

**Assessing Genetic Associations with Depressive Features and Body Mass Index in Samoans**

by

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## **Abstract**

The co-occurrence of depression and obesity has significant public health implications due to their potentially compounding and debilitating effects. The Samoan population provides a unique opportunity to further investigate the relationship, a component of which may be genetic, between obesity and depression because of the high prevalence of obesity. The first aim of this research is to determine if the three genetic variants associated with depression in Europeans are associated with the depressive features of helplessness and hopelessness in a sample of 519 Polynesians. The second aim is to determine if there is an association between the three genetic variants and BMI. In ordinal regression of helplessness and hopelessness on age, sex, BMI, and genotype I observed no significant associations, except for an association between higher age and higher reported hopelessness. In linear regression of BMI on age, sex, and genotype I observed associations between both lower age and female sex with higher BMI. However, there were no significant associations between genotype and BMI. Although I did not see associations between three genetic variants and the depressive features of helplessness and hopelessness or BMI, additional study of genetic variation and depressive features and BMI could identify pleiotropy between these phenotypes. Association between age and hopelessness is intriguing and additional exploration to investigate the robustness of this association and its underlying causes could enhance awareness, prevention,

and treatment of depression among Samoans. The lack of an observed association between these depressive features and body size is contrary to what is observed in most analyses and additional study with this population is needed to validate whether depression and obesity are decoupled in this context. If this decoupling is borne out in follow-up studies in this context, it would imply that independent strategies are needed to address obesity and depression in Samoa. Investigating further could also inform interventions that might interrupt the bidirectional causality that occurs between these two noncommunicable diseases.

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## Preface

I would first like to thank Dr. Ryan Minster for giving me the opportunity to pursue this research interest and for his support and guidance throughout the creation of this essay. I am also extremely grateful to my advisors Dr. Candace Kammerer and Dr. Andrea Durst for their unwavering support and advice throughout this process and my entire academic career at the University of Pittsburgh. I would also like to extend my sincere thanks to Dr. Jenna Carlson for her willingness to read my essay and provide valuable feedback.

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We would like to thank the Samoan participants and local village authorities and research assistants over the years. We acknowledge the support of our research collaboration with the Samoa Ministry of Health; the Samoa Bureau of Statistics; the Samoa Ministry of Women, Community and Social Development; and the American Samoa Department of Health. The Samoan Obesity, Lifestyle, and Genetics Adaptations (OLaGA) Study Group investigators are Ranjan Deka, Jenna C. Carlson, Kima Fa'asalele-Savusa, Nicola L. Hawley, Vaimoana Lupematisila, Stephen T. McGarvey, Ryan L. Minster, Leausa Toleafoa Take Naseri, Muagututi'a Sefuiva Reupena, Melania Selu, John Tuitele, Asiata Satupa'itea Viali and Daniel E. Weeks.

## **1.0 Background**

### **1.1 Introduction**

The co-occurrence of depression and obesity has significant public health implications due to their potentially compounding and debilitating effects. Obesity can make daily work and life tasks more difficult, therefore decreasing an individual's productivity and sense of accomplishment. Prolonged feelings of inadequacy can lead to depression and further perpetuate the behaviors that lead to obesity, such as decreased physical activity and increased caloric intake (Simon et al. 2008). The reverse relationship has also been observed in which depression leads to decreased desire to complete daily tasks, thus reducing the amount of daily physical activity an individual experiences, possibly leading to weight gain and eventually obesity (Milaneschi et al. 2019; Wray et al. 2018). Both have been linked to high healthcare use, and, when co-occurring, can result in longer illness and hospital stays (Robinson et al. 2016; Opel et al. 2015).

The Samoan population provides a unique opportunity to further investigate the relationship between obesity and depression as a large portion of the population has clinical obesity. The most recent estimates available from 2013 are that, in Samoa, 41.2% of men and 65.1% of women (Lin et al. 2017) were at or above the ethnic-specific cut-off point for having clinical obesity (body mass index [BMI]  $\geq 32$  kg/m<sup>2</sup>) (Swinburn et al. 1996). On the other hand, depression is understudied in Samoa. This is concerning because, as described previously, studies have identified a bidirectional relationship between depression and obesity. Having one significantly increases an individual's risk for developing the other (Milaneschi et al. 2019). Therefore, treating one of these

conditions has the potential to impact the other, but if depression is underdiagnosed in Samoa this potentially beneficial treatment route is lost.

While previous studies have focused on a variety of shared biological mechanisms between the two conditions, I am interested in further investigating the genetic mechanisms that contribute to the relationship between depression and obesity.

## **1.2 Depression**

Depression is characterized by the American Psychiatric Association (APA) in their *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) as, “discrete episodes of a least 2 weeks’ duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, and neurovegetative functions and inter-episode remissions” (APA, 2013). Some of the common symptoms associated with depression lasting over a two-week period include “depressed mood for most of the day; diminished interest or pleasure in all, or almost all activities; significant weight loss or significant change in appetite; insomnia; fatigue; diminished ability to think or concentrate; and recurrent thoughts of death” (APA, 2013). In order for an individual’s mental status to be diagnosed as a major depressive episode, at least one of the symptoms has to be either a depressed mood or loss of pleasure in nearly all activities for no less than 2 weeks (APA, 2013). The World Health Organization (WHO) defines recurrent depressive disorder as having repeated depressive episodes during which a person experiences “depressed mood, loss of interest and enjoyment, and reduced energy leading to diminished activity for at least two weeks” (World Health Organization, 2020). In both the APA and WHO definitions of depression there is

a temporal element of two weeks, this time period is what aids in distinguishing depression from other, more temporary, mental disorders.

### **1.2.1 Depression and Public Health**

The WHO reports that there are more than 264 million people affected worldwide by depression (WHO, 2020). Depression is a major public health concern due to its association with disability, loss of quality of life, greater service use, substantial productivity losses, and increased mortality (Ormel et al. 2020). One of the areas of greatest concern is the increased risk of death by suicide for depressed individuals. The WHO reports that nearly 800,000 people take their life by suicide each year, equivalent to one person every 40 seconds (WHO, 2019). However, these figures do not capture the extent of disability in all the individuals who struggle with depression, as many more could be contemplating suicide or have attempted suicide but were unsuccessful and therefore are not reported. Death by suicide is particularly prevalent globally among 15–29-year-olds and is the second leading cause of death among this age group (WHO, 2019).

### **1.2.2 Depression Measures**

There is a wide array of depression measures currently used in clinical settings. Many of them target a specific age-group or population. Two commonly used instruments for assessing depression across the lifespan are the Beck Depression Inventory (BDI) (Beck et al. 1961) and the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977). The BDI is intended

for ages 13 to 80 and consists of twenty-one self-report items presented in a multiple-choice format. The entire inventory is estimated to take an individual ten minutes to complete (APA, 2019). The responses are then scored on a four-point scale to indicate the degree of severity.

The CES-D contains twenty self-reported items also scored on a four-point scale. However, unlike the BDI, the CES-D scoring is weighted by frequency of occurrence in the past week (Smarr & Keefer 2011). With the CES-D, an individual rates each prompt from 0 to 3 based on the frequency of the symptom experienced in the last week. A rating of 0 is “less than 1 day,” and a rating of 3 is “5–7 days.” This results in a possible range of scores from 0 to 60, with the higher scores denoting a greater occurrence of depressive symptoms experienced by the individual in the past week. The CES-D was designed to capture the common symptoms of: “depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance” (Radloff 1977).

The CES-D is publicly available for access at no cost; whereas the BDI must be purchased through Pearson Assessments (Smarr & Keefer 2011). Due to the accessibility of the CES-D and its validation in several distinct populations, the proxy features for depression that I used in this study were selected based on their similarity to statements found in the CES-D.

### **1.2.3 Depression Etiology**

The etiology of depression is influenced by many interrelated factors. From the standpoint of biochemistry, the focus is three major monoamines—serotonin, norepinephrine, and dopamine—and the molecules that interact with them (Saveanu & Nemeroff 2012). These three monoamines, as neurotransmitters, are thought to play major roles in the occurrence and severity of depression. Through autopsies conducted on individuals who were depressed and suicidal, it has

been found that those individuals had low concentrations of serotonin and norepinephrine metabolites in their cerebrospinal fluid (Saveanu & Nemeroff 2012). Several postmortem studies of depressed individuals also revealed a decrease in dopamine transporter binding and increased postsynaptic dopamine receptor D<sub>2</sub>/D<sub>3</sub> binding, leading to reduced dopamine neurotransmission (Saveanu & Nemeroff 2012). Many of the antidepressants prescribed to depressed individuals target one or more of these three monoamine neurotransmitters (Elhwuegi 2004).

Stressful events experienced as a child and early life trauma have also been implicated as major contributing factors to the development of depression later in life. In a study of 1,931 women, it was found that those who reported being abused as children were almost four times more likely to report having attempted suicide, more than three times more likely to report having been hospitalized for an emotional or mental problem, and more than twice as likely to report having considered suicide seven days prior to completing the questionnaire (McCauley 1997). In a study of 942 adults aged 65 years and greater, it was found that traumatic events experienced in childhood doubled an individual's risk of late-life depression and also increased the risk of repeated episodes (Ritchie et al. 2009). Additionally, eight out of twenty-five negative factors were found to be significantly associated with late-life depression: verbal abuse from parents, mental cruelty, excessive punishment by parents, abuse by an adult outside the family, parental mental disorder, poverty, home conflict, and excessive sharing of parental problems with children (Ritchie et al. 2009).

