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Randomized Control Trials

Effects of lacto-vegetarian and vegan diets on glycemic responses and metabolite profiles in healthy adults: A randomized trial using continuous glucose monitoring and targeted metabolomics

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SUMMARY

Background: Our previous studies have demonstrated that dairy products protect against type 2 diabetes (T2D) and improve cardiometabolic health outcomes. Given that continuous glucose monitoring (CGM) and metabolomics analysis capture different aspects of T2D, this study investigated the effects of dairy and non-dairy products on the glycemic and metabolite profiles in healthy adults following lacto-vegetarian and vegan diets.

Methods: A parallel randomized feeding trial with 30 participants compared isoenergetic vegan and lacto-vegetarian diets. All participants wore CGM sensors for 14 days to track glucose concentrations. Anthropometric and biochemical characteristics were also measured. In a subgroup of 13 individuals, fasting and postprandial blood samples were collected on days 1 and 15 for metabolomics analysis.

Results: Our CGM data showed higher mean glucose concentrations in the vegan group over 14 days compared to the lacto-vegetarian group ($p = 0.0399$), after adjusting for age, sex, body mass index, and baseline glucose concentrations. Metabolomics analysis from day 1 to day 15 showed increased

Abbreviations: ANOVA, analysis of variance; ASA, argininosuccinic acid; AUC, area under the curve; BH4, tetrahydrobiopterin; BMI, body mass index; C2, acetyl carnitine; CGM, continuous glucose monitoring; CMH, cardiometabolic health; CV, coefficient of variation; FDR, false discovery rate; GMI, glucose management indicator; iAUC, incremental area under the curve; IDF, international diabetes federation; IFCT, Indian Food Composition Table; IGT, impaired glucose tolerance; LC-MS, liquid chromatography–mass spectrometry; MAGE, mean amplitude of glucose excursions; MDRF, Madras diabetes research foundation; EpiNu, nutritional epidemiology; OPLS-DA, orthogonal partial least squares-discriminant analysis; OGTT, oral glucose tolerance test; PCA, principal component analysis; Pcorr, correlation coefficients; Phe, phenylalanine; QRILC, quantile regression imputation of left-censored data; ROS, reactive oxygen species; SD, standard deviation; SE, standard error; SMBG, self-monitoring of blood glucose; T2D, type 2 diabetes; TAR, time above range; TBR, time below range; TIR, time in range; VIP, variable importance in projection.

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postprandial phenylalanine (Phe; $p = 0.0189$) in the vegan group, while the lacto-vegetarian group showed increased acetyl carnitine (C2; $p = 0.00704$) and decreased argininosuccinic acid ($p = 0.0149$). *Conclusions:* Our pilot CGM data suggest a lacto-vegetarian diet may offer better glycemic control, potentially explained by our preliminary metabolomics findings. The increased Phe observed in the vegan group may be explained by a hypothetical mechanism in which higher glucose induces oxidative stress, whereas the increased C2 from dairy in the lacto-vegetarian group may protect against oxidative stress, contributing to lower glucose concentrations. However, larger, longer-term studies with more diverse populations, along with *in vitro* investigations into biomolecular mechanisms, are needed to confirm these findings.

1. Introduction

Diabetes, which contributes to 10 % of global all-cause mortality [1], is characterized by high blood glucose due to defects in insulin secretion, action, or both [2]. According to the International Diabetes Federation (IDF), there were an estimated 451 million people lived with diabetes in 2017, yet almost half of them (49.7 %) remain undiagnosed worldwide [1]. Additionally, individuals with impaired glucose tolerance (IGT) are at high risk of developing diabetes [2], with an estimated 374 million people living with IGT [1]. India, having the second-largest diabetes population in the world [2], has high prevalence of both type 2 diabetes (T2D) (101 million) and prediabetes (136 million) in urban and rural areas [3]. This situation imposes a significant economic burden on individuals and households across different zones in India [4]. Therefore, there is an urgent to focus on preventing prediabetes and T2D in India.

Self-monitoring of blood glucose (SMBG) has traditionally been used to manage glucose concentrations, requiring multiple blood samples throughout the day, which may miss significant glycemic excursions [5]. In contrast, continuous glucose monitoring (CGM) provides better glucose control by measuring interstitial glucose 24 h a day [6], capturing comprehensive glucose profiles. CGM has even predicted the effects of glucose-lowering treatment for T2D over six months with only 14-day data [7], indicating its potential in T2D research. Metabolomics studies (e.g., liquid chromatography–mass spectrometry [LC-MS]) have identified strong associations between prediabetes/T2D risk and plasma/serum metabolites, including branched-chain amino acids, aromatic amino acids, alanine, glutamate, lysine, methionine, glycerolipids, and acylcarnitines [8–10]. Hence, combining CGM and metabolomics profiles may provide deeper insights into T2D.

Given that India's predominant dietary pattern is vegetarian [11], with dairy contributing ~10 % of daily energy intake [12], understanding its link to prediabetes/T2D is crucial. Our previous studies have shown that high dairy intake is associated with lower risks of adverse cardiometabolic health (CMH) outcomes—metabolic syndrome, fasting plasma glucose, high-density lipoprotein, blood pressure, and body mass index (BMI)—in Asian Indians [13,14]. Moreover, dairy products, particularly plain yogurt, are inversely associated with T2D incidence [15,16]. The potential benefits of dairy consumption and lower risks of T2D and adverse CMH outcomes may be explained by multiple mechanisms, including beneficial saturated fatty acids (SFA), short-chain fatty acids, calcium, changes in gut microbiome, and insulinotropic amino acids [17–19].

While observational studies suggest that high dairy consumption (mainly total dairy or fermented dairy) lowers the risks of T2D and adverse CMH outcomes [14–18], few randomized controlled trials exist [18]. Notably, most studies included participants following an omnivorous diet [14–18], which may make it difficult to isolate the effects of dairy due to differences in nutrient profiles between omnivorous and vegetarian diets, including variations in SFA, heme-iron, cholesterol, fiber, protein, and calcium [20,21]. Furthermore, red meat tends to promote the growth of gut bacteria linked to pro-inflammatory metabolites (e.g., trimethylamine N-oxide) [22]. Therefore, to minimize dietary confounding, this study focuses on participants following lacto-vegetarian and vegan diets, as these diets have more similar nutrient profiles compared to an omnivorous diet [20,21]. This approach allows for a clearer investigation of dairy's effects on CGM-derived glycemic metrics and LC-MS-based metabolite profiles in healthy Asian Indians using a parallel intervention design.

2. Methods

2.1. Study design and participants & anthropometric and biochemical data

The LActo-vegetarian and VegAn Diet on the GLycaemic and MetABoLitE Profiles in Healthy Asian Indians (AVAiLABLE) study was conducted at the Madras Diabetes Research Foundation (MDRF) in Chennai, India, in 2022. This 14-day parallel-arm randomized intervention examined the effects of dairy on glycemic and metabolite outcomes in participants following lacto-vegetarian and vegan diets. Lacto-vegetarian diets exclude red meat, poultry meat, seafood, and eggs but include dairy products, while vegan diets avoid all animal products, including honey and dairy.

