The Journal of Nutrition 153 (2023) 1143–1149

American Society for Nutrition
Excellence in Nutrition Research and Practice

JN THE JOURNAL OF NUTRITION

journal homepage: www.journals.elsevier.com/the-journal-of-nutrition

Nutritional Epidemiology

Positive Health Outcomes Associated with Live Microbe Intake from Foods, Including Fermented Foods, Assessed using the NHANES Database

Colin Hill [1,†], Daniel J. Tancredi [2,†], Christopher J. Cifelli [3], Joanne L. Slavin [4], Jaime Gahche [5], Maria L. Marco [6], Robert Hutkins [7], Victor L. Fulgoni III [8], Daniel Merenstein [9], Mary Ellen Sanders [10,*]

[1] *APC Microbiome Ireland, University College Cork, Cork, Ireland;* [2] *Department of Pediatrics, UC Davis School of Medicine, Sacramento, CA, United States;* [3] *National Dairy Council, Rosemont, IL, United States;* [4] *Department of Food Science and Nutrition, University of Minnesota, Minneapolis, MN, United States;* [5] *Office of Dietary Supplements, NIH, Bethesda, MD, United States;* [6] *Department of Food Science and Technology, University of California–Davis, Davis, CA, United States;* [7] *Department of Food Science and Technology, University of Nebraska, Lincoln, NE, United States;* [8] *Nutrition Impact, LLC, Battle Creek, MI, United States;* [9] *Research Programs Family Medicine, Georgetown University Medical Center, Department of Human Science, School of Health, Georgetown University, Washington, DC, United States;* [10] *International Scientific Association for Probiotics and Prebiotics, Centennial, CO, United States*

A B S T R A C T

Background: Live dietary microbes have been hypothesized to contribute to human health but direct evidence is lacking.
Objectives: This study aimed to determine whether the dietary consumption of live microbes is linked to improved health outcomes.
Methods: Data from the NHANES 2001–2018 were used to assess microbial intake and their adjusted associations with selected physiological parameters (e.g., blood pressure, anthropometric measures, and biomarkers) among adults aged 19 y and older. Regression models were constructed to assess the microbial intake with each physiological parameter and adjusted for demographics and other covariates. Microbial intake was assessed as both a continuous variable and a 3-level categorical variable. Fermented foods were assessed in a separate model.
Results: In continuous models, an additional 100-g intake of microbe–containing foods was associated with a lower systolic blood pressure (regression coefficient: −0.331; 95% CI: −0.447, −0.215 mm Hg), C-reactive protein (−0.013; 95% CI: −0.019, −0.008 mg/dL), plasma glucose −0.347; 95% CI: −0.570, −0.124 mg/dL), plasma insulin (−0.201; 95% CI: −0.304, −0.099 μU/mL), triglyceride (−1.389; 95% CI: −2.672, −0.106 mg/dL), waist circumference (−0.554; 95% CI: −0.679, −0.428 cm), and BMI −0.217; 95% CI: −0.273, −0.160 kg/m^2) levels and a higher level of high density lipoprotein cholesterols (0.432; 95% CI: 0.289, 0.574 mg/dL). Patterns were broadly similar when microbial intake was assessed categorically and when fermented foods were assessed separately.
Conclusions: To our knowledge, this study is the first to quantify, in a nationally representative data set of American adults and using stable sets of covariates in the regression models, the adjusted associations of dietary intakes of live microbes with a variety of outcomes, such as anthropometric measures, biomarkers, and blood pressure levels. Our findings suggest that foods with higher microbial concentrations are associated with modest health improvements across a range of outcomes.

Keywords: NHANES, live dietary microbes, fermented food, probiotics, International Scientific Association for Probiotics and Prebiotics, ISAPP, health promotion/disease prevention

Abbreviations: Hi, high—estimated to contain >10^7 live CFU/g; Med, medium—estimated to contain 10^4–10^7 live CFU/g; MedHi, medium/high—estimated to contain >10^4 live CFU/g.

* Correspondence author. *E-mail address:* maryellen@isappscience.org (M.E. Sanders).

† CH and DJT contributed equally to this work.

https://doi.org/10.1016/j.tjnut.2023.02.019
Received 15 December 2022; Received in revised form 6 February 2023; Accepted 14 February 2023; Available online 22 February 2023

Introduction

We recently estimated the number of live microbes in the diet of US children and adults by designing a classification system that assigned each food recorded by the NHANES to 1 of the 3 microbial categories (low, medium, and high) [1]. This cross-sectional study indicated that the consumption of live microbes had increased over recent decades. One purpose for conducting this earlier study was to prepare the groundwork for estimating whether the consumption of live microbes in general—not just probiotics—are associated with health benefits. The hypothesis that the consumption of live microbes could benefit human health was based on a number of concepts [2]. First, the advent of modern food production and processing along with improved hygiene and sanitation has reduced the number of live microbes consumed by modern humans when compared with those consumed by our ancestors [3]. This decline in the consumption of live microbes coincides with a rise in modern auto-immune diseases [4–6]. Although there is little evidence of a causal link, there is considerable data showing that so-called western diets that are typically low in live microbes, affect the diversity and composition of the gut microbiota (reviewed in [7]). Furthermore, it is notable that the gastrointestinal tract contains an elaborate and extensive immunologic and neurologic network that has a vast array of receptors capable of detecting microbes, their components, or their end products [8]. Second, it is now recognized that gut microbes play a significant role in systemic human health, beyond the gut [9]. The human microbiota comprises trillions of microorganisms per individual, and changes in the composition and function of resident microbiota are associated with a number of systemic diseases, such as those involving the immune system [10]. Third, it has been shown that the consumption of live microbes in the form of probiotics (or live biotherapeutics) has also been directly linked to improved health outcomes, such as prevention of necrotizing enterocolitis in infant, managing the symptoms of functional bowel disorders, prevention of antibiotic-associated diarrhea, treatment of ulcerative colitis, and reducing the incidence and duration of common upper respiratory infections and gastrointestinal infections [11].

