)
Prevalent atrial fibrillation	76 (3.9)	90 (5.2)	92 (6.1)
Frailty			
Robust	1021 (51.8)	789 (45.3)	511 (33.9)
Pre-frail or frailty	857 (43.5)	840 (48.3)	815 (54.1)
Missing	93 (4.7)	111 (6.4)	180 (12)
HF stage			
Stage 0	106 (5.4)	69 (4)	50 (3.3)
Stage A	609 (30.9)	509 (29.3)	370 (24.6)
Stage B	1256 (63.7)	1162 (66.8)	1086 (72.1)
Dementia			
No	1962 (99.5)	1719 (98.8)	1361 (90.4)
Yes	9 (0.5)	21 (1.2)	145 (9.6)

Abbreviations: IQR: inter-quartile range; HDL-C: high-density lipoprotein-cholesterol; CHD: coronary heart diseases; HF: heart failure; NT-proBNP: N-terminal pro B-type natriuretic peptide; hs-troponin: high-sensitive troponin

[a] Continuous variables are presented as median (25th, 75th percentile) and categorical variables as number (column percentage).

During up to 9.6 years (median 8.4 years) of follow-up, we identified 622 incident HF hospitalizations, including 212 HFrEF, 250 HFpEF, and 160 with unknown LVEF. There were 185 incident HF among participants with good olfaction, 214 among those with moderate olfaction, and 223 among those with poor olfaction. Participants with worse olfaction had higher crude cumulative incidence of HF and its competing event of death during the follow-up with a *P* value of the equality test <0.001 (**Figure 7.1**).





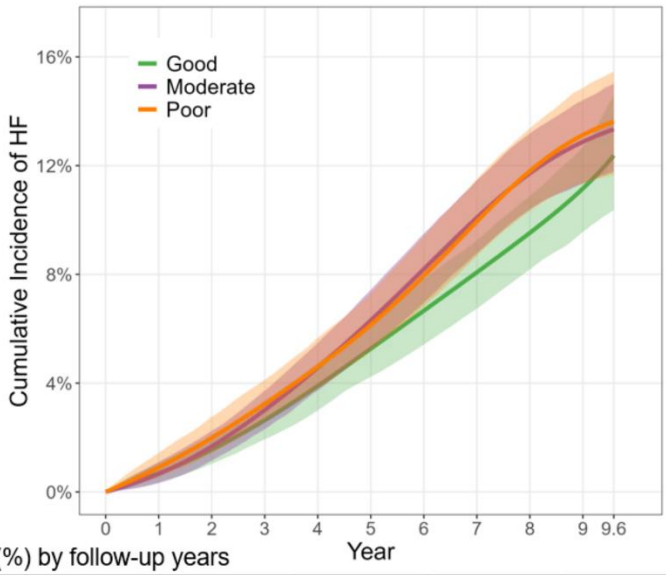
No. at risk

Year	0	2	4	6	8
Good	1971	1912	1824	1701	1409
Moderate	1740	1681	1561	1419	1112
Poor	1506	1403	1263	1079	764

Figure 7.1 Crude cumulative incidence function of heart failure (HF) in the ARIC Study

The multivariable analyses confirmed that worse olfaction was associated with higher risk of HF, while the difference in HF risk across olfactory statuses attenuated after accounting for the imbalance of baseline covariates and competing event of death (**Figure 7.2**). Compared with good olfaction, the magnitude of the total association between poor olfaction and HF risk reached statistically significance at year 8 with the RR of 1.24 (95% CI: 1.03,1.51) (**Table 7.2**). The association of moderate olfaction with HF over time showed a similar pattern with the corresponding RR of 1.23 (95% CI: 1.00,1.50). The decline in the RR scale after year 8 for both

poor and moderate olfaction was largely affected by one incident case at year 9.5 in the good olfaction group. Cause-specific HRs measuring the direct association between olfaction and incident HF showed in general consistent results with the primary analyses (**Table A6.1**). For example, the cause-specific HR at year 8 was 1.42 (95% CI: 1.13, 1.78) for poor olfaction and 1.29 (95% CI: 1.04, 1.61) for moderate olfaction. However, the cause-specific HR for poor olfaction remained statistically significant at year 9.6 with a cause-specific HR of 1.26 (95% CI: 1.02, 1.56) as the direct association between poor olfaction and HF was not attenuated by the positive association between poor olfaction and death, and the Cox regression is less influenced by the one incident case at the end of follow-up.



Risk difference (%) by follow-up years

Olfactory status	2-year	4-year	6-year	8-year	9.6-year
Moderate vs. good	0.1 (-0.6,0.8)	0.7 (-0.6,1.9)	1.5 (-0.2,3.2)	2.2 (0,4.2)	1 (-1.8,3.9)
Poor vs. good	0.4 (-0.3,1.4)	0.7 (-0.4,2.1)	1.3 (-0.2,3.1)	2.3 (0.3,4.4)	1.2 (-1.6,3.8)

Figure 7.2 Marginal adjusted cumulative incidence of heart failure (HF) by olfactory status and the risk difference for moderate and poor versus. good olfaction over time. The cumulative incidence was estimated by discrete-time sub-distribution hazard model, adjusting for covariate in Model 3

Table 7.2 Adjusted marginal risk ratios [a] of heart failure for moderate/poor vs. good olfaction during the follow-up in the ARIC Study (n=5,217)

	Risk ratio (95% confidence interval) by years of follow-up

Table 7.2 (cont'd)

Follow-up year	2-Year	4-Year	6-Year	8-Year	9.6-Year
Model 1[b]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.12 (0.68,1.78)	1.22 (0.9,1.67)	1.29 (1.02,1.63)	1.28 (1.04,1.57)	1.11 (0.88,1.4)
Poor	1.46 (0.98,2.52)	1.34 (1.02,1.91)	1.35 (1.09,1.74)	1.37 (1.14,1.69)	1.18 (0.95,1.45)
Model 2 [c]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.09 (0.65,1.72)	1.18 (0.87,1.64)	1.24 (0.97,1.56)	1.23 (1.00,1.50)	1.07 (0.86,1.33)
Poor	1.34 (0.9,2.27)	1.25 (0.94,1.76)	1.25 (1.01,1.61)	1.26 (1.04,1.56)	1.09 (0.87,1.34)
Model 3 [d]					
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.08 (0.66,1.68)	1.17 (0.86,1.62)	1.23 (0.97,1.55)	1.23 (1.00,1.50)	1.08 (0.86,1.37)
Poor	1.28 (0.85,2.28)	1.18 (0.91,1.66)	1.19 (0.97,1.54)	1.24 (1.03,1.51)	1.1 (0.89,1.35)

[a] Marginal risk ratio was calculated through multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples.
[b] Model 1 includes age, sex, and race-center, plus interaction terms between time and olfaction & education levels.
[c] Model 2 further includes self-reported general health status, smoking status, BMI, prevalent coronary heart disease, atrial fibrillation, diabetes, hypertension, total cholesterol, HDL-cholesterol, lipid lowering medication, and renal function, plus interaction terms between time and sex & body mass index & coronary heart disease.
[d] Model 3 further includes frailty plus interaction terms between time and frailty.

Poor olfaction showed distinct associations with HFrEF and HFpEF during the follow-up (**Table 7.3 and Figure A6.1**). Its association with HFrEF was evident during the first 6 years of follow-up and was modest in year 8. Specifically, the RR was 2.07 (95% CI: 0.97, 5.98) at year 2, 1.95 (95% CI: 1.15, 3.32) at year 4, 1.76 (95% CI: 1.12, 2.74) at year 6, and 1.50 (95% CI: 1.04, 2.21) at year 8. In contrast, no significant association of poor olfaction with HFpEF was observed during the follow-up.

Table 7.3 Adjusted marginal risk ratio [a] of heart failure classified by ejection fraction (EF) for moderate/poor vs. good olfaction during the follow-up (n=5,217)

Olfactory status	No. of incident cases	Risk ratio (95% confidence interval) by years of follow-up				
		Year 2	Year 4	Year 6	Year 8	Year 9.6
Reduced EF						
Good	59	Reference	Reference	Reference	Reference	Reference
Moderate	69	0.8 (0.24,2.29)	1.27 (0.66,2.25)	1.38 (0.88,2.15)	1.33 (0.93,1.86)	0.93 (0.63,1.29)
Poor	84	2.07 (0.97,5.98)	1.95 (1.15,3.32)	1.76 (1.12,2.74)	1.5 (1.04,2.21)	1.1 (0.75,1.64)
Preserved EF						
Good	73	Reference	Reference	Reference	Reference	Reference
Moderate	89	1.45 (0.76,3.15)	1.37 (0.86,2.25)	1.29 (0.87,1.93)	1.29 (0.94,1.85)	1.26 (0.94,1.76)
Poor	88	1.21 (0.56,2.99)	1.15 (0.75,1.98)	1.2 (0.87,1.81)	1.3 (0.97,1.85)	1.25 (0.9,1.79)

[a] Marginal risk ratio was calculated through multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, self-reported general health status, smoking status, BMI, prevalent coronary heart disease, atrial fibrillation, diabetes, hypertension, total cholesterol, HDL-cholesterol, lipid lowering medication, and renal function, plus interaction terms between time and olfaction & body mass index & coronary heart disease & frailty.

We did not observe statistically significant heterogeneity of the association between olfaction and HF risk by age groups, sex, race, HF stages, self-reported general health status, and frailty with all *P* values for the joint Wald test of >0.05. Separating poor olfaction into anosmia and hyposmia, the positive association with HF risk appeared to be more evident for anosmia than hyposmia (**Table A6.2**). The results barely changed after using a more restrictive definition of HF hospitalizations or deleting prevalent dementia cases from the analysis (**Table A6.3** and **A6.4**).