Participants were recruited from the clinical registry of volunteers and workplaces near the MDRF facility. Fifty participants were screened using an oral glucose tolerance test (OGTT) using an 82.5g oral glucose load (equivalent to 75g of anhydrous glucose), measuring the 2-h post-load venous blood glucose concentration, with normal glucose tolerance defined as <140 mg/dL (7.8 mmol/L) [2]. Inclusion criteria included men or women aged 25–50 years, with a BMI between 18.5 and 23.0 kg/m^2 [23], diverse dietary patterns, and no family history of diabetes. Exclusion criteria included self-reported diabetes, prediabetes, dairy allergy, use of any nutritional supplements, on a weight loss diet, pregnancy or lactation, any debilitating illness disease (i.e., cancers, liver, kidney, thyroid, or other endocrine disorders), eating disorders, or any condition hindering compliance (Fig. 1).

Eligible participants were randomized 1:1 into lacto-vegetarian and vegan groups, except for two participants with dietary restrictions assigned to the vegan group. Randomization was conducted in Excel using the rand(.) function. Anthropometric (i.e., weight, height, BMI, body fat, and waist circumference) and biochemical data (i.e., fasting capillary blood glucose, fasting insulin, and insulin resistance (HOMA-IR)) were assessed at the beginning and end of the study. Measurement procedures are detailed in Table S1.

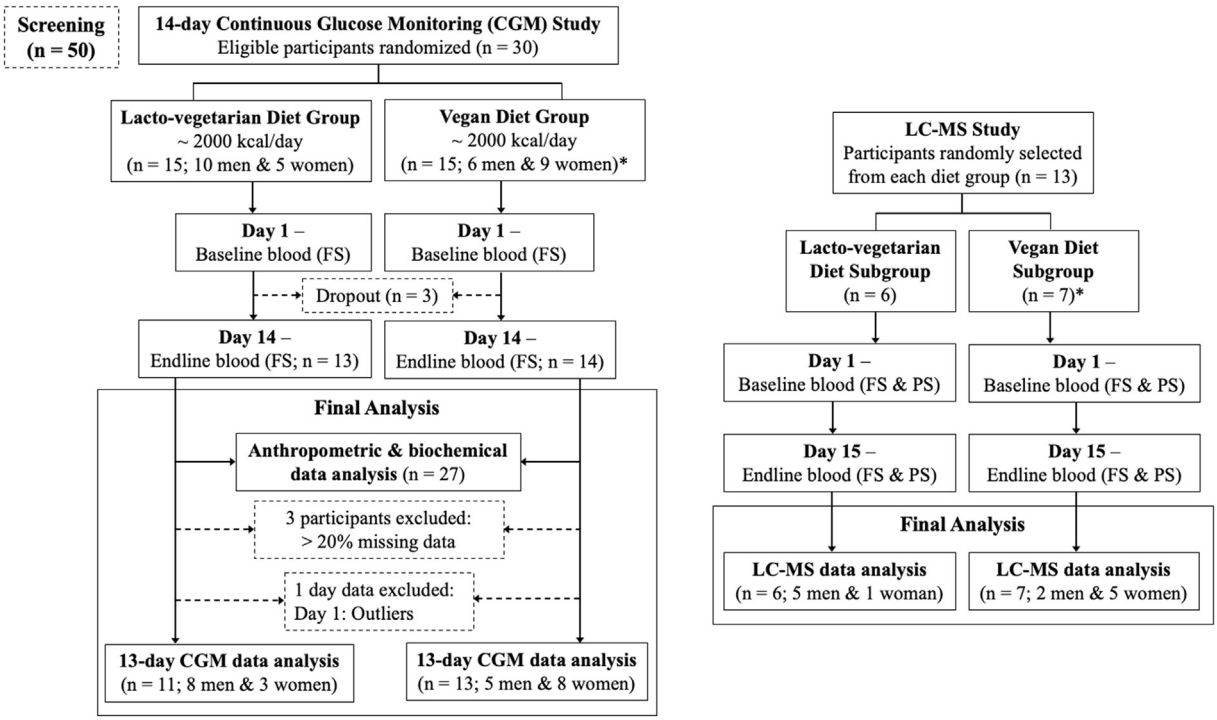

Fig. 1. Schematic representation of the study: Investigating the effects of dairy on glycemic and metabolite profiles in healthy adults following lacto-vegetarian and vegan diets. Three participants dropped out due to bloating, relocation, and difficulty consuming the required food quantity. *: Two participants already on vegan diets prior to the study were assigned to the vegan group for both CGM and LC-MS studies. The remaining participants were randomized into the two diet groups. Abbreviations: FS, fasting state; PS, postprandial state; LC-MS, liquid chromatography-mass spectrometry.

The study protocol was approved by the Institutional Review Board of Madras Diabetes Research Foundation and was registered in the Clinical Trials Registry of India (*CTRI/2022/02/040661 [Registered on: 28/02/2022]*). Written informed consent was obtained from all participants before enrollment in the study.

2.2. Dietary intervention and meal preparation

Trained dietitians designed five-day isoenergetic cyclic lacto-vegetarian and vegan diets that were culturally appropriate and followed dietary guidelines for Asian Indians (Table S2). Both diets provided approximately 2,000 kcal/day (8.4 MJ/day) and were matched for energy, macronutrients, fiber, and added sugar (Table S3). Menus were planned with the in-house Nutritional Epidemiology (EpiNu) software. The lacto-vegetarian diet included dairy (i.e., milk-tea with sugar, boiled milk with sugar, paneer, and curd), whereas the vegan diet included non-dairy products (i.e., sweetened chocolate soy milk, tofu, and peanut curd). Notably, non-dairy products were selected due to their similar protein content to dairy products, affordability, and community acceptance.

All meals were prepared in a controlled kitchen environment at the MDRF facility. Morning tea, breakfast, and lunch were served at the facility, while mid-morning, evening snacks, and dinner were taken home by the participants. Meals were portioned and labeled daily, and participants were instructed to consume them as provided and to report any deviations. 24-hour dietary recalls (i.e., on screening, days 1, 4, 7, 11, and 15) were administered to measure participants' compliance.

2.3. Continuous glucose monitoring data collection, preprocessing, and analyzing

The CGM devices (Freestyle Libre Pro) were used to measure interstitial fluid glucose concentrations every 15 min (96 readings per day) for 14 days, placed on the back of the upper arm of participants on day 1. Participants were blinded to real-time glucose readings. The devices recorded data in a text-format file, including glucose values (in mg/dL) and measuring times (in minutes). On day 15, the devices were removed, and data were transferred to a computer via USB using the manufacturer's software for further analysis.

CGM data were preprocessed in R and aligned in Excel. Briefly, three participants with >20 % data missing were excluded from the dataset. Day 1 data for all participants were excluded due to delayed sensing following CGM sensor insertion. After these exclusions, we achieved a dataset completeness of 99.1 %, with 0.9 % of the values missing. The data were then aligned based on identified postprandial windows using global and local alignment methods. Daily baseline glucose concentrations, defined as the average readings from 04:00 AM to 07:00 AM, were calculated for each participant. Missing values were imputed with the average of neighboring time points if there were fewer than five consecutive missing values. For more than five consecutive missing values, which usually skew the remaining data, we adjusted those values by adding the average of the standard deviation (SD) of differences between values from preceding and succeeding days at each time point. Detailed methods for data preprocessing are outlined in Figs. S14–S23 and Table S11.

