DIET QUALITY AND DEPRESSION IN A COHORT OF AMERICAN INDIANS: THE STRONG HEART FAMILY STUDY

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Abstract: Diet quality has been shown to be inversely associated with depression, but this has not been studied in American Indians (AIs). We examined the prospective association of diet quality and probable depression in a family-based cohort of rural AIs. Using data from the Strong Heart Family Study, we included 1,100 AIs ≥14 years old who were free of probable depression at baseline. We defined probable depression as the presence of moderate or severe depressive symptoms on the Center for Epidemiologic Studies Depression Scale or current use of antidepressant medications. We calculated baseline diet quality from food frequency questionnaires using the Alternative Healthy Eating Index-2010 (AHEI). We used GEE-based multivariate logistic regression to estimate the odds ratio of probable depression at follow up associated with a 10-point higher AHEI score at baseline, adjusted for demographic, psychosocial, and health factors. At follow up, 19% (n = 207) of the sample reported probable depression. Diet quality was not associated with report of probable depression at follow up (OR = 1.16, 95% CI [0.96, 1.39]). Research is needed to examine other temporal dimensions of this relationship and unique aspects of rural AI diets and psychosocial factors that may influence depression.

INTRODUCTION

Rural American Indian (AI) communities experience some of the highest rates of diet-related cardiometabolic diseases in the United States (Benjamin et al., 2019; Hutchinson & Shin, 2014; Breathett et al., 2020). Colonization, loss of land, subsequent food insecurity, and federal food assistance programs led to a rapid transition from traditional to "Western" diets for many AI communities (Compher, 2006; Howard et al., 1999; Kuhnlein & Receveur, 1996; Warne &

Wescott, 2019). Before this nutrition transition, cardiometabolic diseases such as diabetes and coronary heart disease were largely absent in AIs (Howard et al., 1999; Welty et al., 2002).

Traditional or subsistence diets consist of nutrient-dense, minimally processed foods such as wild game, berries, squash, legumes, and whole grains. Hunting, gathering, and harvesting practices of traditional diets are intrinsically linked with physically active lifestyles and spiritual and cultural well-being (Conti, 2006). In contrast, a "Western" dietary pattern is characterized by frequent consumption of highly processed, energy-dense, and nutrient-poor food, and accompanies a sedentary lifestyle and cardiovascular disease risk factors (Eilat-Adar et al., 2013). Commonly consumed foods in rural AI communities, like soda and processed meat, align with this dietary pattern (Fretts et al., 2012; Taylor et al., 2006). Other common foods that have been historically consumed, but differ from pre-colonial, traditional diets, such as hydrogenated vegetable fats for frying, are also associated with similar risk profiles to that of the "Western" dietary pattern (Eilat-Adar et al., 2013).

There is growing interest in understanding how dietary patterns that prevent cardiometabolic diseases may additionally reduce the risk of common mental health conditions (Jacka et al., 2012). While depression is attributable to biological, environmental, and social factors (Lopresti et al., 2013; Urban Indian Health Institute, Seattle Indian Health Board, 2012), some evidence from non-AI populations suggests that healthy diet quality may protect against the development of depression. Dietary patterns characterized by high consumption of vegetables, fruits, whole grains, and healthy fats are associated with reduced risk of depression in recent meta-analyses (Lassale et al., 2019; Molendijk et al., 2018; Nicolaou et al., 2019; Opie et al., 2017). Diets high in ultra-processed foods and red and processed meat may increase the risk (Bear et al., 2020; Lopresti et al., 2013; Marx et al., 2017). Nutritional quality of the diet influences systemic inflammation, oxidative stress, insulin resistance, and gut microbiota, which are related to neuronal health and cognitive functioning (Bear et al., 2020; Opie et al., 2017; Sánchez-Villegas et al., 2013), and could lead to onset or persistence of depressive symptoms. Dietary sources of antioxidants, fiber, omega-3 fatty acids, and folate, consumed in higher amounts in healthy dietary patterns, are thought to play protective, beneficial roles in these mechanisms (Bear et al., 2020; Opie et al., 2017).

However, further investigation of the prospective relationship between diet quality and depression is warranted. Studies that examined adherence to a Mediterranean dietary pattern produced the most robust evidence (Lassale et al., 2019), but this pattern does not reflect a culturally appropriate diet for all populations. While other healthy dietary patterns have produced

generally consistent evidence, the associations are weaker (Nicolaou et al., 2019), and most occurred in cohorts of majority-white populations in Europe, Australia, and North America (Lassale et al., 2019). Additionally, it has been difficult to control for psychosocial factors like social support and environmental stress that influence diet quality and depression (Bear et al., 2020; Molendijk et al., 2018).

To our knowledge, no prior studies have focused on AI populations. Diets of AI populations on reservations and in rural areas differ substantially from populations in the existing literature (Zamora-Kapoor et al., 2019). The prevalence of depression in rural AI populations varies across communities and tribal settings (Asdigian et al., 2018; Beals et al., 2005; Brave Heart et al., 2016; Finkbonner & Kaiser, 2002; Urban Indian Health Institute, 2012). In an earlier analysis of the Strong Heart Family Study, nearly 28% of the population reported current moderate or severe depressive symptoms (Zhao et al., 2016). Importantly, depression has been linked with poor glucose control and higher diabetes mortality in AI communities (Calhoun et al., 2010; Goins et al., 2019; Knaster et al., 2015; Sahota et al., 2008). Efforts to prevent depression can help address disparities in diabetes risk (CDC, 2020). The Strong Heart Family Study is an opportunity to investigate the relationship between diet quality and depression in rural AI communities and identify implications for cardiometabolic and mental health interventions.

Objectives

The primary objective of this study was to determine whether baseline diet quality was associated with the presence of depressive symptoms or antidepressant use after five years of follow up among AIs from primarily rural AI communities. Our secondary, exploratory objectives were to assess for interactions between diet quality and age, and diet quality and sex in this population because susceptibility to depressive symptoms can vary over the life course and differ by sex (Abrams & Mehta, 2019; Akbaraly et al., 2013; Brave Heart et al., 2016; Rice et al., 2015). We additionally conducted sensitivity analyses to assess the robustness of our findings with narrower definitions of depression and, separately, within a more restricted baseline population.

We hypothesized that higher diet quality is associated with lower odds of reporting depressive symptoms and/or antidepressant use at follow up, and secondarily, that the association is stronger among younger individuals and females. Since we aimed to estimate an unbiased association between diet quality and depression, we adjusted for demographic characteristics, measures of physical health, and psychosocial factors in all analyses.

METHODS

Study Design

We analyzed data from the Strong Heart Family Study, a prospective, family-based cohort study designed to identify risk factors for cardiovascular disease among AIs from 12 tribal communities in Arizona, Oklahoma, North Dakota, and South Dakota. Details on the original study are described elsewhere (Lee et al., 1990; North et al., 2003).

