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Food Insecurity is Associated with Nonalcoholic Fatty Liver Disease, Cognitive Impairment, and Immune Activation in People Living with HIV

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FOOD INSECURITY IS ASSOCIATED WITH NONALCOHOLIC FATTY LIVER DISEASE, COGNITIVE IMPAIRMENT, AND IMMUNE ACTIVATION IN PEOPLE LIVING WITH HIV

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Javier A. Tamargo

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To: Dean Tomás R. Guilarte
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This dissertation, written by Javier A. Tamargo, and entitled Food Insecurity is Associated with Nonalcoholic Fatty Liver Disease, Cognitive Impairment, and Immune Activation in People Living with HIV, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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Date of Defense: March 22, 2021

The dissertation of Javier A. Tamargo is approved.

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Florida International University, 2021

The following chapters have been published in their entirety in peer-reviewed journals. According to the stated policy of each journal, they can be included in this dissertation without obtaining formal copyright permission.

CHAPTER III

Tamargo JA, Sherman KE, Campa A, Martinez SS, Li T, Hernandez J, Teeman C, Mandler RN, Chen J, Ehman RL, Baum MK. Food insecurity is associated with magnetic resonance–determined nonalcoholic fatty liver and liver fibrosis in low-income, middle-aged adults with and without HIV. *Am J Clin Nutr*. 2021;113(3):593-601. doi:10.1093/ajcn/nqaa362

CHAPTER IV

Tamargo JA, Meade CS, Campa A, Martinez SS, Li T, Sherman KE, Baum MK. Food Insecurity and Cognitive Impairment in the Miami Adult Studies on HIV (MASH) Cohort. *J Nutr*. 2021. doi:10.1093/jn/nxaa416

DEDICATION

I dedicate this dissertation, with all the work and sacrifice that it took, to my parents.

To my father, Jesús Rafael Tamargo, who loved me unconditionally and instilled in me an unquenchable thirst for knowledge.

To my mother, Gloria Cisneros, who would be extremely proud of the person I am today.

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ABSTRACT OF THE DISSERTATION

FOOD INSECURITY IS ASSOCIATED WITH NONALCOHOLIC FATTY LIVER DISEASE, COGNITIVE IMPAIRMENT, AND IMMUNE ACTIVATION IN PEOPLE LIVING WITH HIV

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Food insecurity (FI) is a socioeconomic condition characterized by inadequate access to enough food and nutrition to sustain health and wellbeing. Food insecurity is a risk factor for chronic and age-related conditions, raising concerns for the aging population of people living with HIV (PLWH), in whom food insecurity is disproportionately prevalent. PLWH are at increased risk of nutrition-related complications and chronic co-morbidities, thus food insecurity may exacerbate adverse health outcomes in this population. This study investigated whether food insecurity was associated with nonalcoholic fatty liver disease (NAFLD), cognitive impairment, and immune activation among socioeconomically disadvantaged adults living with and without HIV.

This study was conducted with participants from the Miami Adult Studies on HIV (MASH) Cohort, predominantly comprised of low-income Black and Hispanic middle-aged adults. Food insecurity was measured with the U.S. Household Food Security

Survey. Magnetic resonance technology was used to assess liver steatosis and fibrosis. The Mini-Mental State Examination was used to assess cognitive impairment. Biomarkers of monocyte/macrophage (sCD14 and sCD163) and lymphocyte (sCD27) activation were measured from blood samples.

Approximately a third of participants experienced food insecurity. Food insecurity modified the effect of BMI on NAFLD, increasing the risk associated with increasing BMI among those who experienced food insecurity. Additionally, food insecurity was independently associated with increased risk for any and advanced liver fibrosis. Baseline food insecurity and its frequency over a 2-year period were associated with cognitive decline, particularly when food insecurity was persistent. The effects of food insecurity on liver disease or cognitive impairment were not significantly different between PLWH and HIV-uninfected participants. Among PLWH, food insecurity was associated with increased sCD14 and sCD27, which also correlated with the severity of food insecurity. The severity of food insecurity also appeared to moderate the relationship between CD4 cell count and sCD163.

Food insecurity may contribute to the NAFLD and cognitive decline among low-income U.S. minorities. Although food insecurity did not have greater effects for PLWH compared to those HIV-uninfected, food insecurity may promote immune activation in PLWH, suggesting a biological link between food insecurity and adverse health outcomes. Improving financial security and access to high-quality foods could reduce the high burden of disease in vulnerable populations.

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ABBREVIATIONS AND ACRONYMS

AALD	Alcohol-associated liver disease
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANI	Asymptomatic neurocognitive disorder
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body mass index
CAD	Coronary artery disease
CES-D	Center for Epidemiological Studies–Depression Scale
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
FI	Food insecurity
FIB-4	Fibrosis-4 Index
FS	Food security
HAND	HIV-associated neurocognitive disorder
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HFSS	U.S. Household Food Security Survey

HIV	Human Immunodeficiency Virus
Hs-CRP	High-sensitivity C-reactive protein
I-FABP	Intestinal fatty-acid binding protein
IgG	Immunoglobulin G
IL	Interleukin
IQR	Interquartile range
IR	Insulin resistance
LFS	Low food security
LPS	Lipopolysaccharide
LS	Liver stiffness
MAFLD	Metabolic (dysfunction)-associated fatty liver disease
MASH	Miami Adult Studies on HIV
MetS	Metabolic syndrome
MMSE	Mini-Mental State Examination
MND	Mild neurocognitive disorder
MR	Magnetic resonance
MRE	Magnetic resonance elastography
MRI-PDFF	Magnetic resonance imaging-derived proton density fat fraction
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCD	Neurocognitive disorder
NCI	Neurocognitive impairment

NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PLWH	People living with HIV
sCD	Soluble cluster of differentiation
SCFA	Short-chain fatty acid
SD	Standard deviations
SNAP	Supplemental Nutrition Assistance Program
T2D	Type II diabetes
TNF	Tumor necrosis factor
TyG	Triglyceride and Glucose Index
VLFS	Very low food security

CHAPTER I: INTRODUCTION

Statement of Problem

Over 1.2 million adolescents and adults in the United States (U.S.) are living with the human immunodeficiency virus (HIV).[1] People living with HIV (PLWH) are, in its majority, a marginalized group disproportionately affected by socioeconomic hardships and stigma.[2,3] In the United States, HIV infections are mostly concentrated in poor communities, where racial-ethnic minorities – particularly Black Americans – are over-represented.[2] As a result of social disparities, PLWH are disproportionately affected by food insecurity,[4-6] a socioeconomic condition of inadequate access to sufficient, safe, and nutritious foods to sustain health and wellbeing. Although population-wide studies are needed, 40-60% prevalence of food insecurity among PWLH in the United States have been reported,[7-10] making it approximately four to six times greater than in the general U.S. population.[5]

Advances in antiretroviral therapy (ART) have improved HIV-related health outcomes and made it possible for PLWH to live longer lives, achieving lifespans that are similar to those of the general population.[11-13] As a result, the prevalence of HIV infections in the United States continues to rise although the incidence rate has declined.[14] As PLWH live longer, chronic and age-related conditions have become the predominant causes of morbidity and mortality, impacting their health and quality of life.[15-20] Indeed, PLWH are at increased risk for many chronic, non-communicable diseases,[19,21-23] and have higher rates of multi-morbidity.[20,24,25]

Food insecurity raises particular concerns for PLWH. On one hand, food insecurity is associated with poorer adherence to ART,[26,27] lower odds for viral suppression,[28] and

lower CD4 cell counts.[29] Thus, food insecurity promotes immunodeficiency and HIV disease progression, increasing the risk for mortality.[4,30] By contributing to poor HIV control, food insecurity may be a barrier for the eradication of HIV. On the other hand, food insecurity also increases the risk for compromised nutritional status (e.g. malnutrition, micronutrient deficiencies)[6,31] and the development and/or progression of comorbidities.[8,9,32-39] There are several nutrition-related complications in HIV infection, such as increased nutritional and metabolic demands,[40,41] as well as altered gastrointestinal function resulting in decreased food intake and poor absorption of nutrients.[42-45] Both HIV infection and ART can lead to metabolic abnormalities and increase the risk for cardiometabolic conditions.[46,47] Given the high rates of food insecurity among PLWH, their susceptibility and vulnerability to chronic diseases, and the associations of food insecurity with poor health outcomes, food insecurity may significantly contribute to the burden of disease among U.S. adults living with HIV.

While several studies have explored the associations between food insecurity and chronic diseases in the general U.S. population,[34-38,48,49] relatively fewer studies have done so specifically in PLWH.[8,9,32,33] In particular, two emerging health concerns have garnered recognition in recent years. Nonalcoholic fatty liver disease (NAFLD) has become the most prevalent liver disease in the world, with a rise in prevalence that parallels that of obesity, type 2 diabetes (T2D), and metabolic syndrome (MetS).[50] While precise estimates are needed, the rate of NAFLD tends to be higher in PLWH than in the general population[51] and PLWH have almost twice the rate of nonalcoholic steatohepatitis (NASH)[52] – a more progressed stage of the disease. In fact, liver disease is a leading cause of morbidity and mortality among PLWH,[53] and it has been associated

with cognitive impairments in PLWH even in the absence of viral hepatitis.[54-56] Despite advances in treatments, cognitive dysfunctions continue to affect a significant portion of PLWH.[57-64] Indeed, HIV-associated dementia is now relatively rare with 2-4% prevalence, but milder neurocognitive disorders are found in approximately 20-50% of PLWH[63] and persist despite long-term viral suppression.[62] Regardless of a growing interest in these conditions, few studies have examined their associations with food insecurity, particularly among PLWH.

Persistent inflammation and immune activation are considered key factors in HIV disease progression and are implicated in chronic conditions in PLWH.[65-68] Activation of the immune system refers to the immune response to invading pathogens.[69] More specifically, immunologic activation is the process by which immune cells are stimulated, triggering specific immune defenses. While these systems are beneficial in the short term, chronic activation of immune systems can be deleterious.[69] Indeed, chronic inflammation and immune activation have been reported in association to liver disease[70-72] and cognitive disorders[73-75] in PLWH. Food insecurity has been associated with pro-inflammatory diets and inflammation,[76-79] suggesting a biological pathway between food insecurity and chronic diseases. However, few studies to date have directly examined whether food insecurity contributes to immune activation in PLWH. In particular, food insecurity, and the poor-quality diets associated with it, could contribute to gut permeability and the translocation of pathogens and other toxic microbial products through the intestinal epithelial barrier (known as microbial translocation)[80] – a significant source of immune activation in PLWH.[81]

Significance of Study

The issues examined in this study have implications that expand from the local community to the globe. Food insecurity affects all levels of society – global, regional, national, community, household, and individual.[82] This study was conducted in Miami-Dade County, which has one of the highest rates of HIV infections in the United States.[83] Yet, there are currently 37.9 million people in the world living with HIV, most of whom live in countries where food insecurity and undernutrition are endemic.[84] Globally, an estimated 26% of the world population (approximately 2 billion people) experienced moderate-to-severe food insecurity in 2019 and 8.9% were undernourished.[82]

NAFLD, paralleling obesity, has reached pandemic proportions[85] and its global prevalence has been estimated at approximately 25%.[86] NAFLD is associated with increased risk for morbidity and mortality, particularly at the more advanced stages of the disease.[87] Still, some have argued that NAFLD remains underappreciated and understudied among PLWH.[88]

Furthermore, an estimated 16% (12-20%) of older adults have mild cognitive impairment and 34% (27-40%) progress to dementia.[89] Cognitive impairments and dementia are seen in approximately 18-21% and 5-8%, respectively, of older adults in the United States.[90,91] Nutritional risk factors such as food insecurity, malnutrition, and obesity can contribute to cognitive impairments. Both food insecurity[8] and obesity[92] are prevalent among PLWH, and food insecurity has been associated with both malnutrition and obesity in PLWH.[6,93] Also, food insecurity[94] and obesity[95,96] have been identified as risk factors for cognitive impairments in PLWH, while underweight is associated with progression of mild cognitive impairment to dementia in the elderly.[97] Others have

reported associations between decreased cognitive function and central or abdominal obesity.[98-100] Additionally, obesity is tightly associated with fatty liver and is a risk factor for progression of liver disease to cirrhosis,[101] further contributing to the risk of cognitive impairment.

Innovation

At the time of this writing, only one study has evaluated the relationship between food insecurity and liver disease, conducted with data from the National Health and Nutrition Examination Survey (NHANES).[102] However, the investigators used indirect measures of hepatic steatosis and fibrosis with poor sensitivity. In this study, we used magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) to quantify liver fat content and magnetic resonance elastography (MRE) to assess liver stiffness, a measure of fibrosis. These measures are non-invasive and highly accurate,[103,104] providing an innovative approach to investigate the problem. Additionally, no studies to date have examined the link between food insecurity and liver disease among PLWH. In the Miami Adult Studies on HIV (MASH) cohort, 98% of participants living with HIV report taking ART and over 80% are virally suppressed (viral load <200 copies/mL). This is similar to other cohorts of PLWH in care,[105] but markedly higher than in the general United States (57%).[106] The MASH cohort, therefore, presents a rare opportunity to examine health outcomes among free-living PLWH who are engaged in care and virally suppressed, but are at increased risk for food insecurity and comorbidities.

Moreover, food insecurity has an inverse correlation with cognitive function,[107] but only two cross-sectional studies have examined this association in PLWH with conflicting results.[94,108] Yet, for many households, food insecurity is a frequent or

persistent problem that occurs for an average of 7 months out of the year.[109] However, no studies to date have examined the longitudinal relationship between food insecurity and cognitive impairment among people living with HIV, while considering the impact of the frequency of food insecurity over time.

Lastly, to the best of our knowledge, only one study previously examined whether food insecurity is associated with immune activation in PLWH – as measured by plasma levels of CD4+ and CD8+ T-cell %CD38+HLADR+.[110] Immune activation is thought to contribute to non-AIDS co-morbidities in PLWH.[65] Previous studies have associated food insecurity with markers of chronic inflammation.[76,77,79] Therefore, immune activation may be a potential biological pathway between food insecurity and the high burden of comorbidities in this population. Indeed, persistent immune activation has been implicated in liver disease[70,72] and neurocognitive disorders[73,75] among PLWH.

Altogether, the results of this study serve to improve public health by improving our knowledge regarding major public health concerns of local, national, and global relevance, with implications for clinical settings and policymakers. The following aims and hypotheses are presented as three distinct chapters, each written as a research article.

Specific Aims and Hypotheses

Chapter III: Association of Food Insecurity with Nonalcoholic Fatty Liver Disease

Specific Aim 1: To determine whether food insecurity is associated with NAFLD using accurate, non-invasive magnetic resonance (MR) technology.

***Hypothesis 1a*:** Food insecurity (assessed with the U.S. Household Food Security Survey) will be associated with increased risk for NAFLD (liver fat >5%) as determined by MRI-PDFF.

Hypothesis 1b: Food insecurity will be associated with increased risk for liver fibrosis as determined by MRE.

***Hypothesis 1c*:** The effects of food insecurity on liver outcomes will be significantly higher in PLWH than HIV-uninfected participants.

Chapter IV: Association of Food Insecurity with Cognitive Impairment

Specific Aim 2: To determine whether food insecurity is associated with cognitive impairment cross-sectionally and after a 2-year follow-up.

Hypothesis 2a: Food insecurity will be independently associated with increased risk for cognitive impairment as determined by the Mini-Mental State Examination (MMSE).

Hypothesis 2b: The risk for cognitive impairment will correlate with the frequency of food insecurity.

Hypothesis 2c: The effect of food insecurity on cognitive impairment will be stronger for PLWH than HIV-uninfected participants.

Chapter V: Association of Food Insecurity with Immune Activation in PLWH

Specific Aim 3: To determine whether food insecurity is associated with increased immune activation in PLWH.

Hypothesis 3a: Food insecurity will be associated with increased immune activation in PLWH as determined by plasma levels of sCD14, sCD27, and sCD163.

Hypothesis 3b: The severity of food insecurity will correlate with levels of sCD14, sCD27, and sCD163.

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Table 1.1. Summary of Hypotheses and Methods

Hypothesis	Dependent Variable(s)	Measurement of Dependent Variable(s)	Independent Variable(s)	Measurement of Independent Variable(s)	Statistical Plan
1a	Food insecurity	HFSS	NAFLD	MRI-PDFF (liver fat >5%)	Chi-square test Logistic regression
1b	Food insecurity	HFSS	Liver fibrosis Advanced fibrosis	MRE LS ≥2.9 kPa ≥ stage 1 LS ≥3.8 kPa ≥ stage 3	Chi-square tests Logistic regressions
1c	Food insecurity HIV	HFSS Medical records	NAFLD Liver fibrosis Advanced fibrosis	MRI-PDFF MRE	Logistic regressions with FI*HIV interaction term
2a	Baseline food insecurity	HFSS	Cognitive impairment	MMSE (≤ 24) at baseline and at 2-year follow-up	Chi-square test Logistic regressions
2b	Frequency of food insecurity	HFSS, measured at baseline and 12- and 24-month follow-ups	Cognitive impairment	MMSE (≤ 24)	Logistic regression
2c	Food insecurity HIV	HFSS Medical records	Cognitive impairment	MMSE (≤ 24)	Logistic regression with FI*HIV interaction term
3a	Food insecurity	HFSS	Immune activation	Plasma sCD14, sCD27, sCD163	Linear regressions
3b	Severity of food insecurity	HFSS	Immune activation	Plasma sCD14, sCD27, sCD163	Spearman correlation Linear regressions

Abbreviations: FI, food insecurity; HFSS, U.S. Household Food Security Survey; LS, liver stiffness; MMSE, Mini-Mental State Examination; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction

CHAPTER II: LITERATURE REVIEW

Food Insecurity in the United States

Food insecurity refers to a lack of adequate access to sufficient, safe, and nutritious foods to sustain health and wellbeing. More specifically, food insecurity is characterized by an uncertain ability or inability to procure enough food to feel satiated and live a healthy life.[1] Distinct from hunger, a physiological condition that occurs solely at the individual level,[2] food insecurity is a socioeconomic condition that can be measured at all levels of society – global, regional, national, community, household, and individual.[3] The Food and Agriculture Organization (FAO) of the United Nations identifies four key dimensions of food insecurity: 1) local *availability* of foods through adequate food systems; 2) whether households or individuals have *access* to those foods; 3) *utilization* of foods for optimal nutrition; and 4) temporal *stability* of the previous conditions.[3] Importantly, food insecurity in the United States is conceptualized somewhat differently from countries with fewer resources.[4] In the United States and similar high-resource countries, calories are inexpensive and readily accessible, but adequate nutrition may be inaccessible both financially and physically.[5]

In the United States, an estimated 10.5% of households, or 13.7 million households, experienced food insecurity at some point in 2019, including 2.4 million households with children.[6] Unfortunately, recent rates of food insecurity in the United States are not dissimilar from those seen over two decades ago,[6] although the spike caused by the Great Recession has leveled out.[7] Moreover, the national state of food security is highly volatile and may be precipitated by national crises. In the wake of the novel coronavirus disease of 2019 (COVID-19) pandemic, subsequent to a dramatic rise in unemployment and food

systems affected leading to food shortages, the national rate of food insecurity rose to an estimated 38.3%.[8] Food insecurity is a consequence of limited resources and is associated with poverty, unemployment, and high housing costs.[9] Indeed, the rate of food insecurity is 35% among households with incomes below the federal poverty level compared to 5% in those with incomes above 185% of poverty.[6] Racial/ethnic minorities are particularly affected, with rates above the national average seen in Black non-Hispanic (19.1%) and Hispanic (15.6%) households.[6] In the midst of the COVID-19 pandemic, minorities were disproportionately affected by economic stressors, leading to nearly twice the odds of food insecurity in Blacks and Native Americans compared to Whites, and 30% higher risk among Hispanics compared to non-Hispanics.[8]

Food insecurity can be a chronic or transitory problem. In the United States, food insecurity is often episodic and recurrent, triggered by unemployment, inflation, food prices, and unforeseen costs.[10,11] Nonetheless, for many households, food insecurity is a frequent or persistent problem experienced for an average of 7 months out of the year.[12,13] About 56% of food-insecure U.S. households in 2018 participated in federal food assistance programs,[14] but these are often insufficient to relieve financial constraints.[4,15,16] Moreover, the reliance on food assistance leads to fluctuations in food intake, or a "food stamp cycle," in which food spending and, subsequently, food intake peak early in the month and sharply decrease towards the end of the month.[17,18]

Assessment of Food Insecurity

Several tools have been developed to measure the various aspects of food insecurity at different social levels.[19] The most widely utilized and well-validated instrument has been the U.S. Household Food Security Survey (HFSS).[6] The HFSS has been validated across U.S. demographics[20,21] and has been adapted for use in other settings with favorable results.[19,22] The 18-item questionnaire assesses a respondent's perceived food sufficiency and adequacy, food-related anxiety, and instances of hunger that occurred in the household during the past 12 months.[23] While the HFSS was designed to measure food insecurity at the household level, it has also been validated to measure food insecurity at the individual level.[20]

The HFSS can categorize households into four levels food security, or by increasing severity of food insecurity: high (or full), marginal, low, and very low food security (VLFS). Recent research has demonstrated that the severity of food insecurity seems to influence its association with health outcomes.[24-27] Important distinctions can be observed between households reporting no food insecurity (full food security) and those with one or two food-insecure conditions (marginal food security), although these two categories would be typically considered food-secure. In fact, the demographic characteristics of marginally food-secure households more closely resemble those of food-insecure households than those with full food security.[28] The same is true for households that would otherwise be categorized as food-insecure, which typically combines low and very low food security. Low food security (previously known as "food insecurity without hunger") is defined as reduced quality, variety, or desirability of diet, with little or no indication of reduced food intake.[29] Very low food security, previously

known as “food insecurity with hunger,” is characterized by multiple indications of disrupted eating patterns and reduced food intake.[6,29] Recently, Choi et al. identified several distinguishing characteristics of households with VLFS.[16] Depending on whether the households had children, older adults, or neither, VLFS households could be identified by increased or decreased participation in food assistance programs, as well as health status and access to healthcare, such as unmet medical care needs, poor health, disability, and depression.[16]

Food Insecurity: A Social Determinant of Health

Food insecurity is a risk factor for poor health outcomes at all ages,[4,30-32] making it an important social determinant of health.[33,34] In effect, adults from food-insecure households are at increased risk for chronic cardiometabolic diseases and mental health problems.[24,30,31,35-38] Many factors may contribute to the associations between food insecurity and poor health outcomes, including poor diet quality,[39] increased stress,[40,41] poor adherence to medical recommendations,[42] and misuse of alcohol and other substances.[43-48] Food insecurity may lead to inadequate dietary intakes, poor diet quality, and disrupted eating patterns that result in suboptimal nutritional status.[49-51] In fact, food insecurity is a predictor of poor diet quality and compromised nutritional status among U.S. adults even after accounting for the effect of poverty.[52] Poor quality diets associated with food insecurity can result in inadequate intake of key nutrients and nutritional deficiencies, as well as increased risk for morbidity and mortality.[9,53,54]

On the other hand, food insecurity may contribute to chronic disease through its paradoxical association with obesity.[55] Indeed, in the United States, energy intakes do not seem to be altered by food insecurity; rather, the differences in health outcomes seem to

stem from dietary habits and the quality of the diet. Zizza et al. reported that individuals who experienced food insecurity consumed fewer but larger meals and snacked on sweets more frequently than those who were food-secure, yet energy intakes did not differ.[56] Individuals from households with low food security, compared to those with full food security, tend to shop more frequently at convenience/dollar stores, which carry limited choices and fewer fresh foods (e.g. fruits and vegetables) than grocery stores and supermarkets.[57] The differences in food shopping behaviors are often related to difficulties in transportation.[57] Food insecurity is also associated with poor food literacy, thus food labels and other nutritional information material may not be effective in improving food choices among food-insecure individuals.[50]

Furthermore, food-insecure households are often forced to make tradeoffs between buying food or paying for other necessities, such as medical care and medications.[58,59] At the same time, food insecurity is associated with increased healthcare utilization and higher health care expenditures.[60-62]

Food Insecurity Among People Living with HIV

People living with HIV (PLWH) are disproportionately affected by food insecurity in both resource-poor and resource-rich settings.[63] This is also seen in the United States,[64-66] where the prevalence of HIV in poor urban areas is similar to those seen in low-income countries with HIV epidemics.[67] Many PLWH in the United States are unemployed or disabled,[67-69] contributing to financial instability and food insecurity. Likewise, food insecurity is associated with a higher prevalence of HIV. A study using 1999-2012 NHANES data showed that men from food-insecure households were twice as

likely to be infected with HIV than those from food-secure households.[70] Further, women living with HIV are at higher risk for food insecurity than men living with HIV.[71]

To be sure, food insecurity and HIV have a complex, multifaceted, and bidirectional relationship. Food insecurity can increase the risk for HIV infections and disease progression (usually measured as a rise in HIV-RNA copies and a decline in CD4 cell counts), and in turn, HIV contributes to and reinforces food insecurity.[63,72] Frega et al. described how food insecurity and HIV are interconnected at the community, household, and individual levels.[72] Weiser et al. described nutritional, mental health, and behavioral pathways for the effect of food insecurity on HIV and vice versa.[63] The bidirectional relationship between food insecurity and HIV is illustrated in Figure 2.1 and summarized below. Importantly, mental health, comorbidities, and HIV-related morbidity and mortality are at the intersection of food insecurity and HIV.