It is also thought that numerous genetic polymorphisms can affect how an individual will respond to stressful events encountered during their lifetime (Saveanu & Nemeroff 2012). In a study of 1,037 children, those who carry the short ("s") allele at a polymorphic region linked to

the serotonin transporter (5-HTT) gene (*SLC6A4*)—this so called 5-HTT-linked polymorphic region is widely known as 5-HTTLPR—showed increased susceptibility to stressful life events and subsequent development of depression symptoms compared to long (“l”) allele homozygotes (Caspi et al. 2003). 5-HTTLPR is an ideal candidate for depression studies since the serotonin system is the target of many antidepressant drugs (Caspi et al. 2003). However, this region highlights the challenges of genetic studies of highly polygenic behavior traits like depression. Subsequent meta-analyses of this gene  $\times$  environment effect have been mixed (Karg et al. 2011; Munafò et al. 2009; Risch et al. 2009; Culverhouse et al. 2018; Duncan & Keller 2011).

Other genes of interest in the development of depression are those involved in regulation of the corticotropin-releasing factor and the hypothalamic-pituitary-adrenal axis (Caspi et al. 2003). A 2008 study investigating the relationship between child abuse on adult depressive symptoms and genetic polymorphisms within the corticotropin-releasing hormone type 1 receptor gene (*CRHR1*) found seven of the ten tested genetic variants to have a significant interaction with child abuse for the prediction of adult depression (Bradley et al. 2008).

Finally, genome-wide association studies (GWASs) of depression have also identified genetic variants associated with depression. There have been 146 studies of various aspects of unipolar depression or treatment-resistant depression conducted to date (Buniello et al. 2019). The largest GWAS of depression is of participants in the UK Biobank who reported a history of seeking help for problems with “nerves, anxiety, tension or depression” (which the authors refer to as “broad depression”,  $n = 322,580$ ) or who reported depressive symptoms with associated impairment (which the authors refer to as “probable major depressive disorder”,  $n = 174,519$ ) (Howard et al. 2018). The most statistically significant genetic variant associated with broad depression that subsequently replicated in a study of depression by 23andMe (Hyde et al. 2016) was rs6699744



(NC\_000001.11:g.72359461A>T, with the nearest gene > 10 kbp away). I selected this variant as the representative of this inclusive definition of depression for analysis in this report. Two additional variants were associated and replicated with the more robust probable major depressive disorder phenotype: rs10929355, NM\_015909.4(*NBAS*):c.5724+16644A>C (NC\_000002.12:g.15258840T>G), and rs5011432, NM\_018374.4(*TMEM106B*):c.442-637A>T (NC\_000007.14:g.12229042A>T). I will also use these two variants for analysis in this report.

### 1.3 Obesity

Like depression, obesity is also considered a complex multifactorial disease (Chooi et al. 2019). In a study of the prevalence of overweight and obesity among children and adults in 195 countries between 1980 and 2015, it was estimated that, worldwide, 107.7 million children and 603.7 million adults had obesity in 2015 (Afshin et al. 2017). The WHO defines overweight and obesity as “abnormal or excessive fat accumulation that may impair health.” The WHO classifies an adult as having overweight if they have a BMI  $\geq 25$  kg/m<sup>2</sup> and as having obesity if they possess a BMI  $\geq 30$  kg/m<sup>2</sup>. Because body fat levels at a given BMI are lower in Polynesians than in Europeans, Swinburn et al. (1996) proposed that for clinical and epidemiological purposes that Polynesians should be considered to have overweight if they have a BMI  $\geq 26$  kg/m<sup>2</sup> and to have obesity if they have a BMI  $> 32$  kg/m<sup>2</sup>.

### **1.3.1 Obesity and Public Health**

Obesity is a major public health concern due to the relationship between BMI and disease burden. High BMI is a risk factor for several chronic diseases such as cardiovascular disease, diabetes mellitus, chronic kidney disease, many cancers, and numerous musculoskeletal disorders. High BMI contributed to an estimated 4.0 million deaths among adults globally in 2015 (Afshin et al. 2017). The leading cause of death in 2015 that was related to high BMI, accounting for 2.7 million deaths worldwide, was cardiovascular disease. Additionally, in 2015 high BMI accounted for 120 million disability-adjusted life-years lost globally (Afshin et al. 2017). Healthcare costs and work absences have also been correlated with the occurrence of obesity. In a cohort study of more than 73,000 individuals, it was found that individuals with obesity had greater medical and pharmacy costs, as well as a greater number of absence days and reduced productivity at work (Kleinman et al. 2014).

### **1.3.2 Obesity Measures**

One of the most accurate methods for obesity measurement currently in use in clinical practice is dual-energy x-ray absorptiometry (DXA). DXA allows for differentiation between bone mineral content, lipid (“fat mass”), and lipid-free soft tissue (“lean mass”). From these measurements the fat mass index (FMI) can be calculated by dividing an individual’s fat mass in kilograms by their height in meters squared. FMI is thought to be an accurate measurement for obesity because it is a direct adiposity measurement parameter and takes into account a patients’ lean mass.

While DXA may yield better obesity measures, BMI is more accessible to a large portion of the world’s population due to the ease of its collection and its low cost. DXA requires a large

expensive machine, analysis software and an involved multi-step procedure. Whereas BMI can be obtained quickly with a stadiometer, a simple equation (weight in kilograms divided by the square of height in meters), and a calculator or smart phone. A meta-analysis of fifty-seven prospective studies showed that an elevated BMI increases an individual's risk for ischemic heart disease, stroke, and cancers of the large intestine, kidney, endometrium and postmenopausal breast (MacMahon et al. 2009). BMI cut-offs for classifying an individual as having clinical obesity were set based on risks for cardiometabolic morbidity and premature mortality (Aune et al. 2016). Concerns have been expressed that BMI and classification based on BMI does not account for ethnic specific muscle-to-fat ratios (Adab et al. 2018). Due to this concern, additional studies have been conducted and ethnic-specific cut-off points for obesity have been determined for risk assessment of several noncommunicable diseases (NICE, 2013). For Polynesians, the cut-off point for obesity has been proposed to be BMI > 32 kg/m<sup>2</sup>, as they have a higher muscle-to-fat ratio than Europeans (Swinburn et al. 1996; Lin et al. 2017).

### **1.3.3 Obesity Etiology**

Obesity is typically caused by excessive dietary intake and insufficient energy expenditure (Wright & Aronne 2012). There are thought to be many contributing factors to the development of obesity, among them: genetic, physiologic, environmental, psychological, social, and economic factors (Wright & Aronne 2012). Globally there has been an increase in the production and accessibility of highly caloric food, while simultaneously total energy expenditure has decreased due to increasingly sedentary lifestyles and less physically laborious careers (Wright & Aronne 2012).

Numerous genetic loci have been implicated in risk of obesity, with each having an additive effect on the total risk (Goodarzi 2017). A 339,224-person GWAS identified 97 genome-wide significant loci associated with BMI, accounting for 2.7% of the variation in BMI (Locke et al. 2015). Of these 97 loci, several gene sets were found to be related to the etiology of body size in the central nervous system, associated with synaptic function, long-term potentiation, and neurotransmitter signaling. Other gene sets were found to be linked to integration of energy metabolism, polyphagia, secretion and action of insulin and related hormones, mTOR signaling, and the neurotrophin signaling pathway. Obesity is a complex disease with many factors, genetic and environmental, contributing to its development and pathology.

#### **1.4 Relationship between Obesity and Depression**

In a review conducted to explore the link between depression and obesity, it was found that across six meta-analyses comprised of twenty-six cross-sectional studies all identified a positive association between depression and obesity (Milaneschi et al. 2019). Furthermore, they discovered that four longitudinal meta-analyses verified the presence of a bidirectional relationship between obesity and depression, meaning that obesity longitudinally increases the risk of developing depression, and vice versa (Milaneschi et al. 2019). Even so, not all studies report data that support the bidirectionality, and the relationship might be a complex one (Singh et al. 2014; Jantaratnotai et al. 2017). Depression is associated with a 37% higher relative risk of obesity, and obesity, with an 18% higher relative risk of depression (Mannan et al. 2016). Additionally, individuals with obesity who possess two or more chronic conditions are five times more likely to report a major

depressive episode in the last year (Romain et al. 2019). Among Mexican women, those who had obesity had 1.28 times the odds of having depression than normal-weight women (Zavala et al. 2018). However, among Mexican men, there was no statistically significant association between obesity and depression (Zavala et al. 2018). This suggests that there could be sex differences in the relationship between obesity and depression.

Finally, there may be genetic factors at play in the relationship between depression and obesity. Rivera et al. (2012) examined genetic variants in *FTO*—variants in which have been associated with BMI and obesity—and have observed variants that are associated with BMI in participants with depression but not in control participants, suggesting that the effect of these variants is altered by the presence of depression.

## 1.5 Samoa

The Independent State of Samoa (Samoa) consists of two main islands—‘Upolu and Sa-vai‘i—and eight small islets located in the Polynesian region of the Pacific Ocean. In 2017 the population of Samoa was 197,611 and is projected to reach 205,770 by 2022 (Samoa Bureau of Statistics, 2016). As a result of ongoing modernization, Samoa “graduated” from its status as a least developed country in January 2014 (UN, 2018) and is currently considered an upper-middle-income country. As of 2016, Samoa’s gross domestic product was ranked seventh among the Oceanian sovereign states (CIA, 2016).

Coupled with Samoa’s economic growth, there has also been an increase in noncommunicable diseases such as cardiovascular disease, type 2 diabetes, and obesity (Hawley et al. 2012).