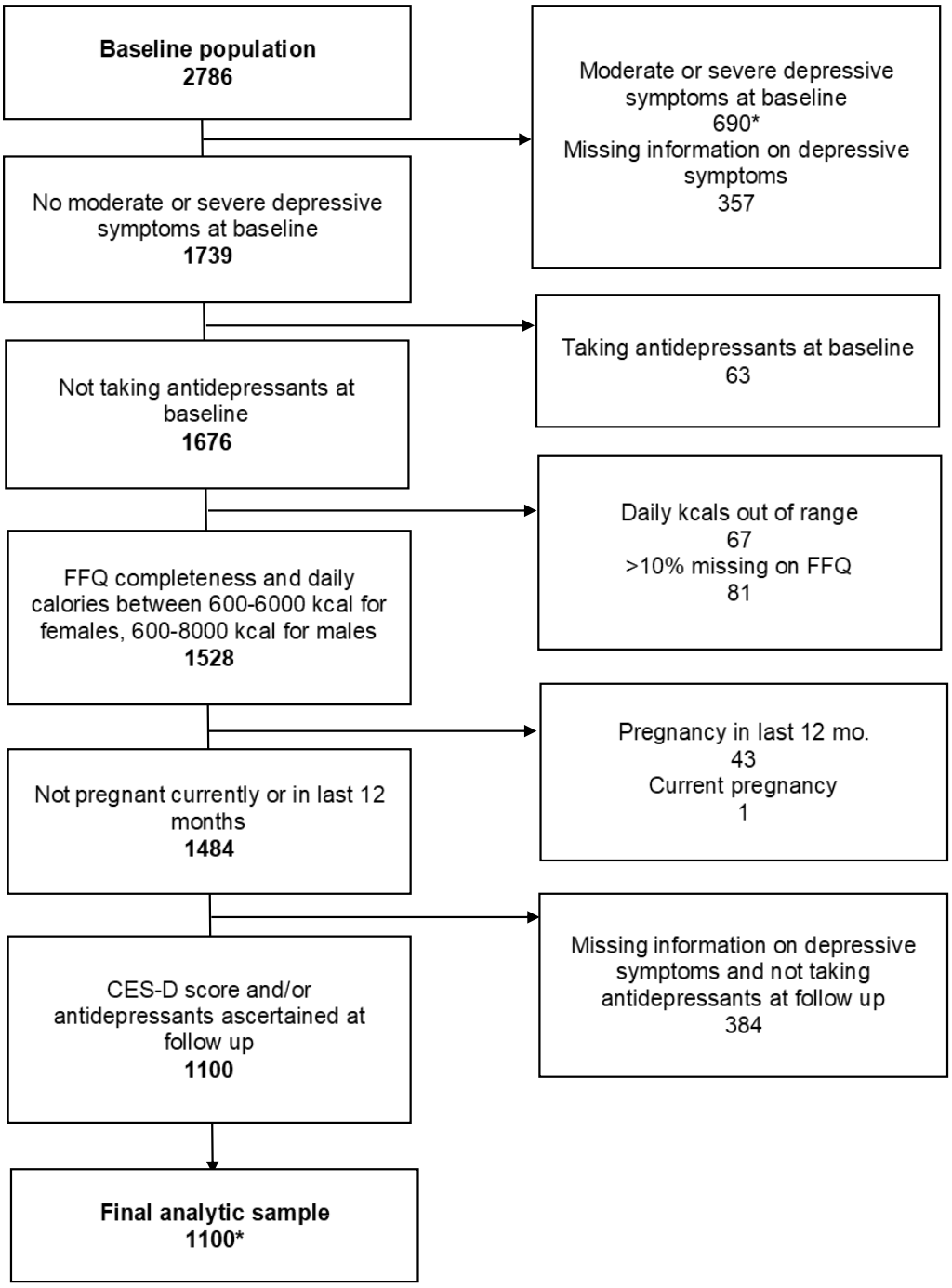
Our study involved two assessments: baseline (2001-2003) and follow up (2007-2009). We selected these assessments because they collected the most recent data on diet and psychosocial measures available in the cohort. Both assessments included a physical examination, detailed personal interview, and one-week pedometer log. The examination consisted of a general physical assessment for overall health, fasting blood glucose testing, pregnancy testing if suspected, and a review of all medications taken in the past two weeks (Lee et al., 1990; North et al., 2003). The personal interview collected information on medical history, demographics, health behaviors, and psychosocial factors. The food frequency questionnaire was only administered at the baseline assessment personal interview. All participants provided written, informed consent at each assessment.

Population

We included 1,100 individuals who completed baseline and follow-up assessments and were free of probable depression at baseline (Figure 1). Participants were ≥14 years old and from 83 large families in 12 tribal communities in Arizona, Oklahoma, North Dakota, and South Dakota. From the initial population of 2,786, we excluded participants from our analysis who, at baseline, had moderate or severe depressive symptoms (n = 690), missing information on depressive symptoms (n = 357), or were taking antidepressant medications (n = 124, 61 of whom also had moderate/severe depressive symptoms). We additionally excluded those with unreliable diet information, defined as reporting daily energy intake outside the bounds of 600-6,000 kcal for females or 600-8,000 kcal for males (Eilat-Adar et al., 2013; Kauffman et al., 2019) or failing to answer >10% of items on the food frequency questionnaire (n = 148). Those with a pregnancy ≤12 months before the baseline assessment were also excluded (n = 44). Finally, we excluded participants who were missing depressive symptom information and not taking antidepressants at follow up (n = 384). Individuals with missing information at follow up were more likely to be

male, older, and have less than a high school education, known diabetes, and slightly higher diet quality compared to the analytic sample (see Appendix Table A1).

Figure 1. Strong Heart Family Study population inclusion and exclusion criteria for the analytic sample



Participants were ≥14 years old at baseline (2001-2003) and from 83 large families in 12 tribal communities in Arizona, Oklahoma, North Dakota, and South Dakota. The follow-up exam occurred in 2007-2009. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D); scores reflect depressive symptoms: none = <10; mild = 10-15; moderate = 16-24; severe = >24. Diet quality and caloric intake were assessed using a Block Food Frequency Questionnaire (FFQ). *321 individuals were additionally excluded in the sensitivity analysis with a baseline population restricted to those with a CES-D score <10 (no depressive symptoms).