Accordingly, we used the framework previously developed to estimate live microbes in foods in the NHANES database [1] to determine whether the consumption of live microbes in meaningful numbers could potentially confer a health benefit. To test this hypothesis, we used regression analyses to estimate the adjusted associations of live microbe consumption with physiological parameters that are collected as part of the NHANES protocols.

Methods

Data set

The NHANES is a nationally representative, continuous survey administered by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention used to assess the health and nutrition of the US population. The dietary data are collected using an in-person 24-h dietary recall component, What We Eat in America, collected using the US Department of Agriculture's (USDA) automated multiple-pass method. As with our previous publication quantifying intakes of foods with microbes [1], we used the NHANES for our analysis. This method identified and recorded all foods and the amounts consumed on the previous day [12]. Adults aged 19 y and older with a day 1 dietary recall in the NHANES 2001–2018 were included in this study. As with our previous study [1], we excluded unreliable dietary records, as determined by the USDA, and pregnant and/or lactating females, resulting in an adult sample of 46,091. NHANES methods have been approved by the NCHS Ethics Review Board [13]. All participants provided written informed consent, and personal information was removed from publicly available data. NHANES procedures and methods are available on its website [14,15].

Determinations of the intakes of foods with microbes and fermented foods were performed as before [1]. In brief, experts in the field (MLM, MES, RH, and CH) estimated the live microbial content and foods with fermentation for 9388 individual food codes within 48 NHANES subgroups. The foods were grouped into categories based on estimated live microbial (bacterial and fungal) content: low [$<10^4$ CFUs/g], medium (Med; 10^4–10^7 CFU/g), and high (Hi; $>10^7$ CFU/g). For each participant, we then computed 3 categories of grams of foods consumed: 1 each for Med, Hi, and Med or Hi foods (MedHi; when referring to dietary intake, MedHi refers to foods that were categorized as either having medium or high microbial content, and when referring to consumers, MedHi refers to persons who consumed some foods from the medium category and/or some foods from the high category). The experts relied on primary literature, manuscript reviews, professional knowledge, and microbial viability in relation to food processing to designate foods into the abovementioned categories. Consensus was required among the experts, with disagreements resolved by discussion.

Given the recent interest in the role of fermented foods in human health, experts also identified foods as fermented or not (Supplemental Table 1). Fermented foods are defined as foods made through desired microbial growth and enzymatic conversions of food components [16]. Fermented foods that do not contain live microorganisms (such as bread and coffee) were excluded. Many of the fermented foods were dairy foods (e.g., buttermilk, cheese, and yogurt). In addition, "pickled" fruits and vegetables foods were also designated as fermented foods with the understanding that despite the possibility to "pickle" (preserve with the use of vinegar), they can also contain live microorganisms if they were refrigerated and not heat-treated.

The mean and median intakes of foods containing live microbes and fermented foods were determined on a per capita basis for the total study population and for consumers of those foods. Although probiotic dietary supplement use was considered in our previous work, given the low consumption (~2% of the population), these were not included in the current analyses. Dietary intake in grams was used in the regression analysis as the primary exposure of interest. As an alternative measure of exposure, we used a 3-level categorical classification of the participants: (G1: nonconsumers; G2: those with intakes greater than zero but less than the median intake for consumers; and G3: those with intakes greater than the median for consumers).

Physiological parameters

Physiological parameters to be analyzed were determined before the start of this study and were selected based on the available evidence linking fermented foods to the cardiometabolic risk. These were C-reactive protein, plasma glucose, plasma insulin, and blood pressure (diastolic and systolic) levels; anthropometric variables BMI, waist circumference, and weight]; and blood lipids [high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and total cholesterol and triglyceride levels]. One-day dietary weights were used in the analyses except, for fasting, subsample weights were used for plasma glucose, plasma insulin, and triglyceride levels. All laboratory variables and manuals with detailed descriptions of laboratory methodologies are directly available from the NHANES website.

Statistical analysis

Regression analyses were used to assess the relationship between the exposures of interest, fermented foods, and foods with live microbes, with each of the physiological parameters. NHANES data were adjusted for the complex sample design, survey nonresponse, and poststratification adjustment to match total population counts from the Census Bureau using survey parameters such as strata, primary sampling units, and sampling weights. Two covariate sets were used for each exposure/outcome analysis. Covariate set 1 included age, sex, ethnicity, poverty income ratios, physical activity levels, current smoking status, and alcohol intake, whereas covariate set 2 included covariate set 1 with the addition of BMI, which is known to affect certain physiological parameters (e.g., glucose, insulin, and lipids). Only covariate set 1 was used when the anthropometric measures were the outcomes. For regression models using grams consumed as a continuous exposure, regression coefficients are reported per 100 g consumed, which describe the adjusted mean difference in the outcome associated with a 100-g increase in the exposure. For regression models using the 3-level classification of patients based on intakes, nonconsumers (G1) were used as the reference level, and regression coefficients are reported for the pair of indicator variables included simultaneously in the model, 1 indicating participants with intakes greater than zero but less than median intakes (G2) and 1 for participants with intakes greater than or equal to median intakes (G3). All analyses used SAS 9.4 software (SAS Institute). We also performed some post hoc regression analyses adding servings of dairy, fruits, vegetables, and yogurt in regression models. These items were added 1 at a time to assess the change in the association of foods with microbes with physiological measures.

