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Original Research Communication

Plant-based meat analogues (PBMAs) and their effects on cardiometabolic health: An 8-week randomized controlled trial comparing PBMAs with their corresponding animal-based foods

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Running head: Plant-based meats and cardiometabolic health

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Trial registration number: NCT05446753

List of abbreviations: ABPM, ambulatory blood pressure monitor; ABMD, animal-based meat diet; BMI, body mass index; CONGA-1, continuous overall net glycemic action; 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; MAG, mean absolute glucose; MAGE, mean amplitude of glycemic excursions; PBD, plant-based diet; PBMA, plant-based meat analogues; PBMD, plant-based meat diet; RCT, randomized controlled trial; SBP, systolic blood pressure; T2DM, type-2 diabetes mellitus; TMAO, trimethylamine-N-oxide

ABSTRACT (300 words)

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

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

Methods: In an 8-week 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 daily) maintaining intake of other dietary components. LDL-cholesterol served as primary outcome, while secondary outcomes included other cardiometabolic disease-related risk factors (e.g. glucose, fructosamine), dietary data, and within a sub-population, ambulatory blood pressure measurements (n=40) at baseline and post-intervention, as well as a 14-day continuous glucose monitor (glucose homeostasis-related outcomes; n=37).

Results: Data from 82 participants (ABMD:42, 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 lipoprotein profile, including LDL-cholesterol. Diastolic blood pressure (DBP) was lower in the PBMD group ($P_{Interaction}=0.041$) although the nocturnal DBP 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: A plant-based meat analogues diet did not show widespread cardiometabolic health benefits compared with omnivorous diets over 8 weeks. The composition of PBMAs may need to be considered in future trials.

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

Introduction

Historically, the consumption of plant-based diets (PBDs) was predominantly practiced based on religious and cultural edicts. More recently, a renaissance of interest in PBDs has evolved due to global concerns surrounding the environment, animal welfare and human health as key motivators. In terms of health, the cardiometabolic advantages of vegetarian and vegan diets compared to omnivorous diets are well established (1–4). Beyond a dichotomous classification (i.e. vegetarians or non-vegetarians), 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 non-communicable 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 (ARIC) study, the PREDIMED (Prevención con Dieta Mediterránea), as well as systematic reviews and meta-analyses that established strong links between an increased adherence to PBDs with modest reductions in cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM) (6–8).

To a large extent, much of these benefits 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 analogues (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 a deconstruction and reconstruction of traditional plant-based foods (e.g. soy protein isolates from soya beans, 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 against 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 to controls that received no intervention (15). Weight loss was likewise detected in another crossover design, 8-week randomized controlled trial (RCT) that compared between dietary interventions with PBMAs against 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. It is hypothesized that dietary substitutions of animal-based meats with PBMA will positively influence cardiometabolic health and lower the risks associated with non-communicable 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 on 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 in-person 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), as well as a semi-quantitative 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 years) 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

levels within these ranges had 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 non-vegan/non-vegetarian and consumed between 2 and 4 servings (approximately 20 g per serving) of protein-rich foods daily (according to the semi-quantitative 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 ≥ 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 months; history of bariatric surgery; present/past diagnosis of clinically relevant cardiovascular, endocrine, gastrointestinal, hematological, hepatic and other relevant disorders as determined by study clinician; uncontrolled hypertension (systolic/diastolic blood pressure (SBP/DBP): ≥ 140/90 mmHg); regular use of chronic 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 month prior to 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 daily); 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 randomized by minimization using R studio (version 1.2.5033) into either the plant-based meat analogue 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 as well as investigator/outcome assessor blinding integrity was maintained.

Study design and intervention

This was an 8-week parallel design RCT. There were a total of 2 in-person study visits at baseline (week 0) and post-intervention (week 8) following a > 10 h overnight fast, and 2 online consultation sessions at weeks 2 and 5. Over the 8-week 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: (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 pre-specified, protein-matched quantities for consumption in 3-day cycles (**Table 1**). This enabled participants to substitute most of their daily intake of dietary protein-rich foods at an acceptable level (approximately 2.5 servings of protein-rich

199 foods daily), with minimal influence on the rest of the diet. A similar dose was used for the
200 SWAP-MEAT (Study With Appetizing Plant-food-Meat Eating Alternative Trial) RCT (16),
201 which is to the best of the authors' knowledge, the only other RCT to rigorously compare the
202 cardiometabolic health effects of PBMA in comparison to their animal-based counterparts.
203 This study also served as the evidence base for power calculations.