Nine standardized CGM measures were applied to the processed data based on published recommendations [24]: 1) mean glucose concentrations (mg/dL), 2) time in range (TIR) of 70–180 mg/dL range (TIR_{70-180}), 3) time above range (TAR) of 180 mg/dL ($TAR_{>180}$), 4) time below range of 70 mg/dL ($TBR_{<70}$), 5) area under the curve (AUC), 6) incremental AUC (iAUC), 7) glucose management indicator (GMI), and 8) glucose variability measured with the coefficient of variation (CV), along with 9) the mean amplitude of glucose excursions (MAGE). Additionally, we reported TIR of 70–140 mg/dL (TIR_{70-140}) and TAR of 140 mg/dL ($TAR_{>140}$).

Mean glucose concentration was calculated as the average of 96 glucose readings per day across days 2–14. TIR measures were calculated using the 'iglu' package [25] in R (version 4.2.2). CV was calculated as $\%CV = 100 \times \sigma/\mu$, where σ and μ represent standard deviation and mean glucose, respectively. GMI was estimated from the average glucose over time using the formula $3.31 + 0.02392 \times$ (*mean glucose in mg /dL*) [26]. AUC of glucose readings was calculated using the trapezoidal rule with the 'caTools' package [27]. iAUC values, excluding the area below the glucose baseline [28], were computed using function i_auc.fn(.) [29] and standardized daily for each participant using the formular ((*SUM of iAUC*)/(#*of time points above the baseline*)). MAGE quantified glucose fluctuations between nadirs and peaks exceeding one SD of daily blood glucose [30], using the 'iglu' package [25].

2.4. Time series analysis

Postprandial values for breakfast, lunch, and dinner were aligned across all participants in each group over 13 days during data preprocessing. Average glucose readings were calculated at each of the 96 time points for both diet groups, providing an aggregated view of daily glucose trends and patterns. These average readings were then transformed into 96-point average data. Seasonal-Trend decomposition using LOESS (STL) with the 'fpp3' package [31] decomposed the glucose data into trend, seasonality, and remainder components to generate representative patterns.

2.5. Metabolomics – targeted LC-MS

A subgroup of 13 participants were randomly selected for metabolomics study, except for two participants with a vegan dietary pattern prior to the study; those two were assigned to the vegan group (Fig. 1). Capillary blood samples were collected from participants after an overnight fast and 2-h post-meal on days 1 and 15 using BD Microtainer® Contact-Activated Lancets. Dried blood specimens were prepared on filter paper and couriered to the third party for sample analysis. Targeted LC-MS was performed by NeoGen Labs (neogenlabs.com) to detect 17 amino acids and 40 acylcarnitines. This analysis used a modified procedure based on a previously established method [32].

We applied a natural log-transformation to raw LC-MS data and used the quantile regression imputation of left-censored data (QRILC) method [33]using the 'imputeLCMD' package [34] to impute 87 missing values (3 %) out of 2,964 (due to the lower limit of detection) across 24 acylcarnitines. Imputed values were then converted back to the original scale (i.e., fasting and postprandial values for each metabolite) using an exponential function. To compare metabolite changes between fasting and postprandial states, we adjusted data by adding a scaling factor of 150 (determined based on the smallest negative changes across the LC-MS dataset) to handle negative values. Subsequently, we applied a base 10 log-transformation and auto-scaling (mean-centered and divided by the SD of each variable) to all data for univariate and multivariate tests using MetaboAnalyst 6.0 software (www.metaboanalyst.ca).

2.6. Statistical analysis

The sample size for this study, based on our previous CGM study [35], was set at 15 participants per diet group, with replicated CGM readings (96 per day over 14 days) to reduce intra-individual variability and provide adequate statistical power. Data normality was assessed using Shapiro–Wilk tests and Q–Q plots. Non-normally distributed data were log-transformed. Between-group comparisons were performed for anthropometric, biochemical, nutrient, CGM, and metabolomics data, while within-group comparisons were performed for anthropometric, biochemical, and metabolomics data.

For univariate tests, independent t-tests and paired t-tests were used for parametric data, while Mann–Whitney tests were used for non-parametric data. Differences among the five menus were tested using one-way ANOVA. Statistical significance was set at $p < 0.05$, with p values from t-tests adjusted with false discovery rate (FDR) ($p_{adjusted} < 0.05$). For multivariate tests, metabolomics data were initially analyzed with unsupervised principal component analysis (PCA) to detect patterns and outliers. Subsequently, supervised orthogonal partial least squares-discriminant analysis (OPLS-DA) was applied to maximize separation between predefined groups. Variable importance in projection (VIP) scores (VIP >1.5) and correlation coefficients (|Pcorr| > 0.6) from OPLS-DA identified influential metabolites and their correlation with the predefined groups, respectively. Q^2 and R^2 values from the OPLS-DA model indicated predictability and goodness of fit, respectively, with p-values assessed using 1,000 random permutations ($p < 0.05$).

3. Results

3.1. Basic characteristics and nutrient comparisons

Table S1 shows the mean differences in anthropometric and biochemical characteristics within each diet group (i.e., lacto-vegetarian or vegan) between days 1 and 14, as well as between the diet groups on day 1, day 14, and changes from day 1 to day 14). In the lacto-vegetarian group, body fat percentage significantly decreased ($p = 0.0276$, p-adjusted $= 0.252$) from day 1 (22.2 ± 6.7) to day 14 (21.3 ± 7.0). In the vegan group, body weight significantly decreased ($p = 0.0304$, p-adjusted $= 0.270$) from day 1 (55.9 ± 6.8) to day 14 (55.4 ± 6.6). HOMA-IR was significantly higher ($p = 0.0469$, p-adjusted $= 0.324$) in the vegan group (2.2 ± 0.9) compared to the lacto-vegetarian group (1.6 ± 0.8) on day 14. However, changes in HOMA-IR from day 1 to day 14 were not significantly different between the diet groups (lacto-vegetarian: -0.3 ± 0.6 vs. vegan: -0.5 ± 1.7, $p = 0.716$). No significant differences were found in nutrient composition (i.e., energy, macronutrient, added sugar, and fiber) between the two isoenergetic diets (Table S3).