Food insecurity is thought to contribute to HIV transmissions through its association to financial stress and living conditions that lead to negative and unsafe coping behaviors, such as risky sexual practices (e.g. bartering sex for money or food)[73,74] and substance use, particularly injection drug use and needle-sharing.[47,75,76] At the individual level, food insecurity can promote immunodeficiency by compromising nutritional status (e.g. malnutrition, nutrient deficiencies),[39,77,78] thereby increasing vulnerability to HIV infection.[79] Furthermore, food insecurity may increase the risk for HIV transmissions by making PLWH more infectious. Indeed, food insecurity is strongly associated with poor adherence to treatment,[73,80] lower odds for viral suppression,[81] and lower CD4 cell counts.[82]

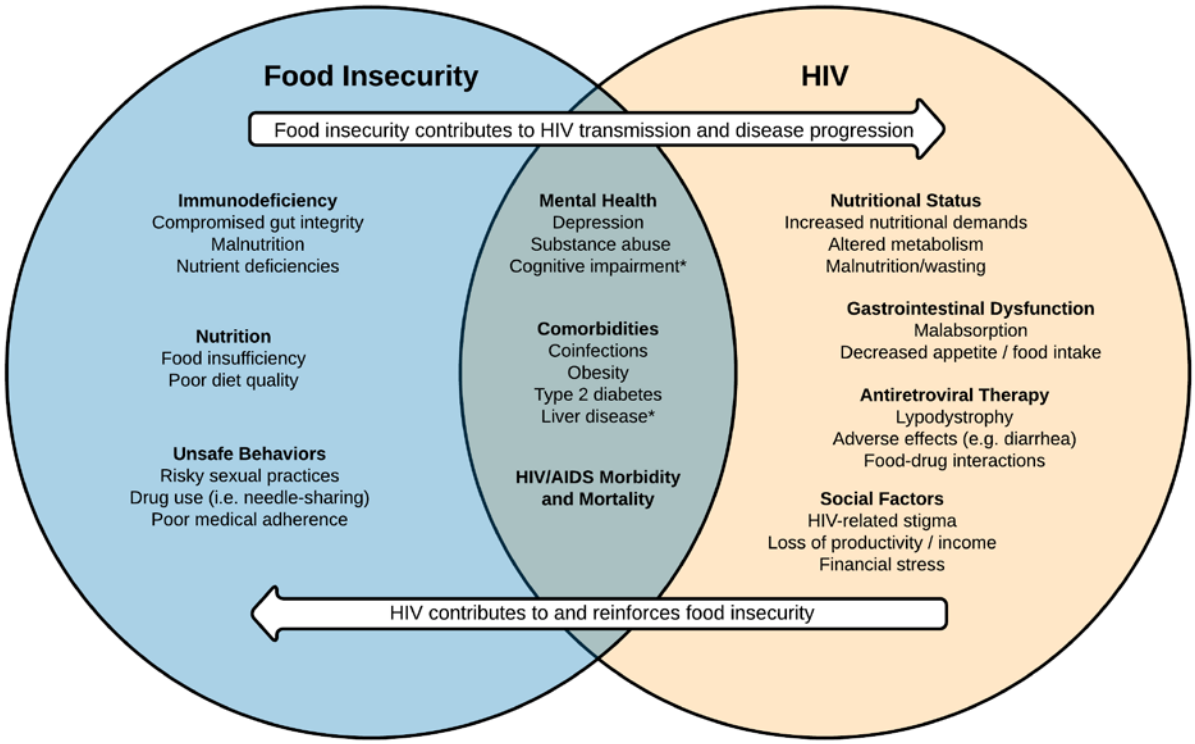

Figure 2.1. Bidirectional Relationship Between Food Insecurity and HIV
* The contribution of food insecurity to liver disease and cognitive impairment among PLWH are hypothesized in this dissertation.

HIV infection leads to incremental metabolic demands as the disease progresses,[83,84] thus food insecurity may further compromise nutritional status in PLWH. Food insecurity can also contribute to non-AIDS-related co-morbidities,[32,85] adding to the burden of morbidity and mortality in PLWH.[86] Thus, food insecurity can promote immunodeficiency, HIV disease progression, and increase overall disease burden, ultimately lowering health-related quality of life[87] and increasing mortality among PLWH. Given all of this, food insecurity may also be a barrier for the eradication of HIV.

On the other hand, HIV may promote food insecurity by impacting the availability, access, and utilization of food.[72] A high prevalence of HIV in a community may decrease food availability by affecting overall productivity and increasing morbidity and mortality;

however, more evidence is needed to ascertain this link. At the household level, HIV-related morbidity and mortality leads to losses in productivity and increased financial burdens that may affect access to food. At the individual level, HIV alters appetite, gastrointestinal function, energy expenditure, and metabolism, ultimately increasing nutritional demands which then may precipitate or exacerbate food insecurity. These HIV-related complications also promote morbidity and mortality among PLWH, which then may contribute to food insecurity at the community and household levels.[63,72]

Nonalcoholic Fatty Liver Disease

Chronic liver disease is a significant cause of morbidity and mortality worldwide. Liver cirrhosis accounts for more than 2.4% (1.3 million) of annual deaths worldwide.[88] Liver cancers account for 8.2% (781,631) of all cancer-related deaths globally, the majority of those (75-85%) being hepatocellular carcinoma (HCC).[89] In the United States, close to 2% of U.S. adults, or 4.5 million, were diagnosed with a chronic liver disease in 2018, a leading cause of mortality among U.S. adults 25 years of age and older.[90] Furthermore, annual deaths in the United States due to liver cirrhosis and HCC increased by 65% and 217%, respectively, from 1999 to 2016.[91] In Western countries, alcohol-associated liver disease and nonalcoholic fatty liver disease (NAFLD), rather than hepatitis viruses, are now the predominant causes of liver-related morbidity and mortality.[92] This is largely due to the availability of hepatitis B virus (HBV) vaccines and effective antiviral treatments for HBV and hepatitis C virus (HCV).[93] What is worse, the burden of fatty liver diseases is expected to rise.[94-99]

Nonalcoholic fatty liver disease (NAFLD) is an increasing public health concern that has paralleled the rising rates of obesity and other metabolic conditions, particularly

MetS – a cluster of conditions which may include abdominal obesity, hyperlipidemia, hypertension, and hyperglycemia.[100] In fact, NAFLD has emerged as the most common liver disease in the United States and other Western countries.[98,101-103] NAFLD is characterized by (1) evidence of hepatic steatosis (≥5% liver fat) and (2) absence of secondary causes for hepatic fat accumulation such as significant alcohol consumption (>21 drinks/week in men and >14 drinks/week in women), use of steatogenic medication, or hereditary disorders.[104] The pathological spectrum of NAFLD encompasses nonalcoholic fatty liver (NAFL; or simple steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis, and HCC. In addition to liver steatosis, NASH is characterized by the presence of inflammation and hepatocyte injury with or without fibrosis.[104] Liver fibrosis (scar tissue) occurs as a consequence of necroinflammation and liver cell injury and may progress to cirrhosis and HCC.

Worldwide, the prevalence of NAFLD has been estimated at approximately 25%.[105] NAFLD is present in both high- and low-resource countries, but in the United States, the estimated prevalence is close to a third of all adults.[106,107] This rate is in stark contrast to an estimated prevalence of 18% in 1988–1991.[107] Among individuals with NAFLD, there is an estimated NASH prevalence of 30%[108] and a 22.8% prevalence of advanced fibrosis.[106] The prevalence of NASH-cirrhosis has increased two and a half times between 1999-2002 and 2009-2012.[109] Moreover, the prevalence of NAFL and NASH are expected to rise by 21% and 63%, respectively, by the year 2030.[96] Subsequently, there will be a higher burden of cirrhosis and HCC.[96] Despite the high prevalence of NAFLD, only about 5% of all individuals with NAFLD in the United States seem to be aware of their condition.[106]

Recently, an International Consensus Panel proposed to replace the nomenclature of NAFLD to metabolic (dysfunction)-associated fatty liver disease (MAFLD) as it more closely reflects its pathological features and our growing understanding of fatty liver disease.[110] Instead of defining NAFLD for what it is not (i.e. "nonalcoholic", viral hepatitis, autoimmune), MAFLD identifies the disease from the underlying pathological processes. Nonetheless, others have urged for caution as the change in nomenclature might be premature.[111] In light of a lack of consensus and the near ubiquitous use of "NAFLD/NASH" in the literature, the traditional nomenclature will be used throughout this text.

NAFLD in People Living with HIV

People living with HIV are especially vulnerable to liver diseases.[112] Historically, PLWH have been vulnerable to coinfection with HBV and HCV,[113] as well as alcohol-related liver disease due to a high prevalence of alcohol use disorder.[114,115] Yet, as viral hepatitis infections are increasingly treated, the burden of fatty liver disease among PLWH has gained recognition.[116] A meta-analysis of imaging studies showed a 35% prevalence of NAFLD among PLWH, with biopsy studies showing NASH in 42% and fibrosis in 22%.[117] These estimates suggest that PLWH have a higher prevalence rate of NAFLD/NASH than the general population. Furthermore, PLWH are more susceptible to liver-related complications since HIV accelerates liver disease progression.[112]

Assessment of NAFLD

Liver biopsy has been the cornerstone of diagnosis, assessment of prognosis, and therapeutic decision-making for liver diseases.[118] However, liver biopsy is an invasive procedure that is costly and fraught with contraindications and potential health

complications.[118] Furthermore, only 1/50,000th of the liver is sampled with biopsy,[119] adding concerns of sampling error. For these reasons, several non-invasive tests have been developed, which in general are more time- and cost-efficient, allowing for repeated assessments and monitoring of liver disease progression.[120,121] These non-invasive assessments include biological and imaging assessments (Table 2.1). Nonetheless, most of these assessments are insufficiently sensitive or specific,[122,123] and frequently used cutoffs may not be appropriate for all age and ethnic groups.[124,125]

Magnetic resonance imaging (MRI)-based assessments have emerged as highly accurate, but direct, non-invasive measures of liver steatosis and fibrosis.[126-131] Chemical shift encoded MRI methods can differentiate protons in water and triglycerides.[132] By quantifying the signals arising from water and fat in tissues, the proton density fat fraction can be calculated (PDFF) – defined as "the ratio of the density of mobile protons from triglycerides and the total density of protons from mobile triglycerides and mobile water" – and expressed as percentages.[132] Thus, liver steatosis can be assessed with MRI-PDFF, which demonstrates high correlation with liver steatosis grade and NAFLD activity score when compared with histologic assessment.[133] However, histologic assessment remains the only available technique to differentiate NASH from simple steatosis.[134] Magnetic resonance elastography (MRE) combines MRI with low-frequency shear waves (vibrations), the speed of which is dependent on the stiffness of tissues, to create an elastogram that can be used to quantify tissue stiffness through an inversion algorithm.[135] Liver stiffness measurement by MRE is considered the most accurate noninvasive assessment of liver fibrosis, with sensitivity and specificity nearly equal to histological assessment.[126]

Natural History of NAFLD

The natural course of NAFLD is a highly dynamic process that has not been fully elucidated. The prevalence of NAFLD is highly associated with metabolic conditions, primarily obesity, type 2 diabetes, and the metabolic syndrome.[104] In fact, historically, NAFLD has been generally considered the liver manifestation of metabolic syndrome.[136] However, new lines of evidence have shown NAFLD as both the cause and consequence of these metabolic conditions. For example, NAFLD has been associated with incident type 2 diabetes and metabolic syndrome,[137,138] which are then predictors of NASH and fibrosis progression.[139,140] Thus, the relationship between NAFLD and metabolic syndrome is better described as mutual and bidirectional. In addition to metabolic risk factors, age, male sex, and Hispanic ethnicity are risk factors (or risk modifiers) for NAFLD.[141] Genetic variations also play an important role in NAFLD risk and disease progression. In particular, the rs738409 variant in human patatin-like phospholipase domain containing 3 gene (*PNPLA3*) for adiponutrin has been extensively studied.[142]

The course of NAFLD is nonlinear and only a portion of NAFLD patients progress to advanced stages of liver disease. Initially, a meta-analysis of 11 paired-biopsy studies by Singh et al. suggested that NASH was associated with twice as rapid fibrosis progression compared to NAFL.[143] Among 411 NAFLD patients, a total of 33.6% had progressive fibrosis (a 1-stage progression of fibrosis), while 43.1% remained stable and 22.3% showed improvements. The fibrosis progression rates among patients with NAFL and NASH were 7.1 (95% CI 4.8–14.3) and 14.3 (9.1–50.0) years per stage, respectively. Furthermore, Singh et al. identified a subset of “rapid progressors;” 21% of NAFLD patients without fibrosis at baseline who progressed to advanced fibrosis (stage 3 or 4

fibrosis) over 5.9±3.7 years. However, NASH has repeatedly failed to predict fibrosis progression,[139,144,145] possibly due to NASH not being a stable, fixed condition. In a study of 446 NAFLD patients with biopsies 4.9±2.8 years apart, Kleiner et al. found that 41.9% of those with NAFL at baseline progressed to borderline or definite NASH and 12.8% had complete resolution of NAFLD.[145] Among those with definite NASH at baseline, 31.5% showed regression to NAFL or borderline NASH and 10.9% had complete resolution of NAFLD.[145] Similar to the findings by Singh et al., 33.9% of participants had fibrosis progression. NAFLD progression (NAFL to NASH, or borderline to definite NASH) was directly associated with fibrosis progression, whereas NAFLD regression was associated with improvement in fibrosis. Thus, Kleiner et al. showed that NASH can progress and regress over time and, subsequently, is not a good predictor of fibrosis progression. Rather, NAFLD disease activity, not the presence of NASH at any given point, predicts fibrosis progression. Likewise, liver fibrosis can progress and regress over time.[143,145]

Co-existing metabolic syndrome components contribute to NAFLD progression and NAFLD-related mortality. Hypertension[143] and type 2 diabetes[139,140] have been associated with fibrosis progression. Comorbid diabetes is associated with increased risk for cirrhosis and HCC.[146,147] Both metabolic syndrome and diabetes can contribute to liver-related mortality in individuals with NAFLD.[148] These relationships are particularly alarming given that 45-65% of individuals with type 2 diabetes also have NAFLD.[149-151]

Extrahepatic manifestations of liver disease result in the development or worsening of comorbidities, such as chronic kidney disease,[152,153] type 2 diabetes,[138,154] and cardiovascular disease.[155,156] Common cardiac complications in NAFLD include coronary

artery disease (CAD), structural myocardial alterations, and cardiac arrythmias.[156] Not surprisingly, NAFLD also leads to significant impairments in health-related quality of life.[157,158] Furthermore, these metabolic comorbidities may limit eligibility for liver transplantation.[159]

NAFLD is associated with increased risks of liver-specific and all-cause mortality.[160-163] NAFLD-related deaths in the United States have been increasing by an average of 2% annually, with cirrhosis and cardiovascular disease (CVD) being the leading causes of death among these.[164] Hepatocellular carcinoma, the fourth leading cause of death overall, is the fastest growing cause of NAFLD-related death, with an average annual increase of 3.8%.[164] While some studies have associated NASH with mortality,[165] emerging evidence has shown that liver fibrosis, not NASH, is a predictor of mortality.[166-168] These findings have been confirmed in a meta-analysis of 5 studies (N=1,495), which showed that the risk for all-cause mortality increased with fibrosis stage in a dose-response fashion.[169] Additionally, liver-related mortality accounted for a greater proportion of all deaths in accordance to increased fibrosis stage. Indeed, liver-related complications become the dominant cause of major health events in patients with cirrhosis, whereas vascular events and non-hepatic malignancies are predominant in those with bridging fibrosis (stage 3 per METAVIR scoring system).[170]

Pathogenesis of NAFLD

Early research on NAFLD led to a “two-hit hypothesis,” which proposed that insulin resistance (IR) and obesity led to the accumulation of fatty acids in the liver (first hit), predisposing the liver to necroinflammation and oxidative stress (second hit), resulting in fibrogenesis.[171] However, a “multiple-hit hypothesis” was later proposed [172]

and has sustained its credibility.[173] The multiple-hit theory describes the pathogenesis of NAFLD as a complex, dynamic interplay between behavioral, environmental, and genetic factors. Insulin resistance (IR), inflammation, and oxidative stress are some of the key mechanisms implicated in the development and progression of NAFLD. Sedentary behaviors and poor dietary habits contribute to IR, which in turn promotes the accumulation of fatty acids in hepatocytes, adipose tissue dysfunction, and inflammation. In the context of NAFL, the accumulation of free fatty acids in the liver, along with compromised disposal of fatty acids, lead to the formation of lipotoxic metabolites that result in inflammation and oxidative stress. As described earlier, individuals may fluctuate between NAFL and NASH over time, resulting in NASH being a poor predictor of NAFLD-related outcomes. However, NASH drives fibrogenesis, which is the most important prognostic factor for health outcomes in NAFLD.[174]

Food Insecurity and NAFLD

A study using NHANES data from the 2005-2006 cohort found that individuals with marginal and low food security, combined, compared to those with high food security, had increased odds for self-reported liver problems (odds ratio [OR]: 2.06, 1.13–3.79; p=0.022).[175] However, to date, only Golovaty et al. have directly examined the relationship between food insecurity and nonalcoholic fatty liver disease (NAFLD).[176] The study used NHANES (2005-2014) data and included 2,627 adults with median age of 43 (30–62) years, who lived below 200% of the federal poverty threshold, were seronegative for hepatitis B and C viruses, and reported no heavy drinking. NAFLD was assessed using the U.S. Fatty Liver Index[177] and advanced liver fibrosis was determined with the NAFLD Fibrosis Score.[178] In total, 29% of participants lived in food-insecure

households. The estimated prevalence of NAFLD was of 32% and that of advanced liver fibrosis was 5%. Food insecurity was significantly associated with higher odds of NAFLD (OR: 1.38, 95% CI: 1.08, 1.77; $p<0.01$) and advanced fibrosis (OR: 2.20, 95% CI: 1.27, 3.82; $p<0.01$), adjusted for sociodemographic (age, sex, household income, household size, ethnicity, education) and behavioral factors (alcohol and smoking history). Food insecurity was also significantly associated with higher odds of obesity and diabetes. Further analysis showed dose-response relationships between the severity of food insecurity and both NAFLD and advanced liver fibrosis.

The analysis by Golovaty et al. suggests that food insecurity may contribute to NAFLD prevalence among low-income U.S. adults. The relationship may be in part due to poor diet quality, which is often a consequence of food insecurity,[39,179] and has been associated with increased risk for NAFLD.[180-182] Moreover, in the United States, patients with chronic liver disease are more likely to be unemployed and disabled, and have higher health care expenditures than those without chronic liver disease.[183] Thus, food insecurity may promote liver disease, and in turn, chronic liver diseases may increase vulnerability to financial instability and food insecurity. Nonetheless, the study is limited by its use of indirect indexes of liver disease. Moreover, whether the effect of food insecurity on NAFLD risk may differ for PLWH remains unknown.

Cognitive Disorders in People Living with HIV

Advances in antiretroviral drugs have increased longevity for PLWH, leading to a growing prevalence of older adults living with HIV.[184] In the United States, over half (51%) of all PLWH are now 50 years of age and older[185] compared to 35% in 2010.[186] As PLWH live longer, age-related comorbidities have become the primary causes of

morbidity and mortality among PLWH.[187-191] Moreover, HIV infection results in accelerated immunosenescence, pre-mature aging,[192-194] and the development of age-associated conditions approximately a decade earlier than HIV-uninfected peers.[195,196] Among these conditions are neurocognitive disorders (NCDs), which despite advances in treatments, continue to affect a significant portion of PLWH.[197]

"Cognitive impairment" is a broad term used to describe losses in mental functions, whereas "neurocognitive impairment" (NCI) emphasizes underlying structural or metabolic brain disruptions that can be objectively measured.[198,199] The American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) recognizes delirium, mild NCDs, and major NCDs (i.e. dementia) that are acquired, rather than developmental, and represent a loss of cognitive function.[200] The DSM-5 defines NCDs as affecting one or more of the following cognitive domains: complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition.[200] Numerous etiologies for NCDs are delineated, including NCD due to HIV infection. The term HIV-associated neurocognitive disorders (HAND) encompasses the different neuropathological complications of HIV.[201] The most widely used diagnostic criteria identifies three distinct categories of HAND: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia.[202] Thanks to widespread use of ART, HIV-associated dementia is now relatively rare with a 2-4% prevalence.[197] However, mild cognitive impairments have been reported in up to 50% of PLWH, depending on prior or current AIDS diagnosis,[197] and persist despite long-term viral suppression.[203] That said, some have

expressed concerns about the clinical validity of ANI,[204] and more conservative diagnostic criteria estimates the prevalence of HAND around 14-28%.[205]

HIV infection directly contributes to cognitive dysfunctions. HIV-associated cognitive impairments are most frequently related to executive dysfunction, particularly affecting working memory.[206] The neurodegenerative effects of HIV infection are thought to occur, at least in part, through its pro-inflammatory properties.[207-209] A number of studies have indicated a role of increased levels of pro-inflammatory cytokines in cognitive impairment and decline.[210,211] HIV infection results in hyper-activation of the immune system, persistent inflammation, and elevated production of pro-inflammatory cytokine/chemokines from monocytes and macrophages.[212-214] Indeed, several studies have supported the association between pro-inflammatory cytokines and HIV-related neurodegeneration.[215-220]

Nonetheless, other factors contribute to cognitive impairments in PLWH. Depression is highly and disproportionately prevalent among PLWH[221] and contributes to substantial cognitive impairments in this population.[222] Liver disease, a major cause of morbidity and mortality among PLWH,[223] has been associated with NCI in PLWH, even in the absence of viral hepatitis.[224-226] Yet, co-infection with hepatitis C virus (HCV) is common among PLWH[227] and is itself associated with cognitive impairments[228,229] irrespective of advanced liver disease, cirrhosis, or substance abuse.[230,231] That said, those who are HIV/HCV co-infected show greater cognitive deficits than HIV and HCV mono-infected individuals.[232,233]

Furthermore, nutritional risk factors such as food insecurity, malnutrition, and obesity may contribute to cognitive impairments in PLWH. Food insecurity[65] and

obesity[234] are prevalent among PLWH, and food insecurity has been associated with both malnutrition and obesity in PLWH.[79,235] Food insecurity[236] and obesity[237,238] have been identified as risk factors for cognitive impairment in PLWH, while underweight has been associated with progression of mild cognitive impairment to dementia in HIV-uninfected elderly.[239] Others have reported associations between decreased cognitive function and central (abdominal) obesity, as measured by waist circumference or waist-to-hip ratio.[240-242] Additionally, obesity is tightly associated with fatty liver and is a risk factor for progression of liver disease to cirrhosis,[243] further contributing to the risk for cognitive impairment.

Assessment of Cognitive Impairment

Neuropsychological assessments are the primary diagnostic measures for NCDs. Cognitive assessments are designed to evaluate specific cognitive domains in an objective, quantitative, and standardized manner. They can be administered non-invasively and are able to detect early signs of cognitive decline in patients unaware of their own cognitive functioning or those that may not present with physical signs of a neurodegenerative disease. Neuropsychological batteries are employed to evaluate broad cognitive function in multiple domains. However, neuropsychological batteries are time-intensive, must be administered by a trained professional, and are not necessary for all patients suspected of NCI. Consequently, several screening tools have been designed to assess global mental status in clinical settings, with low burden to patients and healthcare providers, allowing for monitoring of cognitive decline with repeated assessments over time.[244,245] The most widely used and well-studied cognitive assessment tool for screening NCDs is the Mini-Mental State Examination (MMSE).[246] A comprehensive

meta-analysis of 108 cohort studies and 10,263 patients by Tsoi et al. found that the MMSE had a sensitivity and specificity of 81% and 89%, respectively, for the detection of dementia.[244] However, Tsoi et al. also found that data from 21 cohort studies yielded a 62% sensitivity and 87% specificity for mild NCD using the MMSE.[244] Indeed, cognitive assessment screening tools are insufficiently sensitive to mild NCD. As a general guideline, mild cognitive impairment is considered when performance on cognitive testing that falls between 1-2 standard deviations (SD) below the mean.[198] Importantly, these screening measures cannot diagnose NCDs – a positive result requires further testing.

