The American Journal of Clinical Nutrition 119 (2024) 1405–1416

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Original Research Article

Plant-Based Meat Analogs and Their Effects on Cardiometabolic Health: An 8-Week Randomized Controlled Trial Comparing Plant-Based Meat Analogs With Their Corresponding Animal-Based Foods

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A B S T R A C T

Background: With the growing popularity of plant-based meat analogs (PBMAs), an investigation of their effects on health is warranted in an Asian population.

Objectives: This research investigated the impact of consuming an omnivorous animal-based meat diet (ABMD) compared with a PBMAs diet (PBMD) on cardiometabolic health among adults with elevated risk of diabetes in Singapore.

Methods: In an 8-wk parallel design randomized controlled trial, participants ($n = 89$) were instructed to substitute habitual protein-rich foods with fixed quantities of either PBMAs ($n = 44$) or their corresponding animal-based meats ($n = 45$; 2.5 servings/d), maintaining intake of other dietary components. Low-density lipoprotein (LDL) cholesterol served as primary outcome, whereas secondary outcomes included other cardiometabolic disease-related risk factors (e.g. glucose and fructosamine), dietary data, and within a subpopulation, ambulatory blood pressure measurements ($n = 40$) at baseline and postintervention, as well as a 14-d continuous glucose monitor (glucose homeostasis-related outcomes; $n = 37$).

Results: Data from 82 participants (ABMD: 42 and PBMD: 40) were examined. Using linear mixed-effects model, there were significant interaction (time × treatment) effects for dietary *trans*-fat (increased in ABMD), dietary fiber, sodium, and potassium (all increased in PBMD; *P*-interaction <0.001). There were no significant effects on the lipid-lipoprotein profile, including LDL cholesterol. Diastolic blood pressure (DBP) was lower in the PBMD group (*P*-interaction=0.041), although the nocturnal DBP dip markedly increased in ABMD (+3.2% mean) and was reduced in PBMD (-2.6%; *P*-interaction=0.017). Fructosamine (*P* time=0.035) and homeostatic model assessment for β-cell function were improved at week 8 (*P* time=0.006) in both groups. Glycemic homeostasis was better regulated in the ABMD than PBMD groups as evidenced by interstitial glucose time in range (ABMD median: 94.1% (Q_1:87.2%, Q_3:96.7%); PBMD: 86.5% (81.7%, 89.4%); $P = 0.041$). The intervention had no significant effect on the other outcomes examined.

Conclusions: An 8-wk PBMA diet did not show widespread cardiometabolic health benefits compared with a corresponding meat based diet. Nutritional quality is a key factor to be considered for next generation PBMAs.

This trial was registered at https://clinicaltrials.gov/as NCT05446753.

Keywords: animal protein, blood pressure, cardiovascular disease risk, diet, glycemia, meat, nutrients, plant-based meat analogs, plant protein, randomized controlled trial

Abbreviations: ABPM, ambulatory blood pressure monitor; ABMD, animal-based meat diet; BMI, body mass index; CGMS, continuous glucose monitoring sensor; CVD, cardiovascular diseases; DBP, diastolic blood pressure; GRADE, glycemic risk assessment diabetes equation; HbA1c, glycated hemoglobin; HOMA-β, homeostatic model assessment for β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance; hsCRP, high sensitivity C-reactive protein; iAUC, incremental area under curve; LI, lability index; LDL, Low-density Lipoprotein; HDL, High Density Lipoprotein; PBD, plant-based diet; PBMA, plant-based meat analogs; PBMD, plant-based meat diet; RCT, randomized controlled trial; SBP, systolic blood pressure; T2DM, type-2 diabetes mellitus; TMAO, trimethylamine-N-oxide.

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https://doi.org/10.1016/j.ajcnut.2024.04.006
Received 19 December 2023; Received in revised form 25 March 2024; Accepted 2 April 2024; Available online 8 April 2024

Introduction

Historically, the consumption of plant-based diets (PBDs) was predominantly practiced based on religious and cultural edicts. Recently, a renaissance of interest in PBDs has evolved due to global concerns surrounding the environment, animal welfare, and human health as key motivators. Regarding health, the cardiometabolic advantages of vegetarian and vegan diets compared with omnivorous diets are well established [1–4]. Beyond a dichotomous classification (i.e., vegetarians or nonvegetarians), the PBD index (which positively and negatively scores the intake of plant-based and animal-based foods, respectively) also substantiates the benefits a gradual transition to PBDs may have on noncommunicable disease risk [5]. This was described in large-scale cohorts such as the Nurses' Health Study 1 and 2, Health Professionals' Follow-up Study, Atherosclerosis Risk in Communities study, the Prevención con Dieta Mediterránea, as well as systematic reviews and meta-analyses that established strong links between increased adherence to PBDs with modest reductions in cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM) [6–8].

Much of these benefits largely purported to PBD stem from the wide array of bioactive constituents (e.g., unsaturated fatty acids, phytosterols, dietary fibers, vitamins, minerals, carotenoids, polyphenols, etc.) present in conventional PBDs, characterized by a balanced intake of grains, legumes, nuts, seeds, fruits, and vegetables [9]. Yet despite the advantages of PBDs, adoption, and long-term compliance can be arduous for most habitual omnivores, where meat consumption is deeply ingrained in history, culture, and societal norms [10,11].

The advent of plant-based meat analogs (PBMAs) designed to mimic the organoleptic attributes of their animal-based counterparts sparked remarkable interest globally. Developed from more sustainable plant-based sources, PBMAs have presented our food landscape with a promising opportunity that seemingly addresses both planetary and human health concerns. Its production, however, which involves deconstruction and reconstruction of traditional plant-based foods (e.g. soy protein isolates from soya beans and cassava starch from cassava) introduces potential unintended consequences on various health-promoting constituents inherently present in these plant-based ingredients [12,13]. This is clearly evidenced by the vast differences in nutritional composition when PBMAs are compared with both traditional plant-based protein-rich foods (including nuts, seeds, legumes, or soya-based foods such as *tofu* and *tempeh*), as well as their corresponding animal-based foods [14].

With the growing popularity of PBMAs, it is necessary that we critically examine the health effects of transitioning from a typical omnivorous diet consisting of conventional meats/meat products to diets that substitute PBMAs as the primary protein source. In a previous behavioral intervention, dietary PBMA contributed to a marginally significant reduction in body weight compared with controls who received no intervention [15]. Weight loss was likewise detected in another crossover design, 8-wk randomized controlled trial (RCT) that compared dietary interventions with PBMAs with corresponding animal-based meats. This was coupled with marked improvements in cardiometabolic health, as represented by significant reductions in plasma LDL cholesterol and serum trimethylamine-N-oxide (TMAO) following PBMA intake only [16].

Nevertheless, there remains paucity in clinical evidence that rigorously examined the adaptive responses to diets that incorporated either animal-based meats or a mainstream selection of their corresponding PBMAs, particularly within an Asian dietary context. This will be evaluated by an expanded selection of robust cardiometabolic disease-related risk indicators including ambulatory glucose and blood pressure monitoring, building upon the existing evidence. The objective of this study was to investigate the impacts of dietary patterns that characteristically featured either PBMAs or animal-based meats on cardiometabolic health among males and females in Singapore with an elevated risk of T2DM. We hypothesize that dietary substitutions of animal-based meats with PBMA will positively influence cardiometabolic health and lower the risks associated with noncommunicable diseases, such as CVD and T2DM.

Methods

This study was registered with clincialtrials.gov as NCT05446753 and was approved by the National Healthcare Group Domain Specific Review Board, Singapore (reference number: 2022/00278). Prospective participants provided their written informed consent before study commencement. Recruitment began in June 2022, and all follow-ups were completed before January 2023.

Participants

Research volunteers were identified by means of physical and electronic posters, online advertisements, the research center's recruitment databases, as well as via word of mouth. Individuals who expressed their interest were scheduled for an inperson screening at the Clinical Nutrition Research Center, Singapore, after an overnight fast (>10 h). As part of the screening, validated questionnaires relating to health and lifestyle, physical activity [17], and a semiquantitative food frequency questionnaire [18] were completed. Anthropometric measurements, including height (Seca 763; Seca GmbH), weight (Tanita BC-418, Tanita Inc.), and waist circumference, were recorded in duplicate. The latter was determined standing with a flexible tape measure positioned between the lowest rib and the top of the iliac crest, after consecutive natural breaths [19]. Capillary finger prick blood was collected for fasting blood glucose (HemoCue 201; Radiometer) and glycated hemoglobin (HbA1c) (DCA Vantage Analyzer; Siemens Healthcare GmbH) analyses.