In the cross-sectional analysis of olfaction and subclinical HF biomarkers, participants with poor olfaction had higher crude levels of NT-proBNP and hs-TnT, and a higher prevalence of structural heart disease. After adjusting for covariates, participants with poor olfaction had 13.3pg/mL higher median level of NT-proBNP and 0.8ng/L higher median level of hs-TnT,

compared to those with good olfaction (**Table 7.4**). Further, people with poor olfaction were also more likely to have structural heart disease with an OR of 1.24 (95% CI: 1.06, 1.46).

Table 7.4 The cross-sectional association of olfactory status with NT-proBNP, hs-TnT, and structural heart disease

Olfactory status	NT-proBNP, pg/mL (n=5,012)		hs-TnT, ng/L (n=5,169)		Structural heart disease (n=5,217)	
	Crude value [a]	Adjusted difference [b]	Crude value [a]	Adjusted difference [b]	Crude value [c]	Adjusted OR [d]
Good	111.4 (146.6)	Reference	9 (7)	Reference	624 (31.7)	Reference
Moderate	116.8 (172.1)	7.0 (0,14.1)	10 (8)	0.1 (-0.2,0.5)	573 (32.9)	1.05 (0.90,1.21)
Poor	134.9 (203.4)	13.3 (4.6,22.1)	12 (10)	0.8 (0.3,1.3)	543 (36.1)	1.24 (1.06,1.46)

Abbreviation: NT-proBNP: N-terminal B-type natriuretic peptides; hs-TnT: high-sensitive cardiac troponin T; OR: odds ratio

[a] Median (IQR) is presented by olfactory statuses.

[b] Adjusted differences in median across olfactory statuses (good olfaction as the reference) was estimated by the quantile regression, adjusting for age, sex, race-center, education, smoking status, BMI, self-reported general health status, diabetes, hypertension, total cholesterol, high-density lipoprotein-cholesterol, lipid-lowering medications, coronary heart disease, atrial fibrillation, renal function and frailty.

[c] Number (row %) is presented by olfactory statuses.

[d] OR was estimated by the logistic regression, adjusting for age, sex, race-center, education, smoking status, BMI, self-reported general health status, diabetes, hypertension, total cholesterol, high-density lipoprotein-cholesterol, lipid-lowering medications, coronary heart disease, atrial fibrillation, renal function, and frailty.

7.4 Discussion

In a large community-dwelling cohort of older adults, we found that poor olfaction identified by a single smell test was modestly associated with higher risk of HF hospitalization for 8 years. Interestingly, poor olfaction appeared to have a evident association with HFrEF, but not with HFpEF. Further, we also identified that poor olfaction was associated with pre-HF markers indicating subclinical myocardial pathology and structural dysfunction. Despite the modest association we identified, study findings were robust in multiple subgroup and sensitivity analyses. Notably, this observation is consistent with our recent finding from another cohort of older US

adults, highlighting the potential relevance of this common sensory deficit to future HF risk.

HF is a prevalent cardiac syndrome, especially among older adults[251]. While the clinical onset HF is usually acute, its underlying structural or functional cardiac dysfunction takes time to build[263]. The natural progression of subclinical HF consists of two distinct stages. Stage A is characterized by the presence of major HF risk factors, while Stage B involves the cardiac structural dysfunction[264]. The progressions can be driven by various reasons (such as atherosclerosis and cardiomyopathy) and further complicated by aging-related physiological changes, making the identification and prevention of HF challenging. Frailty is a common geriatric disorder characterized by a declined restoration of homeostasis after stress attacks[254]. While HF may lead to increased systematic vulnerability, frailty may in turn accelerate or signify the development of HF[255]. Accumulating evidence shows that frailty is associated with subclinical markers of structural and functional abnormalities in the vascular system and myocardium in older adults[116,256–258]. Notably, a recent proteomic study provided provocative mechanistic evidence linking frailty with HF[115] by identifying multiple shared biological mechanisms, highlighting the extracardiac pathways of HF development in late life.

Poor olfaction is common but often underrecognized among older adults[2,3]. This neglected sensory deficit, however, may have profound health implications[5,181]. In addition to its robust association with neurodegeneration and mortality, accumulating evidence shows the close association of poor olfaction with frailty[117]. Interestingly, some longitudinal studies have found that poor olfaction may occur prior to frailty and predict faster deterioration of its individual components[105,187,226]. For example, poor olfaction was associated with greater weight loss, including both fat and lean mass[187], and with faster decline in physical functioning among community-based older adults[105]. Despite limited empirical data, poor olfaction in older adults

may contribute to the cascade of events leading to frailty by negatively affecting their nutritional behaviors, emotions, and lifestyles[56,98,100]. Given the increasingly recognized relationship between frailty and HF, it is biologically plausible that poor olfaction signifies future risk of both conditions among older adults.

To the best of our knowledge, only one prospective study has investigated the association between olfaction and incident HF. In the Health ABC Study, we found that poor olfaction was associated with 28% higher cause-specific hazard of congestive HF during up to 12 years of follow-up[1]. Compared with the Health ABC Study, the ARIC Study was designed to study cardiovascular outcomes, was more inclusive with broader age range and functional status at baseline, conducted comprehensive HF adjudication protocols, and adjudicated HF sub-types. Further, in the analysis, we used risk-based association measures to account for the competing risk of death rather than simply treating these competing events as censoring[151]. Nevertheless, our finding supports that from the Health ABC Study. The current Study further suggests the association was limited to HFrEF, a novel observation that has not been reported. In support of these findings, we observed that poor olfaction was significantly associated with well-established subclinical HF biomarkers, including NT-proBNP, hs-cTnT, and structural cardiac abnormalities. While our findings are preliminary, they support a robust albeit modest association between poor olfaction and HF, which warrants further investigation.

Our novel observation on HFrEF versus HFpEF deserves attention. HFrEF primarily involves the impaired contraction of the left ventricle, while HFpEF is characterized by diastolic dysfunction of the left ventricle[252]. Although they have shared risk factors and pathogenesis, HFrEF is more likely to be the consequence of cardiomyocyte loss owing to MI or myocarditis, while HFpEF is more relevant to aging-related inflammation and comorbidities (e.g., diabetes,

hypertension, and chronic obstructive pulmonary disease)[253]. Interestingly, we observed that poor olfaction was evidently associated with higher risk of HFrEF, showing a similar pattern to our independent investigations of the association between poor olfaction and CHD, a primary risk factor for HFrEF (**Chapter 6**). In contrast, we found little evidence for an association between poor olfaction and HFpEF. This is puzzling because frailty may be more relevant to HFpEF than HFrEF[115], and poor olfaction is strongly linked to frailty[117]. Nevertheless, these observations are preliminary and should be further evaluated in future mechanistic studies.

Strengths of this study included the broad representation of community-based US older adults, meticulously adjudicated HF hospitalizations, information on HF biomarkers, and comprehensive statistical analyses. However, this study also has several limitations. First, despite the large sample size and community representation, our findings may not be able to generalize to populations with other demographics, for example, younger populations, Asians, or Hispanics. Second, we only observed a modest association of poor olfaction with HF, which could potentially be explained by residual confounding. However, we have adjusted for a comprehensive list of potential confounders, and the findings appear to be robust within this study and consistent with the previous investigation in the Health ABC Study. Third, despite growing evidence on the relationships between frailty and HF and between olfaction and frailty, the connection and mechanisms between poor olfaction and HF remain largely unexplored. To address this gap, our study was the first to examine the association of olfaction with blood-based and ECG-based subclinical biomarkers for HF. However, since the association was cross-sectional, the longitudinal dynamics between olfaction and these biomarkers is unclear.

In conclusion, among community-dwelling US older adults, we found that poor olfaction identified by a single smell test was associated with modestly higher risk of HF, especially HFrEF.

Future studies should confirm our findings and further investigate the underlying mechanisms.

CHAPTER 8: DISCUSSION

8.1 Summary of Findings

In this project, we leveraged two large community-based cohorts of older adults in the US to comprehensively investigate the associations of poor olfaction with the risk of three major cardiovascular outcomes, including stroke, CHD, and HF.

In the Health ABC Study, we found that poor olfaction measured by a single smell test was modestly associated with higher cause-specific hazard of CHF for up to 12 years of follow-up. This association was more evident among participants who reported very good to excellent health and was robust across subgroups of age, sex, race, and prevalent CHD/stroke. However, we did not observe a statistically significant association of poor olfaction with incident CHD or stroke.

With these preliminary findings, we further investigated olfactory status in relation to each of these cardiovascular outcomes in detail in the ARIC Study. Notably, the ARIC Study was designed specifically to investigate risk factors for atherosclerosis and cardiovascular research with over 30-year continuous contributions to the field. In ARIC, we found an evident association of olfaction with stroke throughout the follow-up, albeit the strength of the association modestly attenuated after year 6. Notably, the magnitude of the association was comparable to established stroke risk factors, such as CHD and atrial fibrillation. A similar finding was observed for CHD, although the association lost its statistical significance after year 6. Finally, we found poor olfaction was associated with a modest risk for incident HF, a finding consistent with that from the Health ABC Study. Further analyses revealed that the association was largely limited to HFrEF. In support of this finding, we found poor olfaction was associated with higher median levels of HF biomarkers of NT-proBNP and hs-cTnT, and a higher odds of structural heart disease among older adults without clinical HF.