The WHO reports that 80% of all deaths in the Western Pacific Region are attributed to noncommunicable diseases, with an estimated 452 deaths reported in 2019 in Samoa due to cardiovascular diseases alone (World Health Organization 2021b, 2016). A study of the trends in diabetes and obesity from 1978 to 2013 in Samoa, found that the increase in the prevalence of type 2 diabetes mellitus (31% in men and 16% in women) over the 35-year interval was attributable to increases in BMI (Lin et al. 2017). As obesity is a known contributing factor affecting the development and pathophysiology of many non-communicable diseases, the estimated 53% of men and 77% women in Samoa with obesity is a major public health concern (Lin et al. 2017).

### **1.5.1 Death by Suicide in Samoa**

Samoa is located in the WHO defined Western Pacific Region of the world, home to an estimated 1.9 billion people (WHO, 2021a), about 24% of the world's population. This region includes Mongolia, China, South Korea, Japan, Vietnam, Laos, Cambodia, Malaysia, Brunei, the Philippines, Australia, Papua New Guinea, and all of the nations and territories in Micronesia and Polynesia. The WHO reports that every year in the Western Pacific Region 200,000 individuals take their life by suicide, approximately 25% of global suicides (WHO, 2021c). In 2016, the WHO reported that the suicide mortality rate for males in Samoa was 6.7 per 100,000 population and 1.9 per 100,000 population for females (WHO, 2016). While, these rates are lower than many of the other countries in the Western Pacific Region, Samoa it is not guaranteed to remain so, as there is a known association between obesity and mental health (Milaneschi et al. 2019). As obesity rates continue to rise in Samoa, its mental health effects should receive increasing attention.

### 1.5.2 Studying Depression in Samoa

When studying depression it must be kept in mind that the term *depression* itself is a Western concept (Kirmayer et al. 2017). Thus it is possible that there are presentations of depression in non-Western populations that fail to be captured by Western diagnostic criteria (Summerfield 2012). Indeed, it was found that among healthcare providers in American Samoa, *depression* is rarely used and is typically not considered to be an illness (Held et al. 2010). *Depression* is used sparingly by healthcare providers in American Samoa because it is perceived that only those who are more educated or who comprise the younger generation would be familiar with the concept (Held et al. 2010). Depression, when translated to Gagana Sāmoa, is translated as “worries of the heart” (Held et al. 2010). This is because among Samoans “feelings” come from the *loto*, which is loosely translated as “heart,” and this is different from the heart as a physical organ. The term *loto* is a comprehensive term for “personal thoughts, feelings and volitions that is resistant to social conditioning” (Held et al. 2010). This nuance between the Western and Samoan interpretations of depression could lead to misunderstandings about whether the symptoms of depression are physical or mental and about the relationship between the two.

Another important factor in depression is the Samoan concept of self. In a 2004 study focused on gaining greater insight into the Samoan perspectives on mental health and culturally appropriate services, the research participants stressed that to assess Samoan concepts of mental health, you must first understand the Samoan concept of self (Tamasese et al. 2005). The Samoan concept of self is different from the Western individualistic concept of self in that the Samoan self is only seen to have meaning in relation with others. This concept of the Samoan self is so strongly held that when an individual seeks psychiatric services without consideration of their community and communal practices, they are seen as being deprived of the most valued source of meaning

and life support to aid in their healing process. Due to this concept of a relational self, mental illness is viewed as a result of fractured relations with others.

Finally, depression is a difficult topic to study in Samoa because there is a significant amount of cultural stigma surrounding the topic of depression. In a 2010 study interviewing healthcare providers in American Samoa many expressed “that depression is taboo, embarrassing, or an indication that someone is crazy” (Held et al. 2010). These beliefs present obstacles for individuals seeking help for depressive symptoms and therefore make it difficult to quantify the number of individuals who are suffering from depression.

### **1.5.3 Obesity in Samoa**

In recent years Samoa has experienced ongoing modernization, which has led to a lifestyle shift for many Samoans from a traditional subsistence culture to a more sedentary lifestyle (Hawley et al., 2012). Coupled with this lifestyle shift and increased urbanization, there has also been a dietary shift toward more processed and less nutritious foods as imported prepared foods and fast foods become more easily accessible (Hawley et al., 2014). As a result of these changes, from 1978–2013 the prevalence of obesity (BMI > 32 kg/m<sup>2</sup>) among men in Samoa increased from 24.7% to 41.2%, and among women it increased from 30.0% to 65.1% (Lin et al. 2017).



## **1.6 Specific Aims**

The goal of this project is to explore potential relationships between genetic variation associated with depression in individuals of European ancestries in among Samoan individuals and then assess those same variants' relationships with body size.

The first aim of this project is to test for association between three genetic variants previously identified as associated with depression and two proxy measurements for depression.

The second aim is to test for association between the three depression-associated genetic variants and BMI.

## 2.0 Methods

This study uses the anthropometric measurements, questionnaires, and genotyping data from the DNA samples previously collected by Hawley et. al (2014) and Hawley et al. (2020) to answer the proposed aims. This study was conducted under the auspices of the Obesity, Lifestyle and Genetic Adaptations (OLaGA, where *ōlaga* means life in Gagana Sāmoa) Study Group.

### 2.1 Participants

The dataset used for this analysis is derived from a population-based genome-wide association study (GWAS) conducted in Samoa in 2010 with around 3,475 participants of Samoan ancestry (the *Soifua Manuia* [Good Health in Gagana Sāmoa] Study). Participants ages 24.5 to 65 were recruited from 33 villages on both ‘Upolu and Savai’i. Participants were excluded if they did not report four Samoan grandparents, were pregnant, or had physical or cognitive impairment that prohibited completion of study examinations. The results of this original study suggested an association between a novel missense variant in *CREBRF* and greater BMI, but lower odds of diabetes among Samoans (Minster et al. 2016). To further characterize this particular association, a follow-up study was conducted between August 2017 and March 2019 which re-recruited 519 participants from the 24 villages on ‘Upolu and which included psychosocial instruments assessing stress and self-efficacy (Hawley et al. 2020). These participants were recruited based on whether they had consent to recontact and the presence or absence of the *CREBRF* variant and were excluded if they were pregnant, had physical or cognitive impairments, had given birth in the prior six months,

were currently lactating, or were or had engaged in a significant weight loss intervention (medication, surgery or had lost > 5% body weight in the prior year). It is from these 519 re-recruited participants that the study described in this report draws its sample.

All participants in these studies gave written informed consent with consent forms in Gagana Sāmoa. The research in Samoa was reviewed and approved by the institutional review boards of The Miriam Hospital; Brown University; the University of Cincinnati; and the University of Pittsburgh. Research in Samoa was also reviewed and approved by the Health Research Committee of the Samoan Ministry of Health.

## **2.2 Phenotypes**

Data collection consisted of two in-person interactions, one in the participant's home and the other 7–10 days later in the Obesity, Lifestyle, and Genetic Adaptations (OLaGA) research laboratory located in the Ministry of Health building in Moto'otua, Apia, Samoa. During the home visit, data were collected on height and weight and questionnaires were administered. The questionnaires were translated into Gagana Sāmoa language and administered in Gagana Sāmoa by local bilingual research assistants. The questionnaires collected information on individual and household demographic and socioeconomic characteristics, current health status and health history, physical activity, dietary intake, sleep patterns and symptoms, and psychosocial measures such as: body image, stress, self-efficacy, and weight control. The second in-person encounter, at the OLaGA research laboratory, consisted of a second measurement of height and weight, as well as measurement of body composition, blood pressure, and hand grip strength and biospecimen

collection. For the analyses in this study, I used the research lab measurements of height and weight.

### **2.2.1 Proxy Measurements for Depression**

The CES-D was not administered to the research participants in 2017–19 because participants identified as at high risk of clinical depression would not have access to treatment. Therefore, I sought to identify items in the psychosocial instruments applied to the participants that aligned with the questions in the CES-D that would provide insight into associations between genetic variation and risk of depression. The selected proxy measurements reflect questions found on the CES-D. Two of the most common symptoms associated with depressed individuals are feelings of helplessness and hopelessness (Pryce et al. 2011). To capture these two feelings from the administered psychosocial instruments, I selected one question that attempted to capture the feeling of perceived helplessness and one that attempted to capture the feeling of hopelessness.

The proxy measurement I selected to capture feelings of helplessness was contained in the self-efficacy instrument. The self-efficacy instrument consisted of 35 items aimed at assessing an individual’s general and social self-efficacy as well as their exercise confidence. Study participants were read 35 statements and for each were asked to select from the options of (1) strongly disagree (matua‘i fevaevaea‘i), (2) disagree (fevaevaea‘i), (3) neither agree or disagree (lē lotomalie toe lē fevaevaea‘i), (4) agree (lotomalie), and (5) strongly agree (matua‘i lotomalie). It was also noted when subjects refused to answer—in this study no one refused to answer. The statement I chose to reflect helplessness was “I do not seem capable of dealing with most problems that come up in life” (“‘Ou te iloa e lē mafai e a‘u ona fōia le tele o fa‘afitāuli o lenei ōlaga.”)

The proxy measurement I selected to capture feelings of hopelessness was contained in the stress instrument. The stress instrument consisted of 18 items aimed at assessing an individual's general and social self-efficacy as well as their exercise confidence. The study participants were read 18 questions and for each were asked to select from the options of (1) never (e le'i tupu lava), (2) almost never (toetiiti lava), (3) sometimes (nisi o taimi), (4) fairly often (seāseā tupu), and (5) very often (tupu so'o). The question I chose to reflect hopelessness was "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?" ("Ua iai se taimi 'ua lagona ai 'ua tele ni fa'afitāuli 'ae 'ua lē mafai ona e fōia, i le māšina 'ua te'a?")