In accordance with inclusion and exclusion criteria stipulated a priori, recruited participants were ethnic Chinese males and females (>30 to ≤70 y) who were without diabetes but with raised blood glucose (defined by a fasting blood glucose concentration ≥5.4 and ≤7.0 mmol/L, and/or HbA1c ≥5.5 and ≤6.4%). Notably, raised blood glucose concentrations within these ranges have been described to provide improved predictive discrimination of T2DM risk, especially among Asians who have a genetic predisposition to metabolic diseases [20–23]. For the maintenance of dietary homogeneity at baseline, participants were also nonvegan/nonvegetarian and consumed between 2 and 4 servings (approximately 20 g per serving) of protein-rich foods daily (according to the semiquantitative food frequency questionnaire completed during screening). The remaining inclusion criteria included full vaccination against COVID-19 and a willingness to adhere to study intervention protocols.

Exclusion criteria included smoking, obesity (defined by BMI of ≥27.5 kg/m^2 based on Asian criteria [24] and/or waist circumference (≥102 cm for male, ≥88 cm for female), ±5% body weight change during the past 3 mo, history of bariatric surgery, present/past diagnosis of clinically relevant cardiovascular, endocrine, gastrointestinal, hematologic, hepatic and other relevant disorders (as determined by study clinician), uncontrolled hypertension [systolic/diastolic blood pressure

(SBP/DBP): ≥140/90 mmHg], regular use of medication (stable use of medication >5 y was allowed), history of drug abuse, use of dietary supplements or traditional medicine which may affect outcomes of interest ≤1 mo before study commencement (e.g., protein concentrates/isolates, omega 3, nutrient blends/meal replacements such as Ensure), adherence to special diets for aesthetic, medical or religious reasons; excessive alcoholic beverage consumption (>2 servings/d), participation in vigorous physical activities [17]; females who were planning pregnancy, pregnant or lactating; as well as staff who were affiliated with either the research organization or study sponsor.

Recruited participants were randomly assigned by minimization using R studio (version 1.2.5033) into either the plant-based meat analog diet (PBMD) or animal-based meat diet (ABMD) groups by an independent research statistician. Sex, age, and the ratio of protein-rich foods intake at baseline (animal-based proteins:plant-based proteins) were selected as prognostic covariates for the randomization. A double-blind was unfeasible due to the nature of the dietary intervention, although allocation concealment and investigator/outcome assessor blinding integrity were maintained.

Study design and intervention

This was an 8-wk parallel design RCT. There were a total of 2 inperson study visits at baseline (week 0) and postintervention (week 8) following a >10 h overnight fast, and 2 online consultation sessions at weeks 2 and 5. Over the 8-wk intervention period, participants were instructed to substitute their habitual protein-rich foods with fixed quantities of either animal-based meats or their corresponding PBMAs provided by the research team. These included a selection of 6 frozen foods that were broadly categorized as follows: *1)* beef mince, *2)* pork mince, *3)* chicken breast, *4)* burger patty, *5)* sausage, and *6)* chicken nuggets provided via scheduled deliveries to each participant's home. Corresponding to this list, the PBMD group was provided with the following foods: *1)* Impossible Beef (Impossible Foods), *2)* OmniMeat Mince (OmniFoods), *3)* Chickened Out Chunks (The Vegetarian Butcher), *4)* Beyond Burger (Beyond Meat), *5)* Beyond Sausage Original Brat (Beyond Meat), and *6)* Little Peckers (The Vegetarian Butcher). Meats provided to the ABMD group were as described and sourced from a local butcher (Baggie's Butcher & Deli) apart from the chicken nuggets (Frozen chicken nuggets, Farmland). All intervention foods were sourced from independent retailers that were unaffiliated with the study sponsor and research team.

Frozen foods were provided in prespecified, protein-matched quantities for consumption in 3-d cycles (Table 1). This enabled participants to substitute most of their daily intake of dietary protein-rich foods at an acceptable level (~2.5 servings of protein-rich foods daily) with minimal influence on the rest of the diet. A similar dose was used for the Study With Appetizing Plant-food-Meat Eating Alternative Trial (SWAP-MEAT) RCT [16], which is, to the best of the authors' knowledge, the only other RCT to rigorously compare the cardiometabolic health effects of PBMA with their animal-based counterparts. This study also served as the evidence base for power calculations.

Throughout the 8 wk, participants were encouraged to minimize their consumption of other protein-rich foods (≤ 1 serving per 3-d cycle) beyond the intervention foods provided. The mode of preparation for intervention foods, including the method of cooking, type of seasoning used, and meal accompaniments, were at the discretion of the participants, although as much as possible, participants were instructed to keep the other components of their habitual diet consistent (e.g., staple foods, fruits, and vegetables). Hedonic acceptability of the foods provided (in terms of appearance, taste, aroma, and texture) and ease of dietary incorporation were evaluated using a continuous visual analog scale after the 8-wk dietary intervention.

TABLE 1
Quantity of protein-matched intervention foods consumed every 3-d in the animal-based meat diet (ABMD) and plant-based meat analog diet (PBMD) groups.

	ABMD		PBMD	
	Weight (g)	Protein (g)[1]	Weight (g)	Protein (g)[1]
Chicken breast	150	33.8	160	34.0
Beef mince	250	44.3	339	57.0
Burger patty	160	28.3	113	20.0
Pork mince	150	29.3	230	28.8
Sausage	100	16.5	100	16.0
Chicken nuggets	100	9.8	90	8.4
Average protein intake (g/day)	54.0		54.7	

[1] Protein content as defined by USDA FoodData Central nutritional database, and nutritional information panels of respective foods.

A comprehensive macro- and micronutrient profiling of the cooked PBMAs and animal-based meats (as provided in their original packaging) was conducted by an external accredited food testing laboratory (Eurofins Food Testing Singapore Pte Ltd). The nutritional profiles of foods provided to each group every 3 d are tabulated in Supplemental Table 1.

Dietary and compliance assessment

In either small groups or individually, participants were instructed on how to complete 3-d food records (2 weekdays and 1 weekend) properly. The 3-d food records were collected 4 times across the intervention period [at baseline (week 0), week 2, week 5, and week 8]. In addition to monitoring the overall dietary intake during the intervention period, these food records also provided an opportunity for researchers to offer tailored advice and suggestions for each participant to improve compliance with the dietary intervention. Dietary data from the food records were analyzed with FoodWorks Professional software (version 10, Xyris Software) for the determination of daily energy in macro- and micronutrient intakes. Nutritional information was primarily based on the AusFoods and AusBrands 2019 databases, supplemented with the USDA FoodData Central nutritional database [25] and nBuddy (HeartVoice) for local Singaporean cuisines. To monitor compliance and adherence levels, participants were additionally tasked to record their consumption of intervention foods daily, throughout the 8-wk intervention duration.

Outcomes of interest

The primary outcome of interest is LDL cholesterol. Secondary outcomes included a 14-d continuous monitoring of glucose concentration, cardiometabolic health-related risk factors such as fasting glucose, fructosamine, and insulin values, clinic and 24-h ambulatory blood pressure measurements, serum lipid-lipoprotein concentrations (triglycerides, HDL cholesterol and total cholesterol), and high sensitivity C-reactive protein (hsCRP) values. Additional outcomes, which included protein metabolism-related biomarkers (e.g., urea, creatinine, and albumin concentrations) and body composition (by dual energy x-ray absorptiometry) were analyzed, although not reported at present, to maintain focus on cardiometabolic health outcomes.

At baseline and week 8, fasting venous blood (~ 33 mL) was drawn by venipuncture into EDTA-coated, sodium fluoride/potassium oxalate

(NaF/KOx)-coated, and plain tubes (Becton-Dickinson). The EDTA and NaF/KOx tubes were placed on ice and centrifuged immediately (2000 × *g*, 10 min at 4 °C), whereas plain tubes were left to clot in an upright position at room temperature for 30 min before centrifugation under similar conditions. Aliquots (0.5 mL) of plasma and serum were stored in –80 °C until thawed for analysis.