Food Insecurity and Cognitive Impairment

Overall, studies show that food insecurity is associated with cognitive impairments. Some studies have associated food insecurity in early life with cognitive impairments in older age.[247-249] The adverse effect of food insecurity on cognitive outcomes has been reported in poor-resource countries.[248,250,251] Table 2.2 summarizes the available literature on food insecurity and cognitive impairment from studies conducted in the United States In a sample of 350 homeless older adults, cognitive impairment was associated with greater odds of VLFS (adjusted OR: 2.21, 95% CI 1.12–4.35).[252] Gao et al. investigated the relationship between food insecurity and cognitive function among 1,358 Hispanic adults of ages 45–75 years from the Boston Puerto Rican Health Study (BPRHS).[253] Very low food insecurity was associated with lower MMSE scores (adjusted means 22.5±0.4 vs 23.4±0.1, $p<0.001$) and higher odds for cognitive impairment (adjusted OR: 2.28; 95% CI: 1.26, 4.12). On the MMSE subscales, food insecurity was associated with lower scores on executive function ($p=0.003$ for trend), but not memory or attention. The

investigators also performed a neurocognitive battery and food insecurity was associated with lower scores for word-list learning, percentage retention, letter fluency, and digit span backward. In a subsequent study from the BPRHS, Wong et al. used a longitudinal design to assess the relationship between food insecurity and changes in cognitive function over a 2-year period.[254] The study included 597 Hispanic adults ages 45–75 years, without cognitive impairment (MMSE ≥ 24) at baseline. Food insecurity, measured only at baseline, was associated with a 2-year decline in global cognition, even after adjustment for sociodemographic characteristics, baseline MMSE score, BMI, and depression symptoms. Again, VLFS was associated with a decline in executive function, but was not associated with changes in the memory domain. Furthermore, the investigators observed that the association between food insecurity and global cognitive decline was more pronounced in participants with baseline MMSE ≥ 27 or those who lived in poverty.

Frith & Loprinzi used NHANES 1999-2002 data from 1,851 older adults (60–85 years old) to assess the effect of food insecurity on cognitive function, as measured by the Digital Symbol Substitution Test.[255] The results of the study showed lower cognitive function in participants with marginal, low, and VLFS compared to participants who were fully food-secure. Although the study was limited by its use of a single cognitive measure, a later study by Portela-Parra & Leung showed similar results using a more robust cognitive assessment. Using NHANES 2011–2014 data from 1,823 older adults with incomes below 300% of the federal poverty level, Portela-Parra & Leung found that food insecurity was inversely associated with cognitive function.[256] Specifically, food insecurity was associated with worse performance on processes related to executive

function: processing speed, sustained attention, verbal fluency, working memory, and immediate learning ability.

Food Insecurity and Cognitive Impairment in PLWH

Despite the high prevalence of food insecurity and cognitive impairments among PLWH, only two cross-sectional studies have examined how food insecurity may contribute to cognitive impairment in PLWH. In a study by Hessol et al., food insecurity was not associated with cognitive impairment as determined with the Montreal Cognitive Assessment (MoCA) in 229 PLWH ages 50 years and older.[257] On the other hand, Hobkirk et al. used a neurocognitive battery to assess the effects of food insecurity on the neurocognitive performance of 61 PLWH and 36 HIV-uninfected middle-aged adults.[236] The investigators found significant interaction effects of HIV and food insecurity on speed of information processing, learning, memory, and motor function, as well as a global deficit score–an average of the deficit scores for all domains. Among PLWH, food insecurity was associated with significantly higher domain deficit scores in the domains of speed of information processing, learning, motor function, and the global deficit score, but not memory. On the other hand, there were no significant differences in domain deficit scores in relation to food insecurity among participants uninfected with HIV; however, this may be a result of the small sample size. Moreover, food insecurity was not associated with viral load suppression, nadir or recent CD4 cell count, length of HIV infection, AIDS diagnosis, HCV infection, or ART adherence, suggesting that the effects of food insecurity were independent of these factors.

These studies demonstrate a need for further research to understand the relationship between food insecurity and cognitive impairment in PLWH. The lack of findings by

Hessol et al.[257] may be due to insufficient sensitivity of screening assessments for mild[258] or HIV-associated cognitive impairments.[259] While the findings by Hobkirk et al. provide robust evidence for the effect of food insecurity on cognitive dysfunction, the small sample of HIV-uninfected participants does not allow to infer that this effect differs in PLWH from HIV-uninfected persons.[236] Additionally, the cross-sectional design does now allow for temporality to be established.

Although the findings are generally consistent, the existing evidence is limited by heterogeneity in samples, food insecurity measurements, and time-frames.[260] Few longitudinal studies are available, and none have applied multiple food insecurity measures to determine the effects of frequency and duration of food insecurity on cognitive impairment.

Immune Activation in HIV Infection

Infection with HIV results in chronic activation of the immune system. While activation of immune responses is beneficial in removing pathogens and resolving infectious processes, chronic activation can be deleterious.[261] Left untreated, rapid and persistent HIV replication leads to progressive immunodeficiency, accelerated immune senescence (age-associated decline in immune function), and the development of AIDS.[192,262] Modern ART has been effective at controlling viral replication and improving longevity for PLWH.[263,264] Nonetheless, persistent immune activation and inflammation, even with effective ART and virologic suppression,[265,266] contribute to high rates of chronic comorbidities among PLWH, including cardiovascular disease, type 2 diabetes, liver disease, non-AIDS-defining cancers, and HIV-associated neurocognitive disorders.[267-276]

One of the major mechanisms thought to contribute to systemic immune activation in PLWH is the infiltration of pathogens and other toxic microbial products through the intestinal epithelial barrier, known as microbial translocation.[277,278] Early in the infection, HIV targets CD4+ T-cells in the gut-associated lymphoid tissue, where the majority of immune cells reside in the human body.[279] Subsequently, HIV weakens gut integrity, leading to microbial translocation and an inflammatory cascade.

Biomarkers of Immune Activation

Monocytes and macrophages play an essential role in innate immunity against pathogens and contribute to adaptive, long-term immunity. These cells promote phagocytosis, release reactive oxygen species (ROS), produce inflammatory cytokines, and modulate T-cell immune response.[280] Inflammatory conditions, such as atherosclerosis, stimulate circulating (inactive) monocytes, leading to macrophage polarization into M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes, depending on the stimuli.[281] Therefore, activation of monocytes and macrophages is critical in immune responses to acute stimuli, but chronic activation leads to adverse downstream effects. Several blood biomarkers of monocyte/macrophage activation have shown great prognostic value for health outcomes in PLWH. In particular, sCD14 and sCD163 have been well-characterized in the context of HIV.[282]

Soluble CD14 (sCD14) is shed by CD14-expressing monocytes after stimulation by lipopolysaccharide (LPS), also known as endotoxin, a marker of microbial translocation derived from the cell wall of gram-negative bacteria.[283] Consequently, sCD14 highly correlates with LPS levels[284,285] and serves as an indirect, yet non-specific marker of microbial translocation.[277,283] Elevated levels of sCD14 persist during effective

suppressive ART and correlate with HIV disease progression.[283,286] Additionally, elevated sCD14 has been associated with several chronic conditions, including cardiovascular disease,[287-289] chronic kidney disease,[290] alcoholic and nonalcoholic liver diseases,[291-295] dementia[296] and HIV-associated neurocognitive disorders,[276] as well as mortality in PLWH.[297,298]

CD163, also known as hemoglobin scavenger receptor, is expressed almost exclusively on monocytes and macrophages.[299,300] Shedding of sCD163 in plasma has been implicated in chronic inflammatory conditions.[299,300] Effective ART decreases sCD163 levels in PLWH, but these only return to HIV-seronegative levels among those who initiate ART early in the infection.[286,301] Consequently, sCD163 serves as a marker of HIV disease progression, correlated directly with HIV viral loads and inversely with CD4 cell count,[301] and shown to predict mortality in PLWH.[302] Moreover, sCD163 serves as a marker of Kupffer cell activation that is highly correlated with liver disease severity and mortality.[303] Elevated sCD163 was associated with advanced liver fibrosis and cytokeratin-18 (a marker of hepatocyte apoptosis) among histologically-determined NAFLD patients.[304] In one study, levels of sCD163 in plasma, but not in cerebrospinal fluid (CSF), correlated with the severity of HAND.[305] In another study, however, levels of sCD163 in cerebrospinal fluid were inversely correlated with cognitive function.[306]

Another useful biomarker is CD27, a transmembrane glycoprotein of the tumor necrosis factor receptor (TNF-R) family that is expressed on peripheral T and B lymphocytes.[307] Soluble CD27 is secreted by antigen-stimulated T-cells, thus considered a direct marker of early-stage T-cell activation. Levels of sCD27 are responsive to ART

but remain elevated in HIV infection, correlate with HIV disease progression, and have been particularly associated with AIDS-associated lymphoma.[265,307-310]

Food Insecurity and Immune Dysfunction in HIV

Several lines of evidence have linked food insecurity with inflammation and immune dysregulation (Table 2.3). Studies conducted with NHANES data have consistently demonstrated that food insecurity is associated with elevated levels of C-reactive protein (CRP), a common marker of systemic inflammation.[311-313] Moreover, Gowda et al. showed that the relationship between food insecurity and CRP was partially mediated by elevated white blood cell counts, suggesting a potential role of immune activation.[311] Also using NHANES data, Bergmans et al. reported on the association between food insecurity and the inflammatory potential of the diet, showing a dose-response relationship between the severity of food insecurity and Dietary Inflammatory Index (DII) scores.[314] Based on a meta-analysis of 1,943 studies, the DII was designed to assess the impact of diets on the following six inflammation biomarkers: interleukin(IL)-1β, IL-4, IL-6, IL-10, tumor necrosis factor-alpha (TNF-α), and CRP.[315]

Recently, the Women's Interagency HIV Study (WIHS) has associated food insecurity with inflammation and immune dysregulation in women living with HIV on stable ART.[316,317] Leddy et al. showed that food insecurity was significantly associated with higher concentrations of pro-inflammatory cytokines IL-6 and TNFR-1.[316] Peters et al. found that food insecurity was associated with increased CD4+ and CD8+ activation (%CD38+HLADR+), increased senescence of CD8+ T cells (%CD57+CD28−), increased exhaustion of CD4+ T cells (%PD-1+), and decreased co-stimulation of CD4+

and CD8+ T cells (%CD57− CD28+), after adjusting for confounders.[317] These association were particularly pronounced among those with higher viral loads and lower CD4 cell counts.

The associations between food insecurity and markers of inflammation and immune dysregulation point to a biological pathway between food insecurity and chronic disease. For example, among 121 Latinos with type 2 diabetes, cortisol and CRP partially mediated the relationship between food insecurity and insulin resistance, the precursor to type 2 diabetes.[40] Notably, insulin resistance is a key pathological mechanism in NAFLD development and progression,[173,318] a relationship likely mediated by inflammation.[319] Insulin resistance is also associated with cognitive dysfunction[320] and cognitive decline.[321] In another study, food insecurity was associated with the primary allostatic system (neuroendocrine and inflammatory), which incorporated serum cortisol and CRP as biomarkers of stress and inflammation, respectively.[322] Thus, the overall findings of these studies suggest that food insecurity has the potential to promote immune activation (and inflammation) among PLWH, and thereby contribute to chronic diseases, including NAFLD and cognitive dysfunction, in this population.

Summary of Literature Review

Food insecurity is an important social determinant of health that disproportionately impacts PLWH. Already at increased risk for nutrition-related complications, chronic metabolic diseases, and mental health disorders, food insecurity may have a significant impact on the disease burden of PLWH. While food insecurity has been associated with NAFLD risk factors, such as obesity, diabetes, and the metabolic syndrome, only one

study has examined its association with NAFLD using indirect indexes of liver disease.[176] Whether food insecurity contributes to NAFLD in PLWH, a population at increased risk for liver disease,[112,116] poor diet,[323] and their related consequences, has not been previously investigated. There is evidence that food insecurity is associated with cognitive impairments; however, only one cross-sectional study has previously examined how food insecurity impacts cognitive function in PLWH.[236] Moreover, few longitudinal studies are available in this area of research, and no studies have examined the role of transient or persistent food insecurity on cognition.

Several mechanisms are thought to mediate the relationship between food insecurity and chronic diseases. Poor diet quality, unhealthy eating behaviors, and negative coping mechanisms have been suggested to play a role in the effects of food insecurity on health outcomes. Some studies have also indicated that inflammation may be a potential biological pathway in this relationship. However, the relationship between food insecurity and immune activation, considered a key factor in adverse health outcomes among PLWH, has not been examined.

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Table 2.1. Non-invasive Assessments for NAFLD

	Biological	Imaging
Liver Steatosis	Fatty Liver Index (FLI) *BMI, waist circumference, triglycerides, and GGT* U.S. FLI *Age, race/ethnicity, waist circumference, GGT, fasting insulin, and fasting glucose* Hepatic Steatosis Index (HSI) *BMI, diabetes, and ALT/AST ratio* NAFL Screening Score *Age, fasting blood glucose, BMI, triglyceride, ALT/AST ratio, and uric acid*	Ultrasound (US) Computed tomography (CT) Controlled attenuation parameter (CAP) Magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF)
Liver Fibrosis	Fibrosis-4 Index (FIB-4) *Age, AST, ALT, platelets* AST-to-Platelet Ratio Index (APRI) *AST, platelets* NAFLD Fibrosis Score (NFS) *Age, BMI, hyperglycemia, AST/ALT ratio, platelets, and albumin* Enhanced Liver Fibrosis (ELF) *2.278+0.851 ln(HA)+0.751 ln(P3NP)+0.394 ln(TIMP-1)*	Transient elastography (TE) Shear wave elastography (SWE) Acoustic radiation force impulse (ARFI) Magnetic resonance elastography (MRE)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HA, hyaluronic acid; P3NP, propeptide of procollagen type III; TIMP-1, tissue inhibitor of matrix metalloproteinases-1

Table 2.2. Summary of Studies on Food Insecurity and Cognitive Impairment

Author, Date Design	Population	Food Insecurity	Cognitive Impairment	Main Findings
Gao, 2009 Cross-sectional	1,358 Hispanic adults from the BPRHS, ages 45-75 years	HFSS	Primary: MMSE < 24 Secondary: 16-word list learning test, digit span forward and back, Stroop test, verbal fluency, clock drawing, figure copying	87.9% were food-secure (high and marginal food security), 6.0% had LFS, 6.1% had VLFS. VLFS was associated with lower MMSE scores (adjusted means 22.5±0.4 vs 23.4±0.1, p<0.001) and higher odds of cognitive impairment (adjusted OR: 2.28; 95% CI: 1.26, 4.12) compared to high-marginal food security. On the MMSE subscales, FI was associated with lower scores on executive function (p=0.003 for trend), but not memory or attention. FI was also associated with lower scores for word-list learning, percentage retention, letter fluency, and digit span backward.
Wong, 2016 Longitudinal	597 Hispanic adults from the BPRHS, ages 40-75 years, MMSE ≥ 24 at baseline	HFSS	Global Deficit Score (GDS): a composite score of the MMSE, 16-word list learning test, digit span forward and back, Stroop test, verbal fluency, clock drawing, figure copying	At baseline, 87.9% were food-secure (high and marginal food security), 5.5% had LFS, 4% had VLFS. VLFS was associated with a significant decline in the global cognitive score (Mdiff: -0.26, 95% CI: -0.41, -0.10) compared to food security. VLFS was associated with a decline in executive function (Mdiff: -0.47, 95% CI: -0.77, -0.18), but not memory (Mdiff: -0.08, 95% CI: -0.46, 0.30).
Hessol, 2017 Cross-sectional	230 PLWH, ages ≥50	HFSS	MoCA < 26	68% were food-secure (high and marginal food security), 15% had LFS, and 17% had VLFS. Cognitive impairment was not associated with LFS (OR: 1.15, 95% CI: 0.65–2.03) or VLFS (OR: 1.27, 95% CI: 0.75–2.16).
Hobkirk, 2017 Cross-sectional	61 PLWH (mean age 46.3±10.7) and 36 HIV-uninfected adults (mean age 44.4±12.0)	HFIAS	Neuropsychological battery: information processing, learning, memory, executive functioning, verbal fluency, attention, motor skills Global Deficit Score (GDS): average of the deficit scores on all cognitive domains	49% of PLWH and 44% of HIV-uninfected participants endorsed at least one FI criteria. Across all participants, FI was associated with deficit scores speed of information processing, but not any other domain or GDS. There were significant FI-HIV interaction effects on information processing, learning, memory, motor function, and the GDS. Among PLWH, but not HIV-uninfected, FI was associated with deficit scores on information processing, learning, motor function, and the GDS.

Author, Date Design	Population	Food Insecurity	Cognitive Impairment	Main Findings
Frith, 2018 Cross-sectional	1,851 adults from NHANES (1999-2002), ages 60-85 years	HFSS	Digit Symbol Substitution Test (DSST)	88.5%, 5%, 4.4%, and 2.1% had full, marginal, low, and VLFS, respectively. Compared to fully food security, marginally (β= -13.4; 95% CI: -17.6, -9.2), LFS (β=-10.9; 95% CI: -17.6, -4.1) and VLFS (β= -22.2; 95% CI: -28.6, -15.8) had significantly lower DSST scores.
Portela-Parra, 2019 Cross-sectional	1,823 adults from NHANES (2011-2014), ages ≥60 years, < 300% poverty level	HFSS	CERAD word learning, CERAD delayed word recall, the Animal Fluency Test (AFT), DSST Overall cognitive function score: average of individual tests	23.7% were food-insecure. FI was associated with lower scores on the CERAD word learning subtest (β= −0.14, 95% CI: −0.26, −0.01), AFT (β= −0.13, 95% CI: −0.25, −0.002), DSST (β=−0.24, 95% CI: −0.33, −0.15), and overall cognitive function (β= −0.15, 95% CI: −0.26, −0.05).
Tong, 2019 Cross-sectional	350 homeless adults, ages 58 (54-61) years	HFSS	Modified MMSE (3MS) < 1.5 SD from the mean (< 7th percentile)	44.6% had high-marginal food security, 31.1% had LFS, 24.3% had VLFS. 25.8% had cognitive impairment. Cognitive impairment was associated with 2.21 (1.12, 4.35) times the odds for VLFS, adjusted for confounders.

Abbreviations: BPRHS, Boston Puerto Rican Health Study; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSST, Digit Symbol Substitution Test; FI, food insecurity; GDS, global deficit score; HFIAS, Household Food Insecurity Access Scale; HFSS, U.S. Household Food Security Survey; LFS, low food security; Mdiff, mean difference; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NHANES, National Health and Nutrition Examination Survey; VLFS, very low food security

Table 2.3. Summary of Studies on Food Insecurity and Immune Dysfunction

Author, Date Design	Population	Food Insecurity	Outcome	Main Findings
Gowda, 2012 Cross-sectional	12,191 adults from NHANES 1999-2006, ages ≥18 years	HFSS	CRP, WBC	7.5% were marginally food-secure and 14.0% had low or VLFS. FI (low or VLFS) was associated with 1.21 (95% CI: 1.04, 1.40) times the odds of being in the highest quartile of CRP and 1.36 (95% CI: 1.11, 1.67) times the odds of having high WBC count (>10,000/µL) compared to food security, adjusted for confounders. WBC count was a partial mediator between FI and CRP (Sobel test $p<0.001$).
Ford, 2013 Cross-sectional	10,455 adults from NHANES 2003-2008, ages ≥20 years	HFSS	CRP > 3 mg/L	6.7% had marginal, 5.8% had low, and 3.6% had VLFS. VLFS was associated with higher mean CRP (4.8 vs. 3.9, $p=0.04$), a higher prevalence of elevated CRP (42.4 vs. 31.5%, $p<0.001$), and 1.25 (95% CI: 1.03, 1.51) times the odds for elevated CRP compared to full food security, adjusted for confounders. However, the increased risk for elevated CRP was lost when additionally adjusted for HbA1c, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, and urinary albumin-creatinine ratio (adjusted OR: 0.98, 95% CI: 0.82, 1.18).
Bergmans, 2018 Cross-sectional	10.630 adults from NHANES 2007-2014, ages ≥20 years, and income-to-poverty ratio ≤3.0	HFSS	DII	14.4% had marginal, 17.3% had low, and 10.7% had VLFS. FI was associated with a dose-response effect on DII scores: marginal (β=0.14, 95% CI: -0.04, 0.32), low (β=0.17, 95% CI: 0.02, 0.32), and VLFS (β=0.31, 95% CI: 0.12, 0.49) having increasingly higher mean DII scores compared to full food security, adjusted for covariates.
Bermudez-Millan, 2019 Cross-sectional	121 Latino/Hispanic adults with type 2 diabetes, ages 60.7±11.6 years	6-item HFSS, short form	hs-CRP	68% were classified as food insecure. FI was associated with higher hs-CRP (10.5±12.9 vs. 9.7 ± 26.1, $p=0.008$). Hs-CRP (and cortisol) partially mediated the relationship between FI and HOMA-IR.

Author, Date Design	Population	Food Insecurity	Outcome	Main Findings
Leddy, 2019 Cross-sectional	421 HIV+ women on ART, ages 47 (40–52) years 79% were virally suppressed (<20 copies/mL) and 70% had CD4 cell count ≥500 cells/mm^3	HFSS	IL-6 TNFR1	31% were food-insecure (marginal, low, or VLFS). FI was associated with 1.23 times higher IL-6 (95% CI: 1.06–1.44) and 1.13 times higher TNFR1 (95% CI: 1.05–1.21), adjusted for confounders. Dietary intakes were not associated with the inflammatory markers.
Peters, 2020 Cross-sectional	241 HIV+ women on ART, ages 46 (40–50) years 74.6% were virally suppressed (<40 copies/mL) and 68.3% had CD4 cell count ≥500 cells/mm^3	HFSS	CD4+ and CD8+: %CD38+HLADR+ %CD57+CD28− %PD-1+ %CD57− CD28+	43% were food-insecure (marginal, low, or VLFS). FI was associated with increased CD4+ and CD8+ activation (%CD38+HLADR+), increased senescence of CD8+ T cells (%CD57+CD28−), increased exhaustion of CD4+ T cells (%PD-1+), and decreased co-stimulation of CD4+ and CD8+ T cells (%CD57− CD28+), after adjusting for confounders. There were no significant differences in sCD14, sCD163, or I-FABP

Abbreviations: CRP, C-reactive protein; DII, Dietary Inflammatory Index; FI, food insecurity; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; I-FABP, intestinal fatty acid binding protein; IL, interleukin; TNFR, tumor necrosis factor receptor; WBC, white blood count

CHAPTER III: ASSOCIATION OF FOOD INSECURITY WITH NONALCOHOLIC FATTY LIVER DISEASE[1]

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease in the United States. Food-insecure individuals often depend on low-cost, energy-dense but nutritionally-poor foods, resulting in obesity and chronic diseases related to NAFLD.

Objective: To determine whether food insecurity is associated with NAFLD in a cohort of HIV and HCV infected and uninfected adults.

Methods: Cross-sectional analysis of low-income, middle-aged adults from the Miami Adult Studies on HIV (MASH) cohort without history of excessive alcohol consumption. Food security was assessed with the USDA's Household Food Security Survey. Magnetic resonance imaging was used to assess liver steatosis and fibrosis. Metabolic parameters were assessed from fasting blood, anthropometrics, and vitals.

Results: Of the total 603 participants, 32.0% reported food insecurity. The prevalence of NAFLD, fibrosis, and advanced fibrosis were 16.1%, 15.1%, and 4.6%, respectively. For every 5 kg/m^2 increase in BMI, the odds of NAFLD increased by a factor of 3.83 (95% CI: 2.37, 6.19) in food-insecure participants compared to 1.32 (95% CI: 1.04, 1.67) in food-secure participants. Food insecurity was associated with increased odds for any liver fibrosis (OR:1.65, 95% CI: 1.01, 2.72) and advanced liver fibrosis (OR: 2.82, 95% CI:

[1] Reprinted from: Tamargo JA, Sherman KE, Campa A, et al. Food insecurity is associated with magnetic resonance–determined nonalcoholic fatty liver and liver fibrosis in low-income, middle-aged adults with and without HIV. *Am J Clin Nutr*. 2021;113(3):593-601. doi:10.1093/ajcn/nqaa362

1.22, 6.54), adjusted for confounders. HIV and HCV infections were associated with increased risk for fibrosis, but the relationship between food insecurity and liver fibrosis did not differ from uninfected participants.