### 2.3 Genotypes

rs5011432, rs6699744, and rs10929355, my genetic variants of interest from Howard et al. (2018), were not directly genotyped in the *Soifua Manuia* Study. However, these variants were observed in whole-genome sequences generated for *Soifua Manuia* participants sequenced as part of the Trans-Omics in Precision Medicine Program (Taliun et al. 2021). Unfortunately, these genotypes and genotypes imputed based on them were not available at the time for this report, so genetic variants directly genotyped in the *Soifua Manuia* Study that are in high linkage disequilibrium with rs10929355, rs5011432, and rs6699744 were selected for use as proxies in this study.

For rs5011432, rs4721059 (NM\_018374.4[*TMEM106B*]:c.442-1810G>A [NC\_000007.14:g.12227869G>C]) was selected as the proxy variant. The correlation between these variants in the *Soifua Manuia* Study is  $r^2 = 0.998$ .

For rs6699744, rs11581382 (NC\_000001.11:g.72363664C>T) was selected as the proxy variant. The correlation between these variants in the *Soifua Manuia* Study is  $r^2 = 0.883$ .

For rs10929355, rs2042144 (NM\_015909.4(NBAS):c.5725-14506A>G [NC\_000002.12:g.15253192T>C]) was selected as the proxy variant. The correlation between these variants in the *Soifua Manuia* Study is  $r^2 = 0.967$ .

rs4721059, rs11581382, and rs2042144 were genotyped as part of Genome-Wide Human SNP 6.0 arrays (Affymetrix). Extensive quality control was conducted on the basis of a pipeline developed by Laurie et al. (2010). Additional details of sample genotyping and genotype quality control are described in Minster et al. (2016).

## 2.4 Statistical Analyses

Data was coded in a Microsoft Excel spreadsheet and subsequently imported into R 3.6.0 (R Core Team 2019) for analysis. Descriptive statistics (mean, standard deviation, and range) of age, BMI, helplessness, and hopelessness were calculated for the sample. The mean and standard deviation of age and BMI and the proportion female were calculated for each of the five levels of helplessness and hopelessness. To test for association between rs4721059, rs11581382, and rs2042144 and each of helplessness and hopelessness, I performed ordinal regression with age, sex, and BMI as covariates. I used ordinal regression in the analyses of helplessness and hopelessness because I did not want to assume numerical linearity for the responses to the helplessness statement and the hopelessness question. To test for association between rs4721059, rs11581382, and rs2042144 and BMI, I performed linear regression with age, sex, and BMI as covariates. In all analyses the genetic variants were modeled additively.  $p$  values  $< 0.05$  were considered statistically significant.

## 3.0 Results

### 3.1 Participant Demographics and Descriptive Statistics

The study sample of 491 participants was 55% female and ranged in age from 30.7 to 72.7 years, with a mean age of 52.2 years. The mean BMI of the participants was 35.8 kg/m<sup>2</sup>. The mean score for helplessness was 3.31 (for which “3” meant they neither agreed nor disagreed, and “4” meant they agreed, that they do not seem capable of dealing with most problems), and for hopelessness was 2.70 (for which “2” meant that they almost never, and “3” meant that they sometimes, felt difficulties were piling up so high that they could not overcome them). See Table 1 for additional details of the descriptive statistics.

**Table 1. Select Characteristics of Sample**

	<b>Mean ± SD</b>	<b>Range</b>
<b>Age (years)</b>	52.2 ± 10.0	30.7–72.7
<b>BMI (kg/m<sup>2</sup>)</b>	35.8 ± 7.7	20.2–76.7
<b>Helplessness</b>	3.31 ± 1.3	1–5
<b>Hopelessness</b>	2.70 ± 1.1	1–5

The allele frequencies of the higher-risk alleles of rs4721059, rs11581382 or rs2042144 can be found in Table 2. The allele frequencies in Samoans are those observed in the *Soifua Manuia* Study (Minster et al. 2016). The allele frequencies of East Asians, South Asians, Admixed Americans, Europeans and Africans are those observed in the 1000 Genomes Project (Auton et al. 2015).

**Table 2: Allele Frequencies of rs4721059, rs11581382, and rs2042144 Risk Alleles**

	Allele	Samoans	East Asians	South Asians	Americans	Europeans	Africans
rs4721059	C	0.319	0.651	0.638	0.571	0.403	0.688
rs11581382	C	0.937	0.945	0.688	0.821	0.833	0.917
rs2042144	T	0.050	0.139	0.370	0.425	0.539	0.049

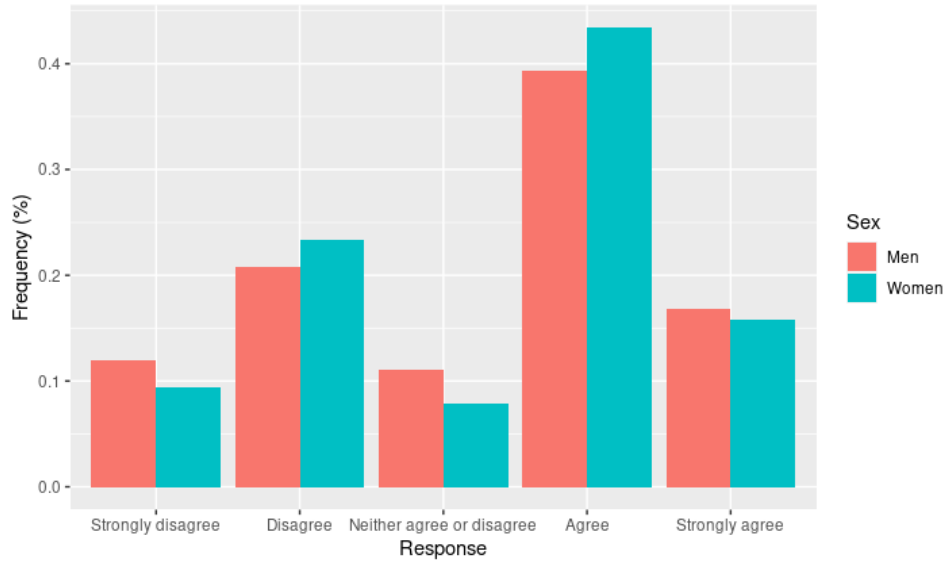
### 3.2 Helplessness

Of the 491 helplessness responses, 58% of the participants “agreed” or “strongly agreed” with the statement “I do not seem capable of dealing with most problems that come up in life,” and 33% of the participants “disagreed” or “strongly disagreed.” The remaining 9% “neither agreed or disagreed.” There were 28 individuals who were not asked to agree or disagree with this statement; the reason for this omission was not recorded. Descriptive statistics for the participants in each reported helplessness category can be found in Table 3. The distributions of sex, age, and BMI per helplessness response are shown in Figures 1, 2, and 3, respectively.

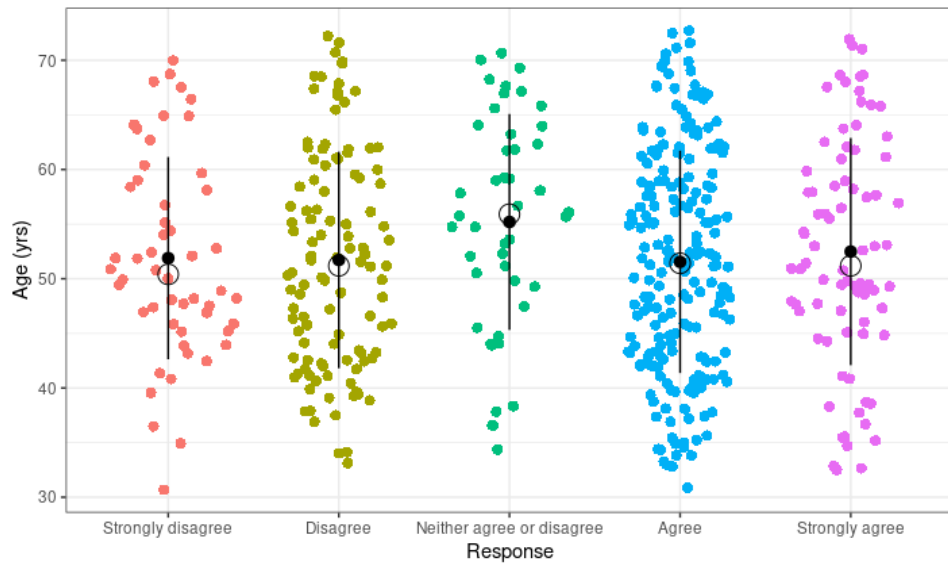
**Table 3. Select Characteristics of Sample Stratified by Helplessness Response**

Helplessness	“I do not seem capable of dealing with most problems that come up in life”					
	1	2	3	4	5	NA
	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree	
<b>Total Number</b>	52	109	46	204	80	28
<b>% Female</b>	48.1	56.9	45.7	56.4	52.5	75.0
<b>Age (years) mean ± sd</b>	51.9 ± 9.3	51.7 ± 10.0	55.2 ± 9.9	51.5 ± 10.2	52.5 ± 10.4	53.0 ± 8.4
<b>BMI (kg/m<sup>2</sup>) mean ± sd</b>	34.1 ± 7.3	36.1 ± 8.7	35.2 ± 6.9	36.6 ± 7.7	34.9 ± 7.0	33.8 ± 5.2