3.2. Effects of lacto-vegetarian and vegan diets on the glycemic profile – CGM study

Table 1 presents CGM-derived parameters (i.e., mean glucose, $TBR_{<70}$, $TAR_{>140}$, $TAR_{>180}$, $TIR_{70\text{-}140}$, $TIR_{70\text{-}180}$, GMI, and CV) averaged over 13 days (i.e., days 2–14). All parameters, except $TAR_{>180}$ and CV, significantly differed between the diet groups. Specifically, the vegan group showed higher mean glucose and GMI compared to the lacto-vegetarian group from day 11 onwards, while significantly higher $TIR_{70\text{-}180}$ and lower $TBR_{<70}$ were observed in the vegan group starting from day 12 onwards (Fig. 2). After FDR adjustment, only mean glucose and GMI remained significant on days 11 and 13. Both diet groups showed increase in mean glucose, GMI, $TIR_{70\text{-}140}$, and $TIR_{70\text{-}180}$ from day 2 to day 7. After day 7, these parameters decreased in the lacto-vegetarian group but continued increasing in the vegan group. $TBR_{<70}$, decreased in both diet groups from day 2 to day 7, remaining stable in the lacto-vegetarian group but increasing in the vegan group afterward. $TAR_{>140}$ was consistently higher in the vegan group compared to the lacto-vegetarian group apart from day 12. Glucose trends over the 13 days were analyzed using STL decomposition (Fig. S1). The trend component showed a pattern similar to the mean glucose in Fig. 2, with linearity values of −5.70 for the lacto-vegetarian and 83.6 for the vegan groups,

Table 1
Descriptive statistics for 13 days averaged continuous glucose monitoring derived parameters.

CGM metrics	Lacto-vegetarian (n = 11)	Vegan (n = 13)	*P* value (*Q* value)
Mean glucose concentration (mg/dL)	78.5 ± 3.7	85.5 ± 3.8	< **0.001** (<**0.001**)
Time in range 70–140 mg/dL (%)	66.9 ± 10.8	79.7 ± 9.3	**0.00125** (**0.00195**)
Time in range 70–180 mg/dL (%)	67.4 ± 10.8	81.1 ± 9.7	< **0.001** (**0.00171**)
Time above range 140 mg/dL (%)	0.5 ± 0.5	1.4 ± 0.7	**0.00146** (**0.00195**)
Time above range 180 mg/dL (%)	0.03 ± 0.11	0.08 ± 0.11	0.0568 (0.0649)
Time below range 70 mg/dL (%)	32.6 ± 10.8	18.8 ± 9.7	< **0.001** (**0.00171**)
Glucose management indicator (%)	5.2 ± 0.1	5.4 ± 0.1	< **0.001** (<**0.001**)
Coefficient of variation (%)	18.4 ± 1.3	19.0 ± 1.1	0.186 (0.186)

Data for each group presented as means ± SD. Mann–Whitney tests were used to determine statistical significance ($p < 0.05$, indicated by bolded values), and the false discovery rate was used to adjust p values, indicated by Q ($p < 0.05$).
Note: The CGM-derived parameters, particularly time below range (70 mg/dL), should be interpreted in conjunction with Fig. 2. During data cleaning, we observed that all CGM baseline readings were consistently lower than actual fasting glucose concentrations in each participant. We believe these apparent "hypoglycemia events" were likely due to batch effects caused by the CGM sensors. For instance, baseline glucose concentrations (i.e., lacto-vegetarian: 58.5 ± 3.9 [day 1], 63.8 ± 10.7 [day 14]; vegan: 63.8 ± 6.8 [day 1], 73.7 ± 7.0 [day 14]) were classified as "hypoglycemia". However, fasting capillary blood glucose concentrations (i.e., lacto-vegetarian: 80.5 ± 7.0 [day 1] and 80.5 ± 6.1 [day 14]; 81.9 ± 8.2 [day 1], 84.9 ± 11.1 [day 14]); Table S1) were within the normal range.

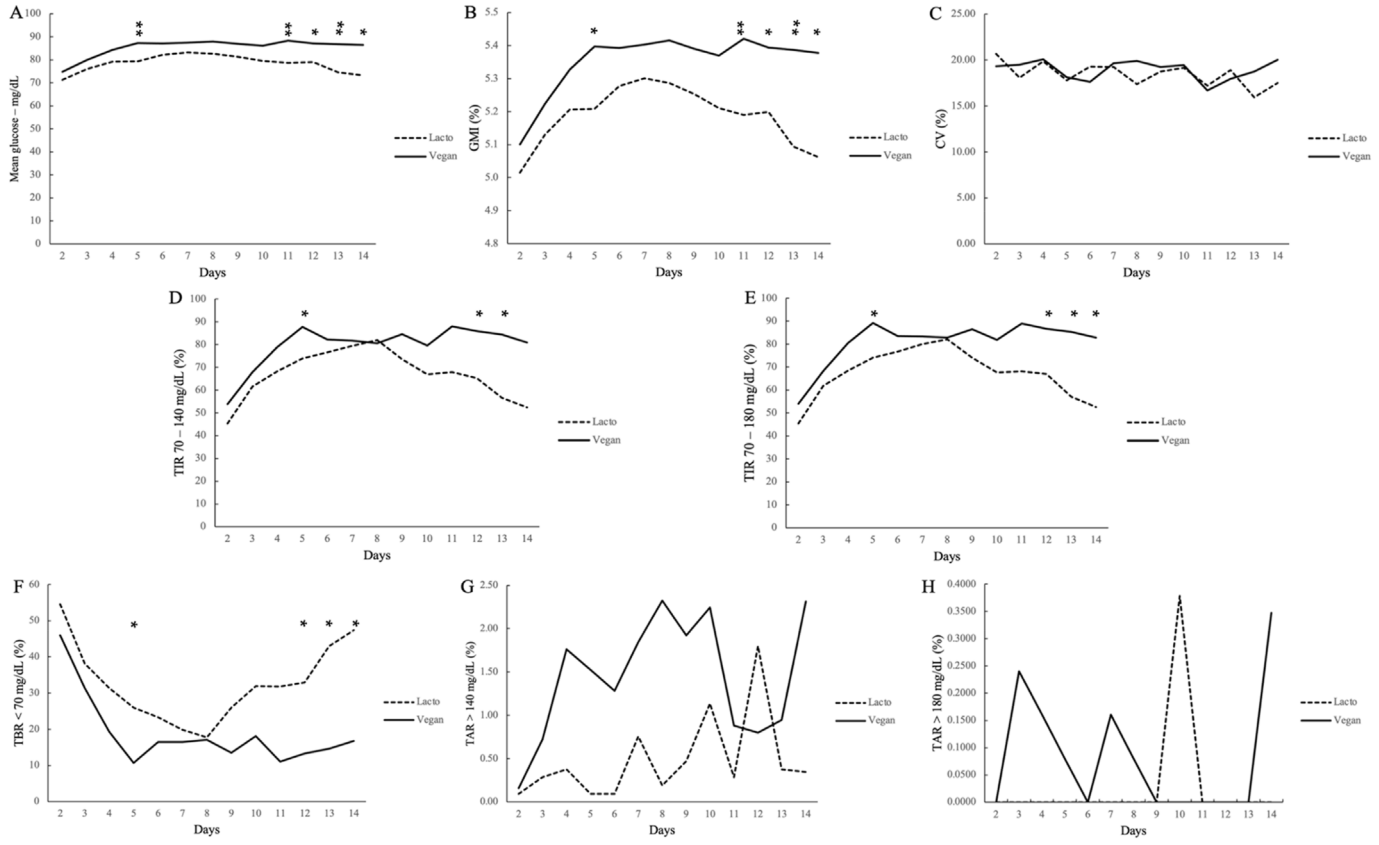

Fig. 2. Continuous glucose monitoring derived glycemic parameters of lacto-vegetarian and vegan groups over 13 days (n = 24). *: Independent t-tests were used for mean glucose and GMI, while Mann–Whitney tests were used for other variables ($p < 0.05$). **: False discovery rate adjusted values ($p < 0.05$). Abbreviations: CV, coefficient of variation; GMI, glucose management indicator; TAR, time above range; TBR, time below range; TIR, time in range.

where a higher linearity value indicates a stronger linear relationship (Table S4).