Assessment of Diet Quality

The validated Block 1998 Food Frequency Questionnaire (FFQ) was used to estimate the usual dietary intake during the previous year at the baseline assessment (Block et al., 1986; (Boucher et al., 2006). The FFQ food list included 110 items that reflected the most common nutrient sources and food groups in American diets based on National Health and Nutrition Examination Survey dietary recall data (Block et al., 1986). Nine additional items that are commonly consumed in AI communities were added to the FFQ (Strong Heart Study Coordinating Center, 2001). The items were selected by community-based study staff and community members in consultation with local dieticians to represent a non-exhaustive list of popular AI foods that may contribute meaningfully to usual dietary intake. The items were Spam, menudo, pazole, guysava, red/green chili stew, Indian taco, frybread, and corn and flour tortillas. For all food items on the FFQ, participants estimated a frequency of consumption (seasonally, never, few times per year, 1x/month, 2-3x/month, 1x/week, 2x/week, 5-6x/week, daily), and quantity (small, medium, large portion size).

Using standard Block FFQ analysis methods with a Block Dietary Database, average daily intakes of food groups, nutrients, and energy were calculated for each participant (Block et al., 1986). We used the Alternative Healthy Eating Index-2010 (AHEI) to determine diet quality from these average daily intakes. The AHEI is based on 11 nutrients and food groups that are associated with risk of cardiometabolic disease: vegetables, fruits, whole grains, sugar-sweetened beverages and fruit juice, nuts and legumes, red and processed meat, *trans* fat, long-chain n-3 fatty acids (EPA + DHA), polyunsaturated fatty acids, sodium, and alcohol (Chiuve et al., 2012). Absolute intake of each nutrient or food item was scored 0 (worst) to 10 (best) using standardized serving sizes and cut points known to influence disease risk (Appendix Table A2) (Chiuve et al., 2012; Kauffman et al., 2019). AHEI scores can range from 0 (least healthy) to 110 (most healthy). We did not include alcohol intake in the AHEI score; therefore, the maximum possible AHEI score in this study was 100. Since the relationship between alcohol use and depression is complex (Boden & Fergusson, 2011), we did not consider alcohol use in the characterization of diet quality. We included categorical, self-reported alcohol use (current, former, never) as a covariate in our statistical analysis instead.

Measurement of Depression

The primary outcome was the presence of moderate or severe depressive symptoms or initiation of antidepressant medications at follow up, which we defined collectively as probable

depression (APA, 2011; Ferrari et al., 2013; Zhao et al., 2016). Depressive symptoms were assessed using the validated Center for Epidemiologic Studies Depression Scale (CES-D) for nonclinical measures of depressive symptomology (Radloff, 1977), which has been used and validated in AI populations (Calhoun et al., 2010; Zhao et al., 2016; Schure & Goins, 2017; Dick et al., 1994; Somervell et al., 1993). The CES-D has also been used in prospective studies of diet quality and depression in other populations (Adjibade et al., 2018; Akbaraly et al., 2013; Le Port et al., 2012; Vermeulen et al., 2018). Participants rated 20 items on a 4-point Likert scale indicating how often in the past week they experienced symptoms associated with depression (Radloff, 1977). Items were summed to produce an overall CES-D score (0-60) to create four categories of depressive symptoms: none = <10, mild = 10-15, moderate = 16-24, severe = >24 (APA, 2011). We considered a participant's overall score missing if they failed to respond to > 4 items (Radloff, 1977).

Participants with any of the following current medications documented in their review were classified as taking antidepressants: Amitriptylin, Bupropion, Buproprion SR, Celexa, Citalopram, Cymbalta, Desipramine, Effexor, Effexor XR, Elavil, Escitalopram, Fluoxetine, Fluvoxamine, Imipramine, Lexapro, Nortriptylin, Paroxetine, Paroxetine HC, Paxil, Prozac, Remeron, Sertraline, Trazodone, Venlafaxine, Wellbutrin, Wellbutrin SR, or Zoloft.

Measurement of Covariates

We selected covariates *a priori* based on their potential to confound the relationship between baseline diet quality and presence of depression and/or use of antidepressants at follow up. Dietary habits and depression are known to vary by age, sex, and tribal community (Beals et al., 2005; Finkbonner & Kaiser, 2002). We used educational attainment as a proxy for socioeconomic status, which is known to influence diet quality and depression (Darmon & Drewnowski, 2008; Lorant et al., 2003). Smoking, smokeless tobacco use, and alcohol use are associated with diet quality and depression (Boden & Fergusson, 2011; Breslow et al., 2010; Liu et al., 2017; Noble et al., 2015). Body size and physical activity are also known correlates of diet quality and depression (Liu et al., 2017). Diabetes status influences diet quality and depression (Al-Ibrahim & Jackson, 2019; Calhoun et al., 2010; Sahota et al., 2008). We hypothesized that the psychosocial measures of self-reported social support, health locus of control, and identification with one's tribal traditions would also influence diet quality and depression through potential

pathways related to health behavior norms, coping, and cultural buffers to environmental stressors (Berk et al., 2013; Roh et al., 2015; Walters & Simoni, 2002).

At the baseline assessment personal interview, participants' field center location (Arizona, Oklahoma, and South Dakota), sex (male, female), age (years), and education (years) were collected in the personal interview. Participants also reported their status for smoking (never, former, current), smokeless tobacco use (current, no), and alcohol use (never, former, current). Body mass index (BMI) was calculated from height and weight measurements at the baseline physical examination.

Daily step counts were measured over seven days immediately following the baseline assessment using Accusplit AE120 pedometers (Yamax, Japan). We calculated average steps per day after excluding the minimum and maximum step counts for each participant; all observations were included if more than two observation days were missing (Fretts, Howard, McKnight, Duncan, Beresford, Calhoun, et al., 2012).

Diabetes status was assessed with blood glucose testing as part of the physical examination at baseline. Known diabetes was defined as ≥126 mg/dL fasting blood glucose at baseline or reported history of diabetes and any of the following: on insulin treatment, hypoglycemic agent, renal dialysis, or had kidney transplantation. Impaired glucose tolerance was defined as fasting blood glucose 110-125 mg/dL and no diabetes treatment. Normal glucose tolerance was <110 mg/dL at baseline and no diabetes treatment (Strong Heart Study Coordinating Center, 2001).

The following psychosocial measures were ascertained during the baseline personal interview. A social support questionnaire measured perceived emotional support, social networks, tangible social support, and negative social support on a Likert scale and produced a summary score of 0-40 (Roh et al., 2015; Strong Heart Study Coordinating Center, 2001). The Multidimensional Health Locus of Control Scale measured beliefs about internal versus external determinants of health, and thus, tendencies towards healthy behaviors and reactions to health outcomes (Strong Heart Study Coordinating Center, 2001; Wallston, 2005). We calculated summary scores of 0-18 for participants' agreement with each construct (internal, external: chance, and external: powerful others); only internal scores were included in the model due to weak inter-construct correlations (Wallston, 2005). Self-identification with tribal traditions was measured by asking, "How much do you identify yourself with your own tribal tradition?" Responses were dichotomized as "a little" (not at all or a little) and "a lot" (some or a lot).