In summary, the ARIC Study confirmed our preliminary finding in the Health ABC Study about the association of poor olfaction with HF but showed different results on stroke and CHD. Potential explanations for these different findings are not clear. While these two studies had similar study designs, population demographics (i.e., sex, race, and mean age at the smell test), and data collection strategies, there are important differences between the two cohorts. First, the ARIC Study was originally designed to study cardiovascular health and has presumably more rigorous assessments of cardiovascular outcomes, biomarkers and covariates. In contrast, the Health ABC Study was designed to assess how body composition changes in the context of aging, with research focusing on body composition and functional outcomes. Second, there are minor yet important differences between these two study populations. The Health ABC Study recruited well-functioning older adults with a narrow age range (ages 70-79) at enrollment. In comparison, the ARIC Study had a much wider age range at baseline (ages 65-90) with no selection of health or functional status. Nevertheless, whether these differences could explain the differential findings on stroke and CHD is unclear, highlighting the importance of further investigations in other aging cohorts.

8.2. Summary of Limitations

In this project, we leveraged extensive data from two large well-established cohorts of US older adults to investigate the associations of poor olfaction with major adverse cardiovascular outcomes among older adults. We conducted comprehensive statistical analyses and carefully accounted for a wide range of covariates and the competing risk of death. However, this project has several notable limitations. First, in both cohorts, the sense of smell was tested in participants with an average age of 75.5 years. Therefore, our findings may not be generalizable to younger populations. Further, our participants were exclusively White and Black individuals from the US,

limiting generalizability to populations of other races, ethnicities, and regions. Second, olfaction declines fast with advanced age, so it will be interesting to investigate how olfactory change may be related to future cardiovascular events. Although the ARIC Study tested participants olfaction again at Visit 6, we did not perform analyses due to a high attrition rate (over 40%) and a limited number of incident cases afterwards given the advanced age of our study population. We argue that this should be investigated in relatively young populations where olfactory loss begins to accelerate, informing whether olfactory decline could be an early marker of adverse cardiovascular events in older adults. In the next section (***8.3.1***), we will briefly present key methodological considerations for investigating time-varying olfactory function in the time-to-event analyses of olfaction and cardiovascular outcomes. Third, despite our comprehensive statistical analyses and relatively large sample size in both cohorts, our findings, even the consistent observation on olfaction and HF, were subject to chance and residual confounding. Fourth, the cross-sectional analyses on poor olfaction and pre-HF markers in the ARIC Study are preliminary, awaiting future longitudinal analysis to examine the temporality of this relationship. Finally, while we found statistical associations of poor olfaction with future risks of major CVDs in one or two cohorts, their clinical implication and underlying mechanism remains elusive, awaiting future investigation.

8.3 Future Directions

8.3.1 Mechanistic Investigations on the Associations

The relationships between poor olfaction and cardiovascular health can be dynamic and complex in the life course. Most poor olfaction in older adults is idiopathic and emerges with advanced age[2,20]. This sensory loss itself, however, may be the consequence of lifelong physiological and pathological changes with age, including those due to metabolic disorders and other cardiovascular

risk factors. It may also be attributed to exposure to adverse environmental hazards, such as air pollutants and viral infections, as the peripheral olfactory system is directly exposed to the external environment[265–267]. Given that age, sex, and genetic variations together may only explain ~10-20% of smell perception variations[268], it is essential to examine whether and how the exterior and interior pressures lead to olfactory loss in later life.

Accumulating evidence, including that from the current project, implicates that olfactory dysfunction may have profound implications on the health of older adults. It therefore necessitates subsequent research on potential biological mechanisms. It is possible that poor olfaction may be a signal of accelerated aging across multiple physiological systems. In support, poor olfaction has been robustly linked to declines in physical, cognitive, and mental functioning[52,105,106]. As such, this sensory loss may also be a marker of the aging of the cardiovascular system in older adults. On the other hand, despite limited evidence, it is also plausible that poor olfaction may lead to poor dietary intake. This may further interact with mental and functional declines in the context of aging and accelerate a cascade of adverse health outcomes, including CVDs. While the investigation of the interplays of these possibilities will be challenging, thorough investigations of the role of poor olfaction in older adults will critically inform the maintenance of cardiovascular and overall health of older adults.

8.3.2 Olfactory Change with Incident Cardiovascular Disease

As human olfaction starts to decline appreciably after age 50, it will be interesting to investigate if and how olfactory change is associated with the risk of cardiovascular disease among younger older adults. However, such investigations will require additional methodological considerations beyond what we did in the current project, for example, attrition during the follow-up and time-varying confounding. We will briefly describe the statistical issues and the potential solutions

using the ARIC Study as an example.

In the ARIC Study, the first smell testing was conducted at Visit 5 (2010-2013, ages 75.6±5.2 years), and the second smell testing was conducted at Visit 6 (2016-2017, ages 79.5±4.7 years), with an average 4.9 years apart. **Figure 8.1** shows the DAG incorporating the time-varying exposure, time-varying confounders, and missingness at Visit 6 (including both attrition at Visit 6 and missing measurements at Visit 6). The existence of U_0 and U_1 suggests that the censoring during the follow-up was not complete at random. The existence of the arrow from Y to Mis_1 suggests that the missingness of olfactory status and other covariates at visit 6 was not complete at random. Therefore, we need to use statistical methodologies to mitigate the biases due to missingness and attrition. Of note, in this DAG, we did not include the competing risk of death for simplicity, as the total association (detailed in **Chapter 3.5**) does not require additional assumptions.

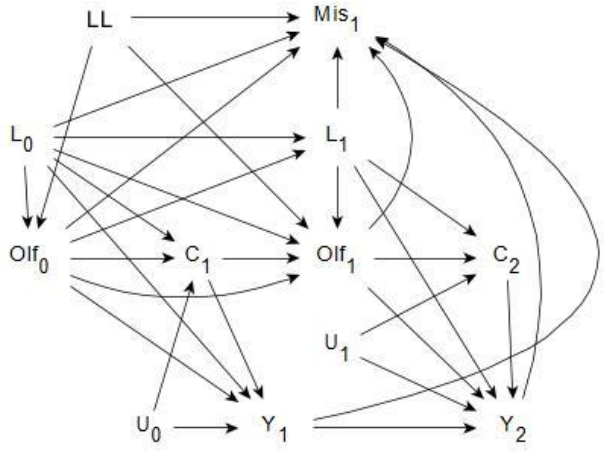


Figure 8.1 The directed acyclic graph for repeated smell testing and incident stroke. Olf_0 and Olf_1 is the olfactory assessment at Visit 5 and Visit 6, respectively. C_1 is censoring between Visit 5 and Visit 6; C_2 is censoring after Visit 6. Y_1 is incident stroke between Visit 5 and Visit 6; Y_2 is incident stroke after Visit 6. U_0 is unmeasured confounding at Visit 5 between censoring and stroke events; U_1 stands for unmeasured confounding at Visit 6. L_0 and L_1 are known confounders at Visit 5 and at Visit 6. Mis_1 stands for the missingness of olfaction or other covariates at Visit 6

Among 5,799 participants who were free of stroke (as an example) at Visit 5, we will have to delete those who died before/at Visit 6. Our final study population, therefore, will include 5,169 participants. This exclusion is critical because the subsequent multiple imputation for missingness in Visit 6 would be meaningless for those individuals who died before Visit 6.

Of the 5,169 surviving participants, 2,712 (52.5%) had at least one missing value in covariates or olfactory status at Visit 6. In the multiple imputation, we will use the random forest method with 50 imputations and 100 iterations per imputation[269], including three sets of covariates. The first set of variables are all the variables used in the primary analysis, including time-fixed and time-varying covariates, olfactory score and category at Visits 5 and 6, the indicators and the Nelson-Aalen estimates of the cumulative hazard to the survival time for incident stroke and the competing event of death during the follow-up[270]. The second set of covariates are potential variables related to non-response, including household income at Visit 1, and dementia status and depressive symptoms at Visit 5. The third set of covariates include those that could explain a considerable amount of variance in smell testing scores, such as the interval between Visit 5 and Visit 6 (i.e., the date of Visit 6 or the estimated median date of Visit 6), and cognitive function at Visit 5. While imputation relies on untestable assumptions, some graphs, e.g., the convergence plot and density plots of the variable distribution before and after the imputation, may assist in diagnosing the imputation.

Similar analyses will be performed for all 50 imputed complete datasets. We will use the marginal structural model with IPW to address issues of treatment-confounder feedback and censoring at random. We will then estimate the marginal absolute risk across groups of olfactory changes and calculate the risk ratio with the reference level of constant good olfaction. The 95% CI was estimated by using bootstrapping.

Last, we will use Rubin's Rule to pool the results from all the imputed datasets[271]. Point estimate is

$$\bar{Q} = \frac{1}{m}\sum_{l=1}^{m} \hat{Q}_l$$

, where $\hat{Q}_l$ is the estimated RR from each imputed dataset, m=50. The total variance T comes from three sources:

$$T = U + B + B/m$$

1) U: conventional statistical measure of variability, as we include a sample from a population; 2) B: extra variance because of missingness in the sample; 3) B/m: the extra simulation variance as $\overline{Q}$ is estimated from a finite m. If the target association measure is RR. There are two ways to obtain the right pooled RR and its 95% CIs through bootstrapping. The first approach is to output $\log(R1) - \log(R2)$ after bootstrapping. Accordingly, pooled point estimate of $\log(R1/R2)$ and its 95% CI can be calculated based on the Rubin's Rule and further transferred to RR. However, when the absolute risk is very low, the estimate of RR from the first approach can be inflated, thus the second approach may be preferable. Instead of directly outputting results for $\log(R1) - \log(R2)$, we can derive the point estimate and variance of $\log(R1) - \log(R2)$ using the delta method[272] from the bootstrapping output for $R1$ and $R2$.