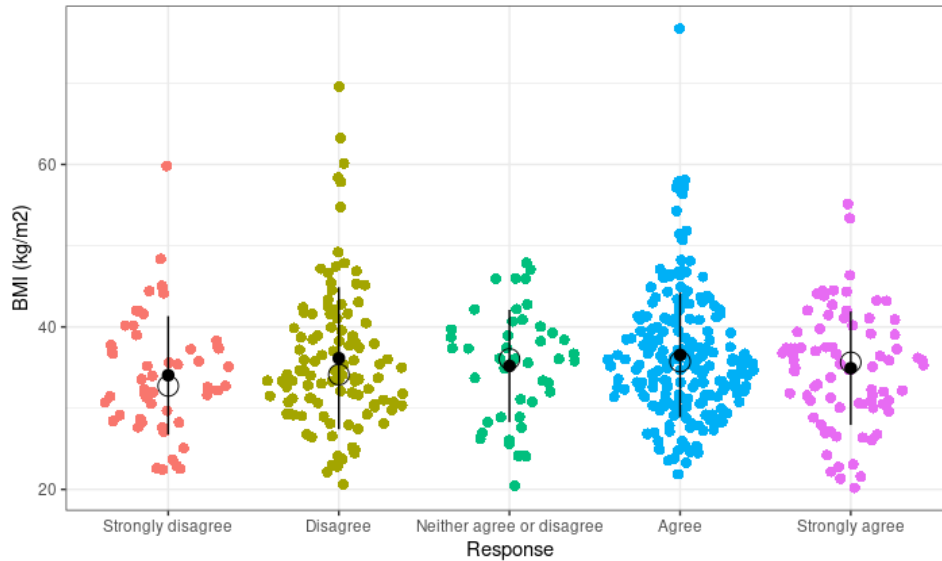




**Figure 1: Helplessness by Sex**



**Figure 2: Age and Helplessness**



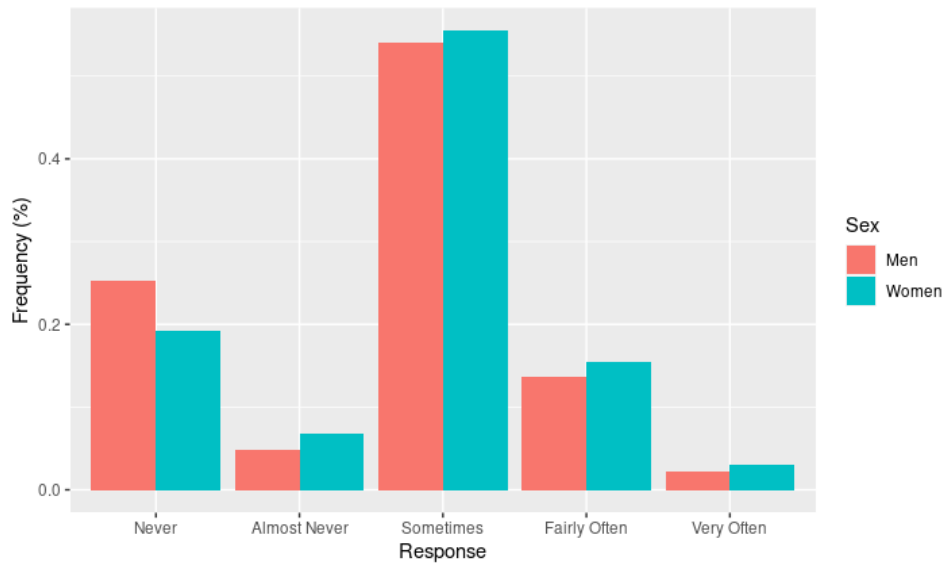
**Figure 3: BMI and Helplessness**

### 3.3 Hopelessness

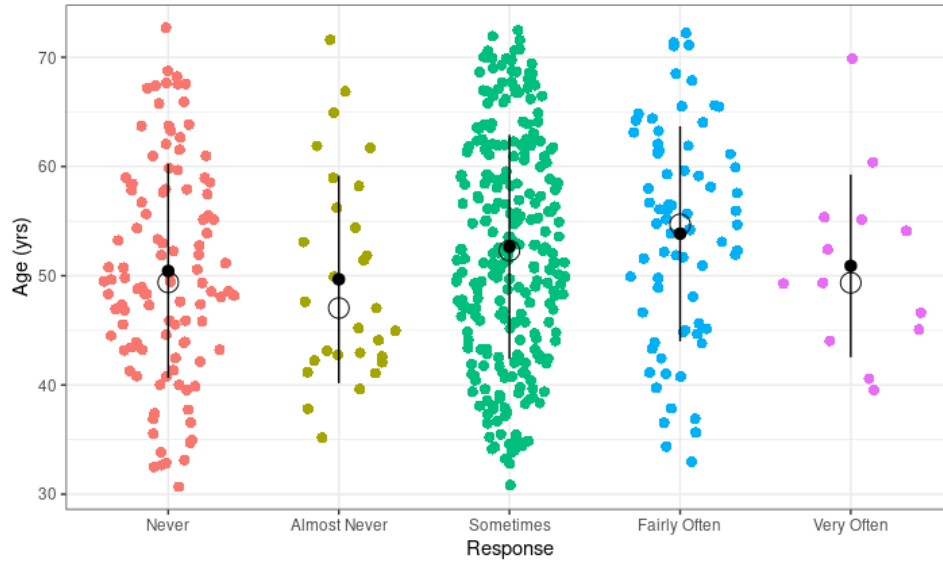
Out of the 491 hopelessness responses 28% of the participants responded “never” or “almost never” to the question “In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?” and 17% responded “fairly often” or “very often.” The greatest majority (54%) selected the third of the five options, “sometimes.” There were 28 individuals who were not asked this question; the reason for this omission was not recorded. Descriptive statistics for the participants in each category can be found in Table 4. The distributions of sex, age, and BMI per helplessness response are shown in Figures 4, 5, and 6, respectively.

**Table 4. Select Characteristics of Sample Stratified by Hopelessness Response**

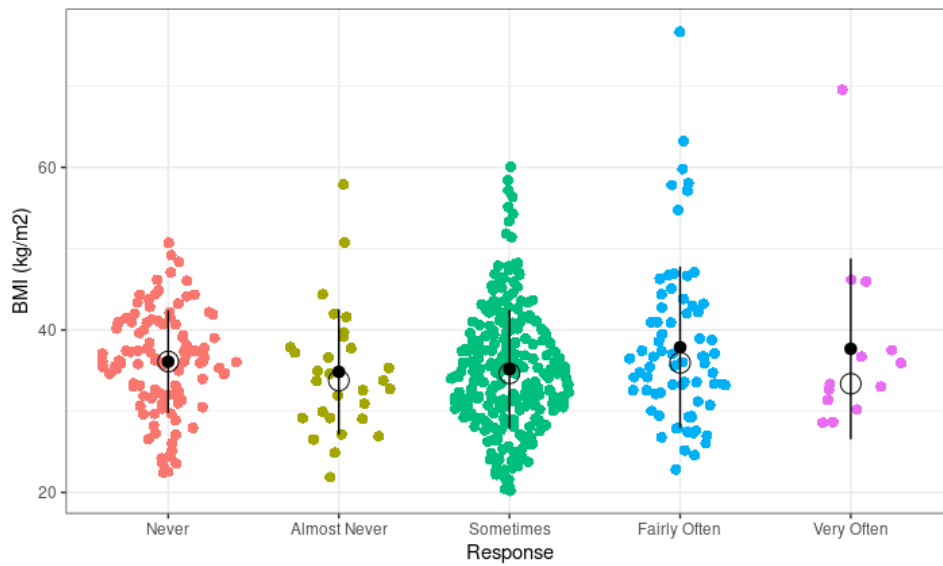
Hopelessness	“In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?”					
	1 Never	2 Almost Never	3 Sometimes	4 Fairly Often	5 Often	NA
<b>Total Number</b>	108	29	269	72	46	28
<b>% Female</b>	47.2	62.1	54.6	56.9	61.5	75
<b>Age (years) mean ± sd</b>	50.4 ± 9.8	49.7 ± 9.5	52.6 ± 10.3	53.8 ± 9.8	50.9 ± 8.4	53.0 ± 8.4
<b>BMI (kg/m<sup>2</sup>) mean ± sd</b>	36.1 ± 6.3	34.8 ± 7.7	35.2 ± 7.3	37.9 ± 9.9	37.7 ± 11.1	33.8 ± 5.2