Analyses

For the primary analysis, our objective was to determine whether baseline diet quality was associated with report of probable depression at follow up in a population free of probable depression at baseline. To achieve this, we estimated the population odds ratio and 95% confidence interval for probable depression at follow up associated with baseline AHEI score. We fit a multivariate logistic regression model using generalized estimating equations with an independence working correlation and robust standard errors. The use of generalized estimating equations accounts for clustering of the data at the family level. We estimated the odds ratio for a ten-point AHEI score difference because this was similar to AHEI score comparisons made in other populations, and standard cut points are not specified (Akbaraly et al., 2013; Miller et al., 2020; Sánchez-Villegas et al., 2015).

We imputed missing observations for covariates using multiple imputation by chained equations (Schafer, 1999) to adjust for potential confounders in our primary analysis. Missing observations for covariates did not exceed 7% for any one variable. The imputation model included all variables in the primary analysis model and produced ten imputations with 100 iterations per round. We evaluated convergence with trace plots of means and standard deviations for each imputed variable and compared distributions of imputed versus observed values to assess whether the imputed variable distributions were realistic.

We conducted two exploratory analyses to evaluate whether the association between diet quality and probable depression differed by baseline age and sex. For age, we added an interaction term for age (years) and AHEI score in the primary model. Due to statistical power limitations, we qualitatively examined the exponentiated interaction term and 95% confidence interval for a deviance from one, meaning we did not evaluate the term based on it being statistically significantly different from one. To explore differences by sex, we stratified the primary model by sex and qualitatively assessed whether the AHEI score coefficient for males differed meaningfully from the coefficient for females.

We conducted several sensitivity analyses to assess the robustness of our findings. First, we repeated the primary analysis with a narrower definition of the outcome: severe depressive symptoms or antidepressants (instead of moderate/severe depressive symptoms or antidepressants). Second, we repeated the primary analysis with a baseline population restricted to participants with less than mild depressive symptoms (instead of less than moderate symptoms). We did this to try to rule out a bidirectional effect of depressive symptoms on diet, since subclinical

(i.e., mild) depressive symptoms at baseline may influence diet quality at baseline and progress to clinical depression at follow up (Le Port et al., 2012). Third, we regressed the primary outcome on AHEI components hypothesized to be most strongly associated with depression (vegetables, fruit, red and processed meat, sugar-sweetened beverages and fruit juice, *trans* fats, and long-chain n-3 fatty acids) to examine whether certain components were driving the association in the primary model (Molendijk et al., 2018; Opie et al., 2017). Fourth, we estimated the mean change in depressive symptoms at follow-up associated with baseline diet quality. We did this to assess whether our findings were materially different with a continuous outcome and omission of antidepressants from the outcome definition.

Finally, to investigate possible selection bias due to the exclusion of individuals with missing depression outcome information, we imputed such values using the approach for missing covariates and included these individuals in the analytic sample. All analyses were performed using Stata 15 (StataCorp LLC, 2017).

Ethics Approvals

This study was approved by the Strong Heart Study Publications and Presentations Committee (under reference numbers T28 and SHS641) and institutional review boards (IRB) from all participating tribes and each Indian Health Service (IHS) region serving the participating tribes, including the Phoenix Area IHS IRB, Great Plains Area IHS IRB, and Oklahoma City Area IHS IRB. This study was not considered human subjects research by the University of Washington IRB because the authors exclusively used deidentified, secondary data from the Strong Heart Family Study and did not have access to any identifying information.

RESULTS

In the analytic sample of 1,100 individuals, AHEI scores ranged from 19.6 to 74.0 with a median of 39.6 (inter-quartile range [IQR]: 34.2-46.1; Table 1). Compared to the highest AHEI quartile, individuals with scores in the lowest quartile were more likely to be male and younger; have less than a high school education; report current smoking, smokeless tobacco use, and alcohol use; have normal BMI; and report mild depressive symptoms. Individuals in the lowest quartile were less likely to report sedentary levels of physical activity, have known diabetes, and identify

with their own tribal traditions. Social support and health locus of control scores were similar across AHEI quartiles.

Table 1
Baseline characteristics of the analytic sample population by quartiles of AHEI diet quality score

	AHEI Score Quartiles				
	Q1 (19.6-34.2)	**Q2 (34.3-39.6)**	**Q3 (39.7-46.1)**	**Q4 (46.1-74.0)**	**Total *N* = 1100**
	N (column %) or mean (SD)				
Male	152 (55)	118 (43)	105 (38)	94 (34)	469 (43)
Age, years					
15-25	104 (38)	72 (26)	44 (16)	32 (12)	252 (23)
26-45	129 (47)	116 (42)	120 (44)	111 (40)	476 (43)
46-65	35 (13)	70 (25)	89 (32)	96 (35)	290 (26)
66-90	7 (3)	17 (6)	22 (8)	36 (13)	82 (7)
Education, years					
0-11	84 (31)	65 (24)	62 (23)	47 (17)	258 (23)
12-15	168 (61)	176 (64)	172 (63)	185 (67)	701 (64)
16-20	23 (8)	33 (12)	40 (15)	41 (15)	137 (12)
Missing	0	1 (<1)	1 (<1)	2 (1)	4 (<1)
Smoking status					
Never	112 (41)	112 (41)	130 (47)	120 (43)	474 (43)
Former	44 (16)	72 (26)	55 (20)	79 (29)	250 (23)
Current	119 (43)	91 (33)	90 (33)	76 (28)	376 (34)
Smokeless tobacco use, current	31 (11)	20 (7)	15 (5)	14 (5)	80 (7)
Missing	0	2 (1)	5 (2)	5 (2)	12 (1)
Alcohol use status					
Never	30 (11)	38 (14)	36 (13)	32 (12)	136 (12)
Former	55 (20)	87 (32)	81 (29)	102 (37)	325 (30)
Current	190 (69)	150 (55)	157 (57)	141 (51)	638 (58)
Missing	0	0	1 (<1)	0	1 (<1)
BMI category[a]					
Underweight	4 (1)	6 (2)	1 (1)	1 (<1)	13 (1)
Normal	68 (25)	44 (16)	46 (17)	39 (14)	197 (18)
Overweight	75 (27)	76 (28)	79 (29)	95 (35)	325 (30)
Obese	126 (46)	148 (54)	146 (53)	140 (51)	560 (51)
Missing	2 (1)	1 (<1)	2 (1)	0	5 (<1)
Pedometer average steps/day					
<5,000	105 (38)	100 (36)	124 (45)	133 (48)	462 (42)
5,000-9,999	115 (42)	119 (43)	102 (37)	99 (36)	435 (40)
≥10,000	40 (15)	38 (14)	31 (11)	32 (12)	141 (13)
Missing	15 (5)	18 (7)	18 (7)	11 (4)	62 (6)