8.3.3 Incorporating Frailty into the Investigation

Frailty is an increasingly appreciated geriatric clinical construct to characterize decreased physiological reserves and increasing vulnerability to adverse health consequences in the presence of stressors[108]. In older adults, frailty is highly predictive of morbidity, loss of independence, hospitalization, and mortality[273,274]. Interestingly, recent studies have robustly linked poor olfaction to frailty[117] and frailty to cardiovascular health[114–116]. However, to our knowledge, no

study has explored the potential interplays between these two ageing phenotypes in the context of cardiovascular health. Such investigation may improve our understanding of both phenotypes and their relevance to cardiovascular health, identifying novel approaches to improve the health and quality of life of older adults.

8.4 Conclusions

Using data from two well-established US cohorts of older adults, we found preliminary evidence that poor olfaction assessed by a single smell test is associated with the risks of major adverse cardiovascular outcomes. The data from both cohorts are mostly consistent for HF, supported by analysis involving subclinical cardiovascular biomarkers. The association of poor olfaction with stroke and CHD are only found in the ARIC Study but not the Health ABC Study. Nevertheless, the findings are provocative and deserve independent investigations.

To our knowledge, this project is the first comprehensive investigation on olfaction and cardiovascular health in older adults. Poor olfaction is common in older adults but has long been overlooked by the medical community and the public. While the COVID-19 pandemic has suddenly brought this sensory deficit to people's attention, we are far from understanding how it may affect human health, particularly in older adults. We expect my dissertation work, together with emerging findings on poor olfaction and a broad range of adverse outcomes, will fuel the research interest to unveil the potentially profound implications of olfaction on the health of older adults.

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APPENDIX 1: LITERATURE REVIEW ON PREVIOUS INVESTIGATIONS

The empirical evidence of olfaction and major cardiovascular adverse outcome consists of two sections. **Table A1.1** includes studies with olfaction as the outcome of interest and cardiovascular disease, cardiovascular subclinical markers, and/or cardiovascular risk factors as the exposures of interest. **Table A1.2** includes olfaction as the exposure of interest and major adverse cardiovascular disease as the outcome of interest, which is in line with our study goal.

Note: () under Exposure and Outcome means the approach of measurements.

Table A1.1 Previous studies regarding cardiovascular disease, cardiovascular subclinical markers, and cardiovascular risk factors in relation to olfaction

Study	Study design	Population	Exposure	outcome	covariates	effect	Estimate
Murphy, 2002, JAMA[2]	Cross-sectional	The Epidemiology of Hearing Loss Study: n=2800 (≥ 55 y, White, WI)	stroke (unknown); smoking status(unknown); diabetes	Self-reported and objective measured olfaction impairment (SDOIT)	Age, sex, occupation, sinus infection, nasal congestion, history of allergies, head injury, deviated septum, nasal polyps, chemotherapy, PD, epilepsy, use of medications	↑ ↑ -	OR: [Yes vs. No] 1.99 (1.13-3.51); [Current vs. never] 2.15(1.49-3.10); [Yes vs. No] 1.08 (0.79,1.47)

Table A1.1 (cont'd)

Schubert, 2011, Laryngoscope[3]6	Longitudinal Study	The Epidemiology of Hearing Loss Study: n=1556 (≥ 55 y, White, WI)	(Self-reported) Statin use	objective measured olfaction (SDOIT) decline between baseline and five years later	Age, sex, history of nasal polyps and deviated septum, oral corticosteroids used, history of heavy alcohol use, exercise	↓	OR: 0.68 (0.46, 0.99)
Schubert, 2014, J Gerontol A Biol Sci Med Sci[90]	Longitudinal cohort	The Beaver Dam Offspring Study (Epidemiology of Hearing Loss Study) (n=2302) (≥ 55 y, White, WI)	Carotid IMT, Number of carotid plaque	objective measured olfaction (SDOIT) decline between baseline and five years later	Age, sex, hypertension, BMI, alcohol and smoking status	- ↑	OR: [per 0.1mm] 1.13 (0.98, 1.31) [per site] 1.24 (1.01, 1.53)
Schubert, 2015, Age and aging[91]	Longitudinal cohort	The Beaver Dam Offspring Study (Epidemiology of Hearing Loss Study) (n=1611 without olfactory impairment)	Carotid IMT, carotid plaque	Incident objective measured olfaction (SDOIT) impairment between baseline and five years later	Age, sex, smoking, exercise, nasal steroids, oral steroids, nasal polyps/ deviated septum	- - ↑ ↑	HR: {≥60 years} [T3 vs. T1] 1.03 (0.70-1.52) [per site] 1.00 (0.91-1.10) {<60 years} [T3 vs. T1] 4.35 (1.69-11.21) [per site] 1.56 (1.17-2.08)

Table A1.1 (cont'd)

Wehling, 2015, BMC Neurology[118]	Cross-sectional study (Hospital-based)	Hospital-based study: n=74 stroke patients vs. age and sex-matched controls (age: 67.2 years)	Stroke occurrence within one year	Objective (SOIT) and self-reported olfactory function	Age and sex	↑	Linear correlation
Seubert, 2017, J Gerontol A Biol Sci Med Sci[119]	Cross-sectional	Swedish National Study: N=2234 (60-90 y, no neurodegeneration)	History of coronary heart disease; Heart faulire; Afib; CBVD; Hypertension; TC;	Olfactory dysfunction (16-item odor identification task)	Age, education, APOE Ɛ4 carrier, BDNF, depression, Migraine, physical activity, BMI, occupation, appetite	- - - - - -	Unknown of the exact value as only a forest plot is provided.
Okamoto, 2019, Chemical Senses[121]	Cross-sectional	Hospital-based patients in Japan: n=19 acute ischemic stroke patients (69.8 y)	No hypoperfusion vs. hypoperfusion in thalamus area	the T&T olfactometer (smell detection and recognition); olfactory identification using the Open Essence	/	↑	Unknown of the exact value as only *P* value is provided

Table A1.1 (cont'd)

Ekstorm, 2020, J[125] Gerontol A Biol Sci Med Sci	Longitudinal cohort	the Swedish National Study on Aging and Care in Kungsholmen: n=1780 (70.5 y, 61.9% female, with ≥2 follow-ups)	(Inpatient registries) cerebrovascular disease; cardiovascular disease burden (Afib, heart failure, coronary heart disease); diabetes;	Average olfactory change per year (Sniffin' Sticks battery)	Age, education, and test version, profession, vocabulary, number of medications, gait speed, APOE Ɛ4 carrier, BDNF	- - ↑	Predictor * time -0.077 (-0.155, 0.002) -0.009 (-0.041, 0.023) -0.09 (-0.161, -0.026))
Palmquist, 2020, J Gerontol A Biol Sci Med Sci[126]	Longitudinal cohort	Swedish National Study on Aging and Care: n=1004 (60-90 y, without OD)	(Inpatient registries) Smoking; atrial fibrillation; CBVD; Hypertension	Incident olfactory impairment (Sniffin' Sticks battery:≤10)	Baseline odor identification, age, APOE Ɛ4 carrier, Episodic memory, Perceptual speed, MMSE, Physical inactivity, Head trauma, Complex leisure activity, social network index	↑ ↑ ↑ ↓	OR: 1.92 (1.12-3.29) 2.07 (1.15, 3.75) 2.35 (1.02, 5.39) 0.66 (0.44, 1.00)

Table A1.1 (cont'd)

Schlosser, 2020, American J Rhinology and Allergy[122]	Cross-sectional	A clinic at the Medical University of South Carolina (MUSC): N=176, (20-93 y)	Heart problems;	Threshold, discrimination, and identification, (TDI) score (Sniffin' Sticks test)	Age, MMSE, anxiety	↑	TDI score: -1.665, *P*=0.01
Roh, 2021, Scientific Report[123]	Cross-sectional	Korean National Health and Nutrition Examination Survey: n=20016 (≥40 y)	(self-reported) diabetes; hypertension; CAD; stroke; obesity; abdominal obesity hypertriglyceridemia; low HDL	(Self-reported) history of olfactory dysfunction	Age, sex, household income, educational level, smoking status, heavy drinking, sleep duration, lack of exercise, history of rhinosinusitis and rhinitis	- - ↑ - - ↑ - -	OR: 1.08 (0.85, 1.38) 1.05 (0.88-1.27) 1.68 (1.15,2.47) 1.33(0.88, 2.00) 0.80 (0.64,1.01) 1.30 (1.03,1.63) 1.06 (0.88, 1.27) 1.05 (0.88, 1.26)
Kultur, 2022, Neurological Sciences[124]	Cross-sectional	Hospital-based population: n=82 (mean age: 54.3 y)	Stroke	MRI imaging: Olfactory bulb volume, olfactory sulcus depth Insular gyrus area, corpus amygdala area	age	↑	Independent sample t test showed significant correlation between stroke and all olfactory MRI markers

Table A1.1 (cont'd)

Shrestha, 2023, Nutrient[35]	Cross-sectional	ARIC Study: m=6053 (mean age: 75.6 y)	Smoking; Obesity; Total cholesterol; Diabetes; Hypertension; MI history; CHD history; Stroke history	Olfaction-Sniffin' Sticks	Age, sex, education, race-site, alcohol, APOE Ɛ4, physical activity, CRP, vitamin B12, blood Hemoglobin	↑ - - ↑ ↓ - - -	RR: 1.051 (1.000, 1.103); 1.127 (1.035, 1.227) 0.941 (0.881, 1.005); 0.920 (0.831, 1.020) 0.977 (0.952, 1.002) 1.075 (1.023, 1.129) 0.931 (0.881, 0.983) 0.982 (0.895, 1.077) 1.046 (0.970, 1.129) 1.037 (0.928, 1.160)

Abbreviations: SDOIT: the San Diego Odor Identification Test; SOIT: Scandinavian odor identification test; PD: Parkinson's disease; TC: total cholesterol; HDL-C: high-density lipoprotein-cholesterol; BMI: body mass index; IMT: intima media thickness; Afib: atrial fibrillation; CBVD: cerebrovascular disease; MMSE: Mini-Mental State examination; CAD: coronary artery disease.