Fig. S2 presents the glucose fluctuations and variability, measured using MAGE, in the two diet groups. A significant difference in MAGE between the diet groups was observed over the 13-day average ($p < 0.001$). Specifically, the vegan group showed higher MAGE on day 13 ($p = 0.00294$, p-adjusted = 0.0382) and day 14 ($p = 0.0244$, p-adjusted = 0.159) compared to the lacto-vegetarian group. Repeated menus for specific days did not show significant glucose variability between the two diet groups in menu 3 (Days 3, 8, and 13) and menu 4 (Days 4, 9, and 14) after excluding days 13 and 14 (Table S5).

Fig. S3 shows the iAUC for overall glucose and postprandial glucose (i.e., breakfast, lunch, and dinner) for both diet groups. Vegan group showed higher iAUC on day 14 ($p = 0.0240$, p-adjusted = 0.312), at breakfast on day 10 ($p = 0.00107$, p-adjusted = 0.0140), and at lunch on day 13 ($p = 0.0212$, p-adjusted = 0.276) compared to the lacto-vegetarian group. However, neither 13-day average for iAUC was significantly different between the two diet groups. Fig. S4 shows the AUC of overall glucose between the two diet groups, consistent with mean glucose and GMI results.

Because baseline glucose concentrations in the two diet groups differed, a multiple regression was conducted to predict the mean

glucose over 13 days based on two diet groups, age, sex, BMI, and baseline glucose concentrations (Fig. S5). The overall model significantly predicated the 13-day mean glucose concentrations, $F(5, 18) = 6.01$, $p = 0.00194$, $R^2 = 0.625$, adjusted $R^2 = 0.521$ (Table 2). Diet group ($\beta = 5.92$, $SE = 2.67$, $t = 2.22$, $p = 0.0399$; Table 2), BMI ($\beta = 1.97$, $SE = 0.843$, $t = 2.34$, $p = 0.0311$; Table 2, Fig. S6), and baseline ($\beta = 0.537$, $SE = 0.236$, $t = 2.27$, $p = 0.0354$; Table 2, Fig. S7) were significantly associated with the 13-day mean glucose concentrations. Notably, a clear separation of 13-day mean glucose concentrations between the two diet groups were observed, except for four vegan participants who had similar glucose profiles to the lacto-vegetarian group (Fig. S5).

3.3. Effects of lacto-vegetarian and vegan diets on the metabolites profile – metabolomics study

PCA was conducted to compare metabolites of two diet groups at fasting and postprandial states on days 1 and 15 (Fig. S8). Due to sex ratio imbalance (only one man or woman in each diet group; Fig. 1), we created three PCA models to observe sex-related outliers: Model 1 – all participants; Model 2 – lacto-vegetarian men and mix-sex vegan groups; and Model 3 – lacto-vegetarian men and vegan women group. However, since clear separations between the two diet groups were observed at the postprandial state on days 1 and 15 compared to the fasting state, we also conducted a PCA to compare metabolite changes between fasting and postprandial states (Fig. 3). Across all models (Fig. 3), p-values (1,000 random permutations) for Q^2 and R^2 values from OPLS-DA were not significant on days 1 and 15. However, on day 15, vegan participants clustered together, unlike the lacto-vegetarian group. This pattern is most evident in Model 3, followed by Model 2, and then Model 1 (Fig. 3).

In Model 3, three differential metabolites out of 57—phenylalanine (Phe), acetyl carnitine (C2), and arginino-succinic acid (ASA)—were identified using multivariate (i.e., VIP >1.5 and |Pcorr| > 0.6) and univariate tests (i.e., $p < 0.05$) on day 15 between the two diet groups (Table 3, Fig. 4). On day 15, we observed an 8.1-fold increase in postprandial Phe in vegan women, whereas the lacto-vegetarian men showed a 5.7-fold increase in postprandial C2 and a 24-fold decrease in postprandial ASA. However, these metabolites were not significant after FDR adjustment. Additionally, we plotted the changes in these three metabolites from fasting to postprandial states against 13-day mean glucose concentrations, observing a clear separation between the two diet groups on day 15 compared to day 1 (Fig. 5). Notably, three vegan participants, with similar glucose profiles to the lacto-vegetarian group (Fig. S5), also had similar metabolite profiles to the vegan group.

PCA plots (Fig. S9) illustrate within-group comparisons (lacto-vegetarian or vegan) of fasting and postprandial states on day 1, day 15, and changes between these days. Despite non-significant p-values (1,000 random permutations) for Q^2 and R^2 values from OPLS-DA, the same influential metabolites (i.e., Phe, C2, and ASA) were identified (Table S6). Significant differences were observed for C2 ($p = 0.011$) and ASA ($p = 0.021$) in the lacto-vegetarian group and for Phe ($p = 0.019$) in the vegan group between days 1 and 15, but these metabolites were not significant after FDR adjustment. Fig. S10 shows no distinct patterns between days 1 and 15 at the fasting state for both diet groups, but a clear separation was observed at the postprandial state for lacto-vegetarian men ($Q^2 = 0.613$, $p = 0.038$), while no clear separation was observed for vegan women. To ensure the three identified metabolites were not influenced by left-censored metabolites (i.e., 24 acylcarnitines with missing values and low concentrations), only 17 amino acids and 16 acylcarnitines without left-censored data were also analyzed using PCA and OPLS-DA. Results from the model without left-censored data (n = 33; Figs. S11–S13, Tables S7&S8) aligned with the original model with left-censored data (n = 57; Figs. 3, S8–S10 and Tables 3, S7).

3.4. Additional analysis – pairwise comparison between diet group and sex & Phe content

Since Model 3 from the metabolomics study showed better separation between lacto-vegetarian men and vegan women, and the CGM study showed higher 13-day mean glucose concentrations in the vegan group, we investigated the role of sex in 13-day mean glucose concentrations using pairwise comparison (Table S9). The CGM study showed the following glucose trends: vegan men (91.9 ± 6.5) > vegan women (81.6 ± 5.8) > lacto-vegetarian men (79.0 ± 5.4) > lacto-vegetarian women (77.5 ± 2.8). However, neither the CGM nor metabolomics studies showed significant differences.

To further investigate the reduced significant differences in Phe changes after FDR adjustment (Tables 3 and S6), we calculated the Phe content in two diets using the EpiNu software with the Indian Food Composition Table (IFCT) database. No significant difference in Phe intake was observed between the lacto-vegetarian (all meals: 5.05 ± 1.18; morning tea & breakfast: 1.54 ± 0.756) and vegan (all meals: 4.87 ± 0.797; morning tea & breakfast: 1.29 ± 0.201) diets (Table S10). Notably, the Phe content in morning tea and breakfast, where postprandial samples were collected for metabolomics, was 1.1 times higher on day 1 compared to day 15 for both diets (Table S10).