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

213 A comprehensive macro- and micro-nutrient profiling of the cooked PBMAs and animal-
214 based meats (as provided in their original packaging) was conducted by an external
215 accredited food testing laboratory (Eurofins Food Testing Singapore Pte Ltd). The nutritional
216 profiles of foods provided to each group every 3 days are tabulated in **Supplemental Table**
217 **1.**

218 **Dietary and compliance assessment**

219 In either small groups or individually, participants were instructed on how to complete 3-
220 day food records (2 weekdays and 1 weekend) properly. The 3-day food records were
221 collected 4 times across the intervention period (at baseline (week 0), week 2, week 5 and
222 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, macro- and micro-nutrient 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-week intervention duration.

Outcomes of interest

The primary outcome of interest is LDL-cholesterol. Secondary outcomes included a 14-day continuous glucose monitor, cardiometabolic health-related risk factors such as fasting glucose, fructosamine and insulin, 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). Additional outcomes which included protein metabolism related biomarkers (e.g. urea, creatinine, albumin) 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) while 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 it was thawed for analysis.

Serological 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-year CVD risk prediction and vascular age (27).

Continuous glucose monitor

During the 8-week intervention period, a subset of the original study population volunteered for an optional component of the study, which included both an additional 14-day continuous glucose monitoring, as well as two sessions of 24-h ambulatory blood pressure monitoring. This was completed by a total of 37 and 40 participants respectively. The optional component required two additional study sessions that were scheduled 2-days prior to the baseline and post-intervention 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-day CGMS period, participants first completed a full-feeding period, that spanned from day 0 dinner to day 3 dinner. This comprised of 13 meals including breakfast (0800 h), lunch (1200 h), snack (1600 h) and dinner (2000 h) that were consumed at fixed timings 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 non-fried 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 three days. This comprised of a muesli bar (Uncle Tobys wholegrain muesli bar, Nestlé) and a packet of plain crackers (Jacob's hi-fibre cracker, Jacob's). Details of the specific 3-day full-feeding menu as well as general nutritional information of these additional foods provided are described in **Supplemental Table 2**.

Glycemic response variables including the incremental area under the curve (iAUC) and area under the curve (AUC) were calculated daily (from 0600 h to 0600 h the following day) and across the 3-day 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 (MAGE), continuous overall

net glycemic action (CONGA-1), Mean Absolute Glucose (MAG) 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 at least 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 two 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, two days prior to the baseline (week 0) and post-intervention (week 8) visits. SBP and DBP readings were taken every 30 minutes when participants were awake and every 60 minutes when asleep. The mean 24-h, awake and asleep SBP, DBP, as well as the 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 two previous RCTs. The first which compared between an 8-week dietary consumption of animal-based meats or PBMA reported significant differences in plasma LDL-cholesterol concentrations after an 8-week 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-analogues and nuts, a significant difference in insulin sensitivity was

observed after 4 weeks 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 previously (effect size = 0.64 and 0.93 for former and latter examples respectively), 84 and 40 subjects will provide an 80 % power at $\alpha = 0.05$ (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 was 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 between 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 $P < 0.05$ (2-tailed).

Results

Participants

Of the 213 volunteers that were screened, 96 were eligible for participation and randomly assigned to either the ABMD or PBMD groups (**Figure 1**). Seven participants withdrew prior to study commencement (i.e., between randomization 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, PBMD: 1), 3 due to an inability to commit to the study schedule (ABMD: 2, 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, 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 (5.8 ± 0.3 %) which was part of the pre-specified 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 of 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.