Conclusions: Among low-income, middle-aged adults, food insecurity exacerbated the risk for NAFLD associated with higher BMI and independently increased the risk for advanced liver fibrosis. People who experience food insecurity, particularly those vulnerable to chronic diseases and viral infections, may be at increased risk for liver-related morbidity and mortality. Improving access to adequate nutrition and preventing obesity among low-income groups may lessen the growing burden of NAFLD and other chronic diseases.

Introduction

Food insecurity is a socioeconomic condition in which households experience inadequate access to sufficient and nutritious foods.[1] Individuals who experience food insecurity often depend on low-cost, energy-dense but nutritionally-poor foods, usually consisting of refined carbohydrates, added sugars, fats, and sodium.[2] Food insecurity is also associated with overconsumption when food is available,[3,4] but not necessarily with lower energy intakes.[5] These factors result in food insecurity contributing to obesity and associated chronic diseases.[6,7] Food insecurity is reported by 14.3 million (11.1%) households in the United States, disproportionately affecting minorities and other marginalized groups.[1,8]

Nonalcoholic fatty liver disease (NAFLD) has become the most prevalent liver disease in the United States and other Western countries, with a rise in prevalence that

parallels that of obesity[9] and metabolic syndrome (MetS).[10] Between a quarter and a third of all U.S. adults[11-13] are estimated to have NAFLD, which encompasses nonalcoholic fatty liver (liver steatosis), nonalcoholic steatohepatitis (NASH), and cirrhosis in the absence of significant alcohol consumption or hereditary disorders.[14] Chronic hepatocyte injury caused by hepatitis infection, heavy drinking, and NAFLD/NASH leads to liver fibrosis, or the scarring of liver tissue. Even after sustained virological response of chronic hepatitis C, older age and high body mass index are associated with persisting fibrosis.[15] Advanced liver fibrosis can result in liver failure, portal hypertension, and cirrhosis, which may require liver transplantation. While the relationship between food insecurity and liver diseases has remained largely unexplored, Golovaty et al. found an association between food insecurity and increased risk of NAFLD and advanced liver fibrosis among low-income U.S. adults.[16]

People living with HIV (PLWH) are among those disproportionately affected by socioeconomic hardships and stigma,[17] including food insecurity.[18-21] Additionally, PLWH are at increased risk for chronic diseases,[22,23] including liver diseases.[24] Moreover, due to several compounding factors, liver disease progression is accelerated in PLWH.[25] As viral hepatitis infections are increasingly treated, the burden of fatty liver disease among PLWH has garnered recognition.[25] In PLWH, NAFLD is estimated in 30-65%[26,27] and liver fibrosis in 8-17%.[28,29] Both in the general population[30,31] and PLWH,[32,33] food insecurity has been linked to substance abuse, which in turn may result in increased risk for liver disease.[34] We have shown that cocaine use is a risk factor for liver fibrosis[35-37] and mortality in PLWH.[36]

While liver biopsy is considered the "gold standard" for determining NAFLD and liver fibrosis, it is costly and invasive with potential health complications in addition to high inter- and intra-observer variability.[38] Magnetic resonance (MR)-based assessments, such as MR imaging-derived proton density fat fraction (MRI-PDFF) and MR elastography (MRE), are currently regarded as the most accurate noninvasive techniques for assessment of liver steatosis and fibrosis, respectively.[39-42] The objective of this study was to determine whether food insecurity is associated with NAFLD using accurate, non-invasive MR technology in a cohort of HIV and/or hepatitis C virus (HCV) infected and uninfected adults.

Methods

Study subjects

The study consisted of a cross-sectional analysis of baseline data from the Miami Adult Studies on HIV (MASH) cohort, which follows people living with and without HIV for patterns of substance use and health disparities, with a focus on liver disease and related comorbidities. From October of 2016 through February of 2020, 1,031 MASH cohort participants had completed a baseline assessment. Participants in the MASH cohort are 40 years of age or older and seronegative for hepatitis B virus. This study was approved by the Florida International University Institutional Review Board and all participants provided written consent for participation in the study, release of medical information, and MR assessments. Exclusion criteria consisted of contraindications for MR (e.g., claustrophobia, ferromagnetic implant, poor fit due to body size [waist circumference greater than ~55 inches/140 cm]), self-reported current or prior alcohol consumption of more than 14 drinks per week for women and 21 for men,[14] underweight, and documented inherited liver disease (e.g., Wilson's disease) from medical records.

Food insecurity

Food insecurity was determined with the USDA's 18-item Household Food Security Survey, which assesses a respondent's perceived food sufficiency and adequacy, food-related anxiety, and instances of hunger that occurred in the household during the past 12 months.[43] The total sum of affirmative responses was used to categorize food security status as food-secure (scores 0–2) or food-insecure (scores ≥3). We further explored food insecurity by levels of severity as follows: full food security (score of 0), marginal food security (scores 1–2), low food security (LFS; scores 3–7 for households

with children and 3–5 without children), and very low food security (VLFS; scores ≥8 with children and ≥6 without children).

Outcomes

The primary endpoints of this study were the presence of nonalcoholic fatty liver (steatosis) and fibrosis. Liver fat content was assessed via magnetic resonance imaging-derived measurement of proton density fat fraction (MRI-PDFF). Liver fibrosis was assessed via liver stiffness (LS) measurement by magnetic resonance elastography (MRE). These were conducted on a 3T Siemens MAGNETOM Prisma scanner. NAFLD was considered present if MRI-PDFF >5%.[14] Liver fibrosis was defined as LS ≥2.9 kPa, which is consistent with histologically-proven liver fibrosis stage 1 or higher, and advanced fibrosis was defined as LS ≥3.8 kPa, consistent with histologically-proven liver fibrosis stage 3 or higher.[44]

Covariates

Demographic data were self-reported. Substance use was determined by self-report and urine drug screen, including tobacco, marijuana, cocaine, methamphetamines, and opiates. Alcohol consumption was determined as drinks per week from self-report. Anthropometrics and blood pressure were measured by trained research staff. Fasting blood samples were used to evaluate serum concentrations of glucose, triglycerides, and liver enzymes. Insulin resistance was measured with the triglyceride and glucose (TyG) index,[45,46] calculated as:

$$Ln(fasting\ triglycerides\ [mg/dL] * fasting\ glucose[mg/dL])/2$$

HIV and HCV viral loads and CD4 cell counts were abstracted from medical records. HIV viral suppression was defined as plasma HIV RNA <200 copies/mL. Body

mass index (BMI) was calculated and expressed in 5 kg/m^2 increments. Obesity was defined as having a BMI ≥30 kg/m^2. Criteria for MetS consisted of the presence of any 3 out of the following: abdominal obesity (waist circumference ≥35 inches for women and ≥40 inches for men), hypertriglyceridemia (TG ≥150 mg/dL), reduced high-density lipoprotein cholesterol (HDL-C) (≤50 for women and ≤40 mg/dL in men), hypertension (≥130 mm Hg systolic or ≥85 mm Hg diastolic blood pressure), or hyperglycemia (fasting plasma glucose ≥100 mg/dL).[47]

Statistical analysis

Descriptive statistics consisted of Chi-square tests for categorical variables and T-test (or nonparametric Wilcoxon rank-sum test) for continuous variables; reported as No. (%) and mean ± standard deviation (SD) or median (interquartile range, IQR). Univariate and multivariable binary logistic regressions were performed for NAFLD, any liver fibrosis, and advanced fibrosis; estimates reported as odds ratio (OR) or adjusted odds ratio (AOR) and 95% confidence intervals (CI). Candidates for multivariable regression models included HIV infection, HCV infection, substance use, and metabolic risk factors. Variables with P<0.25 in univariate analyses were selected for multivariable analyses. MetS and TyG index, if significant in univariate analyses, were included in separate multivariable models in order to avoid multicollinearity since these are composites of other confounders. In multivariable analyses, variables were removed from the model until only those factors with P<0.05 remained. Potential interactions between food insecurity and other confounders were explored by including interaction terms in the multivariable models. Potentially important sociodemographic confounders and alcohol consumption were retained in the models to obtain estimates adjusted for these

confounders. All data analysis was generated using SAS software, Version 9.4. Results were considered statistically significant at $P<0.05$ (two-sided).

Results

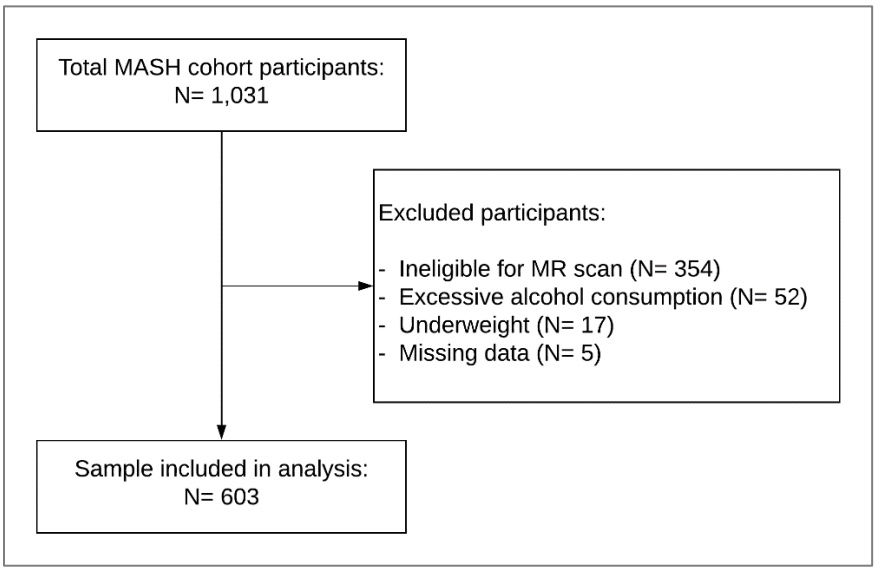

Figure 3.1. Flow Chart for MASH Cohort Participants Included in This Analysis
Abbreviations: MR – magnetic resonance

Study population

The characteristics of the study population are shown in Table 3.1, consisting of 603 adults. Out of the total 1,031 MASH cohort participants at the time this analysis was conducted, 428 were excluded for MR scan ineligibility (n=354), excessive alcohol consumption (n=52), underweight (n=17), or missing important data (n=5) (Figure 3.1). Excluded participants were less likely to be male and infected with HIV or HCV ($P<0.05$), but no other characteristics significantly differed, including food insecurity. Participants were 55.2±6.2 years old and predominantly male (56.0%) and Black non-Hispanic (60.7%). Most were unmarried (89.4%) and without children (91.7%), with 1.8±1.3 members per household. In total, 51.4% of participants were disabled and 36.0%

were otherwise unemployed. Accordingly, 76.6% of participants lived in households that fell under the Federal Poverty Level, with 92.5% falling under 185%, and all below 200% of poverty.

A total of 263 (43.6%) participants were living with HIV, 144 (23.9%) were seropositive for HCV, 64 (10.6%) were coinfected with both HIV and HCV, and 260 (43.1%) were HIV/HCV-uninfected. Of those participants living with HIV, 98.5% reported antiretroviral therapy (ART) and 84.7% were virally suppressed.

Food insecurity, metabolic parameters, and liver outcomes

A third of participants (32.0%) reported FI, with 87 (14.4)% and 106 (17.6)% having low and very low food security, respectively, and an additional 107 (17.7%) who reported marginal food security. Food-insecure participants had lower incomes than those who were food-secure. Higher proportions of food-insecure participants tended to be smokers (P=0.09) and cocaine users (P=0.07) than those who were food-secure. Participants with VLFS were more likely to use more than one illicit substance than food-secure participants (OR=1.63, 95% CI: 1.11, 2.39; P=0.013). No other characteristic significantly differed between the two groups (Table 3.1). Most of the participants were overweight (33.6%) or obese (41.5%), and 21.1% met the criteria for MetS. No significant difference was observed between food-secure and food-insecure individuals in any of the metabolic parameters evaluated.

There were 96 (16.1%) participants with NAFLD, 91 (15.1%) with liver fibrosis, and 28 (4.6%) with advanced fibrosis. As shown in Figure 3.2, food-insecure individuals had higher proportions of advanced fibrosis (7.8 vs. 3.2%; P=0.01), as well as a tendency for any liver fibrosis (19.2 vs. 13.2%; P=0.06) compared to food-secure individuals, but

the frequency of NAFLD did not significantly differ (16.0 vs. 16.1%; *P*=0.97). However, food insecurity was associated with a slightly higher but significant mean liver fat content among obese participants (4.8±2.0 vs. 3.8±1.9%; *P*=0.03), but not among non-obese participants (2.5±1.5 vs. 2.8±1.8%; *P*=0.18); *P*=0.001 for FI-obesity interaction. No significant differences were observed in serum values for AST, ALT, and AST/ALT ratio between food-secure and insecure participants or by levels of food insecurity.

Nonalcoholic fatty liver

Univariate analyses for NAFLD risk are reported in Table 3.2. Food insecurity was not independently associated with NAFLD. The use of tobacco, cocaine, and cannabis were significantly associated with decreased odds for NAFLD. People living with HIV or HCV showed tendencies for lower odds of steatosis compared to uninfected individuals. Of the metabolic risk factors, BMI, and obesity, MetS, hyperglycemia, hypertriglyceridemia, abdominal obesity, and TyG index, were associated with NAFLD. Hypertension and reduced HDL-C were not significantly associated with NAFLD.

Multivariable analyses, shown in Table 3.3, revealed a significant interaction effect between food insecurity and BMI on the risk for NAFLD (*P*<0.0001). For every 5-unit increase in BMI, the odds of NAFLD were 3.83 (95% CI: 2.37, 6.19; *P*<0.0001) times higher in food-insecure participants compared to 1.32 (95% CI: 1.04, 1.67; *P*=0.02) times higher in food-secure participants. This is visually represented in Figure 3.3, which also compares the probability for NAFLD between food-secure and food-insecure individuals; food insecurity was associated with reduced odds for NAFLD at lower BMIs and with increased odds for NAFLD at higher BMIs. To better illustrate the relationship between food insecurity and NAFLD given the interaction with BMI, Table 3.3 also shows results

stratified by the presence of obesity (P=0.003 for interaction). Food insecurity, compared to food security, was associated with significantly lower odds of NAFLD in non-obese participants (AOR: 0.30, 95% CI: 0.11, 0.83; P=0.02) and a trend was observed for higher odds of liver steatosis in obese participants (AOR: 1.85, 95% CI: 0.98, 3.53; P=0.06).

We further explored the FI-BMI interaction effect on NAFLD risk by levels of food insecurity and 5-unit increases in BMI; see Table 3.4. Compared to full food security, VLFS was associated with increased risk for NAFLD at BMIs of 35 and 40 kg/m^2, which correspond to the cutoffs for class II and class III obesity, respectively.

In addition to these findings, hyperglycemia (AOR: 2.48, 95% CI: 1.46, 4.20; P=0.0008), hypertriglyceridemia (AOR: 2.18, 95% CI: 1.29, 3.67; P=0.004), MetS (AOR: 3.20, 95% CI: 1.92, 5.32; P<0.0001), and TyG index (AOR: 2.57, 95% CI: 1.78, 3.71; P<0.0001) were significantly associated with NAFLD. The use of tobacco, cocaine, and cannabis were no longer significant in multivariable analyses.

Liver fibrosis

In univariate analyses for liver fibrosis (Table 3.2), food insecurity was independently associated with increased odds for advanced fibrosis (OR: 2.57, 95% CI: 1.20, 5.52; P=0.02) and showed a trend in association with any liver fibrosis (OR: 1.56, 95% CI: 0.99, 2.47; P=0.06). Additionally, a trend was seen for a dose-response effect between the severity of food insecurity and the risk for advanced fibrosis (P=0.08 for trend). Marginal, low, and VLFS were associated with 1.81, 2.73, and 3.42 times the risk for advanced liver fibrosis compared to full food security. Of the metabolic risk factors, reduced HDL-C and insulin resistance determined with TyG index were significantly

associated with any liver fibrosis. Hyperglycemia showed trends in association with any fibrosis and advanced liver fibrosis ($P<0.1$). No other metabolic parameter was significantly associated with liver fibrosis or advanced fibrosis. HIV and HCV infections were significantly associated with increased odds for any liver fibrosis, but only HCV was significantly associated with advanced fibrosis.

In multivariable analyses (Table 3.5), food insecurity (AOR: 1.65, 95% CI: 1.01, 2.72 ; $P=0.048$), HIV infection (AOR: 2.07, 95% CI: 1.25, 3.44; $P=0.005$), HCV infection (AOR: 5.05, 95% CI: 3.07, 8.32; $P<0.0001$), hyperglycemia (AOR: 1.86, 95% CI: 1.07, 3.22; $P=0.03$), and TyG index (AOR: 1.59, 95% CI: 1.09, 2.32; $P=0.02$) were significantly associated with any fibrosis after adjustment for confounders. Food insecurity was also associated with advanced fibrosis (AOR: 2.82, 95% CI: 1.22, 6.54; $P=0.02$), as was HCV infection, but HIV infection and hyperglycemia were no longer significant. No significant interaction effects were identified for liver fibrosis. Furthermore, a sensitivity analysis excluding HCV-positive participants showed that food insecurity remained significantly associated with advanced liver fibrosis (OR: 5.23, 95% CI: 1.34, 20.48; $P=0.02$).

Discussion

This report describes a unique study using non-invasive, MR-based objective measures of liver steatosis and fibrosis to determine whether food insecurity is associated with biomarkers of liver disease among a cohort of low-income, minority, middle-aged adults living with and without HIV and HCV infections. Food insecurity was associated with NAFLD depending on BMI; food insecurity was associated with greater liver fat

content only among obese participants. Food insecurity was also an independent risk factor for liver fibrosis, particularly advanced fibrosis. Additionally, the risk for advanced liver fibrosis correlated with the severity of food insecurity. These findings are highly relevant for the food-insecure population, particularly those living with HIV and/or HCV since they are already at increased risk of liver-related morbidity and mortality and suffer from disproportionately high rates of food insecurity. However, our findings did not show a cumulative effect of food insecurity and viral infections on liver disease, therefore indicating that food insecurity may be a clinically relevant independent risk factor for liver disease.

Nearly a third of our participants reported FI, which is consistent with the 29% prevalence among U.S. households with incomes below 185% of the federal poverty level [1]. Using MRI-PDFF, our findings suggest a NAFLD prevalence of 16% within the cohort. The low prevalence of NAFLD compared to 25-33% in the general U.S. population[11-13] might be related to the high proportion of Black non-Hispanic males in the MASH cohort,[8,11] as well as increased accuracy from MRI-PDFF compared to other non-invasive measures of liver steatosis.[40]

To the best of our knowledge, only one study has previously explored the relationship between food insecurity and NAFLD. Using NHANES data, Golovaty et al. estimated that 32% of U.S. adults living under 200% of the federal poverty level had NAFLD and 5% had advanced fibrosis.[16] Similar to our results, food insecurity was associated with more than double the odds for advanced liver fibrosis, determined with the NAFLD Fibrosis Score, a non-invasive index that does not provide a direct measurement of fibrosis, but uses age, BMI, AST/ALT ratio, platelets, and albumin.[48] In

contrast to our findings, Golovaty et al. also found that food insecurity was independently associated with increased odds of NAFLD using the U.S. Fatty Liver Index, also not a direct measure, but an algorithm incorporating race/ethnicity, age, waist circumference, glucose, and insulin levels.[49] We have utilized MRE and MRI-PDFF, which represent valid and highly reproducible measurements of liver stiffness and liver fat.[39,40] In addition, the participants in the Golovaty study were younger and had larger proportions of females and White non-Hispanics. Further, many of the participants in our study used tobacco, cocaine, or cannabis, all of which were significantly associated with decreased odds for liver steatosis. We also observed trends towards higher rates of smoking and cocaine use in food-insecure than food-secure participants, and VLFS was associated with increased polysubstance use. Nicotine, cocaine, and cannabis may lead to lower body weight through several mechanisms, including decreased appetite and altered metabolism.[50] By decreasing body adiposity, substance abuse may partially explain the low prevalence of NAFLD in the cohort, as well as the decreased risk for NAFLD associated with food insecurity among non-obese participants.

There are several potential explanations for the effects of food insecurity on liver disease observed in this study. Food insecurity is associated with inadequate dietary intakes, limited food choices, poor diet quality with low-cost, high-fat, high-sugar, calorie-dense foods, and disrupted eating patterns that contribute to obesity [3,4]. Moreover, food insecurity often forces individuals to make tradeoffs between buying food or obtaining medical care and medications.[51,52] Consequently, food-insecure individuals are at increased risk for metabolic conditions, such as obesity and type 2 diabetes [7], which have bidirectional relationships with NAFLD.[53,54] In this study, hyperglycemia and

insulin resistance were associated with NAFLD and liver fibrosis. Food insecurity may lead to poor glycemic control and insulin resistance by increased stress[55,56] and poor adherence to medical recommendations.[57] Indeed, type 2 diabetes and its precursor, insulin resistance, are key pathogenic mechanisms of NAFLD,[58] promoting progression to NASH, advanced liver fibrosis,[59-61] hepatocellular carcinoma,[62] and mortality.[63,64]

The strengths of the study include the large sample of participants with outcome measures obtained with accurate, non-invasive MR technology, and a balanced study design that included PLWH, people infected or co-infected with HCV, and uninfected participants with similar sociodemographic characteristics. The use of MRI-PDFF and MRE provides a high level of accuracy compared to other non-invasive tests.[40] Several limitations in this study should be noted. While the study included a large sample size, the relatively low frequency of advanced liver fibrosis warrants caution in the interpretation of the results. Alcohol consumption was self-reported, thus, subject to underreporting. It is also possible that some of the effect of food insecurity on liver fibrosis seen in this study may not be metabolic- or NAFLD-related; however, the association between food insecurity and advanced liver fibrosis was significant while controlling for and excluding HCV infection. Lastly, the cross-sectional design does not allow for temporality to be established. Indeed, it is possible that the association between food insecurity and liver fibrosis seen in this study may be related to reverse causation. For example, HIV/HCV infection may result in liver fibrosis and lead to psychosocial factors such as poverty and drug use, which then contribute to food insecurity. Decompensated cirrhosis may also result in hepatic encephalopathy with behavioral changes that contribute to FI; however, none of the participants in this study had

decompensated cirrhosis. Therefore, longitudinal studies are needed to better comprehend the potential role of food insecurity in the development and progression of liver diseases.

Our findings provide further evidence that food insecurity is a social determinant of health that contributes to the prevalence of liver disease.[16] The burden of NAFLD is only expected to rise,[65] and extrahepatic manifestations of NAFLD may promote the development or aggravation of other chronic comorbidities.[66] The fact that food insecurity was independently associated with more than twice the risk for advanced liver fibrosis is particularly relevant to clinical outcomes since fibrosis stage, not NASH, predicts mortality in NAFLD patients.[67]

Conclusions

Among low-income, middle-aged minorities living with and without HIV and/or HCV in the MASH cohort, food insecurity was associated with increased liver fat content among obese participants and increased risk for advanced liver fibrosis. People who experience FI, particularly those vulnerable to chronic diseases and viral infections, may be at increased risk for advanced liver disease, which in turn is associated with greater morbidity and mortality. Improving access to adequate nutrition and preventing obesity among low-income groups in the United States may lessen the growing burden of NAFLD and other metabolic chronic diseases.