Results

For the 29,348 adults who consumed foods containing live microbes in the medium or high categories, mean ± SE consumption was 189.6 ± 2.3 g/d and median ± SE consumption was 138.00 ± 1.44 g/d (Table 1). For fermented foods, the mean and median intakes among the adult consumers were 82.3 and 41.92 g/d, respectively. The analysis of both Med and Hi foods as separate terms simultaneously included in the same model revealed that their coefficients were similar, supporting the simpler model where the exposure combined Med and Hi (MedHi) foods together into a single variable [1]. For simplicity, we present only the model with this combination. For this combination, the relative frequency of patients in G1 (nonconsumers), G2 (below median of consumers), and G3 (above median of consumers) was 36%, 32%, and 32%, respectively. For fermented foods, the breakdown was 79%, 10%, and 10%, respectively.

There were generally modest but statistically significant improvements in health-associated outcomes with increased consumption of foods for all physiological parameters assessed, except for LDL and total cholesterol levels, which did not decrease (Table 2 and Supplemental Table 2). For example, when using covariate set 2, each 100-g increase in such foods was associated with reductions in the systolic blood pressure of −0.331 mm Hg (95% CI: −0.215, −0.447 mm Hg) and plasma glucose of −0.347 mg/dL (95% CI: −0.124, −0.570 mg/dL0 and increases in the HDL of 0.432 mg/dL (95% CI: 0.289, 0.574 mg/dL). Similarly, when using covariate set 1 to permit switching anthropometric measures from covariates to outcomes, each 100-g increase in MedHi foods was associated with mean reductions in BMI of −0.217 kg/m^2 (95% CI: −0.160, −0.273 kg/m^2) and waist circumference of −0.554 cm (95% CI: −0.43,

TABLE 1

Adult[1] intake of foods with live microbes or fermented food, NHANES 2001–2018

Food category[2]	No. of consumers per food category[3]	Mean (g/d) food category per consumer	Mean (g/d) food category per study subject[4]	Median, 75th, and 90th percentile (g/d) food category per consumer	Median, 75th, and 90th percentile (g/d) food category per study subject[4]
Med	26,885	173.3 ± 2.09	105.8 ± 1.85	127.02 ± 2.05 229.84 ± 3.16 381.18 ± 6.49	37.97 ± 1.96 159.14 ± 3.56 301.58 ± 5.64
Hi	9758	82.3 ± 1.41	21.2 ± 0.56	41.9 ± 1.09 122.37 ± 2.28 217.35 ± 3.67	0 ± 0 4.70 ± 1.78 57.47 ± 1.58
MedHi	29,348[3]	189.6 ± 2.26	127.0 ± 2.17	138.0 ± 1.44 257.66 ± 3.84 423.23 ± 6.73	56.7 ± 1.88 187.94 ± 3.20 352.84 ± 6.00
Fermented foods	9671	82.3 ± 1.42	21.0 ± 0.56	41.92 ± 1.09 122.38 ± 2.28 219.01 ± 3.49	0 ± 0 3.24 ± 1.78 57.43 ± 1.58

[1] Combined data from the NHANES 2001–2018 for subjects aged 19 y and older (n = 46,091). Data presented as gram of intake per day ± standard error.

[2] Med, foods containing 10^4–10^7 live CFU/g; Hi, foods containing >10^7 live CFU/g; MedHi, >10^4 CFU/g.

[3] In total, 7295 study subjects consumed both Med and Hi foods; hence, the sum of the number of consumers of Med and Hi foods exceeds the total of Med or Hi foods. When referring to dietary intake, MedHi refers to foods that were categorized as either having medium or high microbial content; 16,743 study subjects consumed neither Med nor Hi foods. When referring to consumers, MedHi refers to persons who consumed some foods from the medium category and/or some foods from the high category.

[4] Total study subjects: 46,091.

TABLE 2
Adjusted associations of dietary intake (per 100 g) of foods with medium or high microbial concentrations with physiological parameters in adults[1] (19+ y), NHANES 2001–2018

Outcome	Covariate set 1			Covariate set 2		
	n	Regression coefficient (95% CI)	*P*	*n*	Regression coefficient (95% CI)	*P*
Mean diastolic BP (mm Hg)	40,898	−0.131 (−0.228, −0.034)	0.009	40,351	−0.083 (−0.174, 0.009)	0.076
Mean systolic BP (mm Hg)	41,077	−0.405 (−0.523, −0.287)	<0.001	40,521	−0.331 (−0.447, −0.215)	<0.001
Body mass index (kg/m^2)	41,697	−0.217 (−0.273, −0.160)	<0.001	NA	NA	NA
C-reactive protein (mg/dL)	31,439	−0.017 (−0.023, −0.012)	<0.001	30,943	−0.013 (−0.019, −0.008)	<0.001
Plasma glucose (mg/dL)	18,509	−0.535 (−0.780, −0.291)	<0.001	18,258	−0.347 (−0.570, −0.124)	0.003
HDL cholesterol (mg/dL)	40,313	0.578 (0.425, 0.732)	<0.001	39,734	0.432 (0.289, 0.574)	<0.001
Insulin (μU/mL)	18,163	−0.428 (−0.563, −0.294)	<0.001	17,917	−0.201 (−0.304, −0.099)	<0.001
LDL cholesterol (mg/dL)	17,980	−0.200 (−0.727, 0.328)	0.456	17,736	−0.124 (−0.656, 0.408)	0.647
Total cholesterol (mg/dL)	40,314	−0.135 (−0.522, 0.253)	0.493	39,735	−0.071 (−0.463, 0.321)	0.721
Triglycerides (mg/dL)	18,327	−2.068 (−3.374, −0.762)	0.002	18,080	−1.389 (−2.672, −0.106)	0.034
Waist circumference (cm)	40,804	−0.554 (−0.679, −0.428)	<0.001	NA	NA	NA
Weight (kg)	41,847	−0.440 (−0.604, −0.275)	<0.001	NA	NA	NA