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Table 1 continued
Baseline characteristics of the analytic sample population by quartiles of AHEI diet quality score

	AHEI Score Quartiles				
	Q1 (19.6-34.2)	**Q2 (34.3-39.6)**	**Q3 (39.7-46.1)**	**Q4 (46.1-74.0)**	**Total *N* = 1100**
	N (column %) or mean (SD)				
Diabetes diagnosis[b]					
Known diabetes	22 (8)	38 (14)	53 (19)	57 (21)	170 (15)
Impaired glucose tolerance	53 (19)	53 (19)	69 (25)	66 (24)	241 (22)
Normal glucose tolerance	199 (72)	183 (67)	151 (55)	152 (55)	685 (62)
Missing	1 (<1)	1 (<1)	2 (1)	0	4 (<1)
Social support score (0-49)	40.0 (5.7)	40.6 (5.1)	41.6 (4.8)	41.4 (4.9)	40.9 (5.2)
Health Locus of Control scores					
Internal (0-18)	12.6 (2.2)	12.7 (2.4)	12.4 (2.4)	12.8 (2.4)	12.6 (2.4)
External: Chance (0-18)	8.2 (2.5)	7.6 (2.5)	7.7 (2.3)	7.2 (2.8)	7.7 (2.5)
External: Powerful others (0-18)	8.4 (2.5)	8.2 (2.9)	8.5 (2.8)	8.4 (3.0)	8.4 (2.8)
Identify with tribal traditions (yes)	184 (67)	197 (72)	194 (71)	207 (75)	782 (71)
Missing	0	8 (3)	12 (4)	5 (2)	25 (2)
Depressive symptoms (CES-D scale)					
None	183 (67)	198 (72)	202 (73)	196 (71)	779 (71)
Mild	92 (33)	77 (28)	73 (27)	79 (29)	321 (29)

Note: Data are pooled across three field centers in Arizona, Oklahoma, and North and South Dakota.

[a]Body mass index (BMI): underweight <18.5 kg/m^2; normal 18.5-24.9 kg/m^2; overweight 25-29.9 kg/m^2; obese ≥30 kg/m^2.

[b]Known diabetes (DM) defined as ≥126 mg/dL fasting blood glucose, or reported history of DM and any of the following: on insulin treatment, hypoglycemic agent, renal dialysis, or had kidney transplantation. Impaired glucose tolerance: fasting blood glucose 110-125mg/dL and no DM treatment. Normal glucose tolerance: fasting blood glucose <110mg/dL and no DM treatment.

AHEI: Alternative Healthy Eating Index; a dietary index based on absolute intake of 10 nutrients and foods each scored 0-10 using standardized serving sizes (excluding alcohol). Total AHEI score ranges from 0 (least healthy) to 100 (most healthy).

CES-D: Center for Epidemiologic Studies Depression Scale. Scores reflect depressive symptoms: none = <10; mild = 10-15; moderate = 16-24; severe = >24.

The mean follow-up period was 5.35 years (*SD* = 1.13). At follow up, 15% (*n* = 166) of the analytic sample reported moderate or severe depressive symptoms, and 5% (*n* = 58) reported current use of antidepressant medications, which included 17 individuals who reported both outcomes. Altogether, 19% of the sample reported probable depression (*n* = 207). The median baseline AHEI score for those who later reported probable depression was 39.6 (IQR = 33.4-46.8) and for those who did not, 39.7 (IQR = 34.3-45.8; see Figure 2). Mean AHEI scores for those who did and did not report probable depression are presented in Appendix Table A3.

Results from our primary analysis indicate that diet quality at baseline was not associated with report of probable depression at follow up (Table 2). The unadjusted OR associated with a 10-point higher AHEI score was 1.04, 95% CI [0.88, 1.23], and the adjusted OR was 1.16, 95% CI [0.96, 1.39]. We did not find evidence of interaction with age or sex. The exponentiated age interaction term was 1.00, 95% CI [0.99, 1.01], and stratified estimates were similar for males (OR = 1.04, 95% CI [0.78, 1.37]) and females (OR = 1.22, 95% CI [0.94, 1.56]).

Sensitivity analyses echoed the primary results. We did not find evidence of an association after restricting the outcome to only severe depressive symptoms or taking antidepressants. The association appeared more strongly positive, though still non-significant, when estimated among those who reported no depressive symptoms at baseline. We did not detect any associations with specific AHEI components, nor with changes in depressive symptoms as a continuous outcome variable. Imputing values for individuals with missing outcome information (n = 384) and including them in the sample, to investigate potential influences of loss-to-follow-up, did not materially change the estimate for AHEI score and probable depression (adjusted OR = 1.15, 95% CI [0.95, 1.41]).

Table 2

Association between diet quality as measured with the AHEI-2010 and onset of probable depression and alternative definitions of probable depression in sensitivity analyses

Outcome definition, analytic sample	Crude OR[a] (95% CI)	Adjusted OR[a] (95% CI)
Probable depression (moderate/severe depressive symptoms and/or antidepressant use), N = 1100[b]	1.04 (0.88, 1.23)	1.16 (0.96, 1.39)
Probable depression (severe depressive symptoms and/or antidepressant use), N = 1100[c]	1.04 (0.82, 1.33)	1.12 (0.86, 1.46)
Probable depression (moderate/severe depressive symptoms and/or antidepressant use, excluding those with mild depressive symptoms at baseline), N = 779[c]	1.18 (0.94, 1.48)	1.23 (0.96, 1.59)

[a]The OR for each 10-point increase in the AHEI-2010 score.

[b]Primary analysis.

[c]Sensitivity analysis.