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Table 3.1. Sample Characteristics by Food Security Status

Characteristics	Category	Total N=603	Food-Secure N=410	Food-Insecure N=193	
		N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	*P*[1]
Age, years		55.5 ± 6.2	55.6 ± 6.2	55.2 ± 6.0	0.39
Gender	Male	338 (56.0)	234 (57.1)	104 (53.9)	0.46
Race/ethnicity	Black non-Hispanic	366 (60.7)	256 (62.4)	110 (57.0)	
	White Hispanic	130 (21.6)	86 (21.0)	44 (22.8)	0.35
	White non-Hispanic	55 (9.1)	32 (7.8)	23 (11.9)	
	Multiracial/other	52 (8.6)	36 (8.8)	16 (8.3)	
Marital Status	Married	64 (10.6)	45 (11.0)	19 (9.8)	
	Widowed, divorced, or separated	203 (33.7)	132 (32.2)	71 (36.6)	0.53
	Single	336 (55.7)	233 (56.8)	103 (53.4)	
Household size		1.8 ± 1.3	1.8 ± 1.3	1.7 ± 1.2	0.46
Children in Household		50 (8.3)	32 (7.8)	18 (9.3)	0.53
Education	Less than High-School	240 (39.8)	169 (41.2)	71 (36.8)	
	High-School or GED	173 (28.7)	109 (26.6)	64 (33.2)	0.24
	Some College or more	190 (31.5)	132 (32.2)	58 (30.1)	
Employment	Employed	76 (12.6)	59 (14.4)	17 (8.8)	
	Disabled	310 (51.4)	202 (49.3)	108 (56.0)	0.11
	Otherwise unemployed	217 (36.0)	149 (36.3)	68 (35.2)	
Income	Less than $10,000	336 (55.7)	213 (52.0)	123 (63.4)	
	$10,000 - $20,000	164 (27.2)	118 (28.8)	46 (23.8)	**0.01**
	$20,000 - $30,000	56 (9.3)	38 (9.3)	18 (9.3)	
	$30,000 or more	47 (7.8)	41 (10.0)	6 (3.1)	
Poverty	Below federal poverty level	462 (76.6)	303 (73.9)	159 (82.4)	**0.02**
Substance Use	Tobacco	298 (49.4)	193 (47.1)	105 (54.4)	0.09
	Alcohol, drinks/week	0 (0, 1)[1]	0 (0, 1)[1]	1 (1, 2)[1]	0.45
	Cocaine	225 (37.3)	143 (34.9)	82 (42.5)	0.07
	Cannabis	166 (27.5)	108 (26.3)	58 (30.1)	0.34
	Opiates	64 (10.6)	43 (10.5)	21 (10.8)	0.89
Infection	HIV	263 (43.6)	185 (45.1)	78 (40.4)	0.28
	ART	259 (98.5)	183 (98.9)	76 (97.4)	0.58
	HIV viral load < 200 copies/mL	222 (84.7)	160 (87.0)	62 (79.5)	0.12
	CD4 (cells/mL)	597.8 ± 368.0	610.5 ± 384.0	566.6 ± 326.3	0.42
	HCV	144 (23.9)	94 (22.9)	50 (25.9)	0.42
Metabolic	BMI, kg/m^2	29.5 ± 6.1	29.6 ± 6.2	29.2 ± 6.0	0.55
	Obese (BMI ≥ 30 kg/m^2)	250 (41.5)	174 (42.4)	76 (39.4)	0.48

Characteristics	Category	Total N=603	Food-Secure N=410	Food-Insecure N=193	
		N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	*P*[1]
	MetS	127 (21.1)	89 (21.7)	38 (19.7)	0.57
	Hyperglycemia	133 (22.1)	89 (21.7)	44 (22.8)	0.76
	Hypertriglyceridemia	140 (23.2)	89 (21.7)	51 (26.4)	0.20
	Hypertension	331 (54.9)	228 (55.6)	103 (53.4)	0.60
	Reduced HDL-C	63 (10.5)	45 (11.0)	18 (9.3)	0.53
	Abdominal obesity	317 (52.6)	210 (51.2)	107 (55.4)	0.33
	TyG index	8.5 ± 0.6	8.5 ± 0.6	8.5 ± 0.6	0.59
Hepatic	ALT	18 (14, 27)[2]	19 (14, 27)[2]	18 (14, 27)[2]	0.83
	AST	22 (17, 29)[2]	22 (17, 29)[2]	21 (17, 27)[2]	0.55
	AST/ALT	1.23 ± 0.4	1.24 ± 0.4	1.22 ± 0.4	0.49

[1] Tests for group differences performed with Chi-square test for categorical outcomes and T-test (or Wilcoxon rank-sum) for continuous outcomes.
[2] Median (interquartile range)
Abbreviations: ART- antiretroviral therapy; FS- food security; MetS- metabolic syndrome; TyG- triglyceride and glucose index

Table 3.2. Univariate Analyses for NAFLD (Liver Fat >5% via MRI-PDFF), Fibrosis (LS ≥2.9 kPa via MRE), and Advanced Fibrosis (LS ≥3.8 kPa via MRE) (N=603)[1]

Parameter	Category	NAFLD (*n*=96)		Any Fibrosis (*n*=91)		Advanced Fibrosis (*n*=28)	
		OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Food Insecurity	Food insecure vs secure	0.99 (0.62, 1.58)	0.97	1.56 (0.99, 2.47)	0.06	**2.57 (1.20, 5.52)**	**0.02**
	Marginal vs. full security	0.92 (0.50, 1.70)	0.79	0.55 (0.18, 1.73)	0.31	1.81 (0.58, 5.65)	0.31
	Low vs. full security	0.67 (0.33, 1.39)	0.29	1.51 (0.45, 5.13)	0.51	2.73 (0.92, 8.10)	0.07
	Very low vs. full security	1.28 (0.73, 2.26)	0.39	1.89 (0.61, 5.85)	0.27	**3.42 (1.29, 9.11)**	**0.01**
Substance Use	Tobacco	**0.47 (0.30, 0.74)**	**0.001**	0.95 (0.61, 1.49)	0.83	0.76 (0.35, 1.63)	0.48
	Alcohol (drinks/week)	1.03 (0.97, 1.09)	0.40	0.97 (0.91, 1.05)	0.45	1.01 (0.90, 1.12)	0.93
	Cocaine	**0.50 (0.30, 0.81)**	**0.006**	0.85 (0.53, 1.35)	0.49	0.93 (0.42, 2.05)	0.86
	Cannabis	**0.51 (0.29, 0.88)**	**0.02**	1.21 (0.74, 1.96)	0.45	0.87 (0.36, 2.09)	0.76
	Opiates	0.84 (0.40, 1.76)	0.65	1.34 (0.69, 2.63)	0.39	1.43 (0.48, 4.26)	0.52
Infection	HIV	0.73 (0.47, 1.14)	0.16	**1.71 (1.09, 2.68)**	**0.02**	1.31 (0.61, 2.80)	0.49
	HCV	0.81 (0.48, 1.38)	0.44	**4.84 (3.03, 7.72)**	**<0.0001**	**13.62 (5.40, 34.32)**	**<0.0001**
Metabolic	BMI, per 5 kg/m^2	**1.75 (1.46, 2.09)**	**<0.0001**	0.90 (0.75, 1.09)	0.28	0.79 (0.56, 1.10)	0.16
	Obesity	**3.71 (2.33, 5.89)**	**<0.0001**	0.82 (0.52, 1.29)	0.39	0.78 (0.35, 1.71)	0.53
	MetS	**3.95 (2.49, 6.28)**	**<0.0001**	1.33 (0.79, 2.23)	0.29	1.02 (0.41, 2.58)	0.97
	Hyperglycemia	**2.92 (1.84, 4.63)**	**<0.0001**	1.62 (0.98, 2.67)	0.06	2.04 (0.92, 4.54)	0.08
	Hypertriglyceridemia	**2.64 (1.67, 4.18)**	**<0.0001**	0.99 (0.58, 1.68)	0.97	0.54 (0.18, 1.58)	0.26
	Abdominal obesity	**3.47 (2.11, 5.71)**	**<0.0001**	0.82 (0.53, 1.28)	0.38	0.66 (0.31, 1.43)	0.29
	Hypertension	1.41 (0.91, 2.20)	0.13	1.24 (0.79, 1.95)	0.36	1.10 (0.51, 2.37)	0.81
	Reduced HDL-C	1.42 (0.74, 2.72)	0.28	**1.91 (1.02, 3.58)**	**0.04**	1.94 (0.71, 5.29)	0.19
	TyG index	**2.72 (1.95, 3.79)**	**<0.0001**	**1.45 (1.03, 2.03)**	**0.03**	1.28 (0.72, 2.26)	0.39

[1] Statistical tests were performed using univariate logistic regressions and reported as odds ratio with 95% confidence interval (CI).Abbreviations: LS- liver stiffness; MetS- metabolic syndrome; MRE- magnetic resonance elastography; MRI-PDFF- magnetic resonance imaging-derived measurement of proton density fat fraction; NAFLD- nonalcoholic fatty liver disease; TyG- triglyceride and glucose index

Table 3.3. Multivariable Analyses for NAFLD (Liver Fat >5%) Determined by MRI-Determined Proton Density Fat Fraction (MRI-PDFF) (N=603)

Parameter		**AOR (95% CI)[1]**	***P*-value**
Hyperglycemia		2.48 (1.46, 4.20)	0.0008
Hypertriglyceridemia		2.18 (1.29, 3.67)	0.004
MetS[2]		3.20 (1.92, 5.32)	<0.0001
TyG index[2]		2.57 (1.78, 3.71)	<0.0001
Alcohol, drinks/week		1.06 (0.99, 1.13)	0.08
Parameter	**Condition**	**AOR (95% CI)[1]**	***P*-value**
BMI, per 5 kg/m^2	*x Food insecurity*	*(interaction)*	<0.0001
	Food-secure:	1.32 (1.04, 1.67)	0.02
	Food-insecure:	3.83 (2.37, 6.19)	<0.0001
Food insecurity	BMI=25.0	0.20 (0.07, 0.57)	0.002
	BMI=30.0	0.59 (0.31, 1.14)	0.12
	BMI=35.0	1.91 (1.02, 3.59)	0.04
	x Obesity (BMI ≥30)[3]	*(interaction)*	0.003
	Non-obese:	0.30 (0.11, 0.83)	0.02
	Obese:	1.85 (0.98, 3.53)	0.06

[1] The multivariable logistic regression model examined the relationship between food insecurity, BMI, and NAFLD adjusting for age, sex, race/ethnicity, household size, hyperglycemia, hypertriglyceridemia, and included an interaction term for food insecurity and BMI. Estimates for the effect of food insecurity on NAFLD were obtained for BMIs of 25, 30, and 35 kg/m^2, which correspond to the cutoffs for overweight, obesity class I, and obesity class II, respectively.

[2] Due to multicollinearity, separate models were used to obtain estimates for MetS and TyG adjusting for age, sex, race/ethnicity, household size, BMI, alcohol consumption, and food insecurity.

[3] The multivariable logistic regression model examined the relationship between food insecurity and NAFLD among obese and non-obese participants, adjusting for age, sex, race/ethnicity, household size, hyperglycemia, hypertriglyceridemia, and included obesity (BMI ≥30 kg/m^2) as well as an interaction term for food insecurity and obesity.

Abbreviations: AOR- adjusted odds ratio; LFS- low food security; MetS- metabolic syndrome; TyG- triglyceride and glucose index, VLFS- very low food security

Table 3.4. Multivariable Analyses for Any Liver Fibrosis (LS ≥2.9 kPa) and Advanced Liver Fibrosis (LS ≥3.8 kPa) Determined by Magnetic Resonance Elastography (MRE) (N=603)

Parameter	Any Fibrosis[1]		Advanced Fibrosis[2]	
	AOR (95% CI)	***P*-value**	**AOR (95% CI)**	***P*-value**
HIV	2.07 (1.25, 3.44)	0.005	1.79 (0.73, 4.40)	0.20
HCV	5.05 (3.07, 8.32)	<0.0001	12.56 (4.83, 32.64)	<0.0001
Hyperglycemia	1.86 (1.07, 3.22)	0.03	-	-
TyG index[3]	1.59 (1.09, 2.32)	0.02	-	-
Alcohol, drinks/week	0.99 (0.92, 1.06)	0.69	1.00 (0.73, 1.11)	0.95
Food insecurity	1.65 (1.01, 2.72)	0.048	2.82 (1.22, 6.54)	0.02

[1] The multivariable logistic regression model examined the relationship between food insecurity and any liver fibrosis adjusting for age, sex, race/ethnicity, household size, HIV and HCV infections, hyperglycemia, and alcohol consumption.
[2] The multivariable logistic regression model examined the relationship between food insecurity and advanced liver fibrosis adjusting for age, sex, race/ethnicity, household size, HIV and HCV infections, and alcohol consumption.
[3] Due to multicollinearity, a separate model was used to obtain estimates for TyG adjusting for age, sex, race/ethnicity, household size, alcohol consumption, and food insecurity.
Abbreviations: AOR- adjusted odds ratio; MetS- metabolic syndrome; TyG- triglyceride and glucose index

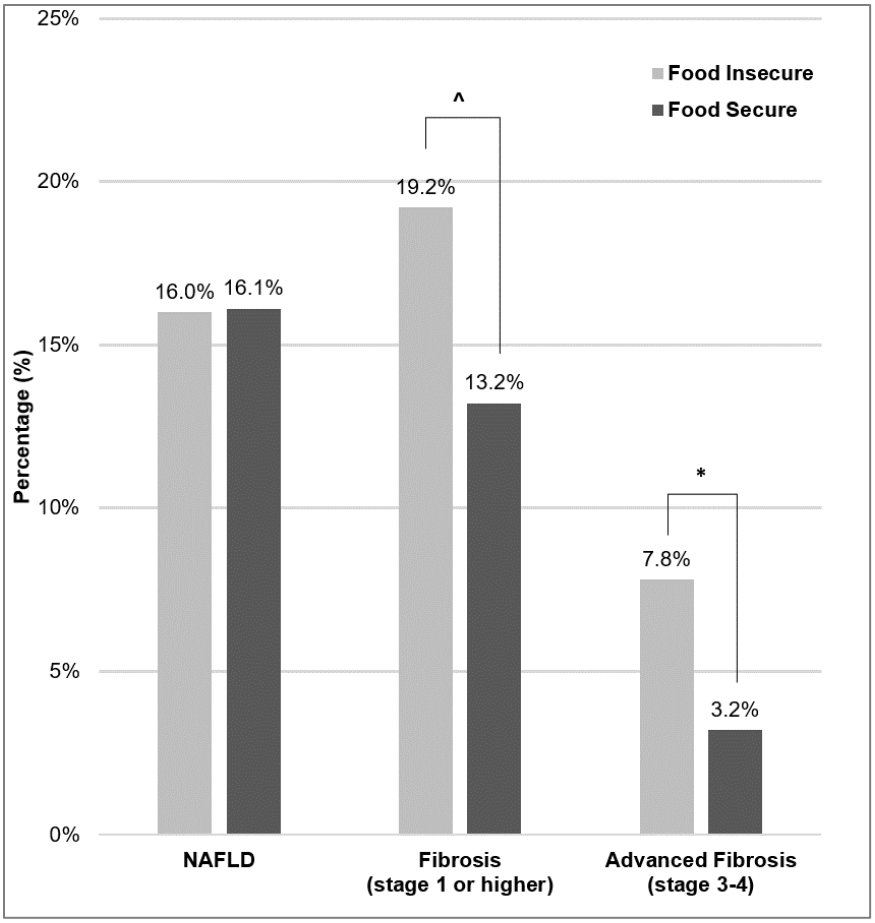

Figure 3.2. Comparison of Liver Parameters by Food Security Status. Of the 603 MASH cohort participants, 97 (16.1%) had nonalcoholic fatty liver, 91 (15.1%) had liver fibrosis, and 28 (4.6%) had advanced fibrosis. Liver fat content was assessed via magnetic resonance imaging-derived measurement of proton density fat fraction (MRI-PDFF). Liver fibrosis was assessed via liver stiffness (LS) measurement by magnetic resonance elastography (MRE). These were conducted on a 3T Siemens MAGNETOM Prisma scanner. Nonalcoholic fatty liver was considered present if MRI-PDFF >5%. Liver fibrosis was defined as LS ≥2.9 kPa, which is consistent with liver fibrosis stage 1 or higher, and advanced fibrosis was defined as LS ≥3.8 kPa, consistent with liver fibrosis stage 3 or higher. Chi-square tests were performed to test for differences between food-secure and food-insecure participants. * $P<0.05$; ^ $P<0.1$

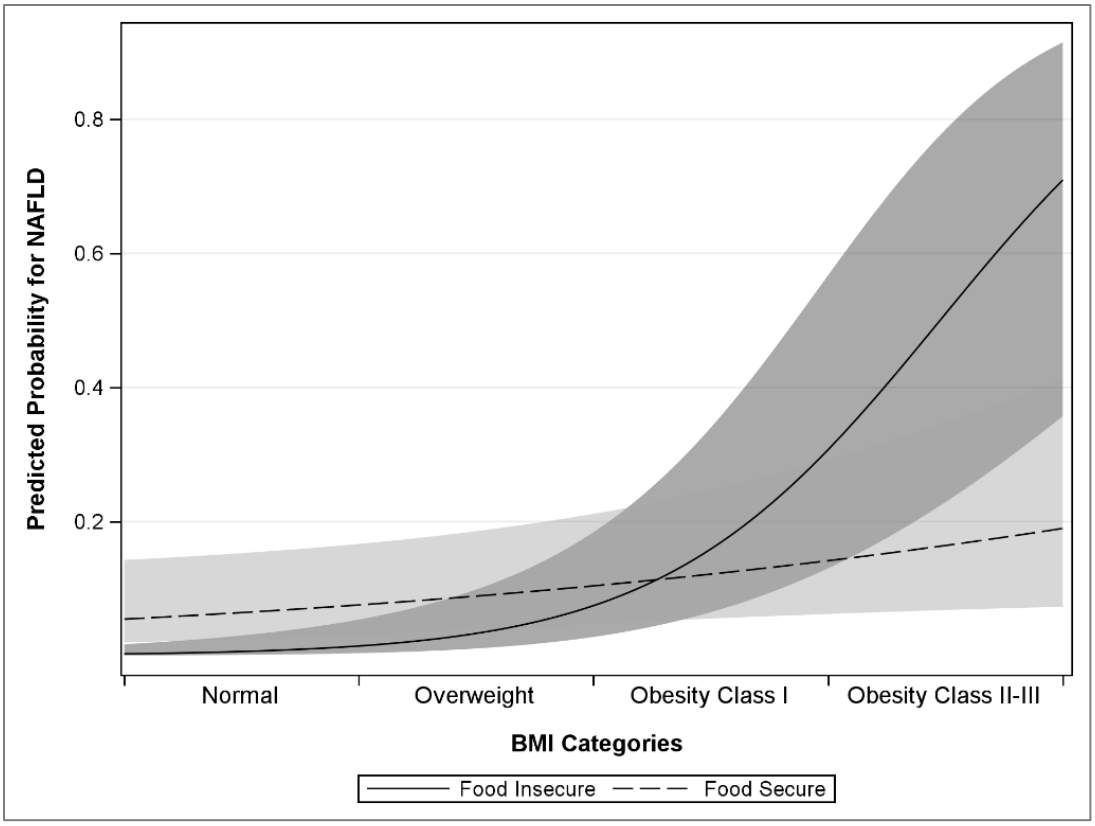

Figure 3.3. Predicted Probability Plot for NAFLD by BMI in Food-Secure vs. Food-Insecure. A multivariable logistic regression model was used to examine the relationship between food insecurity and NAFLD adjusting for age, sex, race/ethnicity, household size, hyperglycemia, hypertriglyceridemia, and included BMI as well as an interaction term for food insecurity and BMI (see Table 3.3). There was a significant interaction effect between food insecurity and BMI (P<0.0001). In other words, the effect of food insecurity on NAFLD was dependent on BMI and vice versa. Estimates for the effect of food insecurity on NAFLD were obtained for BMIs of 25, 30, and 35 kg/m^2, which correspond to the cutoffs for overweight, obesity class I, and obesity class II, respectively. For every 5-unit increase in BMI, the odds of NAFLD were 3.83 (95% CI: 2.37, 6.19; P<0.0001) times higher in food-insecure participants (solid line) compared to 1.32 (95% CI: 1.04, 1.67; P=0.02) times higher in food-secure participants (dotted line). Likewise, compared to food-secure participants, the odds for NAFLD in food-insecure participants were: a) 0.20 (95% CI: 0.07, 0.57) at 25.0 kg/m^2, b) 0.59 (95% CI: 0.31, 1.14) at 30.0 kg/m^2, and c) 1.91 (95% CI: 1.02, 3.59) at 35.0 kg/m^2. Abbreviations: FI- food insecurity; NAFLD- nonalcoholic fatty liver disease

CHAPTER IV: ASSOCIATION OF FOOD INSECURITY WITH COGNITIVE IMPAIRMENT[2]

Abstract

Background: Food insecurity is a social determinant of health associated with cognitive impairments in older adults and people living with HIV (PLWH). Few studies have examined this relationship longitudinally, and no studies have explored how the frequency of food insecurity over time may impact cognitive impairment.

Objective: To examine the impact of food insecurity on cognitive impairment over a 2-year follow-up period in a cohort of people living with and without HIV.

Methods: Two-year longitudinal analysis of primarily economically disadvantaged, middle-aged, Black, and Hispanic participants from the Miami Adult Studies on HIV (MASH) cohort. Food insecurity was assessed with the USDA Household Food Security Module at baseline, 12- and 24-month follow-ups. Food insecurity in all three assessments was considered persistent food insecurity. Cognitive impairment was assessed with the Mini-Mental State Examination (MMSE). Statistical analyses consisted of logistic regressions.

Results: A total of 394 participants (247 HIV+) with 2-year follow-up data were included in this analysis. At baseline, 104 (26.4%) were food-insecure and 58 (14.7%) had cognitive impairment. Very low food security was associated with cognitive impairment at baseline (OR: 3.23, 95% CI: 1.08–9.65). PLWH not virally suppressed had

[2] Reprinted from: Tamargo JA, Meade CS, Campa A, Martinez SS, Li T, Sherman KE, Baum MK. Food Insecurity and Cognitive Impairment in the Miami Adult Studies on HIV (MASH) Cohort. *J Nutr*. 2021. doi:10.1093/jn/nxaa416

higher risk for cognitive impairment compared to HIV-uninfected participants (OR: 2.87, 95% CI: 1.15–7.18). Additionally, baseline food insecurity (OR: 2.28, 95% CI: 1.08–4.81) and the frequency of food insecurity over time (OR: 1.50 per year, 95% CI: 1.08–2.10), particularly persistent food insecurity (OR: 3.69, 95% CI: 1.15–11.83), were associated with cognitive impairment at 2-year follow-up; the results were consistent after excluding cognitively impaired participants at baseline.

Conclusions: Food insecurity is a significant risk factor for cognitive impairment, particularly among individuals who experience food insecurity frequently or persistently. Screening for food insecurity and interventions to secure access to sufficient, nutritious foods may help delay cognitive decline among socioeconomically disadvantaged individuals.

Introduction

Food insecurity (FI) refers to a lack of dependable access to sufficient and nutritious food for an active and healthy life. Food insecurity is the result of limited resources and is associated with poverty, unemployment, and high housing costs.[1] As such, food insecurity is a socioeconomic condition that impacts 14.3 million (11.1%) households in the United States.[2] It is often episodic, triggered by unemployment, inflation, food prices, or unforeseen costs.[3,4] Yet, for many households, food insecurity is a frequent or persistent problem that occurs for an average of 7 months out of the year.[5] Tightly related to sociodemographic factors, food insecurity is disproportionately prevalent among minorities[6] and other marginalized groups, including people living with HIV (PLWH).[7,8]

In the United States, adults from food-insecure households are at increased risk for chronic diseases and mental health conditions.[9,10] Food insecurity has been associated with cognitive deficits among U.S. older adults.[11-13] Fewer studies have examined this association among middle-aged adults, but Wong et al. showed an association between very low food security (VLFS) and cognitive decline among U.S. adults aged 40-75 years.[14] Furthermore, neurocognitive disorders are found in approximately 20-50% of PLWH[15] and persist despite long-term viral suppression.[16] We have previously shown that VLFS was associated with poorer mental health quality of life in PLWH.[17] Hobkirk et al. showed that food insecurity was associated with cognitive impairments among PLWH but not HIV-uninfected participants.[18] Although the findings are generally consistent, the existing evidence is limited by heterogeneity in samples, food insecurity measures, and time frames.[19] Few longitudinal studies are available, and none have applied repeated food insecurity measurements to determine the effects of frequency and duration of food insecurity on cognitive impairment.

Food insecurity and HIV are thought to have a bidirectional relationship, as living with HIV reinforces food insecurity and, in turn, food insecurity may promote immunodeficiency and HIV disease progression.[20,21] Indeed, food insecurity is associated with poorer adherence to antiretroviral therapy (ART), lower odds for viral suppression, and lower CD4 cell counts in PLWH.[22-24] Moreover, PLWH have increased nutritional needs, particularly as the HIV disease progresses.[25,26] Food insecurity can contribute to inflammation in PLWH,[27] a key mechanism in HIV-associated neurocognitive disorders.[28] Therefore, via behavioral and biological mechanisms alike, food insecurity has the potential of contributing to or exacerbating cognitive dysfunction in PLWH.