Serologic assays

Plasma insulin and fructosamine concentrations were determined using the immunochemistry analyzer COBAS e411 and chemistry analyzer COBAS c311 (Roche, Hitachi), respectively. Fasting glucose in NaF/KOx plasma, serum lipid-lipoprotein, and hsCRP concentrations were assayed by National University Hospital Referral Laboratories (Singapore) with standard analytical protocols, using ALINITY c (Abbot Laboratories).

From the outcomes of interest analyzed, homeostatic model assessment for insulin resistance [HOMA-IR = fasting plasma glucose (mmol/L) × fasting plasma insulin (mU/L) / 22.5)] and homeostatic model assessment for β-cell function [HOMA-β = (20 × fasting plasma insulin)/(fasting plasma glucose – 3.5)] were calculated [26]. Overall CVD risk was determined using the primary model of the Framingham risk score to obtain a 10-y CVD risk prediction and vascular age [27].

Continuous glucose monitor

During the 8-wk intervention period, a subset of the original study population volunteered for an optional component of the study, which included both an additional 14-d continuous glucose monitoring, as well as 2 sessions of 24-h ambulatory blood pressure monitoring. This was completed by a total of 37 and 40 participants, respectively. The optional component required 2 additional study sessions that were scheduled 2-d before the baseline and postintervention visits [week 8; ambulatory blood pressure monitor (ABPM) only)] for instructions and device attachment. The continuous glucose monitoring sensor (CGMS; Abbott Freestyle Libre Sensor, Abbott Diabetes Care Ltd) was attached to the underside of the upper right arm during the first session for interstitial glucose measurements at 15-min intervals. Formal data analysis and interpretations of CGMS readings were limited to data acquired after a 48-h equilibration.

As a part of the 14-d CGMS period, participants first completed a full-feeding period that spanned from day 0 dinner to day 3 dinner. This comprised 13 meals, including breakfast (08:00), lunch (12:00), snack (16:00), and dinner (20:00) that were consumed at fixed times daily. Apart from the snack meal, participants cooked and consumed 1 of the 6 frozen 'meats' provided, with a fixed staple that included a serving of either white rice (210 g; HeatBahn, CJ Foods), hamburger bun (55 g; Gardenia hamburger buns, Gardenia Foods Pte Ltd) or plain instant noodles (70 g; Koka nonfried plain instant noodles, Tat Hui Foods Pte Ltd). The type of frozen 'meat' consumed between groups was congruent and protein-matched, with an identical snack eaten on all 3 d. This comprised of a muesli bar (Uncle Toby's wholegrain muesli bar, Nestlé) and a packet of plain crackers (Jacob's hifiber cracker, Jacob's). Details of the specific 3-d full-feeding menu and general nutritional information of these additional foods provided are described in Supplemental Table 2.

Glycemic response variables, including the incremental AUC (iAUC) and AUC, were calculated daily (from 06:00 to 06:00 the following day) and across the 3-d full-feeding period using the trapezoidal rule. Time in range (≥3.9 and ≤7.8 mmol/L), time below range (<3.9 mmol/L), and time above range (>7.8 mmol/L) were defined based on adjusted cut-offs which offered greater clinical representation for the present population who are without diabetes [28,29]. In addition, measurements of glycemic control [J-index, Glycemic Risk Assessment Diabetes Equation (GRADE) and M-value] and glycemic variability [Mean Amplitude of Glycemic Excursions, continuous overall net glycemic action, Mean Absolute Glucose, and Lability Index (LI)] were determined with EasyGV (Version 9.0) [30]. For a confident evaluation of the CGMS metrics, formal analysis and interpretations were limited to participants who had ≥70% valid and representative continuous glucose data collected [31].

Clinic and ambulatory blood pressure

Clinic blood pressure was measured using an automatic sphygmomanometer (HEM-7320, Omron) with a minimum of 2 readings collected for each measurement for all participants. For ambulatory blood pressure, an ABPM (Mobil-O-Graph, IEM GmbH) was worn by a subset of participants (as described above) on their left arm for 24 h, 2 days before the baseline (week 0) and postintervention (week 8) visits. SBP and DBP readings were taken every 30 min when participants were awake and every 60 min when asleep. The mean 24-h, awake, and asleep SBP, DBP, and corresponding nocturnal dips were calculated according to self-reported sleep-wake cycles using formulas described previously (32). Outliers in ambulatory blood pressure measurements were identified using ROUT (Q = 1%), with data analysis and interpretations limited to participants who had >70% valid blood pressure measurements within each 24-h timeframe [32,33].

Power calculation and statistical analysis

Power calculations with G*Power (Version 3.1) [34] were conducted a priori based on 2 previous RCTs. The first, which compared an 8-week dietary consumption of animal-based meats with PBMA, reported significant differences in plasma LDL cholesterol concentrations after an 8-wk intervention (mean difference ± SD after PBMA diet: -17.9 ± 23.5 mg/dL and animal-based meats diet: +4.2 ± 26.6 mg/dL) [16]. In the second study, which investigated the replacement of 30 g/d of animal-based meats (e.g., pork and chicken) with soy-based meat analogs and nuts, a significant difference in insulin sensitivity was observed after 4 wk between groups (mean disposition index ± SD for animal-based meat group: 2899 ± 1878 and soy-based food group: 4974 ± 2543) [35]. Presuming that the present study yields a similar response as previous ones (effect size = 0.64 and 0.93 for former and latter examples, respectively), 84 and 40 subjects will provide an 80% power at α = 0.05 (2-tailed) to statistically confirm a similar effect for the primary outcome (main study) and optional component (continuous glucose monitoring) respectively.

Data distribution and normality were examined using Shapiro-Wilk test and a visual assessment of QQ plots and histograms. Skewed continuous variables were logarithmically transformed before statistical analyses. Comparisons of demographic characteristics at baseline between participants in the ABMD and PBMD groups were evaluated by independent t-test or Fisher's exact test for continuous and categorical variables, respectively. The former was also used for group comparisons of glycemic control and glycemic variability-related indices. The main effects of treatment, time, and interactions (time × treatment) for outcomes of interest were determined by linear mixed-effects model and pairwise comparisons with Bonferroni correction. Statistical analyses were conducted using SPSS version 25 (SPSS, Inc.) and STATA version 13 (StataCorp LP). Data are presented as either mean ± SD or median (quartile 1, quartile 3) unless otherwise stated. Statistical significance was accepted at *P* value of <0.05 (2-tailed).

Results

Participants

Of the 213 volunteers screened, 96 were eligible for participation and randomly assigned to either the ABMD or PBMD groups (Figure 1). Seven participants withdrew before study commencement (i.e., between random assignment and baseline visit) either due to health reasons that were unrelated to study ($n = 1$) or personal reasons such as the inability to commit to the dietary intervention protocol and/or study schedule ($n = 6$). Among the remaining 89 participants, 45 were allocated to the PBMD group and 44 to the ABMD group. During the intervention, 7 participants dropped out of the study; 3 due to medical reasons that were study independent (ABMD: 2 and PBMD: 1), 3 due to an inability to commit to the study schedule (ABMD: 2 and PBMD: 1), and 1 participant from the PBMD group due to difficulties complying with the intervention diet. Data analysis was completed for 82 participants (ABMD: 42 and PBMD: 40) who finished the full intervention duration.

In general, the participants comprised of predominantly older adults (59 ± 8 y) and females (61% females) (Table 2). Besides the raised HbA1c values (5.8% ± 0.3%), which was part of the prespecified inclusion criteria, the population was otherwise apparently healthy in terms of their mean BMI (22.5 ± 2.5 kg/m^2), waist circumference (79.6 ± 7.3 cm), and vascular age (56 ± 15 y) which was slightly younger than their physiological age (59 ± 8 y) [27,36,37]. Habitual dietary protein consumption, including the intake distribution of animal-based (ABMD: 2.4 ± 0.6 servings, PBMD: 2.3 ± 0.6 servings) and plant-based protein-rich foods (ABMD: 0.7 ± 0.4 servings, PBMD: 0.8 ± 0.5 servings) were also matched between groups at week 0, with a distinctly greater contribution from the former.

At baseline, comparisons between groups revealed no significant differences in the demographic characteristics, apart from BMI (ABMD: 21.9 ± 2.5 kg/m^2; PBMD: 23.2 ± 2.4 kg/m^2; $P = 0.011$; data not shown). To adjust for potential confounding that may be consequent to this discrepancy, linear mixed-effects models were repeated with the adjustment of baseline BMI as a covariate. As there were no marked statistical effects either with or without adjustment for any of the variables measured, unadjusted data and P values are presented.