4. Discussion

This study investigated the effects of dairy non-dairy products on glycemic responses and metabolite profiles in healthy Asian Indians following isoenergetic Indian diets, specifically lacto-

Table 2
Regression coefficients for predicting 13-day mean glucose concentrations (days 2–14).[a]

Variables	Coefficient (β)	SE	*t* values	*P* values	95 % CI
(Intercept)	19.7	25.3	0.779	0.446	[−33.5, 73.0]
Group (vegan)	5.92	2.67	2.22	**0.0399**	[0.306, 11.5]
Age	−0.519	0.413	−1.26	0.225	[−1.39, 0.349]
Sex (woman)	−3.92	2.45	−1.60	0.127	[−9.07, 1.23]
BMI	1.97	0.843	2.34	**0.0311**	[0.200, 3.74]
Baseline[b]	0.537	0.236	2.27	**0.0354**	[0.041, 1.03]
R^2: 0.625	Adjusted R^2: 0.521	$F(5, 18) = 6.01$		$p = 0.00194$	

Abbreviation: BMI, body mass index; CI, confidence interval; SE, standard error.

[a] Dependent variable: average mean glucose concentrations of days 2–14; Group coding: 0 = lacto-vegetarian, 1 = vegan; Sex coding: 0 = man, 1 = woman; BMI was the average of days 1 and 15; Statistical significance was defined as $p < 0.05$ and indicated by bolded values.

[b] Since an average of 13 days of baseline masked the effects of other variables in the model due to its high variability throughout the study and correlation with mean glucose (Fig. S7), baseline glucose concentrations were calculated based on the average of days 2 and 3.

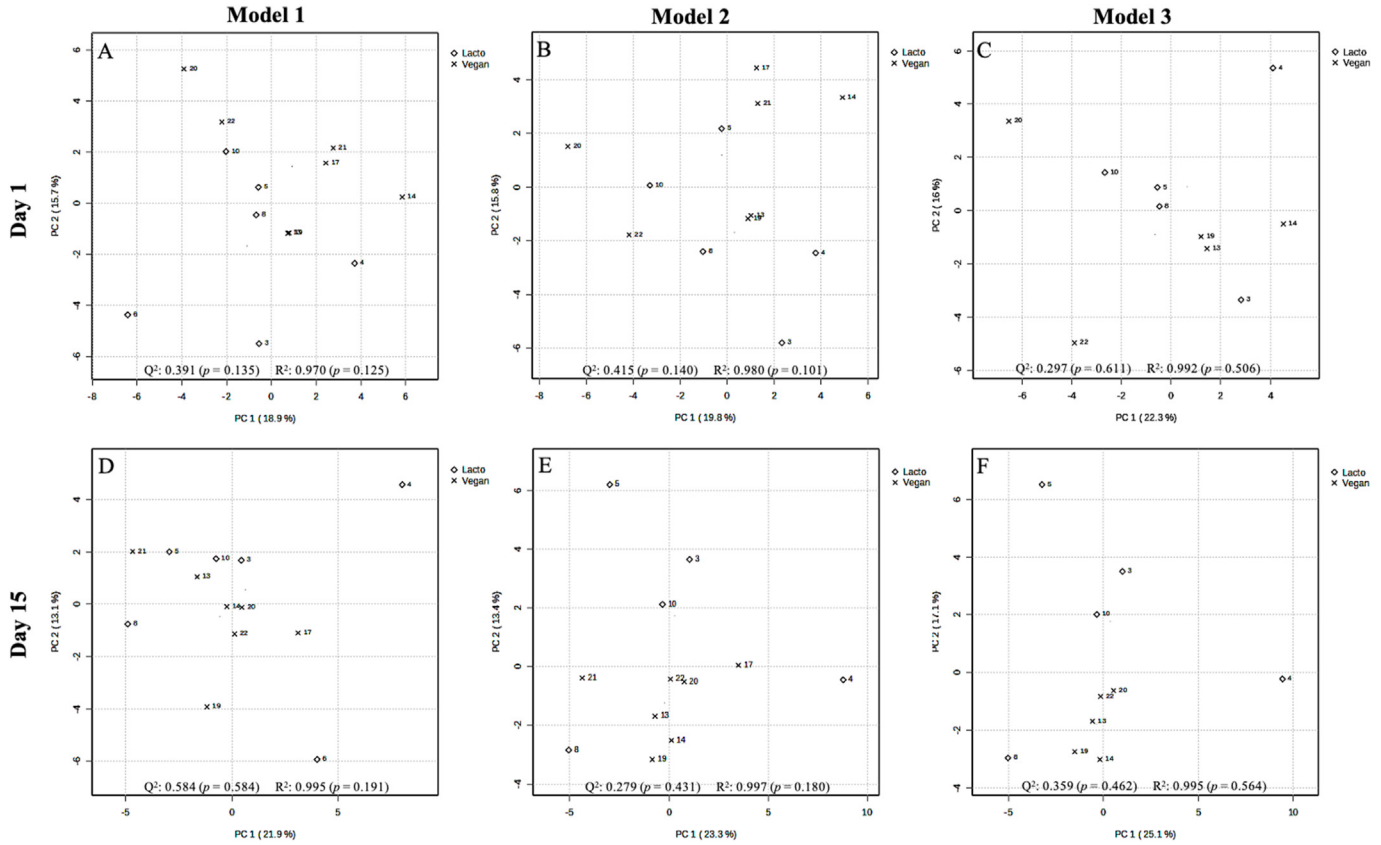

Fig. 3. PCA score plots illustrate the distribution of blood metabolites in health participants. Each data point represents changes between fasting and postprandial metabolites for an individual on day 1 or day 15, with different shapes denoting lacto-vegetarian and vegan groups. Q^2 and R^2 values from OPLS-DA model represent predictability and goodness of fit, respectively, with *p* values from 1,000 random permutation ($p < 0.05$). Model 1 (n = 13): all data; Model 2 (n = 12): lacto-vegetarian men & vegan mix-sex; Model 3 (n = 10): lacto-vegetarian men & vegan women.

Table 3
Inter-group comparisons of metabolite changes between fasting and postprandial on days 1 and 15 using univariate and multivariate tests[a].

Metabolites (μmol/L)	Model 1	Model 2			Model 3			
	P (*Q* value) [day 15]	*P* (*Q* value) [day 15]	Lacto-vegetarian	Vegan	Changes	*P* (*Q* value) [day 1/day 15]	VIP [day 1/day 15]	Pcorr [day 1/day 15]
Phe[b]	**0.0136** (0.689)	**0.0279** (0.529)	4.0 ± 8.8 (5.7)/ 3.0 ± 12.9 (8.5)	9.9 ± 9.6 (6.0)/ 24.3 ± 9.7 (5.6)	↑ Vegan	0.353 (0.928)/**0.0176** (0.335)	1.07/2.03	0.354/0.709
C2[b]	0.0513 (0.701)	**0.00959** (0.273)	−1.7 ± 0.8 (0.5)/ 0.3 ± 0.8 (0.5)	−0.8 ± 2.1 (1.4)/ −1.7 ± 1.0 (0.7)	↑ Lacto	0.359 (0.928)/**0.00715** (0.335)	1.12/2.26	0.312/−0.788
ASA[b]	0.0615 (0.701)	**0.00885** (0.273)	0.4 ± 1.3 (0.9)/ −2.4 ± 1.4 (1.0)	0.1 ± 1.5 (1.0)/ 0.1 ± 1.1 (0.7)	↓ Lacto	0.704 (0.928)/**0.0150** (0.335)	0.369/2.03	−0.122/0.708

Abbreviations: ASA, argininosuccinic acid; C2, acetyl carnitine; CV, coefficient of variation; Phe, phenylalanine; Pcorr, correlation; *Q* value, *P* value adjusted for false discovery rate (FDR); VIP, variable importance in projection.