BP, blood pressure; NA, not applicable.
[1]Combined data from the NHANES 2001–2018.
[2]Covariate set 1: age, sex, ethnicity, poverty income ratio (<1.35, 1.35 ≤ 1.85, >1.85), physical activity level (sedentary, moderate, and vigorous), current smoking status (current, previous, and never), and alcohol intake.
[3]Covariate set: covariate set 1 and BMI.
[4]Regression coefficients represent the adjusted mean change in the outcome associated with each 100-g increase in MedHi foods (those with medium or high microbial concentrations, as explained in the Methods section).

−0.68 cm). For the diastolic blood pressure outcome, the estimated effects were similar between the models with covariate set 1 and with covariate set 2, although statistical significance was not achieved in the latter model. In the post hoc regression analyses, there were very few changes in regression coefficients/statistical significance with the addition of servings of dairy, fruit, vegetables, and yogurt to models (data not shown). However, we did see an attenuation of association of food with microbes with triglycerides when servings of yogurt were added to the models and, for diastolic blood pressure, fasting glucose, and body weight, when servings of fruit was added to the model.

When the intake of fermented foods was the independent variable of interest, the adjusted associations were similar as for the intake of MedHi foods, although statistical significance was lost for C-reactive protein and plasma glucose levels for both covariate sets and for insulin levels when adjusting for covariate set 2 (Table 3 and Supplemental Table 3). Each 100-g increase in fermented foods was associated with, for example, an adjusted mean (95% CI) reduction in systolic blood pressure of −0.638 (95% CI: −0.259, −1.07) mm Hg and an adjusted mean increase in HDL of 0.505 (0.123, 0.886) mg/dL, but effects on plasma glucose were attenuated and did not reach a statistical significance (mean change: −0.202 mg/dL; 95% CI: −1.027, 0.623 mg/dL).

Discussion

This study examined the relationship between the consumption of foods with medium to high amounts of live

TABLE 3
Adjusted associations of dietary intake (per 100 g) of fermented foods with physiological parameters in adults[1] (19+ y), NHANES 2001–2018

Outcome	Covariate set 1			Covariate set 2		
	n	Regression coefficient (95% CI)	*P*	*n*	Regression coefficient (95% CI)	*P*
Mean diastolic BP (mm Hg)	40,898	−0.140 (−0.402, 0.122)	0.294	40,351	−0.067 (−0.330, 0.195)	0.614
Mean systolic BP (mm Hg)	41,077	−0.768 (−1.136, −0.399)	<0.001	40,521	−0.638 (−1.017, −0.259)	0.001
Body mass index (kg/m^2)	41,697	−0.309 (−0.465, −0.154)	<0.001	NA	NA	NA
C-reactive protein (mg/dL)	31,439	−0.010 (−0.027, 0.006)	0.223	30,943	−0.010 (−0.025, 0.005)	0.176
Plasma glucose (mg/dL)	18,509	−0.509 (−1.372, 0.354)	0.246	18,258	−0.202 (−1.027, 0.623)	0.629
HDL cholesterol (mg/dL)	40,313	0.696 (0.294, 1.098)	<0.001	39,734	0.505 (0.123, 0.886)	0.010
Insulin (μU/mL)	18,163	−0.644 (−0.995, −0.292)	<0.001	17,917	−0.277 (−0.571, 0.018)	0.066
LDL cholesterol (mg/dL)	17,980	−0.414 (−1.782, 0.955)	0.551	17,736	−0.330 (−1.684, 1.025)	0.631
Total cholesterol (mg/dL)	40,314	−0.300 (−1.449, 0.848)	0.606	39,735	−0.202 (−1.339, 0.936)	0.726
Triglycerides (mg/dL)	18,327	−4.844 (−7.674, −2.014)	<0.001	18,080	−3.790 (−6.483, −1.098)	0.006
Waist circumference (cm)	40,804	−0.793 (−1.166, −0.421)	<0.001	NA	NA	NA
Weight (kg)	41,847	−0.621 (−1.156, −0.087)	0.023	NA	NA	NA

BP, blood pressure; NA, not applicable.
[1]Combined data from the NHANES 2001–2018.
[2]Covariate set 1: age, sex, ethnicity, poverty income ratio (<1.35, 1.35 ≤ 1.85, >1.85), physical activity level (sedentary, moderate, and vigorous), current smoking status (current, previous, and never), and alcohol intake.
[3]Covariate set: covariate set 1 and BMI.
[4]Regression coefficients represent the adjusted mean change in the outcome associated with each 100-g increase in MedHi foods (those with medium or high microbial concentrations, as explained in the Methods section).

microbes and a range of specific health parameters in a nationally representative sample of adults using the same sets of covariates to permit comparisons across outcomes. The consumption of foods with live microbes was associated with a lower blood pressure, BMI, waist circumference, plasma glucose, C-reactive protein, insulin, and triglyceride levels, along with a higher HDL cholesterol level. The estimated effects were generally modest and directionally favorable to population health. For fermented food consumption, similar findings were observed, although the effects on plasma glucose and insulin were less clear. In general, these results provide additional evidence supporting a link between live microbes and more favorable blood pressure, anthropometric measures, and biomarkers. However, given our analyses were of food intakes and not specifically microbe numbers, we cannot exclude the possibility that other food components besides live microbes contribute to associated health parameters.