TABLE 2
Population baseline characteristics by intervention group.

Characteristics	Combined ($n = 89$)	ABMD ($n = 44$)	PBMD ($n = 45$)
Sex, F/M, *n*	54/35	27/17	27/18
Age (y)	59 ± 8	59 ± 8	60 ± 8
BMI (kg/m^2)	22.5 ± 2.5	21.9 ± 2.5	23.2 ± 2.4
Waist circumference (cm)	79.6 ± 7.3	78.1 ± 7.6	81.0 ± 6.8
Capillary blood glucose (mmol/L)	5.0 ± 0.6	5.0 ± 0.6	5.1 ± 0.6
HbA1c (%)	5.8 ± 0.3	5.8 ± 0.4	5.7 ± 0.2
Framingham vascular age (y)	56 ± 15	55 ± 16	58 ± 14
Dietary protein-rich food intake (servings/d)[1]	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7
Animal-based protein	2.3 ± 0.6	2.4 ± 0.6	2.3 ± 0.6
Plant-based protein	0.8 ± 0.5	0.7 ± 0.4	0.8 ± 0.5

Values reported as means ± SD unless otherwise stated. Between group baseline characteristics analyzed by independent t-test or Fisher's exact test for sex.
Abbreviations: ABMD: animal-based meat diet; HbA1c: glycated hemoglobin; PBMD: plant-based meat analog diet
[1] Determined based on semiquantitative food frequency questionnaire [18].

Laboratory nutritional profiling of intervention foods

Although the average protein content of the intervention foods (both for ABMD and for PBMD) was matched as listed on the products' nutrition information panels, analytical profiling of the macro- and micronutrient contents of cooked foods revealed lower protein contents among foods provided in the PBMD group (ABMD: 226.2 g, PBMD: 192.0 g per 3-d cycle). This was coupled with noticeably higher total carbohydrates (ABMD: 16.1 g, PBMD: 100.6 g per 3-d cycle) and dietary fiber (ABMD: 0.00 g, PBMD: 51.70 g per 3-d cycle) than their corresponding animal-based foods (Supplemental Table 1). The quantity and type of fat indicated largely inconsistent

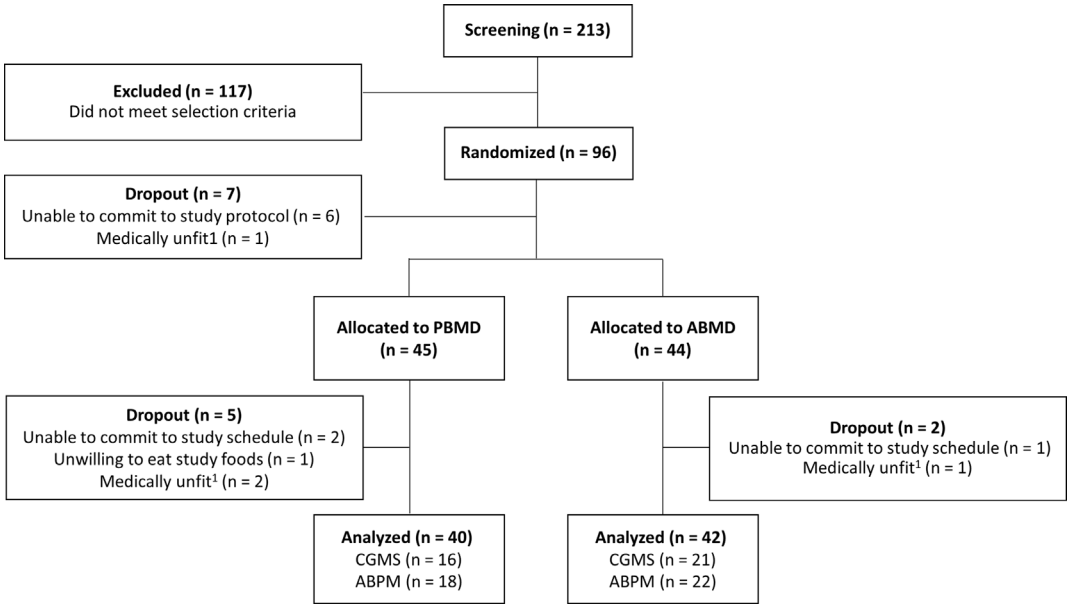

FIGURE 1. CONSORT flow diagram.
[1]Withdrawal due to medical occurrences unrelated to clinical trial participation.

results although most of PBMAs (chicken breast, beef mince, beef burger, and nuggets) trended toward higher polyunsaturated fat (ABMD: 9.47 g, PBMD: 13.12 g per 3-d cycle), whereas animal-based meats (more specifically pork containing foods i.e., pork mince and sausage) were richer in monounsaturated fat (ABMD: 40.52 g, PBMD: 34.82 g per 3-d cycle). As expected, PBMAs contained no cholesterol (ABMD: 600.2 mg, PBMD: 0.0 mg per 3-d cycle).

Examining the micronutrient profile, key differences included folate (ABMD: 48.5 μg dietary folate equivalents (DFE), PBMD: 1207.2 μg DFE per 3-d cycle), calcium (ABMD: 90.4 mg, PBMD: 1316.4 mg per 3-d cycle), iron (ABMD: 15.21 mg, PBMD: 38.78 mg per 3-d cycle) which were higher in PBMAs than their animal-based counterparts. Along with Vitamin B_{12} (ABMD: 15.69 μg, PBMD: 17.31 μg per 3-d cycle), which is absent from most natural plant-based food sources, the higher contents of the above-mentioned micronutrients were likely contributed by constituent ingredients and fortifications used in PBMA formulations.

Dietary data and compliance assessments

The study population's dietary data over the 3-d self-reported food record periods at baseline and week 8 are detailed in Table 3. Dietary intake at baseline was comparable between the 2 groups, apart from carbohydrates and dietary fiber, which was consumed in slightly greater quantities in the PBMD group (carbohydrates: $P = 0.010$; dietary fiber: $P = 0.029$).

Main effects of time were observed for protein (*P time* < 0.001) and saturated fats (*P time* < 0.001) intake, which were significantly higher postintervention, whereas total carbohydrate intake was lowered postintervention (*P time* < 0.001). For protein specifically, this was coupled with an interaction (time × treatment) effect that suggests an increase that was more prominent in the ABMD group [*P-interaction* (interaction coefficient) = 0.002 (10.3)]. Dietary cholesterol, on the other hand, was lowered across both groups (*P time* < 0.001), albeit with markedly greater reduction in the PBMD group [*P-interaction* = 0.001 (11.8)]. Significant interaction effects also revealed contrasting changes in *trans*-fat [*P-interaction* < 0.001 (70.3)], which was markedly raised in ABMD but lowered with PBMD groups, as well as dietary fiber, which was raised specifically in the PBMD group [*P-interaction* < 0.001 (66.3)]. For sodium and potassium, there were likewise significant time and interaction effects, with the post-hoc tests showing a marked increase in the PBMD group.

Population compliance, as defined by daily records of intervention food consumption, was reported to be 87% and 95% for participants completing the PBMD and ABMD interventions, respectively. There were no adverse events related to either the dietary intervention or study participation reported. Between groups, there were also no significant differences in liking for the appearance, aroma, texture, or ease of dietary incorporation for intervention foods. Taste was significantly less preferred for PBMAs compared with their animal-based counterparts (data not shown).

Cardiometabolic health-related outcomes

Descriptive statistics of CVD risk factors, as well as composite risk indicators such as the Framingham 10-y cardiovascular disease risk prediction (D'Agostino et al., [27] 2008), are summarized in Table 4. There were no significant effects on the lipid-lipoprotein profile, including LDL cholesterol. A marginal interaction effect was observed for DBP [ABMD: 77 ± 12 mmHg (week 0) to 77 ± 12 mmHg (week 8); PBMD: 78 ± 9 mmHg (week 0) to 76 ± 8 mmHg (week 8); *P-interaction* (interaction coefficient) = 0.041 (4.31)], with slight reductions in the PBMD group. Among the other cardiovascular health-related outcomes, however, no time and interaction effects were observed in terms of the clinic SBP, hsCRP concentrations, and Framingham 10-y CVD risk following the 8-wk intervention.