Table A1.2 Previous study regarding olfaction in relation to incident cardiovascular disease

Study	Study design	Population	Exposure	outcome	covariates	effect	Estimate
Siegel, Int Forum Allergy Rhinol, 2019[127]	Longitudinal	National Social Like Health and Aging Project, n=3528	Olfactory decline (Sniffin's Sticks) between baseline and year 5	Self-reported first heart attack or new heart disease at year 10	Baseline age, gender, race/ethnicity, level of education, and cognition, baseline BMI and self-reported physical health	-	OR: 1.75 (0.93, 3.31)

APPENDIX 2: LIST OF REGRESSION MODELS IN THE PRESENCE OF COMPETING EVENTS

Table A2.1 The comparison of different regression models in the presence of competing events

Regressions	proportional hazard assumption	Parameter interpretation	Measure of association [a]	Meaning of association [b]	Available package	Convergence	Computation demand	Attrition [c]
Cause-specific hazard proportional model[151,153]	Yes	$\log \frac{\lambda_k^{cs}(t, x=1)}{\lambda_k^{cs}(t, x=0)}$ →derive cause-specific hazard ratio	Cause-specific hazard measures the instantaneous rate ratio of the event[d]	Direct association [Path 1] in the hazard ratio scale	SAS, R "surv" package	Good performance	Low	No
Fine-Gray proportional model (Based on Cox proportional model)[151]	Yes	$\log \frac{\log(1 - F_k(t, x=1)}{\log(1 - F_k(t, x=0)}$ → The parameter does not have straightforward meanings	This model is used for prediction; but can obtain risk ratio/difference[i]	Total association [Path 1+ Path 2] in RR/RD scale	SAS, R "surv" package	Good performance	Using bootstrap→ high	No
Discrete-time Fine-Gray model[155]	No	$\log \frac{\lambda_k^{sd}(t, x=1)}{\lambda_k^{sd}(t, x=0)}$ →derive sub-distribution hazard ratio	Risk difference/ ratio[i]	Total association [Path 1+ Path 2] + direct association [Path 1] in RR/ RD scale	straightforward to implement by directly coding	Good performance	Using bootstrap→ high	Yes

Table A2.1 (cont'd)

Absolute risk regression [275]	With log link	No	$\log \frac{F_k(t, x=1)}{F_k(t, x=0)}$ →derive risk ratio	Risk ratio[d]	Total association [Path 1+ Path 2] in RR scale	R "timereg" package	Too many covariates may cause convergence issue	Low (if not predict the marginal risk)	Yes
	With logit link	No	$\log \frac{F_k(t, x=1)}{1-F_k(t, x=0)}$ →derive risk ratio (when the risk of events is low, so OR≈RR)	≈Risk ratio[d] [d]	Total association [Path 1+ Path 2] in RR scale	R "timereg" package	Some unidentified coding error	Low (if not predict the marginal risk)	Yes

Abbreviations: PH: proportional hazard assumption.

[a] [d] Directly from parameter estimation; [i] from absolute risk prediction and then calculate the corresponding measure of associations

[b] Path 1 and Path 2 refer to Figure 2.1.

[c] Whether can correct the selection bias due to informative attrition.

[d] When the absolute risk of events is low (e.g., <10%), odds ratio ≈ risk ratio.

APPENDIX 3: SUPPLEMENTAL MATERIAL FOR CHAPTER 4

Table A3.1 Age-adjusted population characteristics by baseline olfactory status (n=2,537) [a]

	Olfactory status		
Variable [b]	**Good (n = 845)**	**Moderate (n = 867)**	**Poor (n = 825)**
Male sex	38.6 (35.4,41.9)	48.2 (44.9,51.6)	58.5 (55.1,61.8)
Black race	30.9 (27.9,34.1)	38.1 (34.9,41.4)	46.6 (43.2,50)
Study site of Pittsburgh [c]	55.8 (52.4,59.1)	50.2 (46.9,53.5)	47.7 (44.3,51.2)
Education of >high school [d]	51.2 (47.8,54.6)	43.5 (40.2,46.8)	38 (34.7,41.4)
Body mass index [e]			
25-30 kg/m^2	43.5 (40.2,46.9)	42.1 (38.8,45.4)	41.2 (37.8,44.6)
>30 kg/m^2	23.7 (20.8,26.5)	26.8 (23.8,29.7)	21.5 (18.7,24.3)
Smoking status [f]			
Former & <30 pack-years	27.8 (24.8,30.9)	25.1 (22.2,28)	26.1 (23.1,29.1)
Current or ≥30 pack-years	21.1 (18.3,23.8)	29.9 (26.9,33)	31.8 (28.6,35)
Brisk walking of ≥90 min/wk	11.9 (9.9,14.3)	9.3 (7.6,11.5)	8.6 (6.9,10.8)
General health status [g]			
Good	34.4 (31.2,37.6)	40.5 (37.2,43.8)	38.1 (34.7,41.4)
Fair to poor	15.6 (13.1,18)	15.2 (12.8,17.6)	22.4 (19.5,25.2)
Systolic blood pressure in mmHg	136.1 (134.7,137.5)	135.4 (134,136.7)	134.9 (133.5,136.3)
Antihypertensive drug use	58.9 (55.5,62.1)	61.5 (58.2,64.7)	58.5 (55.1,61.8)
Diabetes	21.5 (18.8,24.4)	24.7 (21.9,27.7)	26.6 (23.7,29.8)
Depressive symptoms	10.3 (8.4,12.6)	12.4 (10.3,14.7)	13.5 (11.3,16)
Heart rate in beats per minute	64.3 (63.6,65.1)	64.8 (64.1,65.5)	65.8 (65.1,66.6)
LVH, n (%)	11.6 (9.6,13.9)	11.2 (9.3,13.5)	11.7 (9.6,14.1)
Abnormal lung function			
Yes	8.6 (6.7,10.5)	11.9 (9.7,14)	12.8 (10.5,15.1)
Missing	9.7 (7.7,11.7)	9.3 (7.4,11.3)	13.3 (10.9,15.6)
Total cholesterol in mg/dL	208.3 (205.7,211)	204.2 (201.6,206.8)	203.7 (201,206.4)
HDL-C in mg/dL	54.8 (53.7,56)	53.3 (52.2,54.4)	53 (51.8,54.1)
Albumin in g/dL	4.00 (3.98,4.02)	3.98 (3.96,4.00)	3.98 (3.96,4.00)
Interleukin 6 in pg/mL	3.3 (3.1,3.5)	3.3 (3.1,3.6)	3.5 (3.2,3.7)
eGFR in mL/min/1.73m^2	79.6 (78.4,80.9)	80 (78.7,81.2)	75.9 (74.6,77.2)
Prevalent major cardiovascular diseases			
Prevalent CHD	23.9 (21.2,27)	23.7 (21,26.7)	24.4 (21.5,27.4)
Prevalent stroke	8.3 (6.6,10.4)	8.3 (6.7,10.4)	7.5 (5.9,9.6)
Prevalent CHF	4.4 (3.2,6)	5.1 (3.8,6.8)	4.2 (3.1,5.9)

Table A3.1 (cont'd)

Abbreviations: IQR: inter-quartile range; HDL-C: high-density lipoprotein-cholesterol; LVH: left ventricular hypertrophy; eGFR: estimated glomerular filtration rate; CHD: coronary heart diseases; CHF: congestive heart failure; CI: confidence interval.

[a] Linear regression for continuous variables, or logistic/ multinomial regression for categorical variables was used to calculate age-adjusted marginal means or percentage in each olfaction group, the average age of which was consistent with that of overall population as 75.6 years.

[b] Continuous and categorical variables are presented as mean (95% CI) and % (95% CI), respectively.

[c] Reference level of study site is Memphis.

[d] Reference level of education is ≤ high school.

[e] Reference level of BMI is <25 kg/m^2.

[f] Reference level of smoking status is never.

[g] Reference level of general health status is very good to excellent.

Table A3.2 The association of baseline olfactory status with incident coronary heart diseases (CHD), stroke and congestive heart failure (CHF) after excluding prevalent cases of dementia or Parkinson's disease [a]

Olfactory function	No. of Event	Person-years	Incidence (per 1,000 person-year)	Model 1[b]		Model 2 [c]		Model 3[d]	
				HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
CHD (n=1,718)									
Good	112	5906.00	19.0	Reference		Reference [e]			
Moderate	116	5532.58	21.0	1.06 (0.81,1.38)	0.667	1.01 (0.77,1.31)	0.963		
Poor	94	4078.08	23.1	1.11 (0.84,1.46)	0.477	1.03 (0.78,1.38)	0.817		
Stroke (n=2,080)									
Good	83	7404.75	11.2	Reference		Reference [f]			
Moderate	70	6927.00	10.1	0.86 (0.63,1.19)	0.374	0.86 (0.62,1.19)	0.354		
Poor	73	5327.25	13.7	1.14 (0.82,1.58)	0.431	1.13 (0.81,1.58)	0.459		
CHF (n=2,160)									
Good	123	7496.92	16.4	Reference		Reference		Reference	
Moderate	165	6976.42	23.7	1.37 (1.08,1.73)	0.009	1.33 (1.05,1.68)	0.019	1.32 (1.05,1.68)	0.020
Poor	137	5403.42	25.4	1.41 (1.1,1.81)	0.006	1.37 (1.07,1.76)	0.014	1.29 (1.00,1.67)	0.051

Table A3.2 (cont'd)

Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval

[a] Associations were estimated from Cox cause-specific models with the robust sandwich standard error estimate to account for the competing risk of death.