Some have proposed a recommendation for live microbes given their link to health, similar to the current recommendations for dietary fiber [2,17]. Recommendations for dietary fiber intake are not focused on any specific fiber type and are based on protection against CVD, although benefits of fiber extend to a wide range of chronic diseases and physiological functions [18]. The adequate intake for dietary fiber was based on the prospective cohort studies that found that 14 g of dietary fiber per 1000 kcal protected against CVD. Although the adequate intake for dietary fiber is based on CVD protection, it is well accepted that fibers have important physiological effects throughout the digestive tract [17,19]. Thus, regulators developing guidelines allowed for a range of physiological effects of dietary fiber, such as laxation, enhanced mineral absorption, lower blood pressure levels, and improvements in glucose response and blood lipid levels, to approve new fiber sources [20]. A similar approach could be applicable to the development of guidelines for dietary live microbes.

We previously estimated the number of live microbes present in individual foods and the total diet of Americans as the first step in proposing a recommended intake of live microbes based on the estimates of the intake and physiological benefits of live microbe consumption [1]. We have expanded on these findings in this study by examining the adjusted associations between foods with live microbes and markers of cardiometabolic health. Consistent with our findings, previous studies have observed significant decreases in cardiometabolic risk factors with either probiotic or fermented food intake. Dixon et al. [21] conducted a systematic review and meta-analysis on the effects of probiotics on risk factors associated with CVD. The results of the meta-analysis showed that probiotics reduced blood pressure, serum glucose, and BMI levels. They also reported a reduction in total and LDL cholesterol levels, which was not observed in our analysis. Similarly, da Silva Pontes et al. reported that probiotics reduced body weight, BMI, waist circumference, and insulin in overweight and obese subjects [22]. Probiotic supplementation has also been shown to reduce blood pressure in subjects with hypertension [23] and type 2 diabetes [24]. In addition, research on probiotics offers mechanistic support for the independent effects of live microbes on cardiometabolic health. Probiotic supplementation has been shown to modulate the gut microbiome, which leads to an increased production of glucagon-like peptide-1 and short-chain fatty acids [25]. Glucagon-like peptide-1 levels affect glucose metabolism and potentially body weight by stimulating insulin secretion, slowing gastric emptying, and reducing food intake [26]. Regarding lipid metabolism, short-chain fatty acids have been shown to decrease hepatic cholesterol synthesis, which impacts cholesterol metabolism [25]. Although the research on health benefits of probiotics is generally conducted on defined probiotic strains, accumulated evidence suggests that some health benefits are likely derived from consuming adequate amounts of probiotics regardless of the strain [27,28]. This suggests that at least some health benefits conferred by probiotics are because of traits that are shared or commonly found among many strains or food-associated microbes.

The consumption of fermented foods has been associated with improved health outcomes such as reductions in BMI, waist circumference, type II diabetes, CVD, and markers of inflammation, in addition to outcomes beyond cardiometabolic health [16,29]. Indeed, the consumption of live and safe microbes from the diet, which would include fermented foods, has been suggested to strengthen immunity, improve gut function, minimize gut-induced inflammation, manage stress, and reduce risks of chronic disease [2,16,30]. Most of the evidence on the health benefits of the fermented foods has been based on epidemiologic studies examining yogurt or other cultured dairy foods. Indeed, yogurt consumption has been linked to a 10% lower risk of high blood pressure [31], decreased risk for CVD [32], and decreased risk for developing type 2 diabetes [25,33] in adults. Furthermore, the results of a randomized controlled trial in healthy premenopausal women showed that women eating 1½ servings of low-fat yogurt every day for 9 wk reduced markers of chronic inflammation compared with women eating a yogurt (nondairy) alternative [34]. Besides fermented dairy, epidemiologic evidence has shown that consumption of fermented soy or fermented vegetables is linked with a reduced risk of type 2 diabetes, blood pressure, and atopic dermatitis [35–37]. More recently, a clinical trial by Wastyk et al. [29] investigated the effects of either a high-fiber or a high-fermented food diet on the markers of immune function and the microbiome. They showed that consumption of fermented foods increased microbiota diversity and decreased inflammatory markers [29]. Beyond immune or physiological effects, a recent randomized controlled trial showed that a diet high in fermented foods, whole grains, fruits and vegetables, and legumes also reduced perceived psychological stress [30]. Future studies are needed to further delineate the effects of the live microbes present in fermented foods from the nutrients and bioactive also found in those same foods. Studies comparing sterile foods with their regular counterparts could be informative in that regard.