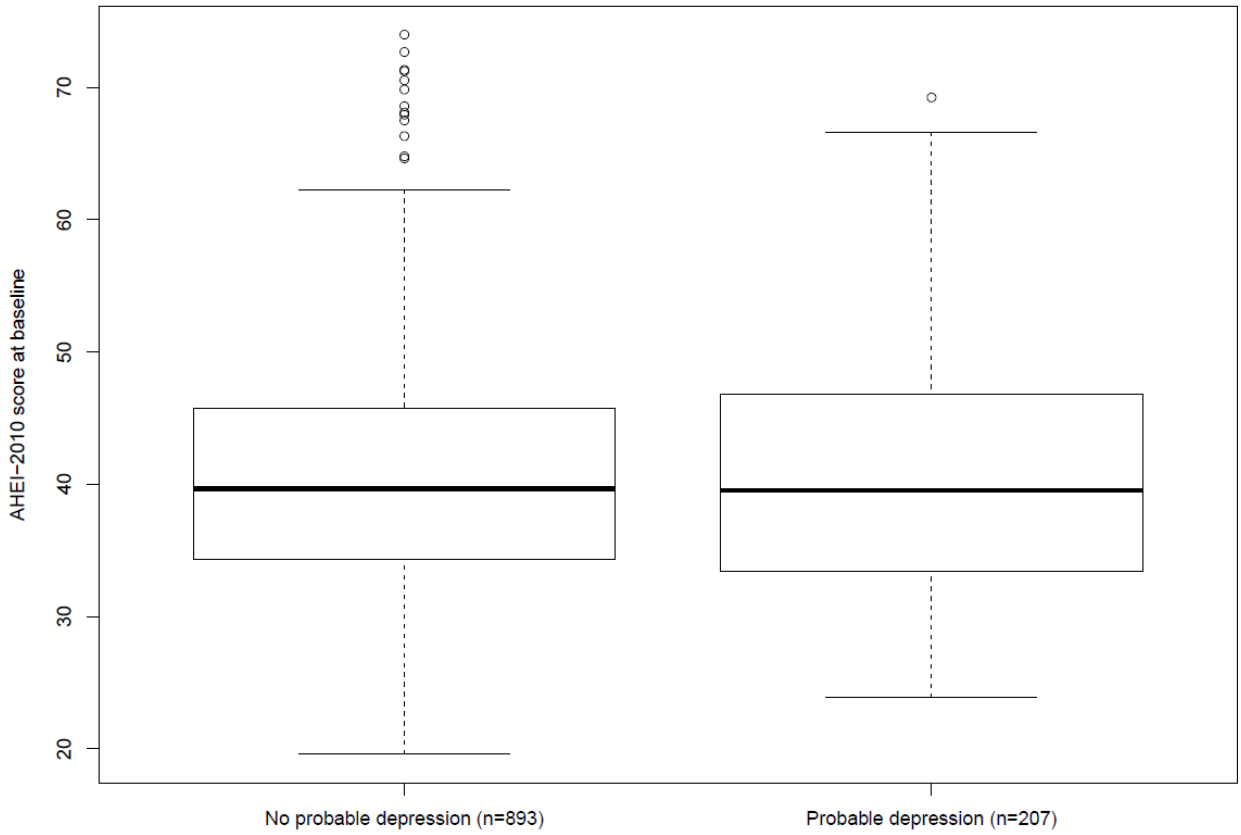
Moderate or severe depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale. Scores reflect depressive symptoms: none = <10; mild = 10-15; moderate = 16-24; severe = >24.

All participants were free of probable depression at baseline.

Adjusted models included baseline measures of field center, sex, age, education, smoking status, smokeless tobacco use, alcohol use, body mass index, physical activity, diabetes diagnosis, social support score, internal health locus of control score, and self-identification with tribal traditions.

AHEI: Alternative Healthy Eating Index; a dietary index based on absolute intake of 10 nutrients and foods; the total AHEI score ranges from 0 (least healthy) to 100 (most healthy).

Figure 2. Baseline AHEI-2010 scores comparing those who did and did not develop probable depression at follow up



The sample included 1,100 individuals ≥14 years old from 83 large families in 12 tribal communities in Arizona, Oklahoma, North Dakota, and South Dakota who were free from probable depression at baseline (2001-2003). Past year diet was collected with a Block Food Frequency Questionnaire and diet quality was determined using the Alternative Healthy Eating Index-2010 (AHEI), a dietary index based on absolute intake of 10 nutrients and foods each scored 0-10 using standardized serving sizes (excluding alcohol). Total AHEI score ranges from 0 (least healthy) to 100 (most healthy). Probable depression was assessed at follow up (2007-2009) and was defined as having moderate or severe depressive symptoms based on the Center for Epidemiologic Studies Depression Scale score (none = <10; mild = 10-15; moderate = 16-24; severe = >24) or taking antidepressant medications. Note: Points outside of the box and whiskers are values greater than 1.5 times the interquartile range.

DISCUSSION

The purpose of this study was to determine whether diet quality was associated with report of probable depression after five years of follow up in a large, family-based cohort of AIs. After adjusting for baseline demographic characteristics, family-level clustering, indicators of health status, and psychosocial factors that may also influence diet and depressive symptoms, our results do not provide evidence of an association. Our overall conclusion did not change in secondary analyses that restricted the population to those with extreme values, nor stratified by age and sex.

Our primary results are inconsistent with much of the literature, as meta-analyses have concluded generally that diet quality is prospectively associated with depression. Dietary patterns such as the AHEI-2010, Healthy Eating Index, Mediterranean Diet Score, Dietary Inflammatory Index, and the Dietary Approaches to Stop Hypertension score are associated with depression symptoms in other studies, including those that used the CES-D as an outcome measure (Lassale et al., 2019; Molendijk et al., 2018; Nicolaou et al., 2019; Opie et al., 2015). Most studies involved large cohorts from majority-white populations in Western Europe, Australia, Canada, and the United States with follow-up periods that were similar to or longer than the follow up in our study (Lassale et al., 2019; Molendijk et al., 2018; Nicolaou et al., 2019). The evidence for interactions between diet quality and sex and age is less consistent in the literature, and in our exploratory analyses, we did not find evidence of either interaction. A harmonized meta-analysis of diet quality and depression found that associations differed by sex for some diet quality scores in some cohorts, but there was not a consistent pattern (Nicolaou et al., 2019). Other studies only observed an association among females (Akbaraly et al., 2013; Wang et al., 2019). Fewer diet-depression studies have investigated interaction with age, despite literature supporting that depression can express differently over the life course (Mirowsky & Ross, 1992). One meta-analysis of diet and depression analyzed studies with and without adolescents and did not find evidence of differing associations (Lassale et al., 2019).

Several inconsistencies in the literature are worth noting in the context of our unexpected findings. Some cohort studies did not find evidence of an association between diet quality and depression. These included the Japan Public Health Center cohort, which assessed adherence to the Japan food guide, and the Whitehall II British cohort, which assessed high intakes of sugar and saturated fats (Okubo et al., 2019; Vermeulen et al., 2018). A meta-analysis found that adjusting for baseline depressive symptoms removed previous associations, suggesting that a bidirectional effect may contribute to mixed findings, since baseline depressive symptoms may influence baseline diet quality (Molendijk et al., 2018). This meta-analysis also found that associations were weaker in studies that assessed clinical diagnosis of depression as the outcome (Molendijk et al., 2018), raising the question of whether other psychosocial factors confound associations with depressive symptoms.