[a] Model 1: lacto-vegetarian mix-sex (n = 6) & vegan mix-sex (n = 7); Model 2: lacto-vegetarian men (n = 5) & vegan mix-sex (n = 7); Model 3: lacto-vegetarian men (n = 5) & vegan women (n = 5). Changes for both diet groups reported as means ± SD (CV%) [day 1]/means ± SD (CV%) [day 15]. Metabolites with a statistical significance ($p < 0.05$, indicated by bolded values) using independent t-tests were reported for all models. Multivariate tests from OPLS-DA were reported in model 3 only.

[b] For the intra-group comparison between day 1 and day 15, Phe was significantly different in the vegan women, while C2 and ASA were significantly different in the lacto-vegetarian men.

vegetarian and vegan diets. Over a 14-day intervention, we identified a potential pathway involving glucose, Phe, and C2 at the postprandial state. The vegan group showed increased Phe, possibly due to higher postprandial glucose inducing oxidative stress. In contrast, the lacto-vegetarian group had higher C2 from dairy, potentially offering protection against oxidative stress and lower glucose concentrations. These findings support our previous studies linking dairy consumption to improved CMH outcomes [13–19]. Given the higher risk of developing T2D among Asian Indians compared to other ethnicities [36] and the burden of uncontrolled glycemic profiles [37], this study provides critical insights into dairy impacts on glycemic control.

Our CGM study showed that the vegan group had increased glucose concentrations compared to the lacto-vegetarian group over 14 days. This interpretation was based on mean glucose, GMI, TIR, AUC, and time series. The regression model, adjusted for age, sex, BMI, and glucose baseline, also supported higher glucose concentrations in the vegan group. However, these parameters did not align with postprandial glucose measured using iAUC, possibly because iAUC measures only the area above the baseline glucose

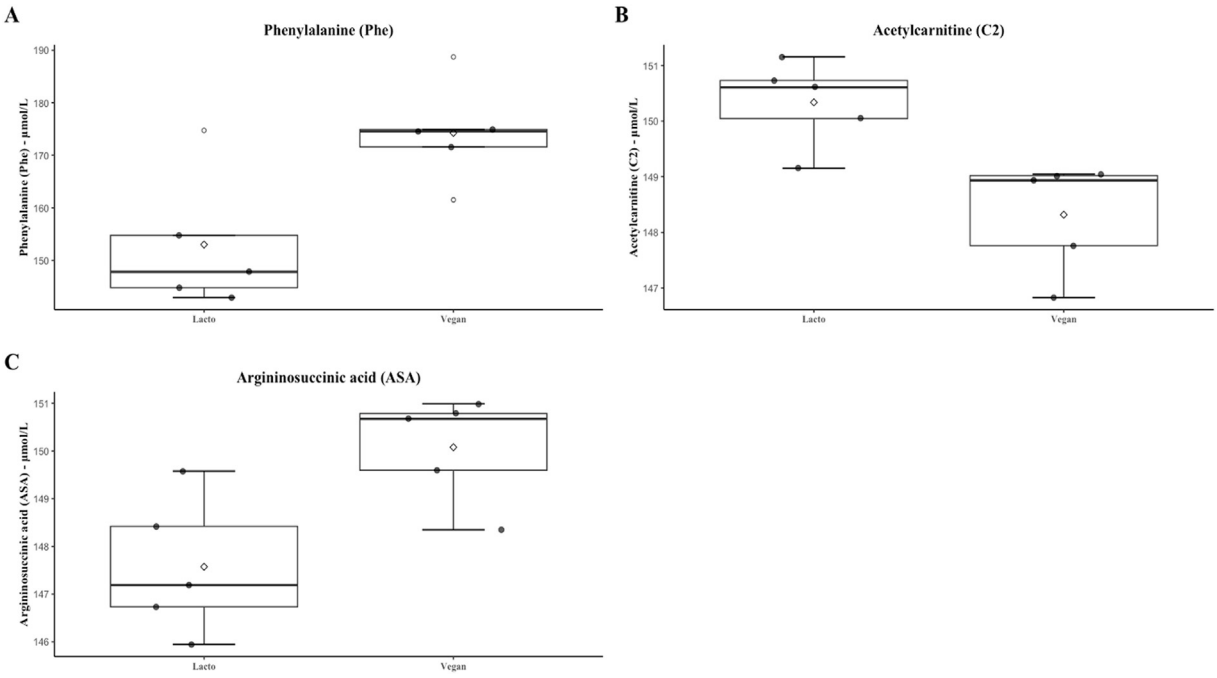

Fig. 4. Box plots illustrate changes of three blood metabolites from Model 3 (Fig. 3). Each participant is represented by a solid black dot, and outliers are shown as hollow circles. Additionally, hollow squares indicate the mean value of each metabolite across all participants. Note: a scaling factor of 150 was applied to metabolites to manage negative values.