Laboratory nutritional profiling of intervention foods

Although the average protein content of the intervention foods (both for ABMD and for PBMD) were matched as listed on the products' nutrition information panels, an analytical profiling of the macro- and micro-nutrient 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-day cycle). This was coupled with noticeably higher total carbohydrates (ABMD: 16.1 g, PBMD: 100.6 g per 3-day cycle) and dietary fiber (ABMD: 0.00 g, PBMD: 51.70 g per 3-day cycle) than their corresponding animal-based foods (Supplemental Table 1). The quantity and type of fat indicated largely inconsistent results although a majority 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-day cycle), while 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-day cycle). As expected, PBMAs contained no cholesterol (ABMD: 600.2 mg, PBMD: 0.0 mg per 3-day cycle).

Examining the micronutrient profile, key differences included folate (ABMD: 48.5 µg DFE, PBMD: 1207.2 µg DFE per 3-day cycle), calcium (ABMD: 90.4 mg, PBMD: 1316.4 mg per 3-day cycle), iron (ABMD: 15.21 mg, PBMD: 38.78 mg per 3-day 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-day 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-day 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 post-intervention, while total carbohydrates intake was lowered post-intervention ($P_{Time} < 0.001$). 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 foods 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, as well as ease of dietary incorporation for interventions foods. Taste was significantly less preferred for PBMAs compared to 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 risk prediction (D'Agostino et al., 2008) are summarized in **Table 4**. There were no significant effects on the lipid 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-week intervention.

The ambulatory blood pressure measurements indicated a time effect in awake DBP (P_{Time} = 0.04) which trended towards 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 ± 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 non-significant ($P_{Interaction}$ (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. However, time in range was significantly higher in the ABMD group, than 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 peaks and a greater proportion of time in range during the full-feeding period. There were no significant differences found in other glycemic control and variability-related parameters during this full feeding period.

Similar patterns were observed during the full 12-day 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 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-day continuous glucose monitoring period.

Anthropometry

453 Post-intervention, there were no clear effects observed in weight and BMI as presented in
454 Table 5. However, a significant marginal decrease in waist-to-hip ratio was reported in both
455 groups over the intervention period (ABMD: 0.87 ± 0.07 (week 0) to 0.85 ± 0.10 (week 8);
456 PBMD: 0.87 ± 0.06 (week 0) to 0.86 ± 0.05 (week 8); P_{Time} = 0.041).

457

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, as well as 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.

While there were no significant effects on the lipid-lipoprotein profile, including LDL-cholesterol, both the 8-week 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, as compared to the corresponding ABMD. Furthermore, in the sub-population who underwent the 3-day 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 its 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 micro-nutrient 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 its 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 carbohydrates consumption, and increase in proteins and saturated fats 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. While this could be considered as a study limitation, the biological effects arising from the difference is likely to be minimal with the maintenance of treatment integrity and average intakes that were comparable between groups.

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, 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 like yeast extract which impart umami flavors to the products (38). These are often complemented with fortifications (i.e. with vitamins B12

505 and D, iron, zinc) to address inherent deficiencies in plant-based ingredients used in the
506 manufacturing and processing of PBMAs (44). A recent analytical comparison revealed
507 similar trends of extensive fortification, whereby PBMAs had significantly higher or similar
508 levels of iron and zinc when compared against their animal-based counterparts (38).
509 Moreover in a recent metabolomics characterization which compared between a Beyond
510 burger patty and conventional ground beef burgers, van Vliet et al. (45) identified significant
511 differences in 90 % of the food metabolome which included discrepancies in the amino acid
512 profile, tocopherols, polyphenols and fatty acids among many others components.

513 Notably, PBMD are distinct not only with omnivorous diets, but also conventional PBD
514 which are often characterized by higher intakes of dietary fiber, and vitamin E whilst lacking
515 in specific micronutrients such as vitamin B12 and iodine (46). A previous cross-sectional
516 study within our own lab which modelled the replacement of animal-based protein foods with
517 plant-based, contemporary alternative protein foods similarly identified a significant increase
518 in dietary fiber and sodium, and decrease in dietary cholesterol following the modelled
519 substitution (42). This suggests that in spite of the carefully curated ingredients, recipes and
520 advances in processing techniques to mimic meat-like textures and flavors, there remain clear
521 discrepancies in nutritional composition between PBMA and their animal-based counterparts
522 (47).