We offer several potential reasons for our null findings. First, we consider unique aspects of diet quality in our study population. Most Strong Heart Family Study participants report fairly simple diets, and there is little variation across individuals due in part to the limited food retail

environment in rural AI communities (Chodur et al., 2016; Eilat-Adar et al., 2013; Fretts et al., 2014, 2018). Having little dietary variety in our sample may have limited our power to detect an association with depression. Further, the AHEI was not designed to directly measure aspects of the diet that are linked with depression, such as antioxidants, fiber, folate, and healthy gut microbiota (Bear et al., 2020; Chiuve et al., 2012; Hébert et al., 2019); limited variety in the diet may have complicated this. Additionally, diet quality is lower, on average, in this AI population compared to other populations in the literature on diet and depression. The median AHEI score in our study was 40 (IRQ: 12). In other studies, median scores range from 45 to 59 (IQRs: 12-16), with the exception of 38 (IQR: 12) in an Italian adult cohort (Nicolaou et al., 2019), though it is unclear whether our exclusion of alcohol from the AHEI explains these differences. If there is a threshold effect of diet quality on depression, diet quality may be too low in our population to observe an association. While there is some suggestive evidence of a threshold effect at the higher end of diet quality (Sánchez-Villegas et al., 2015), it is unknown whether a lower threshold exists.

Another potential explanation is selection bias due to bidirectional effects of diet and depression. Excluding individuals with probable depression at baseline may have biased the sample towards people less susceptible to depression to begin with (Bear et al., 2020), which could be related to past and current diet. A French cohort study found that the influence of diet on depressive symptoms was attenuated when they excluded symptomatic individuals at baseline; the authors hypothesized that those with depressive symptoms are less likely to eat healthily (Le Port et al., 2012). The large body of evidence for cross-sectional associations between diet quality and depression supports this possibility (Lai et al., 2014; Lassale et al., 2019; Nicolaou et al., 2019). A cohort study of Dutch adults found that past and current depressive symptoms were associated with poorer diet quality among men (Elstgeest et al., 2019), providing additional evidence for an inverse association of depression and future diet quality. Other evidence suggests that individuals with subclinical depression (mild symptoms), who are more likely to later report clinical depression, may improve their diets in an attempt to improve symptoms (Bear et al., 2020; Jacka et al., 2015). Indeed, a meta-analysis found that studies that adjusted for baseline subclinical depressive symptoms did not find prospective associations between diet quality and depression, though this adjustment raises concerns for overcorrection (Molendijk et al., 2018). In our study, we were interested in the unidirectional influence of diet as a potential modifiable risk factor for depression. Using a sampling approach common in other diet-depression cohort studies (Nicolaou et al., 2019), we excluded individuals at baseline who reported depression. We did this to limit

potential effects of depressive symptoms on diet quality at baseline. However, we were unable to control for previous depression that resolved before the baseline assessment and possibly influenced current diet quality.

Finally, residual confounding may be present. We adjusted for social support and identification with tribal traditions because we hypothesized that social and cultural factors co-occur with dietary habits that confound the association between diet quality and depression. For example, cultural activities and social gatherings can involve foods that are scored poorly on the AHEI. These foods may confer positive social experiences and mental well-being that contribute to lower odds of reporting depression over time and a lower diet quality score. It is possible the psychosocial measures we included in the model did not fully control for this confounding.

This study has several limitations. First, in contrast to a clinical diagnosis, the CES-D measures past-week depressive symptoms which may vary over time due to the scale's sensitivity to reactions to life events and individual-level cycles of symptomology (Radloff, 1977). However, the CES-D has shown adequate test-retest validity for intervals of up to 12 months (Radloff, 1977) which supports its use in longitudinal studies conducted previously on this topic (Adjibade et al., 2018; Akbaraly et al., 2013; Le Port et al., 2012; Vermeulen et al., 2018). Second, while we included current use of antidepressants in the outcome to indicate depression in the absence of symptoms, there are important limitations to this measure. Some antidepressant medications are prescribed for other conditions like chronic pain and anxiety, and we were unable to distinguish these indications from clinical depression. Additionally, prescribing practices may have changed over time, so data on antidepressant use may not reflect the underlying presence of depression in the population. However, antidepressant use has been included in previous studies of the diet-depression relationship (Chocano-Bedoya et al., 2013; Sánchez-Villegas et al., 2015), and our sensitivity analysis that omitted antidepressants from the outcome did not produce materially different results from our primary analysis. Third, the study is limited by two assessments periods, necessitating our assumption that AHEI scores represented the usual diet before and after the baseline assessment. Diets of the Strong Heart Family Study population are known to be relatively consistent over time (Chodur et al., 2016; Fretts et al., 2018; Kauffman et al., 2019; Kumar et al., 2016), so this may be a reasonable assumption. Additionally, the single follow-up assessment prevents us from estimating time of depression onset and time-varying confounding. Fourth, loss-to-follow-up was greater among male participants. Compared to females, males tend to have poorer diet quality and health

behaviors and are less likely to report depression symptoms (Brave Heart et al., 2016; Noble et al., 2015). In our study, on average, those who were lost to follow up had fewer depressive symptoms at baseline and a slightly higher AHEI score than those with complete data (Appendix Table A1). Although this could have induced a positive, non-significant association between diet quality and reporting depressive symptoms, our sensitivity analysis using imputed outcomes did not offer evidence of this. Fifth, we were unable to exclude participants with possible postpartum depression because we did not have pregnancy information at follow up.

Our study also has numerous strengths. We used standardized, *a priori* measures of diet quality and depression to test for a prospective association in AI communities—a population unique to the literature on this topic yet known to experience higher burdens of related health outcomes. The Strong Heart Family Study is a large, multi-tribal study of risk factors for cardiovascular disease in an underserved and rural population of AIs. We leveraged comprehensive data collected at each assessment to control for potential confounders, including psychosocial factors that have been difficult to control for in previous studies. We were also able to explore interactions by age and sex and impute missing values.

We did not find evidence of a relationship between diet quality and depression after a mean follow up of five years in a population of rural AIs. While nearly one-fifth of our sample reported probable depression at follow up, our findings do not support that past diet quality is an important risk factor. Additional research is needed to confirm this initial interpretation. Future studies with longer follow-up periods and repeated measures of diet and depression will help determine whether a longer-term and bidirectional relationship exists. Further, other aspects of rural AI diets and dietary determinants that may influence depression should be assessed in future studies, such as food insecurity, stress and coping, and social connectedness. Finally, research on possible threshold effects of diet quality and depression in warranted. While current implications for public health and clinical practice are limited without additional research, our results reinforce the need to address low diet quality and high prevalence of depression in rural AI communities represented in this study.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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APPENDIX

Table A1
Characteristics of individuals included in the analytic sample versus those excluded due to missing information on depressive symptoms at follow up