To the best of our knowledge, no studies have examined the longitudinal relationship between food insecurity and cognitive impairment among people living with and without HIV, considering the impact of the frequency of food insecurity over time. The aim of this study was to determine whether food insecurity is associated with cognitive impairment cross-sectionally and after a 2-year follow-up. We hypothesized that (1) food insecurity would be independently associated with increased risk for cognitive impairment, (2) the risk for cognitive impairment would correlate with the severity and frequency of food insecurity, and (3) the relationship between food insecurity and cognitive impairment would be stronger among PLWH than HIV-uninfected persons.

Methods

This was a longitudinal analysis of data collected between October 2016 and February 2020 from the ongoing Miami Adult Studies on HIV (MASH) cohort (NIDA grant # U01-DA040381). Participants are ≥40 years of age, hepatitis B negative, and have documented HIV and hepatitis C virus (HCV) status (positive or negative). For this analysis, we used data collected at baseline, 12- and 24-month follow-ups, excluding participants who were unable to complete cognitive testing (e.g., unable to read or write, n=20) or were missing crucial data (n=9). All participants provided written consent for participation in this study and release of medical records. The protocol for this study was approved by the Florida International University Institutional Review Board.

Food security status

Food insecurity was determined with the Household Food Security Module, which assesses a respondent's perceived food sufficiency and adequacy during the past 12 months.[29] Based on the number of affirmative responses, participants were classified as food-secure (score 0–2) or food-insecure (score ≥3). Food insecurity was further explored by levels of severity: full (score of 0), marginal (score of 1–2), low (score of 3–7 for households with children and 3–5 without children), and VLFS (score ≥8 with children and ≥6 without children). Additionally, we examined the frequency of food insecurity over the 2-year period by using the total sum of time-points with self-reported food insecurity. Food insecurity was measured at baseline and 12- and 24-month follow-ups, thus participants could report food insecurity up to 3 times, equivalent to 3 years of food insecurity. Reporting food insecurity at all times was considered persistent food insecurity.

Cognitive function

Cognitive function was assessed with the Mini-Mental State Examination (MMSE), using scores ≤24 out of 30 as cutoff for impairment.[30] The MMSE is a measure of global cognitive function and the most widely used screening tool for cognitive impairment, with sensitivity and specificity of 81% and 89%, respectively, for the detection of dementia.[31]

Additional covariates

Food insecurity has been associated with several conditions that may have an impact on cognitive function, including obesity, diabetes,[9,10] liver disease,[32] and mental health problems, such as depression[9] and substance abuse.[33-36] Therefore, we considered

these risk factors as potential confounders. Sociodemographic characteristics were self-reported. Substance use was determined by self-report (past 30-days) and urine toxicology (American Bio Medica, Kinderhook, NY, USA). Hazardous alcohol consumption was determined with scores ≥8 in the Alcohol Use Disorders Identification Test (AUDIT).[37] Anthropometric measurements, vital signs, and fasting blood samples were obtained in all study visits. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2, hyperglycemia as fasting blood glucose ≥100 mg/dL, and hypertension as ≥130 mm Hg systolic or ≥85 mm Hg diastolic blood pressure. Liver fibrosis was determined with the Fibrosis-4 Index (FIB-4), using a cutoff of 1.45.[38] Depression symptomatology was assessed with the Center for Epidemiological Studies–Depression Scale (CES-D), with scores ≥16 used to classify the presence of depressive symptoms.[39] HIV viral loads and CD4 cell counts were obtained from medical records. HIV viral suppression was defined as having a plasma HIV RNA <200 copies/mL.

Statistical analyses

Descriptive statistics consisted of Chi-square tests for categorical variables and T-tests or one-way ANOVA for continuous variables, reported as No. (%) or mean ± standard deviation (SD). Comparison of distributions between baseline and 2-year follow-up consisted of paired-sample T-test and McNemar's test for continuous and categorical variables, respectively. The primary exposure of interest was food insecurity, and the primary outcome was cognitive impairment. Separate models were used to examine food insecurity by levels of severity: (1) using the traditional classification of food insecurity (low and very low food security) vs. food secure (full and marginal food security), (2) comparing marginal-to-very low food security to full food security, and (3)

comparing each of marginal, low, and very low food security to full food security. First, a cross-sectional analysis consisted of binary logistic regressions for cognitive impairment at baseline. Second, we performed binary logistic regressions for cognitive impairment at 2-year follow-up, controlling for baseline MMSE scores. In these analyses, we tested the effect of food insecurity at baseline and the effect of the frequency of food insecurity. We additionally performed multivariable regressions adjusting for sociodemographic characteristics (sex, race/ethnicity, income, household size), depressive symptoms, obesity, hyperglycemia, hypertension, liver fibrosis, and HIV and HCV infections. We tested for interaction effects between food insecurity and covariates; these were removed from models if nonsignificant. Results are reported as odds ratios (OR) and 95% confidence intervals (CI) and considered statistically significant at $P<0.05$, two-tailed. The data analysis for this paper was generated using SAS software, version 9.4. Copyright © 2002-2012 SAS Institute Inc., Cary, NC, USA.

Results

Population Characteristics

A total of 394 participants with 24-month follow-up data were included in this analysis. In the ongoing MASH cohort, the overall loss to follow-up has been 3% per year. The study population, as shown in Table 4.1, was largely comprised of economically disadvantaged (all below 200% of the federal poverty level), middle-aged, Black, and Hispanic individuals. At baseline, 104 (26.4%) participants were food-insecure, with low and VLFS in 52 (13.2%) and 52 (13.2%), respectively. An additional 64 (16.2%) participants reported marginal food security. At 2-year follow-up, 104

(26.4%) were food-insecure, with marginal, low and VLFS in 35 (8.9%), 50 (12.7%) and 54 (13.7%), respectively. Compared to food-secure participants, those who reported food insecurity had fewer household members (P=0.003), were more likely to use cocaine (P=0.002), and to report depressive symptoms (63.5 vs. 32.1%; P<0.0001). No differences were observed on metabolic parameters (BMI, obesity, hyperglycemia, and hypertension) or liver fibrosis. A comparison of sample characteristics by levels of food insecurity can be found in Table 4.2.

Food insecure participants tended to be less likely to be infected with HIV than food secure participants (54.8 vs. 65.5%, respectively; P=0.053); conversely, fewer PLWH tended to report food insecurity than HIV-uninfected participants (23.1 vs. 32.0%, respectively; P=0.053). Of the 247 (62.7%) PLWH, 246 (99.6%) were receiving ART and 214 (86.6%) were virally suppressed. Also, 43 (10.9%) participants were infected with HCV, including 21 (5.3%) who were coinfected with both HIV and HCV. No participants acquired HIV or HCV infection throughout the study period.

Prevalence of cognitive impairment

At baseline, 58 (14.7%) participants had cognitive impairment, including 39 food-secure and 19 food-insecure participants. At 2-year follow-up, 49 (12.4%) participants had cognitive impairment, including 20 participants who did not have cognitive impairment at baseline. However, overall, there was no significant change in MMSE scores ($t(393)=1.89$, P=0.06) or in the frequency of cognitive impairment ($\chi^2(1)=1.65$, P=0.20) between baseline and 2-year follow-up.

Cognitive impairment at baseline

Table 4.3 shows the results of logistic regressions for cognitive impairment at baseline. Overall, food insecurity was not associated with cognitive impairment. However, compared to full food security, VLFS was associated with 3.23 (95% CI: 1.08–9.65; *P*=0.04) times the risk for cognitive impairment. Similar results were obtained after adjusting for covariates.

In addition to these results, hypertension was associated with increased risk for cognitive impairment (OR=1.80, 95% CI: 1.01–3.22; *P*=0.048) and there was a marginal association with liver fibrosis (OR=1.67, 95% CI: 0.93–2.99; *P*=0.08). Depressive symptoms (OR=1.35, 95% CI: 0.77–2.36; *P*=0.3), BMI (OR=0.99, 95% CI: 0.95–1.03; *P*=0.7), obesity (OR=0.94, 95% CI: 0.54–1.65; *P*=0.8), hyperglycemia (OR=0.67, 95% CI: 0.32–1.38; *P*=0.3), HIV (OR=1.52, 95% CI: 0.83–2.79; *P*=0.2) and HCV (OR=1.63, 95% CI: 0.74–3.61: *P*=0.2) were not significantly associated with cognitive impairment. On the other hand, the risk for impairment was significantly higher among PLWH who were not virally suppressed (OR: 2.87, 95% CI: 1.15–7.18; *P*=0.02) compared to HIV-uninfected participants.

Cognitive impairment at 2-year follow-up

We performed logistic regression for cognitive impairment at 2-year follow-up, controlling for MMSE scores at baseline (Table 4.4). Baseline food insecurity was associated with cognitive impairment at 2-year follow-up (OR=2.28, 95% CI: 1.08–4.81; *P*=0.03). The association was also significant when comparing marginal-to-VLFS to full food security (OR=2.47, 95% CI: 1.2–5.10; *P*=0.01). Additionally, for every instance that

participants reported food insecurity in the past 12-months (range: 0 to 3 years for food insecurity at baseline and at 12- and 24-month follow-ups), the odds for cognitive impairment at follow-up increased one and a half times (95% CI: 1.08–2.10; *P*=0.02). In particular, persistent food insecurity – reporting food insecurity throughout the entire study – was significantly associated with increased risk for cognitive impairment compared to those who never reported food insecurity (OR: 4.18, 95% CI: 1.29–13.59; *P*=0.02). These relationships remained significant in the fully adjusted multivariable model. None of the covariates were significantly associated with cognitive impairment at 2-year follow-up.

To validate these findings, we repeated the analysis among participants who were not cognitively impaired at baseline (N=336), shown in Table 5.5. The results remained consistent. Baseline food insecurity was associated with 2.32 (95% CI: 0.91–5.93; *P*=0.08) times the odds for cognitive impairment. Likewise, having marginal-to-VLFS was significantly associated with increased risk for cognitive impairment at 2-year follow up compared to full food security (OR=4.24, 95% CI: 1.48–12.10; *P*=0.007). The frequency of food insecurity was associated with 1.53 (95% CI: 1.01–2.32; *P*=0.047) times the odds for impairment for every year that participants experienced FI, and persistent food insecurity was associated with 4.14 (95% CI: 1.09–15.70; *P*=0.04) times the odds for impairment compared to no food insecurity.

Discussion

This study of the MASH cohort found that food insecurity is a predictor of cognitive impairment, both at baseline and after a 2-year follow-up. This is the food insecurity study to establish an association between the frequency of food insecurity, particularly persistent FI, and cognitive decline over time. Furthermore, our findings suggest that even marginal food security is a risk factor for cognitive decline, despite it being traditionally classified as food secure. Food insecurity was also associated with depressive symptoms and cocaine use, but these did not seem to affect cognitive impairment in this study. While food insecurity did not show an impact on HIV treatment and viral load, PLWH who were not virally suppressed showed an increased risk for cognitive impairment at baseline compared to HIV-uninfected individuals. These findings are highly relevant, as food insecurity is intrinsically linked to mental health and substance abuse,[40] and can promote depression[9] and HIV disease progression.[23,24] It is possible that these factors, when compounded, may have additive or exponential effects on cognitive outcomes.

Both at baseline and at 2-year follow-up, VLFS more than tripled the odds for cognitive impairment compared to full food security. This finding is similar to those previously reported among homeless older adults[41] and middle-to-older aged Hispanics.[42] Two studies have also reported associations between food insecurity and cognitive impairment using NHANES data from older adults.[11,13] Studies that have performed cognitive batteries suggest that food insecurity mostly affects executive functions, such as processing speed, sustained attention, verbal fluency, working memory, and immediate learning ability.[13,14,42]

Over the course of 2-years, 20 participants developed cognitive impairment, but the overall prevalence of cognitive impairment in the sample did not change. This may be due to fluctuations in cognitive function as seen in dementia[43,44] and HIV-associated neurocognitive disorders.[45] Nonetheless, similar to the findings in an HIV-uninfected cohort by Wong et al.,[14] food insecurity at baseline was associated with cognitive impairment at 2-year follow-up and the greatest impact was seen in association with VLFS. However, we also found that any level of food insecurity at baseline, including marginal food security, was associated with cognitive impairment at follow-up. Moreover, when we excluded participants with cognitive impairment at baseline, even marginal food security was independently associated with cognitive impairment at follow-up compared to full food security. To the best of our knowledge, we are the first to show this association. Additionally, we are the first to show an association between the frequency of FI, particularly persistent FI, and cognitive impairment; those who consistently experienced food insecurity (reporting past 12-month food insecurity at baseline and at the two yearly follow-ups; equivalent to 3 years of FI) had the highest risk for cognitive impairment at 2-year follow-up. In the Women's Interagency HIV Study, persistent food insecurity (defined as two consecutive 6-month intervals of FI) was associated with increased risk for depression and poor mental well-being.[46]

Despite the high prevalence of food insecurity and cognitive impairments among PLWH, only two cross-sectional studies have previously examined how food insecurity may contribute to cognitive impairment in PLWH. Using the Montreal Cognitive Assessment (MoCA), Hessol et al. were unable to find a significant association between food insecurity and cognitive impairment, possibly related to the high prevalence of

impairment in that sample.[47] In contrast, Hobkirk et al. found a significant interaction effect between HIV and food insecurity on the neurocognitive performance of 61 PLWH and 36 HIV-uninfected middle-aged adults.[18] Among PLWH, food insecurity was associated with significantly higher deficits in the domains of speed of information processing, learning, and motor function, but not memory. There were no significant differences in domain deficit scores among HIV-uninfected participants, possibly due to the small sample. Our findings support the hypothesis that food insecurity may promote cognitive impairment in PLWH independent of adherence to ART and HIV viral load, but we were unable to detect a differential effect between those living with or without HIV possibly due to the vast majority (87%) being virally suppressed. Nonetheless, in our study, PLWH who were not virally suppressed were at a significantly increased risk for cognitive impairment than HIV-uninfected participants. More sensitive neurocognitive testing, such as that performed by Hobkirk et al., with larger sample sizes may be able to identify HIV-associated neurocognitive dysfunctions altered by food insecurity.

Interestingly, food insecurity was associated with depressive symptoms and cocaine use, which can contribute to cognitive dysfunction.[48,49] Notably, 40% of all participants, including 64% of food-insecure participants in this study reported depressive symptoms, which suggests a markedly higher prevalence of depression in this cohort than seen in other U.S. population-based studies of food-insecure individuals.[50,51] It is possible that compounding factors in this population, such as minority status, poverty, FI, chronic disease burden, substance use disorders, and HIV-related stigma, among others, may contribute to the high prevalence of depressive symptoms in this vulnerable population.

Additionally, food insecurity was associated with cocaine use, which has been associated with impaired processing speed and executive functioning.[52] Chronic substance abuse can lead to long-lasting cognitive impairments[49] and may have significant interactions with food insecurity and mental health.[40] For example, cocaine use may contribute to food insecurity by affecting impulse control and reward-based decision making.[53] Interestingly, neurocognitive impairment may play a role in poorer ART adherence among PLWH who use cocaine,[54] thereby furthering the risk for cognitive dysfunction.

It is worth mentioning that while in this study food insecurity was not associated with liver fibrosis (measured with the FIB-4 Index), this association has been made by Golovaty et al. using NHANES data.[32] We have also found food insecurity to be associated with advanced liver fibrosis when measured with magnetic resonance elastography;[55] however, this assessment was not available for all the participants in this analysis. In this study, we observed a trend for liver fibrosis in association with cognitive impairment. Notably, liver disease is a major cause of morbidity and mortality in PLWH[56] and has been associated with cognitive impairments in PLWH.[57,58]

Although the exact mechanisms remain unknown, there are several potential ways by which food insecurity may contribute to cognitive impairment. In resource-rich settings, food insecurity is associated with maladaptive eating behaviors and poor diet quality, although overall energy intake may not be affected.[59] Consequently, food insecurity may result in deficiencies of essential nutrients for brain and cognitive function, such as B-vitamins and *n*-3 polyunsaturated fatty acids, as well as dietary patterns that promote neuroinflammatory processes.[60,61] Our finding that persistent food insecurity was associated with cognitive decline, for example, may be due in part to long-

term nutritional inadequacies. A “neuroprotective dietary pattern,” consisting of antioxidant- and polyphenol-rich foods including fruits, vegetables, monounsaturated fats, and *n*-3 fatty acids (i.e., Mediterranean diet),[61,62] may be inaccessible to people who experience food insecurity. Food insecurity can also contribute to cognitive dysfunction through comorbidities directly affected by diet, such as cardiovascular disease and diabetes. These conditions may be aggravated by poor disease self-management as a result of monetary constraints, such as having to choose between food or medication. Our findings related to food insecurity persistence may be particularly relevant, as persistent food insecurity has been associated with increased cost-related medication non-adherence among older adults.[63] Interestingly, food insecurity has also been associated with shorter leukocyte telomere length in U.S. adults ages 25–45 years, suggesting that food insecurity may advance aging.[64]

Nevertheless, food insecurity is a modifiable risk factor for cognitive impairment. Thus, improving access to sufficient nutritious foods and improving dietary patterns among economically disadvantaged households may allow for lifestyle changes that improve nutritional status and reduce comorbidities, ultimately delaying cognitive decline. In the United States, several food-assistance programs have been implemented to reduce FI, the largest of which is the Supplemental Nutrition Assistance Program (SNAP), also known as food stamps. Although most eligible individuals participate in the program (84% in 2017),[65] many SNAP recipients remain food-insecure even after receiving benefits, as these are often insufficient to relieve monetary constraints.[66] Furthermore, the current criteria for eligibility prevent many individuals from obtaining SNAP benefits.[67] Therefore, there is a need for improved interventions to secure access to

sufficient nutritious foods among socioeconomically disadvantaged groups. Given the consistent findings linking food insecurity to cognitive function, food assistance programs should account for cognitive impairments when planning benefits. Indeed, cognitive impairment has the potential to exacerbate food insecurity by decreasing functional abilities,[68] thereby limiting work opportunities and income, the ability to navigate processes to apply for food assistance programs, and the ability for disease self-management. However, the effect of cognitive impairments on food security status is an interesting area for future research that has not yet been explored.

Limitations of this study include the use of MMSE, a screener that has low sensitivity for identifying mild HIV-associated cognitive disorder. However, in light of our findings, food insecurity may be a clinically relevant risk factor for severe cognitive impairments and dementia. Longitudinal studies using more sensitive neuropsychological batteries and repeated measures of food security will help further our understanding of the long-term effects of FI, including its severity, frequency, and persistence, on cognitive decline. Neuroimaging studies are needed to identify specific brain structures altered by food insecurity. Potential mediators, such as dietary patterns, vascular risk factors, psychiatric comorbidities, and chronic stress should be examined.

Conclusion

Food insecurity is a significant risk factor for cognitive impairment, particularly among individuals who experience food insecurity frequently or persistently. Attention should be paid to PLWH, a population that is disproportionately affected by food insecurity and cognitive dysfunction. Screening for food insecurity and interventions to

secure access to sufficient nutritious foods may help delay cognitive decline among socioeconomically disadvantaged individuals.

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Table 4.1. Population Characteristics at Baseline

Parameter	Total[1] (N=394)	Food-secure[1] (N=290)	Food-insecure[1] (N=104)	P-value[2]
Age, years	53.9 ± 7.9	53.9 ± 8.1	54.2 ± 7.0	0.72
Sex (male)	211 (53.6)	155 (53.5)	56 (53.9)	0.94
Race/ethnicity				
Black non-Hispanic	283 (71.8)	218 (75.2)	65 (62.5)	
White Hispanic	55 (14.0)	37 (12.8)	18 (17.3)	0.07
White non-Hispanic	25 (6.4)	17 (5.9)	8 (7.7)	
Multiracial/other	31 (7.9)	18 (6.2)	13 (12.5)	
Income (below poverty)	309 (78.4)	227 (78.3)	82 (78.9)	0.90
Household size	1.9 ± 1.3	2.0 ± 1.4	1.6 ± 1.0	0.003
Education				
Less than High-School	175 (44.4)	131 (45.2)	44 (42.3)	
High-School or GED	12 (31.7)	92 (31.7)	33 (31.7)	0.82
More than High-School	94 (23.9)	67 (23.1)	27 (26.0)	
Substances				
AUDIT >8	100 (25.4)	72 (24.8)	28 (26.9)	0.67
Smoker (tobacco)	212 (53.8)	151 (52.1)	61 (58.7)	0.25
Cannabis	119 (30.2)	84 (29.0)	35 (33.7)	0.37
Cocaine	159 (40.4)	104 (35.9)	55 (52.9)	0.002
Opioids	40 (10.2)	27 (9.3)	13 (12.5)	0.36
Metabolic				
BMI, kg/m^2	30.0 ± 7.1	30.1 ± 7.3	29.7 ± 6.3	0.65
Obesity	175 (44.4)	129 (44.5)	46 (44.2)	0.96
Hyperglycemia	90 (22.8)	66 (22.8)	24 (23.1)	0.95
Hypertension	210 (53.4)	151 (52.3)	59 (56.7)	0.43
Hepatic				
Liver fibrosis (FIB-4>1.45)	112 (28.4)	82 (29.3)	30 (28.9)	0.91
HIV	247 (62.7)	190 (65.5)	57 (54.8)	0.053
On ART	246 (99.6)	190 (100.0)	56 (98.3)	0.07
<200 copies/mL	214 (86.6)	168 (88.4)	46 (80.7)	0.13
CD4 cells/mL[3]	602 ± 343	605 ± 352	593 ± 315	0.82
HCV	43 (10.9)	31 (10.7)	12 (11.5)	0.81
HIV/HCV coinfection	21 (5.3)	15 (5.2)	6 (5.8)	0.82
Depressive symptoms (CES-D >16)	159 (40.4)	93 (32.1)	66 (63.5)	<0.0001

Abbreviations: ART, antiretroviral therapy; CES-D, Center for Epidemiological Studies–Depression Scale

[1] Values are n (%) or mean ± SD

[2] Chi-square tests for categorical factors and T-test for continuous factors

[3] CD4 cell count data on *n*=232

Table 4.2. Logistic Regressions for Cognitive Impairment (MMSE ≤24) at Baseline (N=394)

Model	Parameter	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)[1]	P-value
1	Food insecurity[2]	1.59 (0.85–2.97)	0.15	1.56 (0.78–3.14)	0.21
2	Full vs. marginal, low, and very low food security	1.11 (0.63–1.95)	0.72	1.05 (0.56–1.98)	0.89
3	Levels of food security				
	Full	Reference	-	Reference	-
	Marginal	1.47 (0.59–3.65)	0.41	1.59 (0.61–4.14)	0.34
	Low	1.45 (0.47–4.50)	0.52	1.29 (0.39–4.32)	0.68
	Very low	3.23 (1.08–9.65)	0.04	4.16 (1.28–13.55)	0.02

[1] Adjusted for age, years of education, race/ethnicity, sex, income, household size, obesity, hyperglycemia, hypertension, depressive symptoms, liver fibrosis, and HIV/HCV infection
[2] Food insecure (low and very low food security) vs. food secure (full and marginal food security)

Table 4.3. Logistic Regressions for Cognitive Impairment (MMSE ≤24) at 2-Year Follow-Up (N=394)

Model	Category	OR (95% CI)[1]	P	Adjusted OR (95% CI)[2]	P
1	Food insecurity at baseline[3]	2.28 (1.08–4.81)	0.03	4.21 (1.66–10.68)	0.002
2	Full vs. marginal, low, and very low food security at baseline	2.47 (1.20–5.10)	0.01	4.41 (1.88–10.35)	0.001
3	Levels of food security at baseline				
	Full	Reference	-	Reference	-
	Marginal	2.01 (0.86–4.70)	0.11	2.31 (0.92–5.80)	0.08
	Low	2.80 (1.21–6.49)	0.02	3.34 (1.32–8.43)	0.01
	Very low	3.02 (1.23–7.41)	0.02	4.62 (1.67–12.80)	0.003
4	Frequency of FI, per year	1.50 (1.08–2.10)	0.02	1.85 (1.23–2.77)	0.003
5	0 years of FI	Reference	-	Reference	-
	1 year of FI	1.62 (0.61–4.30)	0.33	2.37 (0.82–6.89)	0.11
	2 years of FI	2.10 (0.85–5.16)	0.11	3.23 (1.06–9.86)	0.04
	3 years of FI	3.69 (1.15–11.83)	0.03	6.77 (1.72–26.68)	0.006

Abbreviations: FI, food insecurity
[1] Adjusted for MMSE scores at baseline
[2] Adjusted for age, years of education, MMSE scores at baseline, race/ethnicity, sex, income, household size, obesity, hyperglycemia, hypertension, depressive symptoms, liver fibrosis, and HIV/HCV infection
[3] Food insecure (low and very low food security) vs. food secure (full and marginal food security)

CHAPTER V: ASSOCIATION OF FOOD INSECURITY WITH IMMUNE ACTIVATION

Abstract

Background: Persistent immune activation is a hallmark of HIV infection and thought to play a role on chronic diseases in people living with HIV (PLWH). Food insecurity is disproportionately prevalent in PLWH and is associated with adverse health outcomes. We determined whether food insecurity was associated with increased immune activation in PLWH.