523 Amongst the classical CVD risk factors, no clear effects were observed between the
524 ABMD and PBMD groups. In contrast, a PBMD was reported to reduce plasma LDL-
525 cholesterol concentrations in the SWAP-MEAT study (16). The differences in findings
526 between the two studies may be attributed to various reasons. For example, unlike this
527 previous RCT, there were no reductions in total energy and saturated fat reported in our
528 current study. Moreover, it was postulated that the reduction in LDL-cholesterol previously

529 may be modulated by changes in serum trimethylamine N-oxide (TMAO) (48). Although
530 TMAO was not analyzed at present, the key dietary contributors to TMAO production have
531 been reported to be rather heterogeneous between Asian and non-Asian populations (49).
532 Specifically, red meat and poultry were identified as the main TMAO contributing foods in
533 western populations while among Asians, it is usually seafood and soy products (49,50).
534 Hence, the physiological effects of substituting animal-based meats with PBMA may be
535 manifested differently in an Asian population.

536 Nocturnal blood pressure dipping calculated from 24-h ABPM is an independent risk
537 factor for CVD. Nocturnal dipping status is often classified into 3 categories: (1) dippers (>
538 10%), (2) non-dippers (0 – 10%) and (3) reverse dipper (< 0%). According to Boos et al.
539 (51), it was observed that a reduction in nocturnal blood pressure dipping is associated with
540 increased arterial stiffness index and vascular inflammation. Contrary to the PBMD group
541 which reported a reduction in nocturnal DBP dip, the significant increase in the ABMD group
542 could contribute to potential cardiovascular health benefits (52). The difference observed may
543 be attributed to the high sodium content in PBMA as mentioned earlier. When higher sodium
544 levels are consumed and retained during the day, night-time blood pressure increases,
545 resulting in non-dipping (53). Nonetheless, it should be noted that based on the current
546 guidelines by the American Heart Association and American College of Cardiology, both the
547 PBMD and ABMD group remained as non-dippers post-intervention.

548 On the contrary, there was also a discrepancy between ABPM measurements and findings
549 from clinic blood pressure, which suggested improved DBP with PBMD. Although this effect
550 may be linked to the higher dietary potassium levels that positively modulates the renin-
551 angiotensin system alleviating endothelial dysfunction (54), the observations were not
552 reciprocated in the 24-hour awake and asleep blood pressures. It should be highlighted that

553 contrary to the clinic blood pressure that was measured in the full population, ABPM assays
554 were limited to a sub-population who are represented by volunteers that had not been further
555 randomized (randomization conducted for the main study only). Therefore, a degree of
556 caution is warranted for these interpretations. Beyond that, disparities in methodological rigor
557 (between clinic and ambulatory blood pressure measurements) may also contribute to the
558 observed findings. For instance, in spite of the diagnostic agreement between clinic and
559 ambulatory blood pressure measurements, the superiority of the ABPM lies in its frequency
560 and continuity of measurements which enables the unravelling of deeper insights (including
561 nocturnal dips) that may independently improve CVD risk prediction (55).

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

573 These findings were further supported by the CGMS results from the 3-day full-feeding
574 period, which saw a significantly higher time in range (for interstitial glucose) in the ABMD
575 group. The relevance of this difference has been described in Battelino et al (64), which
576 suggested clinically significant benefits among T2DM patients, and an approximately 0.8 %

reduction in HbA1c with every 10 % time in range increase. This was similarly reflected during the 12-day 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 to 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, anti-nutritional factors, as well as food matrix complexity which may impair protein digestibility, absorption, and thus indirectly influence glycemic response (68).

Amongst 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 weeks whilst 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

601 (RE-MAP) study which was a behavioral intervention targeted at reducing meat consumption
602 and substitution with meat-free alternatives (including PBMAs), significant reduction in
603 weight was likewise reported albeit this was coupled with distinct caloric reduction (15). In
604 contrast to this earlier study, the present population had a markedly lower baseline BMI (22.5
605 kg/m^2 compared to 25.4 kg/m^2) and reported maintenance of energy intake at week 8,
606 potentially explaining the absence of weight change.