	Analytic Sample ***N* = 1100**	Missing CES-D score and not taking antidepressants at follow up[a] ***n* = 384**
	n (%) or mean (SD)	
Male	469 (43)	206 (54)
Age, years		
15-25	252 (23)	96 (25)
26-45	476 (43)	138 (36)
46-65	290 (26)	100 (26)
66-90	82 (7)	49 (13)
Missing	0	1 (<1)
Education, years		
0-11	258 (23)	108 (28)
12-15	701 (64)	235 (61)
16-20	137 (12)	39 (10)
Missing	4 (<1)	2 (1)
Smoking status		
Never	474 (43)	141 (37)
Former	250 (23)	110 (29)
Current	376 (34)	133 (35)
Smokeless tobacco use, current	80 (7)	28 (7)
Missing	12 (1)	5 (1)
Alcohol use status		
Never	136 (12)	41 (11)
Former	325 (30)	124 (32)
Current	638 (58)	219 (57)
Missing	1 (<1)	0
BMI category[b]		
Underweight	13 (1)	4 (1)
Normal	197 (17)	73 (19)
Overweight	325 (30)	118 (31)
Obese	560 (50)	186 (48)
Missing	5 (<1)	3 (1)
Pedometer average steps/day		
<5,000	462 (42)	173 (45)
5,000-9,999	435 (40)	129 (34)
≥10,000	141 (13)	50 (13)
Missing	62 (6)	32 (8)

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Table A1
Characteristics of individuals included in the analytic sample versus those excluded due to missing information on depressive symptoms at follow up

	Analytic Sample ***N* = 1100**	Missing CES-D score and not taking antidepressants at follow up[a] ***n* = 384**
	n (%) or mean (SD)	
Diabetes diagnosis[c]		
Known diabetes	170 (15)	79 (21)
Impaired glucose tolerance	241 (22)	84 (22)
Normal glucose tolerance	685 (62)	215 (56)
Missing	4 (<1)	6 (2)
Social support score (0-49)	40.9 (5.2)	38.1 (6.8)
Health Locus of Control scores		
Internal (0-18)	12.6 (2.4)	12.8 (2.3)
External: Chance (0-18)	7.7 (2.5)	8.0 (2.5)
External: Powerful others (0-18)	8.4 (2.8)	8.9 (2.9)
Identify with own tribal traditions (yes)	782 (71)	260 (68)
Missing	25 (2)	7 (2)
AHEI score (no alcohol), quartiles		
1st: 19.6-34.2	275 (25)	96 (25)
2nd: 34.3-39.6	291 (26)	80 (21)
3rd: 39.7-46.1	261 (24)	110 (29)
4th: 46.1-74.0	273 (25)	98 (26)
Depressive symptoms (CES-D scale, baseline)		
None	779 (71)	279 (73)
Mild	321 (29)	105 (27)

[a]Individuals who did not answer any questions on the CES-D questionnaire: *n* = 262; individuals who skipped >4 questions on the CES-D questionnaire: *n* = 122. Individuals with missing CES-D scores, but who were taking antidepressants at follow up are included in the study population (*n* = 13). Individuals not shown in this table are those who, at baseline, had current or recent (≤12 months) pregnancies, CES-D scores ≥16 or missing CES-D scores, or reported taking antidepressants.

[b]Body mass index (BMI): underweight <18.5 kg/m^2; normal 18.5-24.9 kg/m^2; overweight 25-29.9 kg/m^2; obese ≥30 kg/m^2.

[c]Known diabetes (DM) defined as ≥126 mg/dL fasting blood glucose, or reported history of DM and any of the following: on insulin treatment, hypoglycemic agent, renal dialysis or had kidney transplantation. Impaired glucose tolerance: fasting blood glucose 110-125mg/dL and no DM treatment. Normal glucose tolerance: fasting blood glucose <110mg/dL and no DM treatment.

Data are pooled across three field centers in Arizona, Oklahoma, and South Dakota.

AHEI: Alternative Healthy Eating Index; a dietary index based on absolute intake of 10 nutrients and foods; the total AHEI score ranges from 0 (least healthy) to 100 (most healthy).

CES-D: Center for Epidemiologic Studies Depression Scale. Scores reflect depressive symptoms: none = <10; mild = 10-15; moderate = 16-24; severe = >24.

Table A2
The Alternative Health Eating Index-2010 (AHEI) scoring method (Chiuve et al. 2012, Kauffman et al. 2019, Jacobs et al. 2017)

Component	Criteria for Min. Score (0)	Criteria for Max. Score (10)
Vegetables (serv/day)	0	≥5
Fruit (serv/day)	0	≥4
Whole grains (grams/day)		
Males	0	90
Females	0	75
Sugar-sweetened beverages and fruit juice (serv/day)	≥1	0
Nuts and legumes (serv/day)	0	≥1
Red/processed meat (serv/day)	≥1.5	0
trans fat (% of energy)	≥4	≤0.5
Long-chain n-3 fats (EPA and DHA) (mg/d)	0	250
Polyunsaturated fatty acids (% of energy)	≤2	≥10
Sodium (mg/d)	Highest decile	Lowest decile
Total	0	100

Alcohol use was excluded from the AHEI score calculations and was instead included as a separate covariate in analyses. Therefore, the maximum score possible was 100, not 110.

Table A3

Baseline AHEI diet quality scores overall and for each component stratified by those who did and did not develop probable depression at follow up

	Outcome at follow up	
	No probable depression[a] ***n* = 893**	**Probable depression[a]** ***n* = 207**
AHEI components	mean (SD)	
Vegetables (serv/day)	2.6 (2.1)	2.7 (2.2)
Fruit (serv/day)	0.9 (1.0)	1.0 (1.3)
Whole grains (g/day)		
Males	19.9 (25.2)	20.8 (30.6)
Females	20.0 (26.2)	18.2 (19.0)
Sugar-sweetened beverages and fruit juice (serv/day)	2.9 (2.6)	3.0 (2.9)
Nuts and legumes (serv/day)	0.7 (1.0)	0.8 (1.1)
Red/processed meat (serv/day)	1.4 (1.1)	1.4 (1.1)
trans fat (% of energy)	1.6 (0.5)	1.6 (0.6)
Long-chain n-3 fatty acids (EPA and DHA) (mg/d)	67.7 (113.6)	65.0 (104.0)
Polyunsaturated fatty acids (% of energy)	8.6 (2.6)	8.8 (2.7)
Sodium (mg/d)	3114 (1891)	3230 (1892)
Total calories[b]	2322 (1254)	2436 (1327)
AHEI score	40.5 (9.0)	40.8 (9.4)

AHEI: Alternative Healthy Eating Index; a dietary index based on absolute intake of 10 nutrients and foods each scored 0-10 using standardized serving sizes and cut points associated with increased or decreased chronic disease risk. Alcohol use was excluded from the AHEI score calculations and was included as a separate covariate in analyses.

CES-D: Center for Epidemiologic Studies Depression Scale. Scores reflect depressive symptoms: none = <10; mild = 10-15; moderate = 16-24; severe = >24.

[a]Probable depression is defined as having a CES-D score ≥16 or taking antidepressants. All participants were free of probable depression at baseline.

[b]Total calories are not included in AHEI score calculation; shown for descriptive purposes only.