The strengths of this study include using a large, nationally representative data set achieved by combining several sets of NHANES data releases and the use of covariates to appropriately adjust the data and to promote comparability across outcomes. In addition, we were able to examine the effect of whole foods, including those that have traditionally contained live microbes, on health-related parameters. This study has several limitations. The NHANES is a cross-sectional study in which individuals are independently sampled for each survey period and are not followed up over time, therefore cause and effect relationships cannot be determined. Dietary intakes were determined through a self-report, which could lead to underreporting or overreporting of energy and food intakes. In addition, although our study had a large sample size, given we used a single dietary recall, there is a possibility we have under estimated less frequently consumed foods. Another limitation is the potential for residual confounding; thus, the results observed could reflect the effect of other foods co-consumed or not consumed throughout the day. Adults do not consume foods or nutrients in isolation, so the overall eating pattern could influence the metabolic outcomes examined in this study. Furthermore, our analysis is based on a classification scheme that did not differentiate among the types of microbes present and, therefore, does not address the possibility that different types of microbes may differentially affect the health. Finally, because this study is a first step in identifying potential relationships between live dietary microbes and health, no mechanistic underpinnings of the finding, such as alterations in gut microbiota or microbiota-associated metabolites, were assessed.

This study supports that consumption of foods with higher microbial concentrations is associated with a better health across a range of outcomes, such as lower systolic blood pressure, C-reactive protein, plasma glucose, plasma insulin, triglyceride, waist circumference, and BMI levels and a higher HDL cholesterol level. These findings provide preliminary evidence to support the hypothesis that foods containing live microbes may provide health benefits to consumers and suggest the value, if supported by additional research, of a recommendation for live microbes in healthy eating patterns, similar to the current recommendation for fiber [2,38–41]. Furthermore, additional research to disentangle the benefits of the food from the microbes they provide is needed, to clarify our understanding of what drives observed health benefits of foods containing live microbes, including fermented foods. If subsequent research supports a causal relationship between live dietary microbes and health and the magnitude of these effects are confirmed, the potential effect of this dietary change could be substantive.

Inferring from our estimated regression coefficients, our findings suggest that American adults who substitute 400 g of pasteurized, heat-treated, or highly processed foods with 400 g of foods with medium to high amounts of live microbes may contributed to health benefits, such as average reductions in systolic blood pressure from 1 to 4 mm Hg and in waistlines from about two-thirds of an inch to 2 inches. This dietary change could be accomplished consuming an amount that could be obtained by consuming 7 ounces of yogurt (200 g), 1 serving of fresh fruit (75 g), and 1 serving of fresh vegetables (125 g). These potentially important improvements need to be confirmed in large randomized trials comparing the effect of foods containing low with those containing high levels of microbes on blood pressure, weight, and cardiovascular health outcomes, among others. A reduction of systolic blood pressure by 10 mm Hg is known to decrease the risk of cardiovascular events by ~20%–30% [42]. A change of up to 4 mm Hg due to simple dietary substitutions of live microbe–containing foods has the potential to significantly improve human health. Our data, in conjunction with previous research, provides a scientific justification for further exploration into the beneficial role of live dietary microbes.

Funding

The International Scientific Association for Probiotics and Prebiotics (ISAPP) funded the NHANES analysis, which was conducted by Nutrition Impact, Battle Creek, MI. The ISAPP had no role in the design, implementation, analysis, or interpretation of the data.

Author disclosures

CH has consulted for Kyowa Hakko, Adiso Therapeutics, and Winclove BV and serves as a nonpaid member of the Board of Directors of ISAPP. DJT has been a paid consultant for Synbiotic Health, Inc., and International Fragrance & Flavors and serves as a nonpaid member of the Board of Directors of ISAPP. CJC works for the National Dairy Council. MLM serves on the Scientific Advisory Council for the Kerry Health and Nutrition Institute and is the Vice-President of the ISAPP board, a nonpaid position. RH has received grants and honoraria from food and ingredient companies and is a founder of Synbiotic Health. VLF serves as the Senior Vice-President of Nutrition Impact, provides food and nutrition consulting services for food and beverage companies, and conducts analyzes of NHANES data for the members of the food industry. DM has been a paid consultant for HowarU and Bayer, has done legal work for VSL#3, and is the President of the ISAPP board, a nonpaid position. MES has been a paid consultant for Bayer, Bill and Melinda Gates Foundation, California Dairy Research Foundation, Danone North America, Pepsico, Smith, Gambrell & Russell, LLP, and Winclove; has received honoraria for speaking from Associated British Foods, Biocodex, European Federation of Associations of Dietitians, fairlife, Allergosan, Probi, and Sanofi; is paid as the executive director of ISAPP, and has served on advisory boards for Cargill, Danone North America, Danone, Yakult, and Winclove. JLS and JG have no disclosures to report.

Acknowledgments

The authors' responsibilities were as follows—CH: helped in conceiving the research, wrote the introduction, and edited the manuscript; DJT: evaluated the results, wrote the results section, contributed substantively to all other sections, and edited the manuscript; CJC: wrote the discussion section and edited the manuscript; JLS: contributed to writing the discussion section and edited the manuscript; JG: wrote the abstract and edited the manuscript; MLM, RH: contributed to the concept of the research and edited the manuscript; VLF: conducted the NHANES analysis, helped write the results section, and drafted the tables; DM: edited the manuscript; MES: wrote the conclusion section, compiled all sections of the paper, contributed to the concept of the research, and edited the manuscript; and all authors: read and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2023.02.019.

References

[1] M.L. Marco, R. Hutkins, C. Hill, V.L. Fulgoni, C.J. Cifelli, J. Gahche, et al., A classification system for defining and estimating dietary intake of live microbes in US adults and children, J. Nutr. 152 (2022) 1729–1736, https://doi.org/10.1093/jn/nxac074.

[2] M.L. Marco, C. Hill, R. Hutkins, J. Slavin, D.J. Tancredi, D. Merenstein, et al., Should there be a recommended daily intake of microbes? J. Nutr. 150 (2020) 3061–3067, https://doi.org/10.1093/jn/nxaa323.