607 Driven by perceptions of better health and greater environmental sustainability, there has
608 been a societal drive to increase the consumption of alternative protein sources in our diet.
609 While the advantages of PBMAs for planetary health have been pursued with vigor
610 (comprehensively discussed in reviews by Singh et al., (69) and Hu et al., (70)), it is vital not
611 to overlook its impact and implications on human health. With more than 800 companies and
612 brands in the plant-based food market today (71), a key strength of this study lies in the
613 selection of intervention foods which comprised of contemporary PBMAs from established
614 mainstream brands that are widely available to consumers today. The mode of intervention
615 was also intentionally designed with dietary incorporation flexibility to enable an
616 examination of broader dietary consequences following a shift to PBMD in an Asian
617 population. Beyond the cultural and region specific disparities in cuisine and diet, the Asian
618 phenotype is also characterized by inherent differences in cardiometabolic disease
619 vulnerability, and responses to food compared to non-Asian populations (72). Lastly, the
620 controlled full-feeding design of the optional CGMS allowed us to examine, for the first time,
621 a direct and rigorous comparison between different protein food sources in a strictly regulated
622 setting. Where all foods were provided and consumed at fixed times, minimizing the
623 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, whilst 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. While PBMAs have been criticized as being ultra-processed, the selection of corresponding animal-based foods (e.g. sausages, chicken nuggets, burger patties) also limits potential delineation of health impacts that may stem from its "ultra-processed" 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 sub-population 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 possibilities of potential 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 to 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

649 and bioaccessibility. The inclusion of nutrition to the current focus on organoleptic properties
650 and sustainability will be beneficial to both the manufacturers and the consumers in this
651 Asian population and globally.

Author contributions

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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. All authors have read and approved the final manuscript and report no conflicts of interest.

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

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 (years)	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 (years)	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.
[1]Determined based on semi-quantitative food frequency questionnaire (18). ABMD: animal-based meat diet; HbA1c: glycated hemoglobin; PBMD: plant-based meat analogue diet

TABLE 3 Average daily dietary intake of selected nutrients at baseline (Week 0) and following an 8-week animal-based meat diet or plant-based meat analogue diet during each 3-day 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. [1]Effects of ABMD and PBMD were assessed by linear mixed-effects model. [2]Significant difference from baseline (2-tailed, $P < 0.05$) from baseline by Bonferroni's pairwise comparisons. [3]Significant difference at baseline (2-tailed, $P < 0.05$) by independent t-test. ABMD: animal-based meat diet; PBMD: plant-based meat analogue diet

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. [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.
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

TABLE 5 Effects of an animal-based meat diet compared to a plant-based meat analogue 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. [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, 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

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 analogue diet

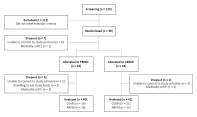
	ABMD (n = 21)	PBMD (n = 16)	*P*[1]
72-h combined AUC (mmol/L × min)	25958 ± 2436	26677 ± 3023	0.43
Day 1 24-h AUC	8637 ± 869	8989 ± 884	0.23
Day 2 24-h AUC	8630 ± 745	8895 ± 1340	0.45
Day 3 24-h AUC	8691 ± 908	8793 ± 971	0.75
72-h combined iAUC (mmol/L × min)	4340 ± 1681	4783 ± 1098	0.37
Day 1 24-h iAUC	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

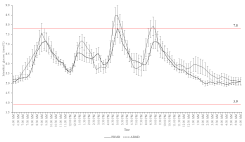
Values reported as means ± SD or median (Q_1, Q_3). Skewed continuous variables were logarithmically transformed prior to statistical analyses. [1]Continuous glucose outcomes were calculated based on the 3-day full feeding period for comparison using independent t-tests. [2]Time in range was calculated 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. 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

Figure legends

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram
[1]Withdrawal due to medical occurrences unrelated to clinical trial participation

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 reported as means and error bars representing SEM. Meals consumed were identical, protein quantity matched and differentiated by the source of dietary protein (animal-based meat vs corresponding plant-based meat analogue) only





Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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