**Figure 4: Hopelessness by Sex**



**Figure 5: Age and Hopelessness**



**Figure 6: BMI and Hopelessness**

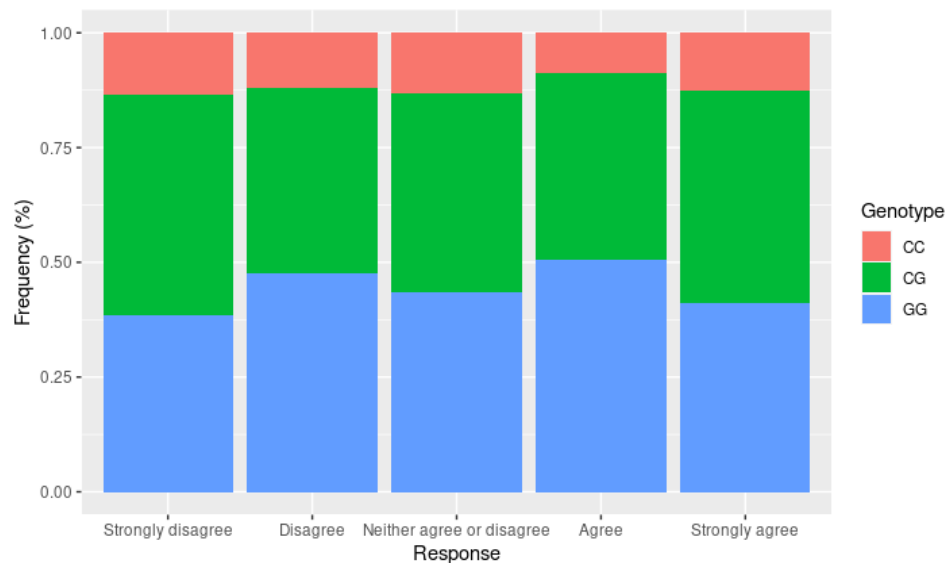
### 3.4 Association of Helplessness with Sex, Age, BMI, and Genetic Variants

I performed ordinal regression to assess the effects of sex, age, BMI, and genotype on response to the statement capturing helplessness. There was no evidence of association in this

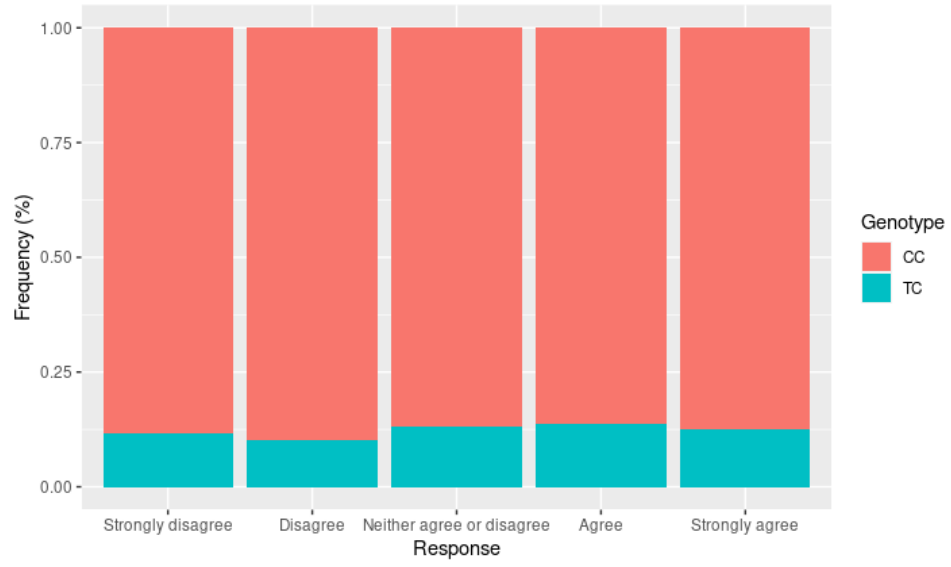
sample between helplessness and age, sex, BMI or rs4721059, rs11581382 or rs2042144. Table 5 contains the regression coefficients ( $\beta$ ) and  $p$  values for the rs4721059, rs11581382 and rs2042144 analyses. Figures 7, 8, and 9 display the distribution of responses to the helplessness statement stratified by genotype for rs4721059, rs11581382, and rs2042144, respectively.

**Table 5. Ordinal Regression of Helplessness on Age, Sex, BMI, and Genetic Variants**

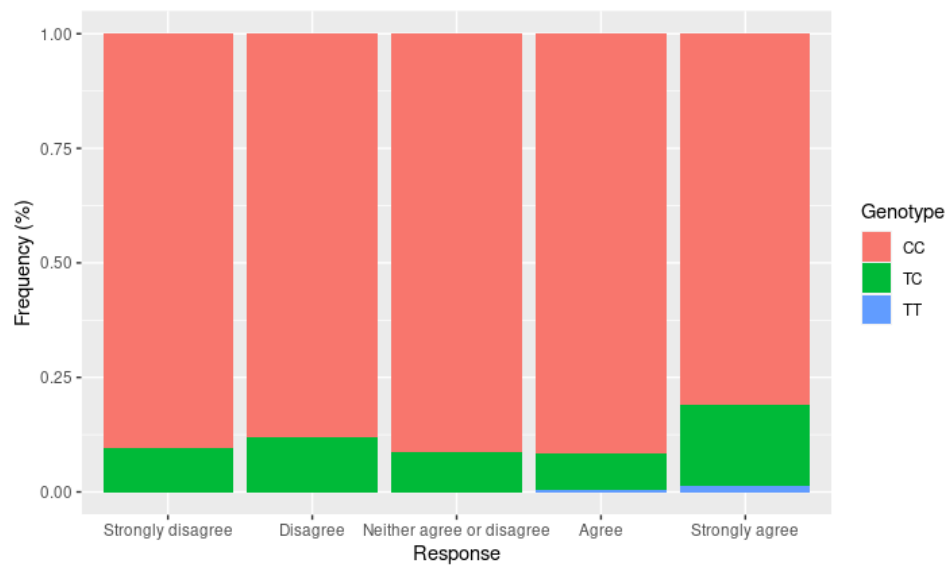
rs4721059			rs11581382			rs2042144		
Covariate	$\beta$	$p$	Covariate	$\beta$	$p$	Covariate	$\beta$	$p$
Age	0.001	0.891	Age	0.001	0.859	Age	0.002	0.790
Sex	0.052	0.764	Sex	0.054	0.754	Sex	0.067	0.697
BMI	0.004	0.703	BMI	0.004	0.704	BMI	0.005	0.642
rs4721059	-0.056	0.649	rs11581382	0.150	0.545	rs2042144	0.361	0.165



**Figure 7: Helplessness and rs4721059**



**Figure 8: Helplessness and rs11581382**



**Figure 9: Helplessness and rs2042144**

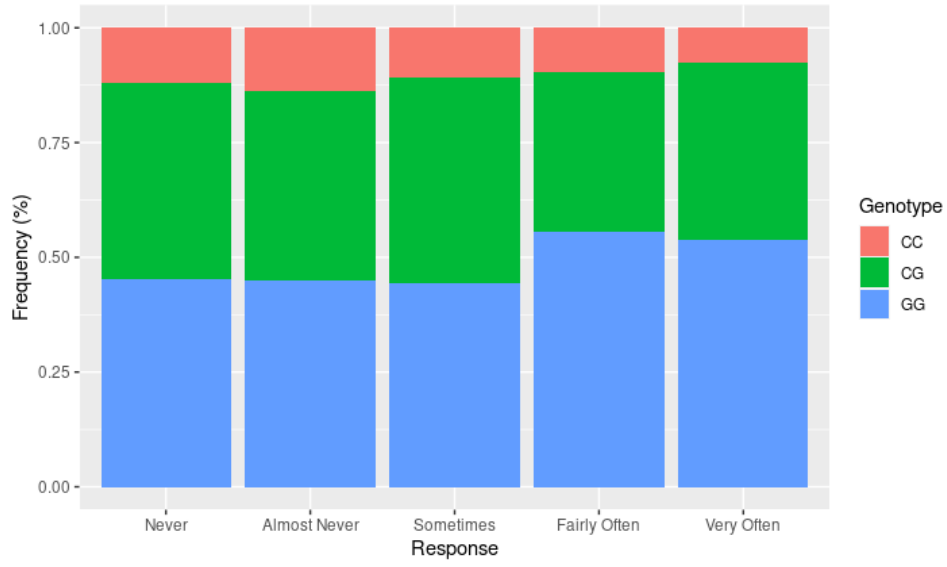
### 3.5 Association of Hopelessness with Sex, Age, BMI, and Genetic Variants

I performed ordinal regression to assess the effects of sex, age, BMI, and genotype on response to the question capturing hopelessness. There was no evidence of association in this sample between hopelessness and sex, BMI or rs4721059, rs11581382 or rs2042144. There was a statistically significant association between higher hopelessness and higher age in all these genetic variant analyses; the odds of being in a higher category of hopelessness is 2.5% higher per year of age ( $p < 0.005$ ) adjusting for sex, BMI, and the genetic variant—calculated as  $e^\beta$ . Table 6 contains the regression coefficients ( $\beta$ ) and  $p$  values for the rs4721059, rs11581382, and rs2042144 analyses. Figures 10, 11, and 12 display the distribution of responses to the helplessness statement stratified by genotype for rs4721059, rs11581382, and rs2042144, respectively.