Methods: Plasma levels of sCD14, sCD27, and sCD163 were quantified in 323 PLWH on antiretroviral therapy from the Miami Adult Studies on HIV (MASH) Cohort. The U.S. Household Food Security Survey was used to assess food insecurity; defined as marginal, low, or very low food security. Dietary intakes were assessed with 24-hour recalls.

Results: Nearly half of participants were food insecure (42.7%) and most (85.5%) had suppressed HIV viral loads (<200 copies/mL). Food insecurity was independently associated with higher levels of sCD14 and sCD27. The severity of food insecurity directly correlated with sCD14 (rho=0.151; p=0.006) and sCD27 (rho=0.154; p=0.006), and showed a tendency to modify the relationship between CD4 cell count and sCD163 (F=2.35, p=0.07). Very low food security was significantly associated with increased sCD163 levels among those with lower CD4 cell count (B=0.534, SE=0.22, t=2.40, p=0.02).

Conclusions: Food insecurity may promote immune activation in PLWH, suggesting a biological link between food insecurity and chronic disease among PLWH. Improving

financial security and access to high-quality foods could reduce the high burden of disease in this highly vulnerable population. Future research should consider diet quality and gut-permeability as potential mediators of food insecurity and immune activation.

Introduction

Infection with the human immunodeficiency virus (HIV) results in chronic immune activation and progressive immunodeficiency.[1,2] Modern antiretroviral therapy (ART) has been effective at controlling viral replication and improving longevity and quality of life for people living with HIV (PLWH).[3,4] Nonetheless, persistent immune activation and inflammation, even with virologic suppression,[5,6] contribute to high rates of chronic comorbidities among PLWH, such as cardiovascular disease, type 2 diabetes, liver disease, and non-AIDS-defining cancers.[7-15] Consequently, non-AIDS-defining illnesses have become the predominant causes of morbidity and mortality among PLWH in settings where ART is readily available.[16-18] Moreover, PLWH suffer from higher rates of multi-morbidities than the general population.[19,20]

In addition to the immune response to HIV infection, many social and lifestyle factors, such as sedentary lifestyle, poor diet quality, and substance abuse, can contribute to inflammation and chronic diseases in PLWH. Food insecurity (FI) is a social determinant of health that refers to a lack of dependable access to nutritious foods, resulting in dependence on low-cost foods and poor quality diets.[21-25] In the United States, approximately 10.5% of the population experienced food insecurity at some point during 2019, with significantly higher rates among minority-headed households and those with incomes below 185% of the federal poverty line.[26] Food insecurity also

disproportionately affects PLWH in both high- and low-resource settings[27] and has been associated with several adverse health outcomes in the general U.S. population[28-34] and PLWH.[35-38] There are several nutrition-related consequences of HIV infection, including increased metabolic demands and altered gastrointestinal absorptive function. Food insecurity further increases the risk for compromised nutritional status (e.g. malnutrition, micronutrient deficiencies).[39]

Studies using data from the National Health and Nutrition Examination Survey (NHANES) have established associations of food insecurity with pro-inflammatory diets [40] and elevated C-reactive protein (CRP).[41,42] Recently, the Women's Interagency HIV Study (WIHS) has associated food insecurity with elevated levels of pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor receptor 1 (TNFR1),[43] as well as T-cell activation (%CD38+HLADR+) in women living with HIV.[44] These studies point to biological mechanisms between food insecurity and chronic disease. However, more studies are needed to investigate the association between food insecurity and immune activation – a precursor to chronic disease – in PLWH. Therefore, we aimed to determine whether food insecurity was associated with increased monocyte/macrophage (sCD14 and sCD163) and lymphocyte (sCD27) activation in PLWH.

Methods

Data from 325 participants from the Miami Adult Studies on HIV (MASH) Cohort were cross-sectionally analyzed for this study. Eligibility in the MASH cohort includes age of 40 years or older, documented HIV and hepatitis C virus (HCV) status (positive or negative), and seronegative for hepatitis B virus. All participants provided written

informed consent for participation in the study and release of medical information. Participants who were HIV-uninfected, HCV-infected, or not taking ART were excluded from this analysis. The protocols for the study were approved by the Institutional Review Board at Florida International University.

Primary outcomes: Biomarkers of immune activation

Plasma levels of sCD14, sCD27, and sCD163 were quantified by analyte-specific bead-based Luminex Multiplex immunoassays (EMD Millipore Corporations). Soluble CD14 (sCD14) is shed by CD14-expressing monocytes after stimulation by lipopolysaccharide (LPS, also known as endotoxin).[45] Consequently, sCD14 serves as a marker of monocyte activation, as well as an indirect, yet non-specific marker of microbial translocation.[45,46] Elevated levels of sCD14 and sCD163 persist during effective suppressive ART and correlate with HIV disease progression.[45,47,48] Shedding of sCD163 in plasma has also been implicated in chronic inflammatory conditions.[49,50] Soluble CD27 is secreted by antigen-stimulated T-cells, thus considered a direct marker of early-stage T-cell activation. Levels of sCD27 are responsive to ART but remain elevated in HIV infection, correlate with HIV disease progression, and have been particularly associated with AIDS-associated lymphoma.[5,51-54]

Food insecurity

The USDA's Household Food Security Survey was used to assess food insecurity.[26] The 18-item instrument determines food security through questions related to conditions and behaviors that characterize food insecure households. Similar to others,[35,43,44] we defined food insecurity as having marginal, low, or very low food security, whereas participants with full food security were considered food-secure.

Diet recalls

Twenty four-hour dietary recalls were collected by trained research staff using the Multiple Pass Method.[55] The participants were provided with visual aids to improve the accuracy of data. Dietary analysis was conducted via NutriBase Pro software, Version 17. Copyright © 1986-2020 Cybersoft Inc. Intakes of total energy, energy from protein, carbohydrates, and fats, and grams of saturated fatty acids (SFAs) and fiber were considered potential confounders.

Additional covariates

Sociodemographic data were self-reported. As both food insecurity and immune activation are associated with several chronic conditions, we incorporated several covariates as potential confounders for the relationship between food insecurity and immune activation. HIV viral load and CD4 cell count were obtained from participants' medical records. Participants were considered virally suppressed if HIV RNA was below 200 copies/mL. Height, weight, vital signs, and fasting blood were obtained for all participants. Body mass index (BMI) was calculated and reported as 5 kg/m^2 increments for more clinically relevant interpretation. Hyperglycemia (fasting plasma glucose ≥100 mg/dL), hypertriglyceridemia (TG ≥150 mg/dL), and hypertension (≥130 mm Hg systolic or ≥85 mm Hg diastolic blood pressure) were determined. Liver fibrosis was assessed with the Fibrosis-4 Index (FIB-4) ≥1.45, calculated from age, platelets, and serum liver enzymes. Systemic inflammation was measured with high-sensitivity C-reactive protein (hs-CRP). Substance use, including cocaine, cannabis, and heroin, was self-reported and confirmed with urine toxicology (American Bio Medica, Kinderhook, NY). Cigarette

smoking was self-reported and hazardous drinking was assessed with the Alcohol Use Disorders Identification Test (AUDIT), using a cutoff of 8.[56]

Statistical analysis

The data analysis for this paper was performed using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002-2012 SAS Institute Inc. The data were analyzed for outliers and assumptions of normality. Descriptive statistics were reported as No. (%) and mean ± standard deviation (or median [interquartile range, IQR] if not normally distributed). Participants were grouped as food-secure and food-insecure (dichotomous), or by levels of food security (4 levels, multicategorical). Group differences were tested with Chi-square tests, T-tests, and one-way ANOVA; due to skewed distributions for sCD14, sCD27, and sCD163, Wilcoxon rank-sum and Kruskal-Wallis tests were performed. Due to the direction of the hypotheses (i.e., food insecurity is associated with higher levels of immune activation), one-sided p-values were reported for Wilcoxon rank-sum tests. Spearman correlations were used to determine the relationships between markers of immune activation and levels of food insecurity. To assess the relationship between food insecurity and immune activation, linear regressions were performed using log-transformed values of the primary outcomes. Potential confounders were explored with linear regressions, including sociodemographic characteristics (e.g., age, sex, race/ethnicity, income, and household size), HIV viral load and CD4 cell count, metabolic and comorbid parameters, substance use, and dietary intake. Parameters that were Statistical significance was set at an alpha level of 0.05 and two-sided p-values are reported unless otherwise specified.

Results

Characteristics

Sample characteristics are shown in Table 5.1. Of the 323 participants in the study, 185 (57.3%) were food secure and 138 (42.7%) were food insecure, with 53 (16.4%), 43 (13.3%), and 42 (13.0%) participants reporting marginal, low, and very low food security, respectively. The participants had a mean age of 53.3±7.8 years, and were predominantly male (n=197, 61.0%) and Black non-Hispanic (n=207, 64.1%) or White Hispanic (n=65, 20.1%). Most households had between 1 and 2 members, with a mean annual income of $13,315 and 73.1% (*n*=233) fell below the federal poverty level (https://aspe.hhs.gov/2020-poverty-guidelines). Most participants had a maximum education of high-school or less (n=226, 70.0%) and were disabled (n=205, 63.5%) or unemployed (n=84, 26.0%).

Only 47 (14.5%) participants did not have suppressed HIV viral loads. The mean CD4 cell count was 602±333 cells/μL, with only 23 (7.1%) participants who had CD4 cell count below 200 cells/μL (indicative of AIDS). The mean BMI was 29.2±6.1 kg/m^2, with 126 (39.0%) of participants classifying as obese, and mean energy intake was 1,967±1,150 kcals. Additionally, 79 (24.5%) had hyperglycemia, 99 (30.7%) had elevated triglycerides, and 162 (50.2%) had hypertension.

Associations with food insecurity

Very low food security was associated with non-suppressed HIV viral load (p=0.02) but not CD4 cell count (p=0.9); data not shown. Food insecurity was associated with a higher percent of total energy intake from fats compared to food security (37.3±10.2 vs. 34.5±12.3%; p=0.04). Neither BMI nor total energy intake differed

between the two groups. No other significant differences in characteristics were observed between food secure and insecure participants, although trends for lower age and lower incomes, as well as higher hs-CRP, hazardous drinking, and use of cannabis were noted among food insecure participants ($p<0.1$).

Distribution of immune activation biomarkers

Table 5.2 shows the median values of sCD14, sCD27, and sCD163. Food insecurity was associated with higher levels of sCD14 (one-sided $p=0.005$) and sCD27 (one-sided $p=0.003$), but not sCD163 (one-sided $p=0.3$), compared to food security. When examining the markers of immune activation by levels of food insecurity, borderline differences for sCD14 ($p=0.05$) and sCD27 ($p=0.051$) were noted. The lowest levels of sCD14 and sCD27 were found among participants with full food security. Additionally, having a non-suppressed HIV viral load was associated with higher levels of sCD14 (one-sided $p=0.009$), sCD27 (one-sided $p<0.0001$), and sCD163 (one-sided $p=0.032$).

The severity of food insecurity was directly correlated with sCD14 (rho=0.151; $p=0.006$) and sCD27 (rho=0.154; $p=0.005$), but not with sCD163 (rho=0.039; $p=0.5$); shown in Table 5.3.

Factors associated with immune activation

We performed univariate linear regressions on log-transformed sCD14, sCD27, and sCD163 to determine potential confounders for the relationship between food insecurity and markers of immune activation (Table 5.4). Older age, race/ethnicity, higher BMI, hypertriglyceridemia, hypertension, higher hs-CRP, and liver fibrosis were also associated with markers of immune activation. Higher CD4 cell counts were associated

with lower sCD27 levels. Trends were observed with cigarette smoking and cocaine use. Dietary intakes of total energy, macronutrients, SFAs, and fiber were not associated with any of the outcomes.

In multiple regressions (Table 5.5), food insecurity remained significantly associated with sCD14 and sCD27 after adjustment for confounders. While food insecurity and CD4 cell counts were not independently associated with sCD163 levels, the severity of food insecurity showed a tendency to moderate the relationship between CD4 cell count and sCD163 (F=2.35, p=0.07). As shown in Table 5.6, compared to full food security, VLFS was significantly associated with increased sCD163 levels when adjusted for the interaction with CD4 cell count (B=0.534, SE=0.22, t=2.40, p=0.02). CD4 cell counts were inversely associated with sCD163 levels only among participants with VLFS (B=-0.086, SE=0.03, t=-2.60, p=0.01).

Discussion

Food insecurity is a social determinant of health that disproportionately affects U.S. minorities[26] and PLWH[27] and is associated with several chronic conditions and mortality among U.S. adults.[28-34] In this study, we show a direct association between food insecurity and immune activation, which is thought to play a key role in HIV disease progression, as well as the development and progression of chronic conditions.[7-15] More specifically, food insecurity was independently associated with increased plasma levels of sCD14 and sCD27, which were also directly correlated with the severity of food insecurity. Our findings suggest that the severity of food insecurity could moderate the relationship between CD4 cell count and sCD163; together, VLFS and low CD4 cell

count predicted higher sCD163 levels. The research presented herein was conducted with PLWH from the MASH Cohort, a vulnerable population that is largely comprised of socioeconomically disadvantaged Black and Hispanic adults who are engaged in HIV care and virally suppressed. At least some level of food insecurity was reported by nearly half of the participants (43%). We also found higher markers of immune activation in association with HIV viremia, lower CD4 cell count, older age, race/ethnicity, higher BMI, hypertriglyceridemia, hypertension, higher hs-CRP, and liver fibrosis. Our findings, therefore, provide insights into a potential link between food insecurity and adverse health outcomes among low-income PLWH who are on suppressive ART.

Notably, the association between food insecurity and sCD14 suggests increased microbial translocation – a major pathway of immune activation in PLWH.[57] The Western diet, characterized by high intakes of meats, refined grains, and added sugars, has also been associated with higher sCD14 concentrations.[58] In turn, elevated sCD14 has been associated with several chronic conditions, including cardiovascular disease,[59-61] chronic kidney disease,[62] alcoholic and nonalcoholic liver disease,[63-67] dementia,[68] HIV-associated neurocognitive disorders,[69] and mortality in PLWH.[70,71]

Food insecurity may affect gut integrity by altering microbiome composition. The poor-quality diets associated with food insecurity may lead to alterations in the diversity of gut microbiota and loss of mucosal barrier defenses, resulting in increased gut permeability, microbial translocation, and metabolic endotoxemia.[72-75] High-fat diets, in particular, have been shown to alter gut microbiota and disrupt the intestinal barrier, inducing systemic inflammation.[74,76] Indeed, in a study of 149 PLWH and 69 uninfected controls, intakes of SFAs and added sugars were associated with intestinal fatty acid

binding protein (I-FABP), a marker of intestinal barrier dysfunction that also correlated with sCD163 and LPS.[77] Similarly, among HIV-infected women, consuming 3 servings of high-fat foods per day was associated with higher IL-6.[43] While we did not find significant relationships between diet and immune activation, food-insecure participants had higher intakes of fat than food-secure participants. Additionally, more than half of participants (53%) consumed over 10% of total energy from saturated fats, exceeding current recommendations.[78] On the other hand, fiber plays an important role in maintaining gut integrity, as certain undigested carbohydrates are metabolized by gut microbes producing beneficial short-chain fatty acids (SCFAs).[79-81] Food insecurity in the United States is characterized by diets that are high in refined carbohydrates and simple sugars, thus low in fermentable fibers.[21,24] We did not find a significant difference in fiber intake between food secure and insecure participants; yet, fiber intakes in these participants of the MASH cohort (mean 13.2±10.7 g) were well-below the recommendations for adults over 50 years of age (22.4 g for females and 28 g for males).[78]

The association between food insecurity and sCD27 may have other implications. CD27 is a transmembrane glycoprotein belonging to the tumor necrosis factor receptor (TNF-R) family. Although the immunological function of sCD27 has not been fully elucidated, circulating sCD27 induces immunoglobulin G (IgG) production[82] and is highly implicated in autoimmune diseases and lymphomas,[83,84] including AIDS-associated lymphoma.[51,52] Thus, our findings may reflect an increased risk for cancer in association with food insecurity, which is consistent with previous observations.[85] With regards to sCD163, we found that VLFS was associated with increased levels of sCD163

once we accounted for an interaction effect between the severity of food insecurity and CD4 cell count. The results therefore suggest that the severity of food insecurity may moderate the relationship between immune activation and immunodeficiency in PLWH. Interestingly, VLFS was associated with not having a suppressed viral load, but not with CD4 cell count. Nonetheless, lower CD4 cell count significantly predicted higher sCD163 levels in participants with VLFS, which could be in part explained by poor engagement in treatment.[35,86] Elevated sCD163 persists in PLWH despite suppressive ART unless treated early in the infection[47,48] and has been associated with mortality.[87] Additionally, elevated sCD163 has been highly associated with states of chronic inflammation, such as obesity,[88] cardiovascular risk,[89] type 2 diabetes,[90] the metabolic syndrome,[91] and nonalcoholic fatty liver disease.[67]

The findings in this report are consistent with previous research. Population-based studies have established an association between food insecurity and CRP, a marker of systemic inflammation.[41,42] Notably, Gowda et al. showed that the relationship between food insecurity and CRP was partially mediated by elevated white blood cell counts, suggesting a potential role of immune activation.[41] Recently, data from the WIHS cohort has shown that food insecurity was associated with elevated inflammation (IL-6 and TNFR1),[43] as well as CD4+ and CD8+ activation (%CD38+HLADR+) and other markers of immune dysregulation in women living with HIV who were mostly virally suppressed.[44] These results, as well as the ones reported herein, point to biological pathways between food insecurity and chronic disease. For example, among 121 Latinos with type 2 diabetes, increased stress (cortisol) and inflammation (CRP) partially mediated the relationship between food insecurity and insulin resistance, the precursor for

type 2 diabetes.[92] In another study, food insecurity was associated with the primary allostatic system (neuroendocrine and inflammatory), which incorporated serum cortisol and CRP as biomarkers of stress and inflammation, respectively.[93] While our data did not show an association between food insecurity and hs-CRP, hs-CRP correlated with sCD14 and showed a trend with sCD27.

Diet quality may explain some of the relationship between food insecurity, immune-activation and inflammation, and chronic disease. Indeed, food insecurity often leads to dependence on low-cost foods, resulting in poor-quality diets that are high in fats, simple sugars, and refined carbohydrates, but low in essential nutrients and fiber.[21-25] Micronutrients play critical roles in immunity and their deficiency can contribute to immune activation and inflammation.[94,95] Moreover, Bergmans et al. reported on the association between food insecurity and inflammatory potential of the diet, showing a dose-response relationship between the severity of food insecurity and the Dietary Inflammatory Index scores.[40] In our study, we found that levels of sCD14 and sCD27 were directly correlated with the severity of food insecurity. One may surmise that as the severity of food insecurity increases, so does the immuno-inflammatory potential of the diet.

However, diet alone does not entirely explain the relationship between food insecurity and health outcomes.[33,37] Other potential mechanisms include poor disease management,[96] chronic stress,[92,97] and competing financial constraints, such as having to make tradeoffs between food and medication[98] while having increased healthcare expenditures.[99,100] Food insecurity is additionally associated with high rates of alcohol and substance abuse,[101-106] which may also contribute to poor health. Indeed, we observed

trends between cigarette smoking and sCD27 levels, as well as between cocaine use and sCD14 levels. Both smoking and cocaine have been associated with immune activation in PLWH.[107-109] For example, use of stimulants (cocaine and methamphetamine) was associated with increased plasma levels of neopterin – a marker of immune activation – among ART-treated PLWH.[109] We found a higher prevalence of hazardous drinking among food insecure participants; however, hazardous drinking was not associated with immune activation. Previous studies have shown contrasting results in regard to excessive drinking and sCD14 levels in PLWH.[110-112]

To summarize, food insecurity was associated with increased biomarkers of immune activation sCD14, sCD27, and sCD163 in PLWH from the MASH cohort. The present study is strengthened by the use of validated assessments among a well-characterized cohort of PLWH. While we controlled for intakes of energy, macronutrients, SFAs, and fiber, future studies may consider the impact of diet quality and microbial translocation on the relationship between food insecurity and immune activation. The cross-sectional design does not allow to establish causality and it is possible that some of the effects observed may be related to unmeasured factors. However, our findings remained consistent even after controlling for several sociodemographic and comorbid confounders. Our findings are also consistent with prior research. Longitudinal studies may provide a more thorough understanding of the causal and temporal relationships between food insecurity, immune activation, and chronic disease outcomes.

Conclusions

Food insecurity was associated with markers of immune activation in the MASH cohort, suggesting a biological link between food insecurity and chronic disease among PLWH. Our findings suggest that improving financial security, access to high-quality foods, and nutrition knowledge could lead to significant health benefits in this highly vulnerable population. Additionally, screening for food insecurity may be a cost-efficient method of risk-assessment and reducing the high burden of disease among PLWH. Mechanisms for the effect of food insecurity on immune activation remain to be elucidated. Future research should consider diet quality and gut-permeability as potential mediators of food insecurity and immune activation.

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Table 5.1. Characteristics of Study Participants

	Total (N=323)	Food Secure (N=185)	Food Insecure (N=138)	
	No. (%) Mean ± SD	No. (%) Mean ± SD	No. (%) Mean ± SD	P
Age, years	56.3 ± 7.8	54.0 ± 7.0	52.3 ± 8.8	.072[a]
Sex, male	197 (61.0)	113 (61.1)	84 (60.9)	.969[b]
Race/ethnicity				
Black non-Hispanic	207 (64.1)	123 (66.5)	84 (60.9)	.724[b]
White non-Hispanic	20 (6.2)	10 (5.4)	10 (7.3)	
White Hispanic	65 (20.1)	36 (19.5)	29 (21.0)	
Multiracial/other	31 (9.6)	16 (8.7)	15 (10.9)	
Household size	1.9 ± 1.4	2.0 ± 1.4	1.8 ± 1.4	.219[a]
Annual household income ($)	13,315 ± 11,206	14,211 ± 12,515	12,115 ± 9,069	.082[a]
Below federal poverty level	236 (73.1)	137 (74.1)	99 (71.7)	.643[b]
Education				
Less than High-School	128 (39.6)	66 (35.7)	62 (44.9)	.159[b]
High-School or GED	98 (30.3)	63 (34.1)	35 (25.4)	
More than High-School	97 (30.0)	56 (30.3)	41 (29.7)	
Employment				
Employed	34 (10.5)	21 (11.4)	13 (9.4)	.584[b]
Disabled	205 (63.5)	113 (61.1)	92 (66.7)	
Otherwise unemployed	84 (26.0)	51 (27.6)	33 (23.9)	
Metabolic				
BMI (kg/m^2)	29.2 ± 6.1	29.4 ± 6.4	28.9 ± 5.7	.436[a]
Obesity	126 (39.0)	74 (40.0)	52 (37.7)	.673[b]
Hyperglycemia	79 (24.5)	49 (26.5)	30 (21.7)	.326[b]
Hypertriglyceridemia	99 (30.7)	58 (31.4)	41 (29.7)	.752[b]
Hypertension	162 (50.2)	94 (50.8)	68 (49.3)	.785[b]
hs-CRP	4.9 ± 8.9	4.1 ± 5.7	6.0 ± 11.9	.082[a]
Substance use				
Hazardous drinking	60 (18.6)	28 (15.1)	32 (23.2)	.066[b]
Cigarette smoking	150 (46.4)	81 (43.8)	69 (50.0)	.268[b]
Cocaine	108 (33.4)	58 (31.4)	50 (36.2)	.358
Cannabis	94 (29.1)	47 (25.4)	47 (34.1)	.090[b]
Heroin	32 (9.9)	17 (9.2)	15 (10.9)	.617[b]
HIV				
HIV RNA <200 copies/mL	276 (85.5)	163 (88.1)	113 (81.9)	.117[b]
CD4 cells/μL	602 ± 333	610 ± 322	591 ± 349	.610[a]
CD4 <200 cells/μL	23 (7.1)	10 (5.4)	13 (9.4)	.165[b]
Dietary				

	Total (N=323)	Food Secure (N=185)	Food Insecure (N=138)	
	No. (%) Mean ± SD	**No. (%) Mean ± SD**	**No. (%) Mean ± SD**	**P**
Total energy (kcals)	1967 ± 1150	1933 ± 1169	2012 ± 1125	.546[a]
Energy from protein (kcal)	327 ± 208	332 ± 228	321 ± 178	.653[a]
% energy from protein	17.5 ± 7.0	18.0 ± 7.8	16.9 ± 5.9	.166[a]
Energy from carbohydrate (kcal)	925 ± 631	916 ± 629	938 ± 635	.765[a]
% energy from carbohydrate	46.7 ± 13.1	47.3 ± 14.1	45.9 ± 11.8	.358[a]
Fiber (g)	13.6 ± 12.3	12.9 ± 11.2	14.6 ± 13.7	.246[a]
Energy from fat (kcal)	710 ± 485	678 ± 489	754 ± 479	.173[a]
% energy from fat	35.6 ± 11.5	34.5 ± 12.3	37.3 ± 10.2	**.040[a]**
SFAs (g)	25.3 ± 21.8	24.1 ± 21.8	27.1 ± 21.8	.228
SFAs, ≥10% total energy	172 (53.3)	100 (54.1)	72 (52.2)	.738

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; SFAs, saturated fatty acids
[a] T-test
[b] Chi-square test

Table 5.2. Distribution of Markers of Immune Activation[1]

	N	sCD14 (ng/mL) Median (IQR)	sCD27 (ng/mL) Median (IQR)	sCD163 (ng/mL) Median (IQR)
All participants	323	1028.5 (801.5, 1371.9)	8.5 (6.2, 11.4)	541.4 (349.0, 961.2)
Food secure	185	956.9 (731.1, 1320.2)	8.1 (5.8, 10.5)	532.8 (370.7, 874.6)
Food insecure[a]	138	1115.2 (843.3, 1432.6)	9.3 (6.9, 12.1)	551.6 (340.9, 1046.4)
p-value[b]		**0.005**	**0.003**	0.311
Full FS	185	956.9 (731.1, 1320.2)	8.1 (5.8, 10.5)	532.8 (370.7, 874.6)
Marginal FS	53	1042.5 (837.0, 1395.8)	9.1 (6.9, 11.5)	517.5 (370.7, 874.6)
Low FS	43	1117.8 (909.5, 1461.4)	8.9 (6.8, 11.6)	567.5 (310.2, 968.4)
Very low FS	42	1171.8 (814.7, 1437.8)	9.6 (6.4, 13.5)	598.7 (344.5, 1070.2)
p-value[c]		0.050	0.051	0.745
Virally Suppressed	276	997.6 (785.9, 1335.2)	8.3 (6.0, 10.8)	535.7 (343.4, 920.7)
HIV RNA >200 copies/mL	47	1184.7 (927.6, 1522.8)	10.4 (8.3, 13.7)	754.9 (379.3, 1207.7)
p-value[b]		**0.009**	**<.0001**	**0.032**

Abbreviations: FS, food security

[a] Food insecure group includes participants with marginal, low, and very low food security. Full food security is the reference group; [b] Wilcoxon rank-sum tests were performed to compare distribution of sCD14, sCD27, and sCD163; one-sided p-values are reported; [c] Kruskal-Wallis omnibus test was performed to test for differences in sCD14, sCD27, and sCD163 by levels of food security (full, marginal, low, and very low food security). Dwass, Steel, Critchlow-Fligner method for pairwise multiple comparisons yielded no significant differences between categories.