[b] Model 1 included age, sex, race, education and study site as covariates.

[c] Model 2 further included smoking status, brisk walking, body mass index, self-reported general health status, systolic blood pressure, use of antihypertensive medications, diabetes, depressive symptoms, total cholesterol and high-density lipoprotein-cholesterol as covariates. For CHF, Model 2 further included prevalent CHD/stroke in addition to above covariates.

[d] Model 3 (only for CHF) further included heart rate, left ventricular hypertrophy, abnormal lung function, albumin, interleukin 6 and estimated glomerular filtration rate.

[e] Age category was stratified in the Cox model.

[f] Brisk walking and antihypertensive medication use were stratified in the Cox model.

Table A3.3 Cause-specific hazard ratios and 95% confidence intervals [a] of each covariate in relation to congestive heart failure among all participants (n=2,421) and among participants who self-reported very-good-to-excellent health (n=1,100)

Variable	Categories	HR (95% CI)	
		All participants [b]	Those with very-good-to-excellent health [c]
Olfaction	Moderate vs. good	1.32 (1.05,1.66)	1.40 (0.96,2.06)
	Poor vs. good	1.28 (1.01,1.64)	1.70 (1.15,2.53)
Age at baseline (year)	–	1.04 (1.01,1.08)	1.04 (0.99,1.10)
Sex	Male vs. female	1.03 (0.83,1.28)	0.99 (0.71,1.38)
Race	White vs. Black	1.10 (0.89,1.36)	0.93 (0.67,1.30)
Study site	Memphis vs. Pittsburgh	0.81 (0.66,0.97)	0.72 (0.53,0.99)
Education	> high vs. ≤ high school	0.8 (0.66,0.97)	0.80 (0.59,1.09)
Smoking status	Former & <30 pack-years vs. never	1.09 (0.87,1.38)	1.12 (0.78,1.62)
	Current or ≥30 pack-years vs. never	1.32 (1.05,1.64)	1.53 (1.06,2.19)
Brisk walking	≥90 vs. <90 min/wk	0.73 (0.50,1.07)	0.73 (0.43,1.23)
Body mass index	25-30 kg/m^2 vs. <25 kg/m^2	0.74 (0.60,0.93)	0.77 (0.53,1.14)
	>30 kg/m^2 vs. <25 kg/m^2	0.9 (0.70,1.17)	0.93 (0.59,1.49)
Antihypertensive drug use	Yes vs. No	1.44 (1.17,1.78)	1.45 (1.04,2.04)
Diabetes	Yes vs. No	1.24 (1.01,1.53)	1.22 (0.84,1.75)
Depressive symptoms	Yes vs. No	0.95 (0.73,1.25)	0.95 (0.53,1.69)
Total cholesterol (mg/dL)	–	1.00 (0.996,1.001)	1.00 (0.996,1.005)
HDL-C (mg/dL)	–	1.00 (0.99,1.01)	0.99 (0.98,1.003)
Prevalent coronary heart disease/stroke	Yes vs. No	1.65 (1.36,2.01)	1.63 (1.18,2.26)
Heart rate (beat/minute)	–	1.01 (1.00,1.02)	1.00 (0.99,1.02)
LVH	Yes vs. No	1.40 (1.08,1.83)	1.39 (0.87,2.20)
Albumin (g/dL)	–	0.73 (0.54,0.99)	0.77 (0.46,1.29)
eGFR (mL/min/1.73m^2)	–	0.99 (0.98,0.99)	0.99 (0.98,1.00)
Abnormal lung function	Yes vs. No	1.44 (1.09,1.90)	1.29 (0.81,2.06)
	Missing vs. No	0.96 (0.71,1.30)	1.00 (0.60,1.66)
General health status	Good vs. very good to excellent	1.17 (0.95,1.45)	/

Table A3.3 (cont'd)

	Fair to poor vs. very good to excellent	1.33 (1.02,1.74)	/
Systolic blood pressure (mmHg)	–	1.01 (1.00,1.01)	Stratified variable
Interleukin 6 (pg/mL)	–	Stratified variable	1.03 (0.99,1.07)

Abbreviations: CHF: congestive heart failure; HR: hazard ratio; 95% CI: 95% confidence interval; HDL-C: high-density lipoprotein-cholesterol; LVH: left ventricular hypertrophy; eGFR: estimated glomerular filtration rate.

[a] The 95% confidence intervals were estimated using the robust sandwich standard error estimate.

[b] Tertile of interleukin 6 was stratified in the Cox model.

[c] The group of systolic pressure (cut-off as 140 mmHg) was stratified in the Cox model.

APPENDIX 4: SUPPLEMENTAL MATERIAL FOR CHAPTER 5

Methods

We imputed missing frailty data and created 10 imputed datasets by using the random forest method with 100 iterations per imputation. In the imputation model, we included olfactory status, all the covariates in the primary analysis, the indicators of incident stroke and competing event of death and their corresponding Nelson-Aalen estimates of cumulative hazards, as well as additional variables that may be related to the missingness, including prevalent dementia, global cognitive function, and depressive symptoms. For each imputed dataset, we conducted the same analysis as the primary analysis and performed the statistical inference via bootstrapping with 300 samples. Finally, we used Rubins' rule to obtain the pooled point estimates of risk ratios with good olfaction as the reference level and their pooled 95% confidence intervals at different time points.

Table A4.1 The period-specific associations of baseline olfactory status with incident stroke (n=5,799)

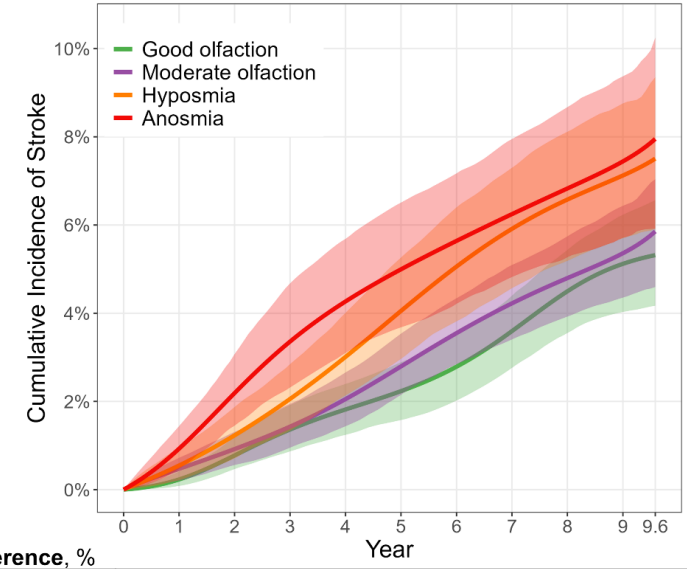
Olfactory status	Cause-specific hazard ratio (95% confidence interval) [a] by follow-up years			
	4-Year [b]	6-Year [c]	8-Year [c]	9.6-Year [c]
Good	Reference	Reference	Reference	Reference
Moderate	1.11 (0.69,1.79)	1.25 (0.88,1.8)	1.13 (0.84,1.54)	1.09 (0.82,1.45)
Poor	1.98 (1.26,3.16)	1.84 (1.3,2.62)	1.76 (1.31,2.38)	1.61 (1.21,2.14)

[a] Associations were estimated from the cause-specific Cox regression, adjusting for age, sex, race-center, education, APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), lipid lowering medication, atrial fibrillation, coronary heart disease, heart failure, estimated glomerular filtration rate, and frailty.
[b] Quartiles of age were stratified in the model.
[c] Quartile of HDL-C and frailty were stratified in the model.

Table A4.2 Marginal adjusted risk ratios of stroke comparing moderate/hyposmia/anosmia with good olfaction during the follow-up (n=5,799)

Olfactory status	Risk ratio (95% confidence interval) [a] by follow-up years				
	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.19 (0.63,2.27)	1.13 (0.73,1.74)	1.27 (0.95,1.82)	1.07 (0.82,1.48)	1.10 (0.80,1.53)
Hyposmia	1.59 (0.85,3.15)	1.66 (1.06,2.59)	1.82 (1.24,2.69)	1.46 (1.06,1.96)	1.41 (1.02,1.96)
Anosmia	2.83 (1.63,5.23)	2.35 (1.52,3.91)	2.02 (1.43,2.97)	1.52 (1.08,2.07)	1.50 (1.06,2.08)

[a] Marginal adjusted risk ratio was calculated through the multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein (HDL)-cholesterol, lipid lowering medication, atrial fibrillation, coronary heart disease, heart failure, estimated glomerular filtration rate, and frailty, plus two-way interaction terms between time and olfaction & education & HDL-cholesterol.



Risk difference, %

Olfactory status	**Follow-up years**				
	2-year	4-year	6-year	8-year	9.6-year
Moderate vs. good	0.1 (-0.4,0.7)	0.2 (-0.6,1.1)	0.8 (-0.2,1.7)	0.3 (-0.9,1.7)	0.5 (-1.2,2.4)
Hyposmia vs. good	0.5 (-0.1,1.2)	1.2 (0.1,2.3)	2.3 (0.8,3.7)	2.1 (0.3,3.9)	2.2 (0.1,4.4)
Anosmia vs. good	1.4 (0.6,2.3)	2.4 (1.1,4.0)	2.9 (1.2,4.6)	2.3 (0.5,4.3)	2.6 (0.4,5.1)

Figure A4.1 Marginal adjusted cumulative incidence function of stroke by 4-category olfactory status and the risk difference comparing moderate, hyposmia, anosmia with good olfaction. The cumulative incidence was estimated by the discrete-time sub-distribution hazard model, adjusting for covariates in Model 3

Table A4.3 Marginal adjusted risk ratios of stroke comparing moderate/poor with good olfaction among participants without dementia, Parkinson's disease, and depressive symptoms (n=5,205)

Olfactory status	Risk ratio (95% confidence interval) [a] by follow-up years				
	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.32 (0.7,2.65)	1.19 (0.77,1.92)	1.31 (0.9,1.99)	1.12 (0.83,1.53)	1.17 (0.86,1.63)
Poor	2.21 (1.24,4.17)	1.92 (1.24,3.09)	1.84 (1.35,2.7)	1.52 (1.16,2.11)	1.52 (1.11,2.09)

[a] Marginal risk ratio was calculated through the multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein (HDL)-cholesterol, lipid lowering medication, atrial fibrillation, coronary heart disease, heart failure, estimated glomerular filtration rate, and frailty, plus two-way interaction terms between time and olfaction & education & HDL-cholesterol.