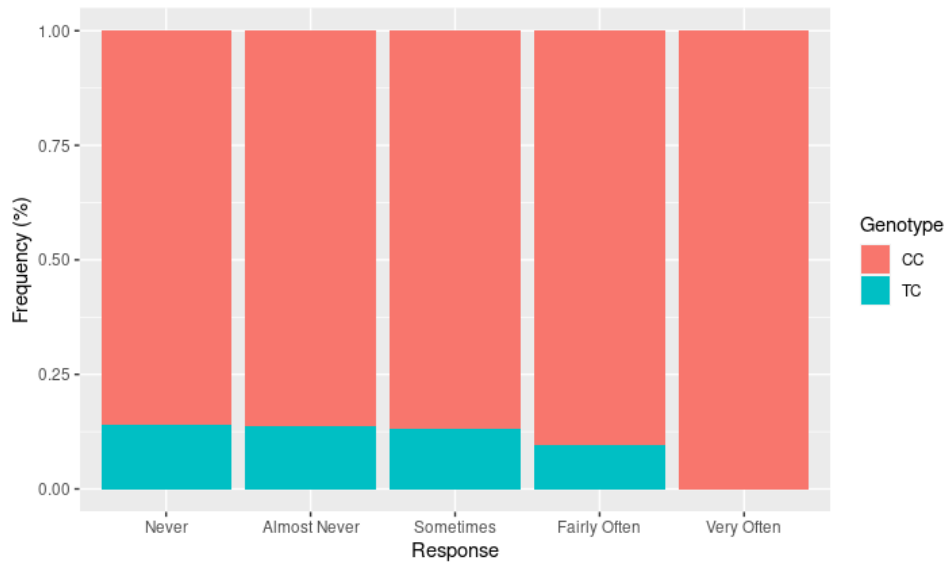
**Table 6. Ordinal Regression of Hopelessness on Age, Sex, BMI, and Genetic Variants**

rs4721059			rs11581382			rs2042144		
Covariate	$\beta$	$p$	Covariate	$\beta$	$p$	Covariate	$\beta$	$p$
Age	0.025	0.004*	Age	0.024	0.006*	Age	0.025	0.005*
Sex	0.257	0.161	Sex	0.245	0.181	Sex	0.237	0.197
BMI	0.015	0.196	BMI	0.016	0.081	BMI	0.016	0.194
rs4721059	-0.156	0.227	rs11581382	-0.249	0.334	rs2042144	0.036	0.893

\*Statistically significant

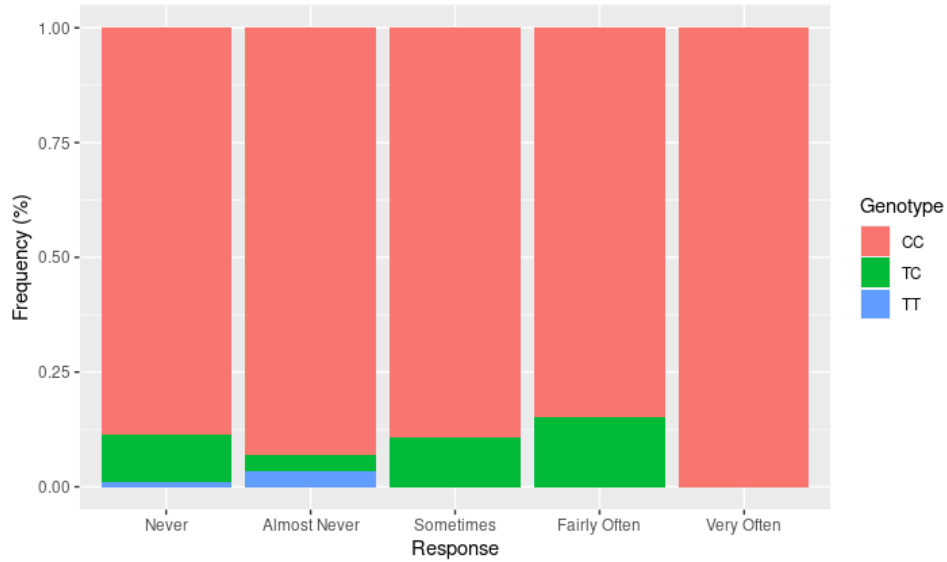


**Figure 10: Hopelessness and rs471059**



**Figure 11: Hopelessness and rs11581382**

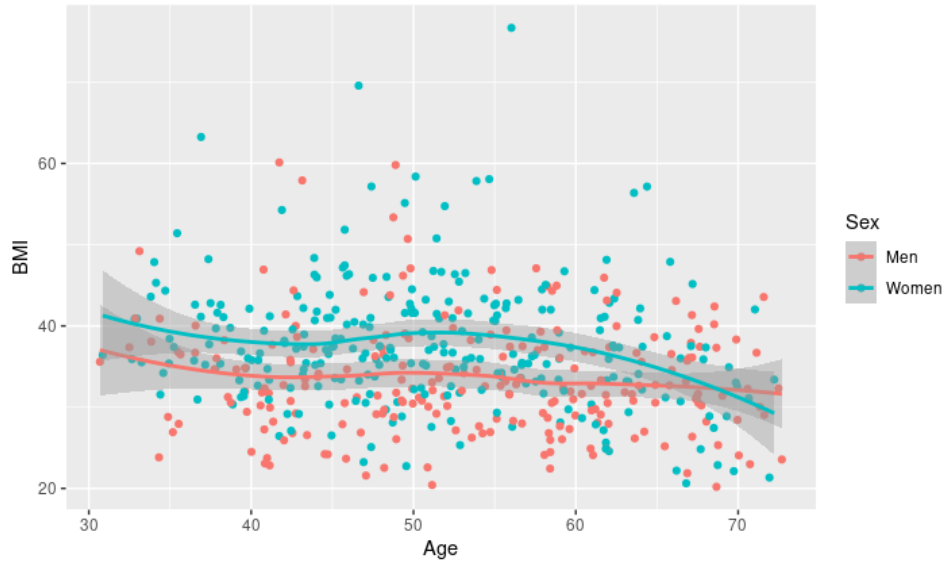




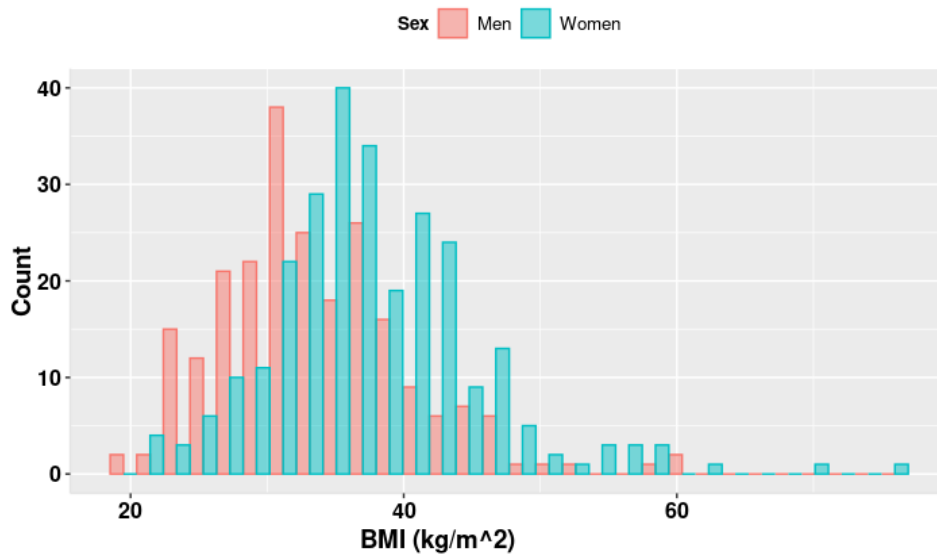
**Figure 12: Hopelessness and rs2042144**

### **3.6 Association of BMI with Sex, Age and Genetic Variants**

The distribution of BMI by age, stratified by sex, can be found in figure 13. BMI is relatively consistent across age in both sexes, except for women above the age of 55 where it tends to be lower with higher age. The distribution of BMI, stratified by sex, can be found in figure 14. There are two bell-shaped and symmetric distributions, one for each sex with separate modes; there is a higher mean BMI in women. This feature can also be observed in figure 13, where the smoothed curve of the mean BMI of women is higher than that of men until about age 68.



**Figure 13: Distribution of BMI by Age Stratified by Sex**



**Figure 14: Distribution of BMI Stratified by Sex**

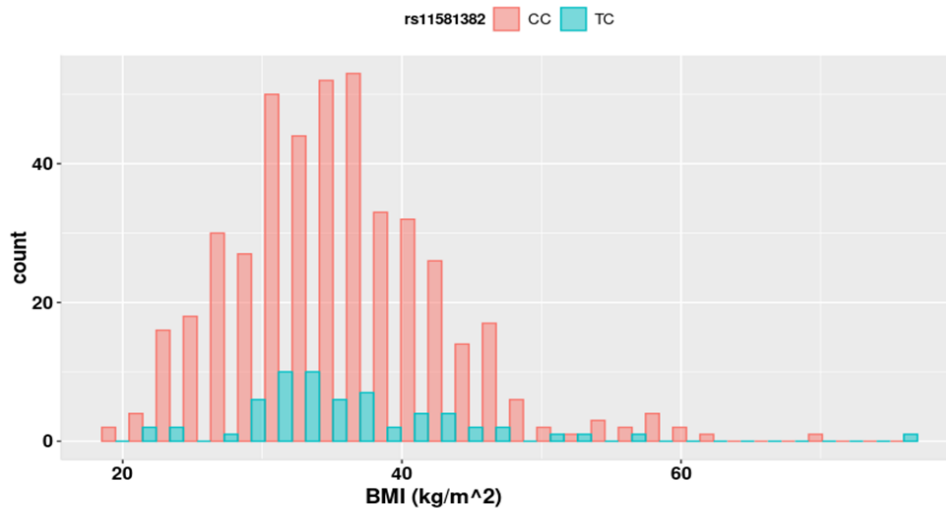
To further explore these observations and to assess the association of rs4721059, rs11581382 and rs2043144 with BMI, I performed linear regression of BMI on sex, age, and genotype. The regression coefficients and  $p$  values can be found in Table 7 for the rs4721059,

rs11581382 and rs2043144 analyses. Both age and sex had statistically significant effects on BMI in all three analyses. BMI was approximately  $-0.1 \text{ kg/m}^2$  lower per year ( $p < 0.003$ ) and was approximately  $4.0 \text{ kg/m}^2$  higher in women than in men ( $p < 3.7 \times 10^{-9}$ ). However, there was no evidence of a statistically significant association between genotype and BMI for any of the variants. The distributions of BMI stratified by genotypes for rs4721059, rs11581382, and rs2043144 are displayed in Figures 15, 16, and 17.