The ambulatory blood pressure measurements indicated a time effect in awake DBP ($P_{Time} = 0.04$), which trended toward a reduction at week 8 [ABMD: 80 ± 9 mmHg (week 0) to 79 ± 11 mmHg (week 8); PBMD: 79 ± 9 mmHg (week 0) to 77 ± 9 mmHg (week 8)]. There was also a significant interaction effect for nocturnal dip in DBP (*P-interaction* (interaction coefficient) = 0.017 (6.20)], which was increased in the ABMD group [7.2% ± 7.0% (week 0) to (9.3% ± 7.3% (week 8)] but decreased in the PBMD group [9.5% ± 5.6% (week 0) to 6.3% ±

TABLE 3
Average daily dietary intake of selected nutrients at baseline (week 0) and following an 8-wk animal-based meat diet or plant-based meat analog diet during each 3-d food record period.

	ABMD ($n = 42$)		PBMD ($n = 40$)		Time	Time × Treatment
	Week 0	Week 8	Week 0	Week 8	*P*	*P* (Interaction coefficient)
Energy (kcal)	1531 ± 314	1640 ± 304	1687 ± 522	1674 ± 357	0.30	0.18 (1.81)
Protein (g)	74.1 ± 18.7	105.8 ± 18.5[2]	77.5 ± 26.7	90.9 ± 13.9[2]	< 0.001	0.002 (10.3)
Total fat (g)	59.76 ± 18.38	69.74 ± 17.44[2]	64.47 ± 29.27	65.82 ± 16.89	0.038	0.11 (2.59)
Saturated fat (g)	19.09 ± 6.46	23.23 ± 4.83[2]	18.82 ± 7.29	21.42 ± 5.61[2]	< 0.001	0.37 (0.82)
Trans-fat (g)	0.60 ± 0.32	1.02 ± 0.27[2]	0.63 ± 0.36	0.34 ± 0.28[2]	0.09	< 0.001 (70.3)
Polyunsaturated fat (g)	11.02 ± 4.50	10.36 ± 5.11	13.66 ± 8.77	12.04 ± 4.35	0.15	0.54 (0.38)
Monounsaturated fat (g)	24.66 ± 9.05	27.61 ± 8.39	26.58 ± 13.81	25.50 ± 7.77	0.47	0.12 (2.48)
Dietary cholesterol (mg)	421 ± 212	346 ± 143[2]	412 ± 152	157 ± 152[2]	< 0.001	0.001 (11.8)
Total carbohydrates (g)	164.0 ± 39.8[3]	139.3 ± 45.3[2]	192.4 ± 56.9[3]	172.4 ± 51.5[2]	< 0.001	0.69 (0.16)
Sugars (g)	45.2 ± 18.6	38.9 ± 22.0	54.9 ± 27.6	38.7 ± 23.5[2]	0.001	0.12 (2.53)
Dietary fiber (g)	16.01 ± 5.29[3]	15.25 ± 5.81	19.25 ± 7.72[3]	30.99 ± 7.76[2]	< 0.001	< 0.001 (66.3)
Sodium (mg)	2430 ± 917	2358 ± 905	2304 ± 716	3283 ± 1168[2]	0.001	< 0.001 (16.3)
Potassium (mg)	2126 ± 633	2421 ± 504[2]	2292 ± 763	3269 ± 798[2]	< 0.001	< 0.001 (15.8)

Values reported as means ± SD.
Abbreviations: ABMD: animal-based meat diet; PBMD: plant-based meat analogue diet
[1]Effects of ABMD and PBMD were assessed by linear mixed-effects model.
[2] Significant difference from baseline (2-tailed, $P < 0.05$) by Bonferroni's pairwise comparisons.
[3] Significant difference at baseline (2-tailed, $P < 0.05$) by independent t-test.

TABLE 4
Effects of an animal-based meat diet compared to a plant-based meat analogue diet on cardiovascular health-related outcomes.

	ABMD ($n = 42$)		PBMD ($n = 40$)		Time[1]	Time × Treatment[1]
	Week 0	Week 8	Week 0	Week 8	*P*	*P* (Interaction coefficient)
Total cholesterol (mmol/L)	5.42 ± 0.90	5.53 ± 0.89	5.81 ± 1.07	5.63 ± 1.08	0.66	0.11 (2.50)
LDL cholesterol (mmol/L)	3.51 ± 0.92	3.47 ± 0.95	3.60 ± 0.90	3.48 ± 0.93	0.21	0.69 (0.15)
HDL cholesterol (mmol/L)	1.60 ± 0.38	1.64 ± 0.31	1.71 ± 0.42	1.66 ± 0.40	0.96	0.26 (1.23)
Triglyceride (mmol/L)	0.85 (0.70, 1.20)	0.90 (0.60, 1.10)	0.80 (0.70, 1.00)	0.90 (0.70, 1.35)	0.56	0.24 (1.39)
Total cholesterol:HDL cholesterol	3.57 ± 1.03	3.52 ± 0.94	3.55 ± 0.92	3.51 ± 0.80	0.54	0.91 (0.014)
SBP (mmHg)	119 ± 19	121 ± 18	122 ± 15	121 ± 15	0.98	0.10 (2.77)
DBP (mmHg)	77 ± 12	77 ± 12	78 ± 9	76 ± 8[2]	0.030	0.041 (4.31)
C-reactive protein (mg/L)	0.60 (0.20, 1.60)	0.90 (0.20, 1.20)	0.70 (0.20, 1.25)	0.60 (0.20, 1.00)	0.99	0.33 (0.96)
Framingham 10-y CVD risk (%)	6.47 (3.01, 12.53)	6.62 (3.74, 11.33)	7.68 (4.67, 12.94)	7.28 (4.36, 11.72)	0.84	0.09 (2.90)
ABPM outcomes	ABMD ($n = 23$)		PBMD ($n = 21$)		Time[1]	Time × Treatment[1]
	Week 0	Week 8	*P*	Week 8	*P*	*P* (Interaction coefficient)
24-h SBP (mmHg)	121 ± 13	120 ± 15	123 ± 12	121 ± 10	0.25	0.48 (0.51)
Awake SBP (mmHg)	122 ± 12	123 ± 15	125 ± 11	123 ± 10	0.39	0.34 (0.92)
Asleep SBP (mmHg)	115 ± 15	112 ± 16	116 ± 15	115 ± 11	0.33	0.47 (0.52)
24-h DBP (mmHg)	79 ± 9	77 ± 11	78 ± 9	76 ± 9	0.09	0.96 (0.003)
Awake DBP (mmHg)	80 ± 9	79 ± 11	79 ± 9	77 ± 9	0.044	0.57 (0.33)
Asleep DBP (mmHg)	74 ± 10	71 ± 11	72 ± 9	72 ± 8	0.20	0.19 (1.78)
Nocturnal SBP dip (%)	6.5 ± 5.0	8.8 ± 6.8	7.1 ± 5.5	5.8 ± 5.8	0.78	0.06 (3.65)
Nocturnal DBP dip (%)	7.2 ± 7.0	9.3 ± 7.3	9.5 ± 5.6	6.3 ± 6.0[2]	0.74	0.017 (6.20)

Values reported as means ± SD or median (Q_1, Q_3). Skewed continuous variables were logarithmically transformed prior to statistical analyses.
Abbreviations: ABMD: animal-based meat diet; ABPM: ambulatory blood pressure; CVD: cardiovascular diseases; DBP: diastolic blood pressure; PBMD: plant-based meat analogue diet; SBP: systolic blood pressure

[1] Effects of ABMD and PBMD were assessed by linear mixed-effects model. Adjustment of baseline BMI as a covariate to the model revealed no marked statistical effect.

[2] Significant difference from baseline (2-tailed, $P < 0.05$) from baseline by Bonferroni's pairwise comparisons.

6.0% (week 8)]. A similar trend was observed for nocturnal dip in SBP [ABMD: 6.5% ± 5.0% (week 0) to 8.8% ± 6.8% (week 8); PBMD: 7.1% ± 5.5% (week 0) to 5.8% ± 5.8% (week 8)] albeit this was marginally nonsignificant [*P-interaction* (interaction coefficient) = 0.06 (3.65)].