[3] J.L. Sonnenburg, E.D. Sonnenburg, Vulnerability of the industrialized microbiota, Science 366 (2019), https://doi.org/10.1126/science.aaw9255 eaaw9255.

[4] G.E. Dinse, C.G. Parks, C.R. Weinberg, C.A. Co, J. Wilkerson, D.C. Zeldin, et al., Increasing prevalence of antinuclear antibodies in the United States, Arthritis Rheumatol 74 (2022) 2032–2041, https://doi.org/10.1002/art.41214.

[5] A. Lerner, P. Jeremias, T. Matthias, The world incidence and prevalence of autoimmune diseases is increasing, Int. J. Celiac Dis. 3 (2016) 151–155, https://doi.org/10.12691/ijcd-3-4-8.

[6] A. Manzel, D.N. Muller, D.A. Hafler, S.E. Erdman, R.A. Linker, M. Kleinewietfeld, Role of "western diet" in inflammatory autoimmune diseases, Curr. Allergy Asthma Rep. 14 (2014) 404, https://doi.org/10.1007/s11882-013-0404-6.

[7] E.D. Sonnenburg, J.L. Sonnenburg, The ancestral and industrialized gut microbiota and implications for human health, Nat. Rev. Microbiol. 17 (2019) 383–390, https://doi.org/10.1038/s41579-019-0191-8.

[8] B.B. Yoo, S.K. Mazmanian, The enteric network: interactions between the immune and nervous systems of the gut, Immunity 46 (2017) 910–926, https://doi.org/10.1016/j.immuni.2017.05.011.

[9] J.A. Wargo, Modulating gut microbes, Science 369 (2020) 1302–1303, https://doi.org/10.1126/science.abc3965.

[10] E.Z. Gomaa, Human gut microbiota/microbiome in health and diseases: a review, Antonie Leeuwenhoek 113 (2020) 2019–2040, https://doi.org/10.1007/s10482-020-01474-7.

[11] D.J. Merenstein, M.E. Sanders, D.J. Tancredi, Probiotics as a TX resource in primary care, J. Fam. Pract. 69 (2020) E1–E10.

[12] A.J. Moshfegh, D.G. Rhodes, D.J. Baer, T. Murayi, J.C. Clemens, W.V. Rumpler, et al., The US Department of Agriculture Automated Multiple–Pass Method reduces bias in the collection of energy intakes, Am. J. Clin. Nutr. 88 (2008) 324–332, https://doi.org/10.1093/ajcn/88.2.324.

[13] National Center for Health Statistics, NCHS Ethics Review Board, 2022 [cited November 11, 2022]. Available from: https://www.cdc.gov/nchs/nhanes/irba98.htm.

[14] National Center for Health Statistics, National health and nutrition examination survey, 2022 [cited November 10, 2022]. Available from: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

[15] J. Dwyer, M.F. Picciano, D.J. Raiten, Members of the Steering Committee, National Health and Nutrition Examination Survery, Collection of food and dietary supplement intake data: what We Eat in America–Nhanes, J. Nutr. 133 (2003) 590S–600S, https://doi.org/10.1093/jn/133.2.590S.

[16] M.L. Marco, M.E. Sanders, M. Gänzle, M.C. Arrieta, P.D. Cotter, L. De Vuyst, et al., The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on fermented foods, Nat. Rev. Gastroenterol. Hepatol. 18 (2021) 196–208.

[17] N.M. McKeown, G.C. Fahey, J. Slavin, J.W. van der Kamp, Fibre intake for optimal health: how can healthcare professionals support people to reach dietary recommendations? BMJ 378 (2022), e054370 https://doi.org/10.1136/bmj-2020-054370.

[18] R. Korczak, J.L. Slavin, Definitions, regulations, and new frontiers for dietary fiber and whole grains, Nutr. Rev. 78 (2020) 6–12, https://doi.org/10.1093/nutrit/nuz061.

[19] I. Hojsak, M.A. Benninga, B. Hauser, A. Kansu, V.B. Kelly, A.M. Stephen, et al., Benefits of dietary fibre for children in health and disease, Arch. Dis. Child. 107 (2022) 973–979, https://doi.org/10.1136/archdischild-2021-323571.

[20] F.J. Dai, C.F. Chau, Classification and regulatory perspectives of dietary fiber, J. Food Drug Anal. 25 (2017) 37–42, https://doi.org/10.1016/j.jfda.2016.09.006.

[21] A. Dixon, K. Robertson, A. Yung, M. Que, H. Randall, D. Wellalagodage, et al., Efficacy of probiotics in patients of cardiovascular disease risk: a systematic review and meta–analysis, Curr. Hypertens. Rep. 22 (2020) 74, https://doi.org/10.1007/s11906-020-01080-y.

[22] K.S.D.S. Pontes, M.R. Guedes, M.R.D. Cunha, S.S. Mattos, M.I. Barreto Silva, M.F. Neves, et al., Effects of probiotics on body adiposity and cardiovascular risk markers in individuals with overweight and obesity: A systematic review and meta–analysis of randomized controlled trials, Clin. Nutr. 40 (2021) 4915–4931, https://doi.org/10.1016/j.clnu.2021.06.023.

[23] C. Chi, C. Li, D. Wu, N. Buys, W. Wang, H. Fan, et al., Effects of probiotics on patients with hypertension: a systematic review and meta–analysis, Curr. Hypertens. Rep. 22 (2020) 34, https://doi.org/10.1007/s11906-020-01042-4.