Table 5.3. Spearman Correlation Coefficients (Rho) Between Markers of Immune Activation, CD4 Cell Count, and Severity of Food Insecurity (N=323)

	sCD27	sCD163	CD4	FI severity[a]
sCD14 (ng/mL)	.398**	.271**	-.019	.151*
sCD27 (ng/mL)		.301**	-.149	.154*
sCD163 (ng/mL)			-.057	.039
CD4 (cells/µL)				.057

[a] From least to highest severity of food insecurity: full (0), marginal (1), low (2), and very low food security (3)

* $p<0.01$; ** $p<0.0001$

Table 5.4. Univariate Regressions for (Log-Transformed) Markers of Immune Activation in The MASH Cohort (N=323)

Parameter		Log sCD14 (ng/mL)				Log sCD27 (ng/mL)				Log sCD163 (ng/mL)			
		β	**SE**	***t***	***p***	**β**	**SE**	***t***	***p***	**β**	**SE**	***t***	***p***
Age, 5 years		.025	.02	1.60	.110	.051	.02	3.21	**.002**	.010	.02	.39	.693
Sex	Female	.095	.05	1.88	.061	.016	.05	.32	.750	.118	.08	1.53	.127
Race/ethnicity	White non-Hispanic	.204	.10	1.96	.051	.232	.10	2.21	**.028**	.385	.15	2.49	**.013**
	White Hispanic	.041	.06	.65	.518	-.089	.06	-1.40	.163	.320	.09	3.40	**.001**
	Multiracial/other	-.023	.09	-.27	.791	-.118	.09	-1.37	.172	.271	.13	2.13	**.034**
Income, $1000		.001	.002	0.25	.806	-.002	.002	-.67	.503	.003	.003	.77	.442
Household size		.008	.02	.46	.643	-.014	.02	-.78	.437	-.022	.03	-.81	.418
Metabolic	BMI, 5 kg/m^2	.007	.02	.34	.732	-.001	.02	-.05	.959	.093	.03	3.05	**.003**
	Hyperglycemia	-.055	.06	-.96	.340	-.086	.06	-1.46	.145	.043	.09	.49	.621
	Hypertriglyceridemia	.104	.05	1.95	.052	.090	.05	1.64	.102	.173	.08	2.13	**.034**
	Hypertension	.083	.05	1.69	.092	.129	.05	2.57	**.011**	.013	.08	.17	.864
	Log hs-CRP	.055	.02	2.62	**.009**	.039	.02	1.81	.072	.019	.03	.59	.559
Hepatic	Liver fibrosis[a]	.124	.05	2.29	**.023**	.123	.05	2.24	**.026**	-.060	.08	-.73	.465
Substance use	Hazardous drinking[b]	.068	.06	1.07	.289	-.041	.06	-.64	.526	.122	.10	1.26	.208
	Cigarette Smoking	.042	.05	.85	.399	.086	.05	1.71	.089	-.010	.08	-1.33	.185
	Cocaine	.101	.05	1.94	.053	.077	.05	1.44	.151	-.028	.08	-.35	.728
	Marijuana	.070	.05	1.29	.199	.041	.06	.74	.458	.094	.08	1.14	.257
	Opioids	.045	.10	.45	.650	-.027	.10	-.27	.790	-.242	.15	-1.63	.105
HIV	HIV RNA >200 copies/mL	.143	.07	2.04	**.042**	.271	.07	3.87	**.0001**	.214	.11	2.02	**.044**
	CD4, 100 cells/μL	-.003	.01	-.40	.690	-.020	.01	-2.75	**.006**	-.010	.01	-.86	.389
Diet	Total energy, 100 kcals	.021	.02	.95	.342	-.016	.02	-.72	.473	.012	.03	.34	.734
	Protein energy, 100 kcals	.019	.01	1.54	.125	.012	.01	1.00	.320	.026	.02	1.41	.159
	Carbohydrate energy, 100 kcals	.002	.004	.61	.544	-.005	.004	-1.31	.190	-.0005	.01	-.08	.936
	Fat energy, 100 kcals	.005	.01	.98	.327	-.002	.01	-.34	.733	.004	.01	.46	.644
	SFAs, g	.008	.01	.66	.512	.0001	.01	.08	.940	.006	.02	.36	.718
	Fiber, g	-.008	.02	-.41	.685	-.025	.02	-1.21	.226	.016	.03	.52	.607
Food insecurity[c]		.132	.05	2.66	**.008**	.120	.05	2.38	**.018**	.022	.08	.29	.768

Abbreviations: SFAs, saturated fatty acids

[a] Fibrosis-4 Index (FIB-4) ≥1.45; [b] Alcohol Use Disorders Identification Test (AUDIT) ≥8; [c] Food insecure group includes participants with marginal, low, and very low food security. Full food security is the reference group.

Table 5.5. Relationship Between Food Insecurity and (Log-Transformed) Markers of Immune Activation Controlling for Demographic, Dietary, Clinical, and Behavioral Factors (N=323)

Model	Log sCD14 (ng/mL)				Log sCD27 (ng/mL)				Log sCD163 (ng/mL)			
	β	**SE**	***t***	***p***	**β**	**SE**	***t***	***p***	**β**	**SE**	***t***	***p***
1) Food insecurity[a] (univariate)	.132	.05	2.66	**.008**	.120	.05	2.38	**.018**	.022	.08	.29	.768
2) Adjusted for sociodemographic characteristics, HIV viral load, and CD4 cell count[b]	.135	.05	2.73	**.007**	.122	.05	2.50	**.013**	-.004	.07	-.06	.955
3) Additionally adjusted for diet[b]	.138	.05	2.65	**.009**	.128	.05	2.54	**.012**	.009	.08	.12	.907
4) Additionally adjusted for metabolic parameters and substance use[c]	.117	.05	2.25	**.025**	.129	.05	2.56	**.011**	.024	.08	.31	.758

[a] Food insecure group includes participants with marginal, low, and very low food security. Full food security is the reference group.
[b] Age, sex, race/ethnicity, income, household size, HIV viral load >200 copies/mL, and CD4 cell count
[c] Total energy (kcals), energy from protein, carbohydrates, and fats (kcals), saturated fats (g), and fiber (g).
[d] BMI, hyperglycemia, hyperlipidemia, hypertension, liver fibrosis (FIB-4 ≥1.45), high-sensitivity C-reactive protein, hazardous drinking, cigarette smoking, cocaine, and opioids.

Table 5.6. Regression for Log-Transformed sCD163 with Food Insecurity and CD4 Cell Interaction (N=323)

Parameter	Category	β	SE	*t*	*p*	*F*	*p*
Food insecurity	Marginal FS	.037	.22	.18	.859	1.88	.115
	LFS	.079	.25	.32	.748	-	-
	VLFS	.534	.22	2.40	**.017**	-	-
	Full FS	Reference	-	-	-	-	-
CD4, 100 cells/μL		.007	.02	.43	.664	1.88	.171
Food insecurity*CD4	CD4*Marginal FS	-.013	.03	-.42	.678	2.35	.072
	CD4*LFS	-.001	.04	-.02	.984	-	-
	CD4*VLFS	-.086	.03	-2.60	**.010**	-	-
	CD4*Full FS	Reference	-	-	-	-	-

Abbreviations: FS, food security; LFS, low food security; VLFS, very low food security

CHAPTER VI: SUMMARY AND CONCLUSIONS

The present study investigated whether food insecurity was associated with NAFLD, cognitive impairment, and immune activation in socioeconomically disadvantaged adults from the MASH Cohort. A summary of the hypotheses and results can be found in Table 6.1. For the first time, this study established: 1) an association between food insecurity and NAFLD in people living with and without HIV using direct and highly-accurate measures of liver steatosis and fibrosis, 2) a relationship between the frequency of food insecurity, particularly persistent food insecurity, and cognitive decline in people living with and without HIV, and 3) an association between food insecurity and immune activation in people living with HIV. Our findings highlight the consequences of social disparities and the insidious impact of food insecurity, a complex socioeconomic issue that encompasses social, behavioral, and biological factors contributing to numerous adverse health outcomes and lower quality of life. Fortunately, food insecurity is a modifiable risk factor, thus the results of this study may inform public health advocacy and aid in policies targeted at reducing social disparities in access to essential components of life, such as safe and adequate nutrition.

Both NAFLD and cognitive disorders are pressing health issues for aging populations, particularly vulnerable groups such as PLWH. Nonalcoholic fatty liver disease has rapidly become the most prevalent liver disease in the Western world,[1] affecting almost a third of all U.S. adults.[2-4] Yet, PLWH are highly vulnerable to liver diseases and susceptible to liver disease progression and related complications.[5] Cognitive impairments and dementia are seen in approximately 18-21% and 5-8%, respectively, of U.S. adults aged 50 and older.[6,7] Over half of all PLWH in the United

States are 50 years of age and older[8] and as many as half of PLWH show signs of cognitive dysfunction,[9] although more conservative estimates place the prevalence of HAND between 14-28% of PLWH aged 50 and older.[10] Persistent immune activation in HIV infection, in addition to its role in HIV disease pathogenesis, has been implicated in liver disease[11,12] and cognitive disorders among PLWH.[13] Furthermore, advanced liver disease has also been linked to immune activation[11,14] and cognitive impairments in PLWH.[15,16]

Approximately a third of the MASH Cohort participants were food-insecure, a prevalence rate that is consistent with that seen in U.S. households earning less than 185% of the federal poverty level.[17] However, there was no significant difference in the prevalence of food insecurity between PLWH and HIV-uninfected participants. Our estimates also suggest that the prevalence of NAFLD, liver fibrosis, and advanced liver fibrosis in the MASH Cohort were 16.1%, 15.1%, and 4.6%, respectively. Compared to HIV-uninfected, PLWH were at increased risk for liver fibrosis, but not NAFLD or advanced liver fibrosis. Also, at baseline, approximately 15% of participants had cognitive impairment and PLWH who were not virally suppressed (HIV RNA > 200 copies/mL) showed a nearly 3-fold increased risk for cognitive impairment compared to HIV-uninfected participants.

With respect to Aim 1, we used MRI-PDFF to assess liver steatosis and MRE to assess liver fibrosis. Food insecurity was associated with greater liver fat content only among obese participants, and we observed a significant interaction effect between BMI and food insecurity on NAFLD. In other words, food insecurity modified the effect of BMI on NAFLD, increasing the risk associated with increasing BMI among those who

experienced food insecurity. Additionally, food insecurity was associated with increased risk for any liver fibrosis (stage 1 or higher) and advanced liver fibrosis (stage 3 or higher). The effects of food insecurity were not significantly different between PLWH and HIV-uninfected participants. Our findings were similar to those by Golovaty et al., who investigated the association between food insecurity and NAFLD using NHANES 2005-2014 data and indirect indexes of liver steatosis and fibrosis.[18] Unlike our observations, Golovaty et al. found that food insecurity was independently associated with higher odds of NAFLD, but similar to us, food insecurity was also associated with increased risk for advanced liver fibrosis. Notably, the effect sizes in both studies were similar.

For Aim 2, we assessed cognitive impairment at baseline and at 2-year follow-up with the MMSE (cutoff of ≤ 24). Our results showed that (1) VLFS was associated with cognitive impairment at baseline, (2) baseline food insecurity was associated with cognitive impairment after a 2-year follow-up, and (3) the frequency of food insecurity over the 2-year period was associated with cognitive decline, (4) particularly when it was persistent. On the other hand, the risk for cognitive impairment associated with food insecurity was not significantly different between PLWH and HIV-uninfected participants. The findings support what has been previously reported by Wong et al., who found that food insecurity at baseline was associated with cognitive impairment at 2-year follow-up and the greatest impact was seen in association with VLFS.[19] However, Hobkirk et al. found that food insecurity was associated with cognitive deficits in PLWH but not HIV-uninfected participants using a neurocognitive battery.[20] The contrasting

results may be related to poor sensitivity of the MMSE in our study and the small sample of HIV-uninfected participants in the Hobkirk study.

Lastly, for Aim 3, we used plasma sCD14, sCD27, and sCD163 as biomarkers of immune activation among HIV-infected participants. Food insecurity was associated with greater immune activation in PLWH, as determined by higher levels of (log-transformed) sCD14 and sCD27. The severity of food insecurity was directly correlated with sCD14 and sCD27 levels. The severity of food insecurity also appeared to moderate the relationship between CD4 cell count and sCD163 (p=0.07). Indeed, VLFS was significantly associated with increased sCD163 levels among those with lower CD4 cell counts. While this is the first report on food insecurity and immune activation, the findings are consistent with prior studies that have associated food insecurity with markers of systemic inflammation.[21-23] The association between food insecurity and sCD14 also suggests increased microbial translocation – a major pathway of immune activation in HIV infection.[24]

The results presented herein add to a growing body of evidence on the adverse effects of food insecurity on health outcomes among vulnerable populations. Although the prevalence of food insecurity in the United States has declined after the aftermath of the Great Recession,[25] it remains now at levels similar to those in the late 1990's.[17] Furthermore, the prevalence of food insecurity remains disproportionately elevated among minorities and other marginalized groups.[17] The burden of food insecurity is particularly worrisome among PLWH, for whom it may have added risks due to the compromising nature of the HIV infection. Notably, food insecurity was not associated with increased effects for PLWH compared to HIV-uninfected participants. Nonetheless,

due to the high prevalence of food insecurity among PLWH, our findings suggest that food insecurity might substantially contribute to the increased burden of morbidity among PLWH. Importantly, food insecurity was associated with immune activation in PLWH, in whom persistent immune activation and inflammation, despite effective ART, contribute to adverse health outcomes, such as HIV disease progression and age-associated chronic comorbidities. The results of this study are therefore highly relevant to U.S adults living with HIV, in whom poverty and food insecurity, along with other social disparities, are highly and pervasively prevalent. Public health strategies to mitigate food insecurity among PLWH are warranted.

It is important to recognize that the results of this study are necessarily not applicable to the general population, as food insecurity predominantly affects low-income households, particularly minority headed-households.[17] This study does, however, characterizes a highly vulnerable subset of the population with high rates of poverty, food insecurity, chronic diseases, and mental health problems, including depression and substance use disorders. The MASH cohort represents those who have the greatest need for improved public health efforts to diminish social disparities, including the insidious food insecurity that contributes to poorer health outcomes.

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Table 6.1. Summary of Hypotheses and Findings

No.	Hypothesis	Results
1a	FI will be associated with increased risk for NAFLD (liver fat >5%) as determined by MR imaging-derived proton density fat fraction (MRI-PDFF).	FI was associated with greater liver fat content only among obese participants (4.8±2.0 vs. 3.8±1.9%; *P*=0.03). There was a significant interaction effect between FI and BMI on the risk for NAFLD (*P*<0.0001). For every 5-unit increase in BMI, the odds of NAFLD were 3.83 (95% CI: 2.37–6.19; *P*<0.0001) times higher in food-insecure participants compared to 1.32 (95% CI: 1.04–1.67; *P*=0.02) times higher in food-secure participants.
1b	FI will be associated with increased risk for liver fibrosis as determined by magnetic resonance elastography (MRE).	FI was associated with increased risk for liver fibrosis (OR:1.65, 95% CI: 1.01–2.72; *p*=0.048) and advanced liver fibrosis (OR: 2.82, 95% CI: 1.22–6.54; *p*=0.02), adjusted for confounders.
1c	The effects of FI on liver outcomes will be significantly higher in PLWH than HIV-uninfected participants.	There were no significant interaction effects between FI and HIV infection.
2a	FI will be independently associated with increased risk for cognitive impairment as determined by the Mini-Mental State Examination (MMSE).	VLFS was associated with cognitive impairment at baseline (OR: 4.16, 95% CI: 1.28–13.55; *p*=0.02). Baseline FI was associated with cognitive impairment after a 2-year follow-up (OR: 4.21, 95% CI: 1.66–10.68; *p*=0.002).
2b	The risk for cognitive impairment will correlate with the frequency of FI.	The frequency of FI over the 2-year period was associated with cognitive decline (OR: 1.85 per year of food insecurity, 95% CI: 1.23, 2.77; *p*=0.003), particularly when it was persistent (OR: 6.77, 95% CI: 1.72–26.68; *p*=0.006).
2c	The relationship between FI and cognitive impairment will be stronger among PLWH than HIV-uninfected participants.	There were no significant interaction effects between FI and HIV infection.
3a	FI will be associated with increased immune activation in PLWH as determined by plasma levels of sCD14, sCD27, and sCD163.	FI was associated with higher levels of (log-transformed) sCD14 (β=0.13, SE=0.05; *p*=0.008) and sCD27 (β=0.12, SE=0.05; *p*=0.018). FI also showed a tendency to moderate the relationship between CD4 and sCD163 (*F*=2.35, *p*=0.07) – VLFS was associated with increased sCD163 levels among those with lower CD4 counts (B=0.53, SE=0.22; *p*=0.02).
3b	The severity of FI will correlate with levels of sCD14, sCD27, and sCD163.	The severity of food insecurity was directly correlated with sCD14 (rho=0.15; *p*=0.006) and sCD27 (rho=0.15; *p*=0.006) levels.

Abbreviations: FI, food insecurity; VLFS, very low food security

CHAPTER VII: STRENGTHS AND LIMITATIONS

Population

The present study was conducted in a well-characterized cohort of predominantly low-income, minority, middle-aged and older adults living with and without HIV. The homogeneity of sociodemographic characteristics among cohort participants is a strength of the study. Moreover, the prevalence of food insecurity in the MASH Cohort is remarkably similar to what is seen among low-income U.S. households.[1] That said, young adults and White non-Hispanics are underrepresented in the MASH Cohort. With respect to PLWH in the MASH Cohort, the vast majority are engaged in care, receiving ART, and virally suppressed, and are therefore similar to those enrolled in the Ryan White Program[2] and other U.S. cohorts of PLWH in care,[3] but it may not represent all PLWH in the United States[4] An additional benefit of this study being conducted with the MASH Cohort is that it allows for longitudinal follow-up to expand on our findings.

Assessments

The study is further strengthened by the use of highly validated assessments. The U.S. Household Food Security Survey (HFSS) is the most widely utilized and well-validated assessment of food insecurity.[5] The HFSS assesses a respondent's perceived food sufficiency and adequacy, food-related anxiety, and instances of hunger that occurred in the household during the past 12 months. Yet, the HFSS does not capture the entire gamut of elements that comprise food insecurity, trading off comprehensiveness for simplicity and comparability.[5] The use of MRI-PDFF and MRE, in particular, provides a high level of accuracy compared to other non-invasive liver assessments.[6] On the other hand, 354 MASH Cohort participants were ineligible for the magnetic

resonance liver scans, which may have led to sampling bias. The frequency of food insecurity, however, did not differ between those eligible and ineligible for liver scans. The MMSE is the most widely used and well-studied screening assessment for neurocognitive disorders[7] and has shown high accuracy for the detection of dementia.[8] Yet, screening tools are generally insufficiently sensitive to mild and HIV-related cognitive disorders. That said, our findings indicate that food insecurity may be a clinically relevant risk factor for severe cognitive impairment. We also used widely studied plasma biomarkers of immune activation, allowing for comparisons across other cohorts.

Covariates

We performed multivariable analyses to account for several potential confounders of the associations between food insecurity and study outcomes, including sociodemographic characteristics (age, sex, race/ethnicity, income, education, and household size), metabolic factors (e.g., BMI, hyperglycemia, hypertension), mood (depressive symptoms), and substance use. While these analyses confirmed the associations and strengthened the results, there may be unmeasured confounders that were unaccounted for. Our analyses on NAFLD are presumptive of no excess alcohol consumption, but this was self-reported, thus, subject to underreporting. This is also no different from what is done in other clinical and research settings. It is also possible that some of the effect of food insecurity on liver fibrosis seen in this study may not be metabolic- or NAFLD-related; however, the association with advanced liver fibrosis was significant while controlling for and excluding HCV infection.

Design

Most of our analyses employed a cross-sectional design, which does not allow for temporality to be established. As a result, we cannot conclude that food insecurity precedes liver disease and immune activation. For example, HIV/HCV infection may result in liver fibrosis and lead to psychosocial factors, such as poverty and drug use, that contribute to food insecurity. Factors associated with immune activation, such as fragility and increased morbidity, may contribute to food insecurity by decreasing functional capability and work opportunities.

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CHAPTER VIII: FUTURE RESEARCH

The findings, as well as the limitations of this study indicate that further research is warranted. Potential mechanisms and mediators for the effects of food insecurity reported in this study should be examined, including dietary patterns and diet quality, negative coping behaviors, and chronic stress. Moreover, all of the outcomes examined in this study are inter-related. Future studies could consider these interrelationships and examine the direct and indirect effect of these variables. For instance, does elevated immune activation mediate the relationship between food insecurity and cognitive decline?

Longitudinal studies are needed to establish whether food insecurity precedes liver disease and immune activation. Longitudinal analyses could help elucidate the long-term effects of food insecurity, including its severity, frequency, and persistence, on the progression of liver disease and cognitive decline. Additionally, such studies may also indicate whether the trajectory of outcomes over time differs between PLWH and HIV-uninfected persons.

Although liver assessments by magnetic resonance have the advantage of increased accuracy, they restrict the sample to only those participants who are eligible for the scans. Future studies could incorporate additional non-invasive assessments of liver disease, compare diagnostic accuracy, and examine how food insecurity relates to the different measures. Based on our findings, other designs including comprehensive neurocognitive batteries would improve on this research via improved diagnostic accuracy, sensitivity to mild cognitive impairments, and elucidation of the specific cognitive domains affected by food insecurity. Neuroimaging studies can identify specific brain structures altered by

food insecurity. Furthermore, further research on immune activation should incorporate additional markers of inflammation and microbial translocation.

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