Table A4.4 Marginal adjusted risk ratios of ischemic stroke comparing moderate/poor with good olfaction (n=5,799)

	Risk ratio (95% confidence interval) [a] by follow-up years				
Follow-up year	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.03 (0.52,2.15)	1.08 (0.67,1.7)	1.33 (0.91,1.92)	1.14 (0.83,1.58)	1.15 (0.83,1.56)
Poor	1.96 (1.13,4.12)	1.84 (1.22,2.95)	1.82 (1.32,2.66)	1.41 (1.09,1.93)	1.39 (1.06,1.95)

[a] Marginal risk ratio was calculated through the multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein (HDL)-cholesterol, lipid lowering medication, atrial fibrillation, coronary heart disease, heart failure, estimated glomerular filtration rate, and frailty, plus two-way interaction terms between time and olfaction & education & HDL-cholesterol.

Table A4.5 Marginal adjusted risk ratios of stroke comparing moderate/poor with good olfaction, after using multiple imputation (n=5,799)

Olfactory status	Risk ratio (95% confidence interval) [a] by follow-up years				
	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.18 (0.61,2.3)	1.13 (0.71,1.79)	1.27 (0.9,1.79)	1.06 (0.8,1.42)	1.1 (0.82,1.46)
Poor	2.13 (1.17,3.87)	1.97 (1.29,3)	1.9 (1.38,2.63)	1.48 (1.13,1.93)	1.44 (1.1,1.89)

[a] Marginal risk ratio was pooled from the results of 10 imputed datasets based on Rubin's rule. For each imputed dataset, marginal absolute risks across olfactory statuses and risk ratios were calculated through the multivariable discrete-time Fine-Gray model; and their 95% confidence intervals were obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein (HDL)-cholesterol, lipid lowering medication, atrial fibrillation, coronary heart disease, heart failure, estimated glomerular filtration rate, and frailty, plus two-way interaction terms between time and olfaction & education & HDL-cholesterol.

Table A4.6 Adjusted marginal risk ratios [a] of stroke for common risk factors during the follow-up (n=5,799)

	Risk ratio (95% confidence interval)				
Follow-up year	Year 2	Year 4	Year 6	Year 8	Year 9.6
Poor vs. good olfaction	2.14 (1.22,3.94)	1.98 (1.43,3.02)	1.91 (1.43,2.77)	1.49 (1.17,2.00)	1.45 (1.16,1.95)
CHD vs. no	1.84 (1.08,3.14)	1.83 (1.24,2.6)	1.66 (1.21,2.29)	1.51 (1.15,2.02)	1.58 (1.14,2.19)
Atrial Fibrillation vs. no	2.33 (1.06,4.13)	1.99 (1.16,3.02)	1.75 (1.14,2.45)	1.61 (1.10,2.21)	1.47 (1.01,1.97)

Abbreviation: CHD: coronary heart disease

[a] Marginal risk ratio was calculated through multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. To make the comparison comparable, the model included the interaction between the risk factor of interest and time. In addition, the model includes olfaction, age, sex, race-site, education, APOE4 carrier, smoking status, body mass index, coronary heart disease, heart failure, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein (HDL)-cholesterol, atrial fibrillation, lipid lowing medication, estimated glomerular filtration rate, and frailty, plus two-way interaction terms between time and education & HDL-cholesterol.

APPENDIX 5: SUPPLEMENTAL MATERIAL FOR CHAPTER 6

Table A5.1 Olfactory status in relation to risk of coronary heart disease (n=5,142) using an alternative approach

Olfactory Status	Cause-specific hazard ratio [a] (95% confidence interval) by years of follow-up			
	4-Year [b]	6-Year [c]	8-Year [d]	9.6-Year [e]
Good	Reference	Reference	Reference	Reference
Moderate	1.34 (0.82,2.22)	1.37 (0.93,2.03)	1.3 (0.96,1.77)	1.25 (0.93,1.68)
Poor	1.75 (1.07,2.91)	1.65 (1.11,2.46)	1.26 (0.91,1.76)	1.25 (0.91,1.72)

[a] Cause-specific hazard ratio was estimated from the cause-specific Cox proportional hazards regression, adjusting for age, sex, race-center, education, APOE4 carrier, smoking status, body mass index (BMI), diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high-density lipoprotein-cholesterol, lipid lowering medication, atrial fibrillation, stroke, heart failure, renal function, and frailty.
[b] BMI is stratified in the model.
[c] BMI and frailty are stratified in the model.
[d] BMI and stroke are stratified in the model. Poor vs. good olfaction does not follow the proportional hazard assumption.
[e] Race-center and stroke are stratified in the model. Poor vs. good olfaction does not follow the proportional hazard assumption.

Table A5.2 Four-category olfactory status in relation to risk of coronary heart disease (n=5,142)

Olfactory status	Risk ratio [a] (95% confidence interval) by years of follow-up				
	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.52 (0.75,3.0)	1.49 (0.95,2.37)	1.34 (0.94,1.94)	1.32 (0.97,1.72)	1.15 (0.86,1.49)
Hyposmia	1.71(0.64,3.84)	2.14 (1.30,3.44)	1.61 (1.12,2.36)	1.25 (0.86,1.71)	1.06 (0.76,1.44)
Anosmia	2.45 (0.9,5.84)	1.93 (0.99,3.38)	1.56 (0.96,2.47)	1.20 (0.79,1.82)	1.10 (0.71,1.69)

[a] Marginal adjusted risk ratio was calculated through the multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein-cholesterol, lipid lowering medication, atrial fibrillation, stroke, heart failure, renal function, and frailty, plus interaction terms between time and olfactory status.

Table A5.3 Olfactory status in relation to risk of coronary heart disease among participants without dementia (n=4,953)

Olfactory status	Risk ratio [a] (95% confidence interval) by years of follow-up				
	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.51 (0.7,3.44)	1.54 (0.96,2.57)	1.37 (0.94,2.15)	1.33 (1,1.83)	1.16 (0.85,1.59)
Poor	2.19 (1.10,4.72)	2.21 (1.43,3.43)	1.68 (1.12,2.5)	1.26 (0.9,1.74)	1.12 (0.81,1.57)

[a] Marginal adjusted risk ratio was calculated through the multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, APOE4 carrier, smoking status, body mass index, diabetes, systolic blood pressure, antihypertensive medication, total cholesterol, high density lipoprotein-cholesterol, lipid lowering medication, atrial fibrillation, stroke, heart failure, renal function, and frailty, plus interaction terms between time and olfactory status.