Significant time effects were observed for both fructosamine and HOMA-β, with both treatment groups reporting a decrease in fructosamine [ABMD: 247.2 ± 17.0 μmol/L (week 0) to 244.7 ± 18.6 μmol/L (week 8); PBMD: 243.9 ± 13.8 μmol/L (week 0) to 241.9 ± 15.8 μmol/L (week 8); *P time* = 0.035] (Table 5), and an increase in HOMA-β [ABMD: 76.8 (49.4, 105.9) (week 0) to 79.0 (57.0, 105.6) (week 8); PBMD: 70.7 (51.6, 108.5) (week 0) to 77.0 (56.1, 132.5) (week 8); *P time* = 0.006] (Table 5). There were, however, no between group differences and, likewise, a lack of significant effects in the other metabolic health-related parameters.

CGMS-derived parameters of glycemic control and variability during the 72-h full-feeding period (day 1 breakfast to day 3 dinner) are summarized in Table 6. Among the glycemic control parameters, no significant differences were observed for combined and daily iAUC and AUC between the 2 groups during the full-feeding period.

TABLE 5
Effects of an animal-based meat diet compared to a plant-based meat analog diet on anthropometry and metabolic health-related outcomes.

	ABMD ($n = 42$)		PBMD ($n = 40$)		Time[1]	Time × Treatment[1]
	Week 0	Week 8	Week 0	Week 8	*P*	*P* (Interaction coefficient)
Weight (kg)	57.3 ± 8.5	57.3 ± 8.4	60.6 ± 9.6	60.4 ± 9.9	0.26	0.32 (1.02)
BMI (kg/m^2)	21.9 ± 2.6	21.9 ± 2.5	23.0 ± 2.3	22.9 ± 2.4	0.22	0.25 (1.34)
Waist-to-hip ratio	0.87 ± 0.07	0.85 ± 0.10	0.87 ± 0.06	0.86 ± 0.05	0.041	0.93 (0.009)
Fasting glucose (mmol/L)	5.41 ± 0.43	5.37 ± 0.50	5.45 ± 0.44	5.38 ± 0.40	0.15	0.78 (0.082)
Fasting insulin (mU/L)	6.86 (4.47, 10.40)	7.17 (4.71, 9.38)	7.39 (4.47, 9.41)	7.60 (4.95, 10.83)	0.06	0.60 (0.30)
Fasting fructosamine (μmol/L)	247.2 ± 17.0	244.7 ± 18.6	243.9 ± 13.8	241.9 ± 15.8	0.035	0.81 (0.058)
HOMA-IR	1.64 (1.12, 2.50)	1.63 (1.15, 2.23)	1.80 (1.02, 2.40)	1.76 (1.14, 2.52)	0.11	0.63 (0.24)
HOMA-β	76.8 (49.4, 105.9)	79.0 (57.0, 105.6)	70.7 (51.6, 108.5)	77.0 (56.1, 132.5)[2]	0.006	0.52 (0.41)

Values reported as means ± SD or median (Q_1, Q_3). Skewed continuous variables were logarithmically transformed prior to statistical analyses.
Abbreviations: ABMD: animal-based meat diet; HOMA-IR: homeostatic model assessment for insulin resistance; HOMA-β: homeostatic model assessment of β-cell function; PBMD: plant-based meat analogue diet

[1] Effects of ABMD and PBMD were assessed by linear mixed-effects model. Adjustment of baseline BMI as a covariate to the model revealed no marked statistical effect.

[2] Significant difference from baseline (2-tailed, $P < 0.05$) by Bonferroni's pairwise comparisons.

TABLE 6
Continuous glucose monitor derived parameters of glycemic management and variability following a 72-h fixed menu, protein-matched full-feeding with either an animal-based meat diet or a plant-based meat analog diet.

	ABMD ($n = 21$)	PBMD ($n = 16$)	P[1]
72-h combined AUC (mmol/L × min)	25958 ± 2436	26677 ± 3023	0.43
Day 1 24-h AUC	8637 ± 869	8989 ± 884	0.23
Day 2 24-h AUC	8630 ± 745	8895 ± 1340	0.45
Day 3 24-h AUC	8691 ± 908	8793 ± 971	0.75
72-h combined iAUC (mmol/L × min)	4340 ± 1681	4783 ± 1098	0.37
Day 1 24-h iAUC	1428 ± 690	1609 ± 400	0.36
Day 2 24-h iAUC	1420 ± 598	1687 ± 584	0.18
Day 3 24-h iAUC	1492 ± 583	1487 ± 610	0.98
Time below range (%)[2]	0 (0.00, 0.00)	0.00 (0.00, 0.96)	0.72
Time above range (%)[2]	5.94 (3.26, 12.76)	11.3 (7.20, 14.61)	0.11
Time in range (%)[2]	94.1 (87.2, 96.7)	86.5 (81.7, 89.4)	0.041
Mean absolute glucose (mmol/L/h)	4.19 ± 1.2	4.60 ± 0.86	0.25
Coefficient of variation (%)	20.2 ± 5.1	21.9 ± 5.2	0.31
MAGE (mmol/L)	3.20 (2.65, 3.72)	3.72 (3.20, 4.37)	0.38
CONGA (mmol/L)	4.94 ± 0.35	4.99 ± 0.61	0.76
Lability index	2.09 (1.48, 3.17)	3.02 (2.57, 3.98)	0.18
J-index	15.6 (14.6, 18.9)	18.0 (14.7, 19.7)	0.29
M-value	1.87 (0.94, 3.72)	1.10 (0.85, 2.65)	0.53
GRADE	0.49 (0.27, 0.56)	0.70 (0.43, 0.92)	0.08

Values reported as means ± SD or median (Q_1, Q_3). Skewed continuous variables were logarithmically transformed prior to statistical analyses.
Abbreviations: ABMD: animal-based meat diet; AUC: area under curve; CONGA: continuous overall net glycemic action; GRADE: glycemic risk assessment diabetes equation; iAUC: incremental area under curve; MAGE: mean amplitude of glycemic excursions; PBMD: plant-based meat analogue diet
[1] Continuous glucose outcomes were calculated based on the 3-day full feeding period for comparison using independent t-tests.
[2] Time in range was calculated based on time spent in range 3.9 to 7.8 mmol/L, time below range was based on time < 4.0 mmol/L and time above range was based on time > 7.8 mmol/L.

However, time in range was significantly higher in the ABMD group than in the PBMD group [ABMD median: 94.1% (Q_1: 87.2%, Q_3: 96.7%); PBMD: 86.5% (81.7%, 89.4%); $P = 0.041$)]. This is shown in Figure 2, where the PBMD group had higher glucose concentration peaks and a greater proportion of time in range during the full-feeding period. No significant differences were found in other glycemic control and variability-related parameters during this full-feeding period.

Similar patterns were observed during the full 12-d continuous glucose monitor, wherein GRADE, which similarly represents the metabolic risk due to hypoglycemic and hyperglycemic events [30], was significantly lower in the ABMD group [0.43 (0.37, 0.77)] than in the PBMD group [0.70 (0.49, 1.36)]; $P = 0.048$, (Supplemental Table 3). No significant differences were identified in other glycemic variability and glycemic control parameters during the 12-d continuous glucose monitoring period.

Anthropometry

Postintervention, there were no clear effects observed in weight and BMI as presented in Table 5. However, a significant marginal decrease in waist-to-hip ratio was reported in both groups over the intervention period [ABMD: 0.87 ± 0.07 (week 0) to 0.85 ± 0.10 (week 8); PBMD: 0.87 ± 0.06 (week 0) to 0.86 ± 0.05 (week 8); P *time* = 0.041].

Discussion

In recent years, PBMAs have seen a dramatic increase in production and availability worldwide. This is driven by several factors that include sustainability concerns, animal welfare, rising population protein demands, and the perceived health halos surrounding these foods [12,13]. With the introduction of PBMAs into population diets, it is vital to develop a greater understanding of these foods nutritionally and to investigate the impact of dietary incorporation on health and chronic disease risk. To the best of the authors' knowledge, this is the first RCT in an Asian dietary context that examined the effects of consuming either PBMAs or their animal-based counterparts on cardiometabolic health.