[24] T. Liang, L. Wu, Y. Xi, Y. Li, X. Xie, C. Fan, et al., Probiotics supplementation improves hyperglycemia, hypercholesterolemia, and hypertension in type 2 diabetes mellitus: an update of meta–analysis, Crit. Rev. Food Sci. Nutr. 61 (2021) 1670–1688, https://doi.org/10.1080/10408398.2020.1764488.

[25] J. Companys, L. Pla–Pagà, L. Calderón–Pérez, E. Llauradó, R. Solà, A. Pedret, et al., Fermented dairy products, probiotic supplementation, and cardiometabolic diseases: a systematic review and meta–analysis, Adv. Nutr. 11 (2020) 834–863, https://doi.org/10.1093/advances/nmaa030.

[26] T.D. Müller, B. Finan, S.R. Bloom, D. D'Alessio, D.J. Drucker, P.R. Flatt, et al., Glucagon–like peptide 1 (GLP–1), Mol. Metab. 30 (2019) 72–130, https://doi.org/10.1016/j.molmet.2019.09.010.

[27] C. Hill, F. Guarner, G. Reid, G.R. Gibson, D.J. Merenstein, B. Pot, et al., Expert consensus document. The International Scientific Association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic, Nat. Rev. Gastroenterol. Hepatol. 11 (2014) 506–514.

[28] M.E. Sanders, A. Benson, S. Lebeer, D.J. Merenstein, T.R. Klaenhammer, Shared mechanisms among probiotic taxa: implications for general probiotic claims, Curr. Opin. Biotechnol. 49 (2018) 207–216, https://doi.org/10.1016/j.copbio.2017.09.007.

[29] H.C. Wastyk, G.K. Fragiadakis, D. Perelman, D. Dahan, B.D. Merrill, F.B. Yu, et al., Gut–microbiota–targeted diets modulate human immune status, Cell 184 (2021) 4137–4153, https://doi.org/10.1016/j.cell.2021.06.019, e14.

[30] K. Berding, T.F.S. Bastiaanssen, G.M. Moloney, S. Boscaini, C.R. Strain, A. Anesi, et al., Feed your microbes to deal with stress: a psychobiotic diet impacts microbial stability and perceived stress in a healthy adult population, Mol. Psychiatry 28 (2023) 601–610.

[31] J.R. Buendia, Y. Li, F.B. Hu, H.J. Cabral, M.L. Bradlee, P.A. Quatromoni, et al., Long–term yogurt consumption and risk of incident hypertension in adults, J. Hypertens. 36 (2018) 1671–1679, https://doi.org/10.1097/HJH.0000000000001737.

[32] L. Wu, D. Sun, Consumption of yogurt and the incident risk of cardiovascular disease: a meta–analysis of nine cohort studies, Nutrients 9 (2017), https://doi.org/10.3390/nu9030315.

[33] J.P. Drouin–Chartier, Y. Li, A.V. Ardisson Korat, M. Ding, B. Lamarche, J.E. Manson, et al., Changes in dairy product consumption and risk of type 2 diabetes: results from 3 large prospective cohorts of US men and women, Am. J. Clin. Nutr. 110 (2019) 1201–1212, https://doi.org/10.1093/ajcn/nqz180.

[34] R. Pei, D.M. DiMarco, K.K. Putt, D.A. Martin, Q. Gu, C. Chitchumroonchokchai, et al., Low–fat yogurt consumption reduces biomarkers of chronic inflammation and inhibits markers of endotoxin exposure in healthy premenopausal women: a randomised controlled trial, Br. J. Nutr. 118 (2017) 1043–1051, https://doi.org/10.1093/jn/nxy046.

[35] M. Nozue, T. Shimazu, S. Sasazuki, H. Charvat, N. Mori, M. Mutoh, et al., Fermented soy product intake is inversely associated with the development of high blood pressure: the Japan Public Health Center–based prospective study, J. Nutr. 147 (2017) 1749–1756, https://doi.org/10.3945/jn.117.250282.

[36] S. Park, J.H. Bae, Fermented food intake is associated with a reduced likelihood of atopic dermatitis in an adult population (Korean National Health and Nutrition Examination Survey 2012–2013), Nutr. Res. 36 (2016) 125–133, https://doi.org/10.1016/j.nutres.2015.11.011.

[37] A. Taniguchi–Fukatsu, H. Yamanaka–Okumura, Y. Naniwa–Kuroki, Y. Nishida, H. Yamamoto, Y. Taketani, et al., Natto and viscous vegetables in a Japanese–style breakfast improved insulin sensitivity, lipid metabolism and oxidative stress in overweight subjects with impaired glucose tolerance, Br. J. Nutr. 107 (2012) 1184–1191, https://doi.org/10.1017/S0007114511004156.

[38] S. Rezac, C.R. Kok, M. Heermann, R. Hutkins, Fermented foods as a dietary source of live organisms, Front. Microbiol. 9 (2018) 1785, https://doi.org/10.3389/fmicb.2018.01785.

[39] V. Bell, J. Ferrão, T. Fernandes, Nutritional guidelines and fermented food frameworks, Foods 6 (2017), https://doi.org/10.3390/foods6080065.

[40] C. Hill, RDA for microbes – are you getting your daily dose? Biochemist 40 (2018).

[41] V. Bell, J. Ferrão, L. Pimentel, M. Pintado, T. Fernandes, One health, fermented foods, and gut microbiota, Foods 7 (2018), https://doi.org/10.3390/foods7120195.

[42] R.M. Carey, A.E. Moran, P.K. Whelton, Treatment of hypertension: a review, JAMA 328 (2022) 1849–1861, https://doi.org/10.1001/jama.2022.19590.