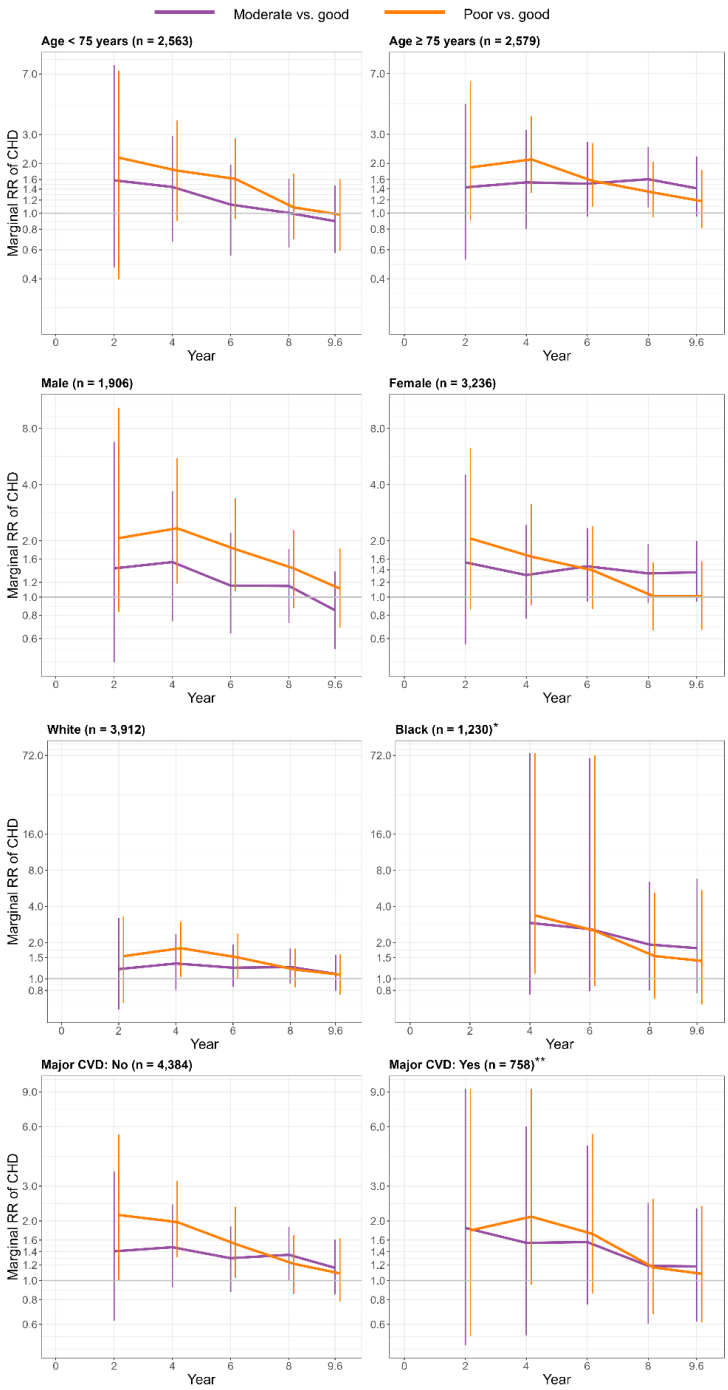
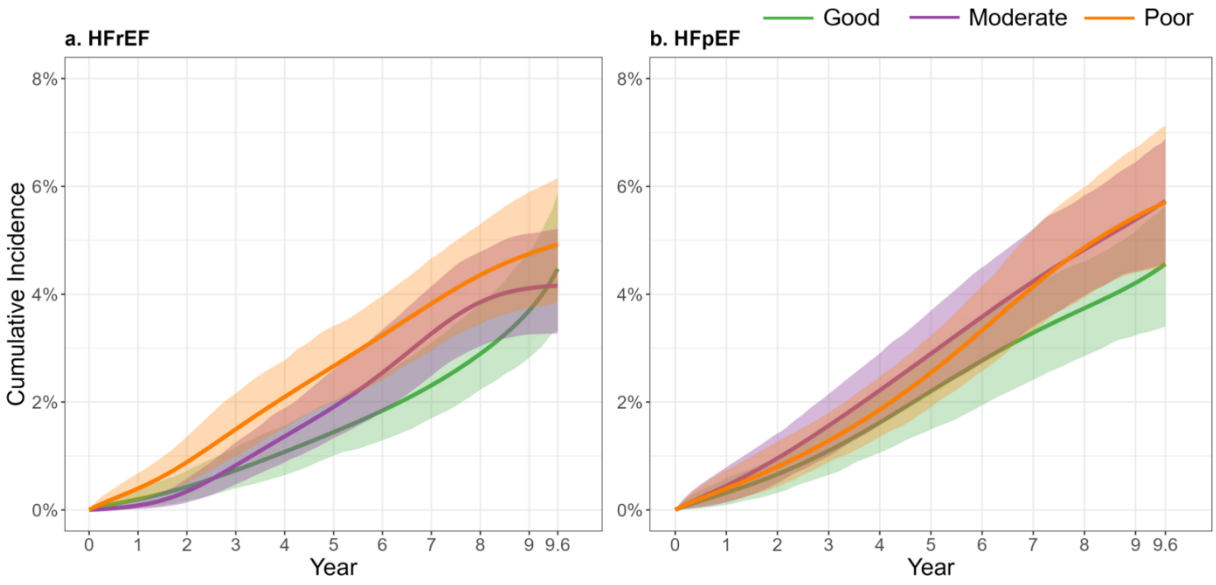


Figure A5.1 Stratified marginal adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) of coronary heart disease (CHD) by a) age groups; b) sex; c) race; d) prevalent cardiovascular disease (CVD). * In subgroup of Black participants, due to the small number of incident events, the point estimate of year-2 RR was imprecise, so the data is not shown in the plot. The adjusted RR of CHD at year 4 was 2.91 (95% CI: 0.74, 3.1×10^{8}) for moderate olfaction and 3.4 (95% CI: 1.1, 2.6×10^{8}) for poor olfaction. ** In subgroup of participants with prevalent CVD, the adjusted RR of CHD at year 2 was 1.84 (95% CI: 0.23, 3.1×10^{12}) for moderate olfaction and 1.79 (95% CI: 0.52, 3.9×10^{12}) for poor olfaction

APPENDIX 6: SUPPLEMENTAL MATERIAL FOR CHAPTER 7



Risk difference (%) by follow-up years

HFrEF

	2-year	4-year	6-year	8-year	9.6-year
Good	Ref	Ref	Ref	Ref	Ref
Moderate	-0.1 (-0.5,0.3)	0.3 (-0.5,0.9)	0.7 (-0.3,1.6)	1 (-0.2,2.1)	-0.3 (-2.2,1.1)
Poor	0.5 (0,0.9)	1 (0.2,1.8)	1.4 (0.3,2.5)	1.5 (0.1,2.8)	0.5 (-1.4,2.2)

HFpEF

2-year	4-year	6-year	8-year	9.6-year
Ref	Ref	Ref	Ref	Ref
0.3 (-0.2,0.8)	0.6 (-0.3,1.5)	0.8 (-0.4,2.0)	1.1 (-0.3,2.5)	1.2 (-0.3,2.8)
0.1 (-0.4,0.7)	0.2 (-0.5,1.1)	0.6 (-0.4,1.8)	1.1 (-0.1,2.7)	1.1 (-0.6,3.0)

Figure A6.1 Marginal adjusted cumulative incidence of a) heart failure with reduced ejection fraction (HFrEF) and b) heart failure with preserved ejection fraction (HFpEF) by olfactory status. The cumulative incidence was estimated by discrete-time sub-distribution hazard model, adjusting for covariate in Model 3

Table A6.1 The period-specific associations of baseline olfactory status with incident heart failure (n=5,217) [a]

Olfactory function	Cause-specific hazard ratio (95% confidence interval) by follow-up years			
	4-Year [b]	6-Year [c]	8-Year [d]	9.6-Year [e]
Good	Reference	Reference	Reference	Reference
Moderate	1.16 (0.83,1.62)	1.21 (0.93,1.57)	1.29 (1.04,1.61)	1.18 (0.97,1.45)
Poor	1.19 (0.85,1.68)	1.28 (0.97,1.68)	1.42 (1.13,1.78)	1.26 (1.02,1.56)

[a] Associations were estimated from Cox cause-specific models, adjusting for age, sex, race-center, education, self-reported general health status, smoking status, BMI, diabetes, hypertension, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), lipid lowering medication, coronary heart disease, atrial fibrillation, renal function, and frailty.
[b] Race-center was stratified in the model.
[c] Race-center, BMI, quartile of HDL-C, and atrial fibrillation were stratified in the model.
[d] Race-center, quartile of HDL-C, atrial fibrillation, and frailty were stratified in the model.
[e] Quartile of HDL-C, atrial fibrillation, and frailty were stratified in the model.

Table A6.2 Adjusted marginal risk ratio [a] of heart failure for moderate/hyposmia/anosmia vs. good olfaction during the follow-up (n=5,217)

Olfactory status	Risk ratio (95% confidence interval) by follow-up years				
	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.07 (0.65,1.65)	1.16 (0.86,1.6)	1.22 (0.96,1.54)	1.22 (1.00,1.49)	1.07 (0.86,1.34)
Hyposmia	1.06 (0.59,1.98)	0.97 (0.68,1.41)	1.09 (0.84,1.48)	1.15 (0.93,1.46)	1.01 (0.8,1.29)
Anosmia	1.47 (0.89,2.58)	1.36 (0.95,2.01)	1.26 (0.95,1.7)	1.28 (1.01,1.64)	1.16 (0.87,1.49)

[a] Marginal risk ratio was calculated through multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, self-reported general health status, smoking status, BMI, prevalent coronary heart disease, atrial fibrillation, diabetes, hypertension, total cholesterol, HDL-cholesterol, lipid lowering medication, and renal function, plus interaction terms between time and olfaction & body mass index & coronary heart disease & frailty.

Table A6.3 Adjusted marginal risk ratio [a] of acute decompensated heart failure for moderate/poor vs. good olfaction (n=5,217)

Olfactory status	No. of incident cases	Risk ratio (95% confidence interval) by follow-up years				
		Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	141	Reference	Reference	Reference	Reference	Reference
Moderate	160	1.1 (0.64,1.94)	1.15 (0.81,1.64)	1.23 (0.94,1.61)	1.22 (0.97,1.49)	1.08 (0.86,1.33)
Poor	167	1.36 (0.89,2.37)	1.27 (0.94,1.92)	1.26 (0.98,1.65)	1.25 (1.01,1.56)	1.06 (0.8,1.35)

[a] Marginal risk ratio was calculated through multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, self-reported general health status, smoking status, BMI, prevalent coronary heart disease, stroke, diabetes, hypertension, total cholesterol, HDL-cholesterol, lipid lowering medication, and renal function, plus interaction terms between time and olfaction & body mass index & coronary heart disease & frailty.

Table A6.4 Adjusted marginal risk ratio [a] of heart failure for moderate/poor vs. good olfaction during the follow-up in participants without dementia (n=5,042)

Olfactory status	Risk ratio (95% confidence interval) by follow-up years				
	Year 2	Year 4	Year 6	Year 8	Year 9.6
Good	Reference	Reference	Reference	Reference	Reference
Moderate	1.08 (0.65,1.68)	1.18 (0.88,1.55)	1.24 (0.99,1.6)	1.23 (1.04,1.52)	1.07 (0.87,1.28)
Poor	1.23 (0.81,1.94)	1.15 (0.84,1.52)	1.19 (0.95,1.52)	1.23 (0.99,1.5)	1.09 (0.88,1.35)

[a] Marginal risk ratio was calculated through multivariable discrete-time Fine-Gray model; 95% confidence interval was obtained through bootstrapping with 300 samples. The model includes age, sex, race-center, education, self-reported general health status, smoking status, BMI, prevalent coronary heart disease, stroke, diabetes, hypertension, total cholesterol, HDL-cholesterol, lipid lowering medication, and renal function, plus interaction terms between time and olfaction & body mass index & coronary heart disease & frailty.