Although there were no significant effects on the lipid-lipoprotein profile, including LDL cholesterol, both the 8-wk dietary regimes contributed to a reduction in fructosamine and higher HOMA-β over time. This was, however, coupled with no clear differences in effects between ABMD and PBMD. Along with the other cardiometabolic health outcomes measured and contrary to our research hypothesis, we failed to substantiate any clear benefits for PBMD on cardiometabolic health compared with the corresponding ABMD. Furthermore, in the subpopulation that underwent the 3-d fixed menu continuous glucose monitoring, glycemic management as represented by the time in range and GRADE was more effective in the ABMD group. The 24-h ambulatory blood pressure assessments likewise revealed modest improvements (in nocturnal systolic and diastolic blood pressure dip) after an ABMD and not a PBMD. These findings suggest that despite the well-documented health benefits of traditional PBDs, their health benefits should not be conflated with PBMD, which are distinct in both their nutrition as well as their impact on cardiometabolic disease risk.

In alignment with previous nutritional comparisons between PBMAs and their corresponding animal-based foods [38,39], our comprehensive assessment revealed vast differences in the macro- and micronutrient profiles. Higher carbohydrates in PBMA, for example, are contributed by starches, fibers, and methylcellulose, which are often incorporated at levels between 2% and 30% primarily for their stabilizing and texture-modifying properties [12,40]. The quantity and type of fat varies between products and influences critical aspects such as the food structure, as well as its flavor and sensorial properties. For instance, the higher proportion of polyunsaturated fatty acids in PBMA may be attributed to the inclusion of sunflower and canola oil which are both rich in linoleic acid [41].

In terms of overall macronutrients, the reductions in carbohydrate consumption and increase in protein and saturated fat intake across groups were likely contributed by the intervention foods introduced. Specifically, higher dietary proteins in the ABMD group may have stemmed from inconsistencies between nutrient estimates (from nutritional databases) referenced during study design [25] and the analyzed nutrient profiles of cooked foods. Although this could be considered as a study limitation, the biological effects arising from the difference are likely to be minimal with the maintenance of treatment integrity and average intakes that were comparable between groups.

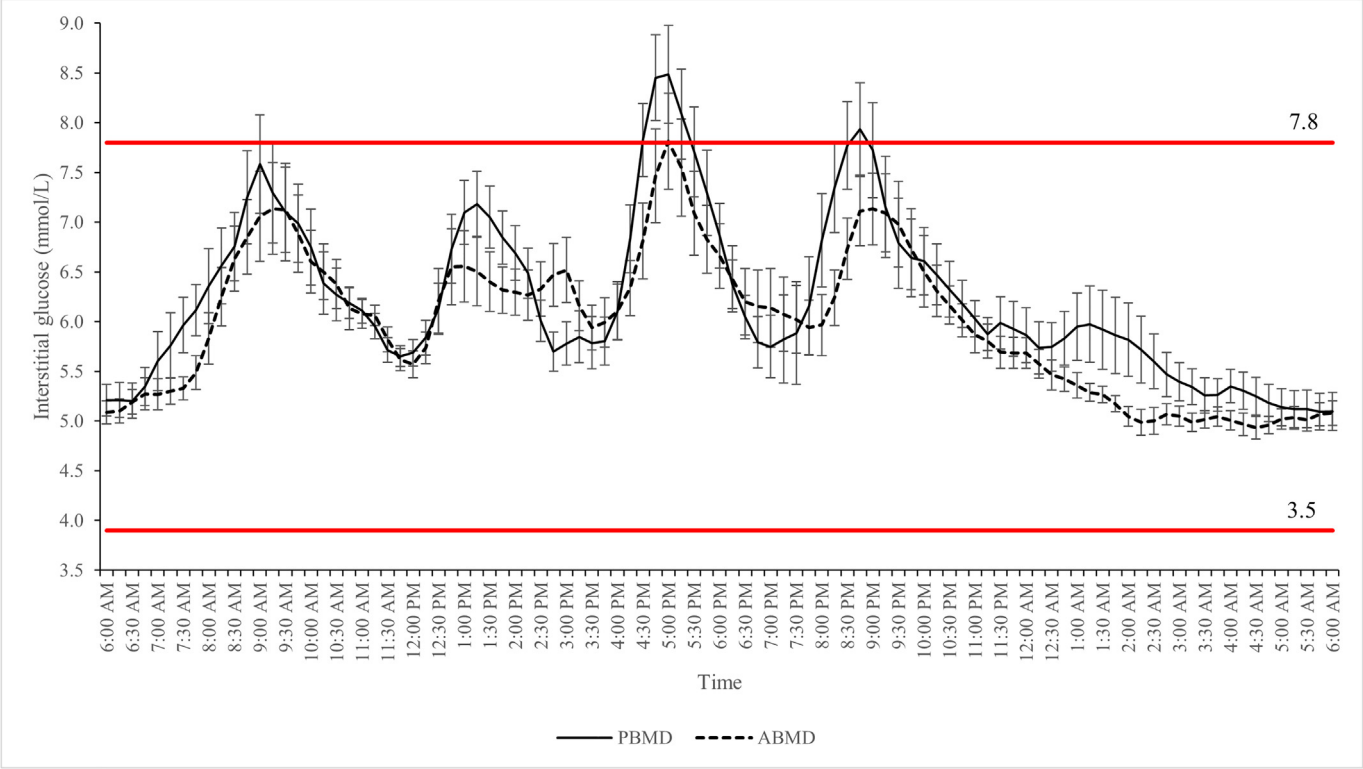

FIGURE 2. Interstitial glucose profile as determined by continuous glucose monitoring sensor during the first 24-h of the fixed menu, fixed time full-feeding period. Values are reported as means, and error bars represent SEM. Meals consumed were identical, protein quantity matched and differentiated by the source of dietary protein (animal-based meat vs. corresponding plant-based meat analog) only.

Among the micronutrients, PBMAs selected for this study were higher in sodium, which aligned with observations from previous comparisons [38,42]. Notably, salt serves a diverse range of functions, from acting as a flavor enhancer and extending the product shelf life to influencing protein structure and texture [43]. Potassium and calcium, which are found to be higher in certain PBMAs, were likely enriched from the usage of protein concentrates, potassium/calcium salts, and flavoring agents, such as yeast extract, which impart umami flavors to the products [38]. These are often complemented with fortifications (i.e., with vitamins B12 and D, iron, and zinc) to address inherent deficiencies in plant-based ingredients used in the manufacturing and processing of PBMAs [44]. A recent analytical comparison revealed similar trends of extensive fortification, whereby PBMAs had significantly higher or similar concentrations of iron and zinc compared with their animal-based counterparts [38]. Moreover, in a recent metabolomics characterization that compared a Beyond burger patty with conventional ground beef burgers, van Vliet et al. [45] identified significant differences in 90% of the food metabolome, which included discrepancies in the amino acid profile, tocopherols, polyphenols, and fatty acids among many other components.

Notably, PBMD is distinct not only from omnivorous diets but also conventional PBD, which are often characterized by higher intakes of dietary fiber and vitamin E while lacking in specific micronutrients such as vitamin B12 and iodine [46]. A previous cross-sectional study within our own laboratory, which modeled the replacement of animal-based protein foods with plant-based, contemporary alternative protein foods, similarly identified a significant increase in dietary fiber and sodium and decrease in dietary cholesterol following the modeled substitution [42]. This suggests that in spite of the carefully curated ingredients, recipes, and advances in processing techniques to mimic meat-like textures and flavors, there remain clear discrepancies in nutritional composition between PBMA and their animal-based counterparts [47].

Among the classical CVD risk factors, no clear effects were observed between the ABMD and PBMD groups. In contrast, a PBMD was reported to reduce plasma LDL cholesterol concentrations in the SWAP-MEAT study [16]. The differences in findings between the 2 studies may be attributed to various reasons. For example, unlike this previous RCT, no reductions in total energy and saturated fat were reported in our current study. Moreover, it was postulated that the reduction in LDL cholesterol previously may be modulated by changes in serum trimethylamine N-oxide (TMAO) [48]. Although TMAO has not been analyzed at present, the key dietary contributors to TMAO production have been reported to be rather heterogeneous between Asian and non-Asian populations [49]. Specifically, red meat and poultry were identified as the main TMAO-contributing foods in Western populations, whereas, among Asians, they are usually seafood and soy products [49,50]. Hence, the physiological effects of substituting animal-based meats with PBMA may be manifested differently in an Asian population.