**Table 7. Linear Regression of BMI on Sex, Age and Genetic Variants**

rs4721059			rs11581382			rs2042144		
Covariate	$\beta$	$p$	Covariate	$\beta$	$p$	Covariate	$\beta$	$p$
Age	-0.100	0.003*	Age	-0.098	0.003*	Age	-0.100	0.002*
Sex	4.006	$2.8 \times 10^{-9}$ *	Sex	3.990	$3.3 \times 10^{-9}$ *	Sex	3.985	$3.7 \times 10^{-9}$ *
rs4721059	-0.208	0.667	rs11581382	0.306	0.759	rs2042144	-0.006	0.995

\*Statistically significant



**Figure 15: BMI and rs11581382**

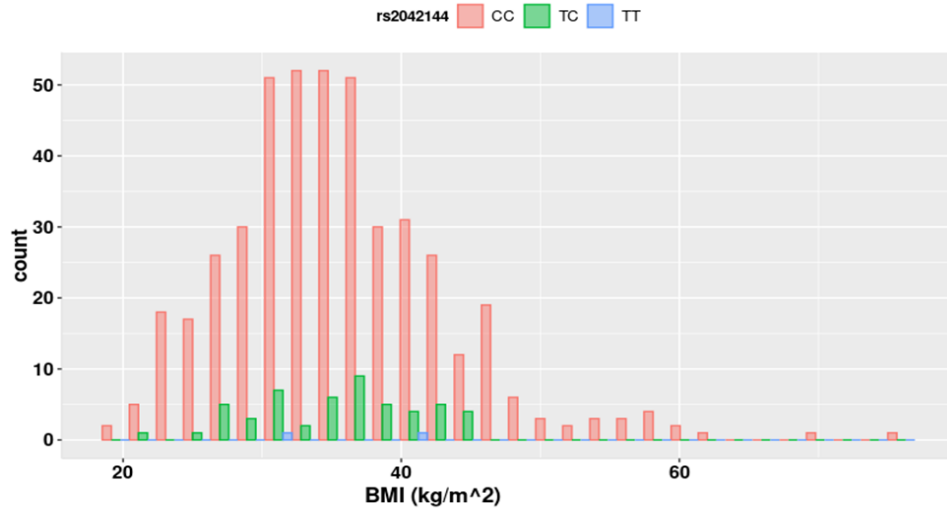


Figure 16: BMI and rs2042144

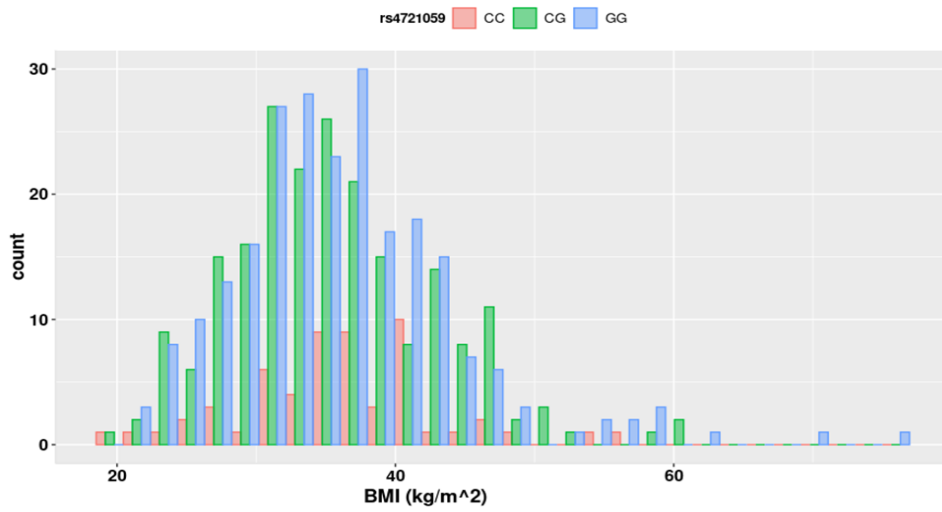


Figure 17: BMI and rs4721059

## 4.0 Conclusions

In this study, I looked at three proxies for genetic variants previously associated with broad depression or probable major depressive disorder. I tested for association between these variants and two depressive features, helplessness and hopelessness, as well as with BMI. I also looked at the relationship between age, sex, and BMI and the two depressive features, as well as between age and sex, and BMI.

I observed no significant association between the three genetic variants (rs4721059, rs11581382 and rs2043144) and helplessness, hopelessness, or BMI. There are several limitations that could have contributed to lack of the observation of an association where one might yet still exist. One possible explanation is that the genetic variants I selected for this study were based on the findings from Howard et al. (2018), who used the UK Biobank and excluded individuals who were not recorded as “white British.” The UK Biobank is clearly not representative of the genetics found on Samoa, as Samoans are indigenous Polynesian people. So, it is possible that the genetic variants I have selected are not appropriate for study of Samoans.

Another possible reason for there not to have been an observed relationship is that the genotypes of the specific genetic variants I was interested in from Howard et al. (2018) were not available in the *Soifua Manuia* Study, and nearby highly correlated variants were used instead, potentially diluting the correlation between the peak Howard et al. (2018) variants’ genotypes and the phenotypes.

The lack of statistical power could also be contributing to the absence of an association. The largest effect size among the three variants in Howard et al. (2018) was an odds-ratio of 1.009.

The power to detect such a small odds-ratio with just 519 participants is likely very low. Additionally, the allele frequencies of all three variants, especially rs2042144 (0.050 in Samoans vs 0.539 in Europeans) are further away from 0.500 than they are in white British individuals, which also contributes to lower statistical power.

Finally, it could be that the proxy measures for depression that I selected from the questionnaires did not accurately or completely capture depression within the sample. As described previously, depression is a complex disorder with numerous presentations that can be specific to the individual and their personal experiences. Additionally, this was the first time that these psychosocial instruments (questionnaires) were used in the Samoan context, so it is possible that the questionnaires did not capture exactly the information the researchers were hoping to acquire.

I did observe an association between hopelessness and age, where higher age was associated with higher reported hopelessness. This is inconsistent with research that has consistently shown that depression is less prevalent (or not more prevalent) among in late life as compared to midlife (Blazer et al. 1991; Charles et al. 2001; Murrell et al. 1983). Furthermore, Alvarez et al. (2011) found that most symptoms of depression do not differ between early- and late-onset depression, and Grayson and Thomas (2013) did not observe any differences in clinical features between early- and late-onset depression. This inconsistency between the finding here and the consensus in the literature could reflect a spurious finding in this study or a unique feature of depressive affects in the Samoan context. Additional studies targeting depression and depressive symptoms more comprehensively could aid in understanding whether this observation is real and, if so, its cause.

Research is also consistent in the observation that depression and obesity are often comorbid and the relationship between them is bidirectional (Milaneschi et al. 2019). However, in

this study, there was no association between the depressive features of helplessness and hopelessness and BMI. This could be due to the imprecision of these two proxy assessments in truly capturing depression. It is intriguing however to consider whether depression and obesity might be decoupled in the Samoan context. Additional research is necessary to confirm that these two diseases are in fact not correlated among Samoans.

#### **4.1 Public Health Implications**

Although this research study did not find a significant association between an individual's genotype at three depression-related variants and depressive symptoms or BMI, this does not mean a relationship does not, in fact, exist. I studied just three genetic variants out of many that have been implicated in influencing depression and BMI through various pathways and mechanisms. There are many more possible relationships that remain to be explored. Also, as more genetics research is conducted with the Samoan people, an increased understanding of genomic variants specific to the Samoan people and the role that they play will become clearer, uncovering more areas of potential research. However, given the levels of obesity present within the Samoan population, it is vital to consider the implications of that in terms of uncaptured comorbidity with depression and the effect of those conditions on quality of life.

If, as potentially suggested by this study, depression and body size are decoupled among Samoans, and the bidirectional nature present in many populations has been interrupted, this could point to social determinants present in the population that could be acting against psychosocial factors that might link depression and obesity. Such factors could point to interventions that might decouple these disorders in other populations.

## 4.2 Further Research

Both depression and obesity are thought to be influenced by many genetic variants as well as various environmental factors, making them ideal candidates for polygenic risk score estimation. This would provide a score predicting the relative risk for a disease. However, to yield accurate results the data used to calculate these scores needs to come from large-scale genomic studies. A recent study conducted by Cao et al. (2021) using polygenic risk scores for depression found that individuals who possessed a high genetic risk as well as what they labeled as unfavorable lifestyle (current smoker, unhealthy diet, moderate alcohol intake, a BMI  $\geq 30$  kg/m<sup>2</sup>, and lack of physical activity) had greater than a two-fold risk of incident depression than those who had low genetic risk and a favorable lifestyle (Cao et al. 2021). However, this study, as with a great many genomic studies before it, was conducted solely on individuals of European ancestries. The limited number of genomic studies conducted on populations of non-European ancestries, and specifically Samoans, makes applying polygenic risk scores difficult because the data on their applicability and efficacy is simply not available. Additional genetics research is necessary in populations of non-European ancestry to allow for scientific advances so that extant health disparities between those of European ancestries and those of non-European ancestries is not further exacerbated as interventions based on genetic information become more prevalent.



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