Nocturnal blood pressure dipping calculated from 24-h ABPM is an independent risk factor for CVD. Nocturnal dipping status is often classified into 3 categories: 1) dippers (> 10%), 2) nondippers (0% – 10%), and 3) reverse dippers (< 0%). According to Boos et al. [51], it was observed that a reduction in nocturnal blood pressure dipping is associated with increased arterial stiffness index and vascular inflammation. Contrary to the PBMD group, which reported a reduction in nocturnal DBP dip, the significant increase in the ABMD group could

contribute to potential cardiovascular health benefits [52]. The difference observed may be attributed to the high sodium content in PBMA, as mentioned earlier. When higher sodium concentrations are consumed and retained during the day, night-time blood pressure increases, resulting in nondipping [53]. Nonetheless, it should be noted that based on the current guidelines by the American Heart Association and American College of Cardiology, both the PBMD and ABMD groups remained as nondippers postintervention.

On the contrary, there was also a discrepancy between ABPM measurements and findings from clinic blood pressure, which suggested improved DBP with PBMD. Although this effect may be linked to higher dietary potassium concentrations that positively modulate the renin-angiotensin system and alleviate endothelial dysfunction [54], the observations were not reciprocated in the 24-h awake and asleep blood pressures. It should be highlighted that contrary to the clinic blood pressure that was measured in the full population, ABPM assays were limited to a subpopulation represented by volunteers who had not been further randomly distributed (randomization was conducted for the main study only). Therefore, a degree of caution is warranted in these interpretations. Beyond that, disparities in methodological rigor (between clinic and ambulatory blood pressure measurements) may also contribute to the observed findings. For instance, in spite of the diagnostic agreement between clinic and ambulatory blood pressure measurements, the superiority of the ABPM lies in its frequency and continuity of measurements, which enables the unraveling of deeper insights (including nocturnal dips) that may independently improve CVD risk prediction [55].

With the rising prevalence of T2DM in Asia and globally, lifestyle modifications are key strategies for primary prevention [56]. Conventional PBDs characterized by higher intakes of minimally processed whole foods, such as grains, legumes, nuts, fruits, and vegetables have been consistently associated with improved cardiometabolic health and lower risks of all-cause mortality [57–60]. However, in a recent meta-analysis, it was concluded that a replacement of red meat with other animal-based white meats and/or plant-based protein sources, such as soy, may not confer beneficial effects on glycemic regulation [61]. Similarly, although the present comparison between PBMD and ABMD identified improvements in fasting fructosamine concentration (representative of the average glycemia in the recent 2 – 3 wk) and HOMA-β (index of beta-cell function) [62,63] in both diets, there were no differences detected between the groups.

These findings were further supported by the CGMS results from the 3-d full-feeding period, which saw a significantly higher time in range (for interstitial glucose) in the ABMD group. The relevance of this difference has been described in Battelino et al. [64], which suggested clinically significant benefits among T2DM patients and ~0.8% reduction in HbA1c with every 10% time in range increase. This was similarly reflected during the 12-d continuous glucose monitoring period according to GRADE scores (reflective of clinical risks attributable to hypoglycemic or hyperglycemic events), which were significantly lower in the ABMD group. For the future adoption of PBMAs, cautionary advice may be warranted for populations with heightened cardiometabolic health risks, where glycemic management is essential. Particularly for these more vulnerable populations, there may be a greater need for a careful reformulation of existing PBMAs with either low- or better-quality carbohydrates.

The ABMD group specific glycemic improvements may be linked to the relatively lower dietary carbohydrates and increased protein consumption compared with the PBMD group. Although protein bioavailability was not evaluated at present, emerging evidence suggests attenuated digestion and absorption of PBMA proteins compared with animal-based meats, which can, in turn, differentially influence insulin secretion and the production of various gut hormones [65–67]. This was linked to several factors, including the higher molecular weight and poorer solubility of plant proteins, antinutritional factors, and food matrix complexity, which may impair protein digestibility absorption and thus indirectly influence glycemic response [68].

Among the anthropometric indicators, there was a lack of clear effects, although previous studies have demonstrated a greater weight loss with the consumption of PBMA. In the SWAP-MEAT study, a crossover design RCT, participants were similarly tasked to consume PBMAs or animal-based meat for 8 wk while maintaining their intake of all other dietary components. A significant weight loss was observed after the consumption of PBMAs only, although the findings were potentially weakened by the lack of a rigorous washout period between the treatments [16]. In the REplacing Meat with Alternative Plant-based products (RE-MAP) study, which was a behavioral intervention targeted at reducing meat consumption and substitution with meat-free alternatives (including PBMAs), significant reduction in weight was likewise reported, albeit this was coupled with distinct caloric reduction [15]. In contrast to this earlier study, the present population had a markedly lower baseline BMI (22.5 kg/m^2 compared with 25.4 kg/m^2) and reported maintenance of energy intake at week 8, potentially explaining the absence of weight change.

Driven by perceptions of better health and greater environmental sustainability, there has been a societal drive to increase the consumption of alternative protein sources in our diet. Although the advantages of PBMAs for planetary health have been pursued with vigor (comprehensively discussed in reviews by Singh et al., [69] and Hu et al., [70]), it is vital not to overlook its impact and implications on human health. With >800 companies and brands in the plant-based food market today [71], a key strength of this study lies in the selection of intervention foods, which are comprised of contemporary PBMAs from established mainstream brands that are widely available to consumers today. The mode of intervention was also intentionally designed with dietary incorporation flexibility to enable an examination of broader dietary consequences following a shift to PBMD in an Asian population. Beyond the cultural and region-specific disparities in cuisine and diet, the Asian phenotype is also characterized by inherent differences in cardiometabolic disease vulnerability and responses to food compared with non-Asian populations [72]. Lastly, the controlled full-feeding design of the optional CGMS allowed us to examine, for the first time, a direct and rigorous comparison between different protein food sources in a strictly regulated setting, where all foods were provided and consumed at fixed times, minimizing the influence of confounders.

Nevertheless, the specificity of the intervention effects may be compromised to an extent since the mode of intervention provided a selection of foods (which restricts detailed investigations into food-specific treatment effects). However, this was deemed necessary, given the demanding nature of the protocol to promote compliance while providing greater external validity. Its efficacy was justified by the high self-reported compliance (>91%) and low dropout rate (7.9%) which enabled adequately powered, robust interpretations that were reflective of dietary intervention effects. Although PBMAs have been criticized as being ultraprocessed, the selection of corresponding animal-based foods (for example, sausages, chicken nuggets, burger patties) limits potential delineation of health impacts that may stem from its “ultraprocessed” nature. In terms of the cardiometabolic health-related outcomes

examined, rigor can also be potentially enhanced with the inclusion of multiple time point measurements (i.e., for blood lipid-lipoproteins), as well as a larger sample size (i.e., specifically for outcomes examined in the subpopulation of the additional optional component). These may be taken into consideration for future research. Finally, while these outcomes of interests were defined a priori, the large panel of secondary outcomes examined could contribute to a higher likelihood of false positives. However, unadjusted values were reported to increase the possibility of future developments.

In conclusion, despite the emergence of PBMAs as a source of alternative protein foods within the global food system, the results of the current study do not substantiate superior cardiometabolic health benefits of PBMDs compared with an omnivorous diet composed of animal-based meats. Dietary incorporation of PBMAs, in particular, may influence nutritional intake and potentially compromise glycemic management. This suggests that assumptions of health benefits from consuming a PBMD may not be directly extrapolated to those consuming a PBD. However, this creates an opportunity and stimulus for the food industry to re-evaluate the production of next-generation PBMAs with improved nutritional attributes and bioaccessibility. The inclusion of nutrition in the current focus on organoleptic properties and sustainability will be beneficial to both the manufacturers and the consumers in this Asian population and globally.

Acknowledgments

We thank Shia Lyn Tay, Rachel Tso for their support and assistance with the clinical study, and Shalini Ponnalagu, Priya Govindharajulu for their guidance during our statistical and laboratory analyses.

Author contributions

The authors' responsibilities were as follows – DWKT, SH, CJK: designed research; DWKT, ASM, KAM, NYLL: conducted research; DWKT, ASM, KAM, NYLL: performed statistical analysis and analyzed the data; DWKT, ASM, NYLL: wrote the paper under the supervision of SH, CJK; DWKT, CJK: has primary responsibility for final content and all authors: have read and approved the final manuscript.

Conflict of Interest

The authors report no conflicts of interest.

Funding

This study was supported by Pinduoduo Incorporated (HongKong Walnut Street Limited). Pinduoduo Incorporated had no role in study design, study conduct, laboratory analyses, data collection, management and interpretation or the writing, reviewing and approval of the manuscript.

Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.04.006.

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