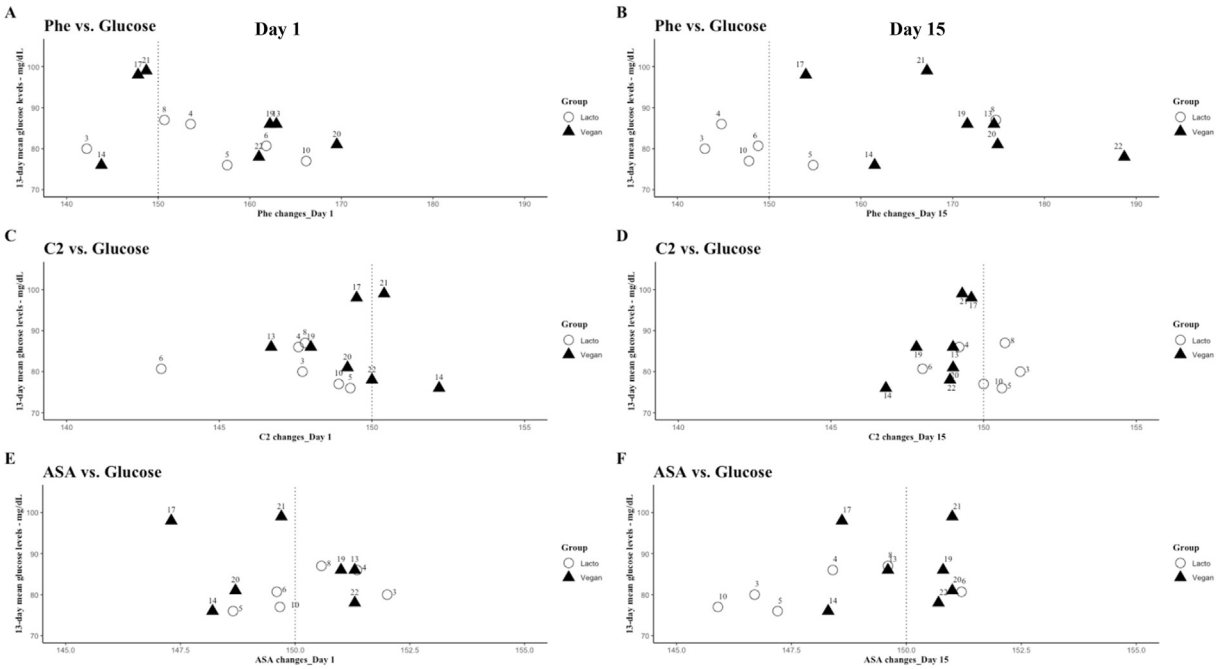

Fig. 5. Scatter plots illustrate blood metabolite changes from Model 1 (Including participants 6, 17, 21) and the 13-day mean glucose in a subgroup of healthy participants on days 1 (A, C, E) and 15 (B, D, F). A scaling factor of 150 (dashed line) was applied to metabolites to manage negative values, with changes being negative on the left of the line and positive on the right. Notably, vegan participants (14, 20, 22) showed similar glucose profiles to the lacto-vegetarian group (Fig. S5) and comparable metabolite profiles. Note: to ensure confidentiality, participants' IDs in this figure are shuffled.

concentration, whereas the other parameters capture the full glucose profile, including carryover effects from the diet. Altogether, our CGM study suggests that a lacto-vegetarian diet may offer benefits for maintaining more stable glucose concentrations over time. However, future study with longer durations and more diverse populations is needed to confirm these findings.

On the other hand, our subgroup metabolomics analysis may offer a potential explanation for the differences that were not captured in the CGM study. Since fewer separations between the two diet groups were observed in Models 1 and 2, possibly due to sex-related outliers, we focused on comparing vegan women and lacto-vegetarian men using Model 3. Our findings suggest that

three metabolites—Phe, C2, and ASA—may contribute to the separation between the two diet groups. On day 15, we observed an 8.1-fold increase in postprandial Phe in vegan women, whereas the lacto-vegetarian men showed a 5.7-fold increase in postprandial C2 and a 24-fold decrease in postprandial ASA. The C2 increase in the lacto-vegetarian group could be attributed to the carnitine content in dairy products (i.e., milk, curd, and paneer). While C2 is primarily recognized for its role in improving cognitive impairment [38], it has also been suggested to possess antioxidant properties [39]. Moreover, carnitine supplementation promotes C2 formation and restores metabolic flexibility in individuals with IGT [40]. Therefore, C2 may offer glycemic control benefits, which could potentially explain the lower glucose concentrations in the lacto-vegetarian group compared to the vegan group. Conversely, the Phe increase in the vegan group may be attributed to glucose-Phe interaction. *In vitro* studies have shown that intermittent high glucose stimulates reactive oxygen species (ROS) production [41], which can oxidize tetrahydrobiopterin (BH4) [42], an essential cofactor for converting Phe to tyrosine, thereby raising postprandial Phe. Phe has been associated with an increased T2D risk [8–10], and recent research suggests that it impairs insulin signaling and inhibits glucose uptake by inactivating insulin receptor beta in a mouse model [43]. Notably, despite blood Phe changes being non-significant after FDR adjustment, which provides a robust statistical measure, our dietary data shows the consistent Phe intake between the two diet groups throughout the study, suggesting these trends should be considered for their biological plausibility. Moreover, dietary Phe intake was on average 1.1 times higher on day 1 in both diets than on day 15, suggesting elevated postprandial Phe could be attributed to glucose-induced oxidative stress. Altogether, it is plausible that without the protective benefits of C2, glucose concentrations in the vegan group may rise over time, resulting in elevated Phe, thereby creating a vicious cycle. Moreover, the ASA decrease in the lacto-vegetarian group may result from efficient conversion from ASA to arginine, indicating sufficient protein intake and, thus, enhanced urea cycle activity. However, it remains unclear whether ASA plays a role in regulating glycemic control. Overall, while our findings suggest the possibility that C2 derived from dairy products (~558g daily—76.3 % milk, 20.5 % curd, and 2.5 % paneer) may offer benefits for glycemic control, future studies with larger sample sizes, longer study durations, and more diverse populations are warranted to investigate the biological mechanism by which glucose-induced ROS may increase postprandial Phe through oxidizing BH4. Notably, dairy products also contain other bioactive nutrients (e.g., lipids, proteins, and micronutrients) that play a key role in regulating inflammation [17–21,44] that contributes to ROS production. Therefore, the benefits of C2 in glycemic control should be interpreted with caution, particularly given the limitations of our sample size.

Our study has several strengths. In the CGM study, we provided five repeated menus for each diet over 14 days, controlling portion sizes and caloric intake for each participant. This approach enabled an accurate assessment of glucose profiles. Additionally, we developed an alignment method to adjust for misaligned CGM data daily, ensuring that the glucose profiles were representative and aligned with mealtimes, thereby enhancing data reliability. Regarding metabolomics data, we observed missing values in acylcarnitines on day 1, likely due to their inherently low concentrations. To address this, we used the QRILC method to impute the left-censored data in the LC-MS dataset and confirmed the identified metabolites, ensuring that the results were not driven by acylcarnitines.

Our study has several limitations. First, variations in the breakfast composition for the metabolomics subgroup on days 1 and 15 may have influenced the non-significant findings for the identified metabolites after FDR adjustments. Nevertheless, we standardized the data by comparing metabolite changes between fasting and postprandial states within and between groups, providing insights into how metabolites change 2 h after a meal. Second, due to limited funding, this study did not include a control group (i.e., an omnivorous diet), which would provide insights into potential dietary confounding [20,21]. Nevertheless, we leveraged existing data on sex-related differences in Phe levels and diabetes susceptibility to interpret our findings. Men generally exhibit higher Phe [45] and greater susceptible to diabetes than women [46]. Thus, in our study, vegan women with significantly higher Phe and glucose served as an “experiment” group compared to the lacto-vegetarian men as a “control” group. Third, our study had a small sample size and limited duration for both the CGM and metabolomics analyses, which may affect representativeness. Future studies with larger sample sizes and longer durations are needed to validate our findings. Notably, anthropometric and biochemical results served as reference measures but may not provide as comprehensive a profile as CGM-derived glycemic variables and LC-MS-based metabolites. Hence, we did not draw strong conclusions from these results.

5. Conclusion

Our study suggests a potential metabolic pathway involving glucose, Phe, and C2, indicating that dairy and non-dairy products may influence glycemic responses in healthy adults following lacto-vegetarian and vegan diets. The better glycemic control observed in the lacto-vegetarian group may be partially explained by the beneficial action of C2 and other bioactive nutrients in dairy products. In contrast, the higher glucose concentrations observed in the vegan group may be explained by a hypothetical mechanism in which accumulated glucose induces ROS, leading to decreased BH4 levels, elevated postprandial Phe, and ultimately impaired glucose uptake. However, the exact molecular mechanisms underlying these interactions remain unclear and warrant further investigation. Future studies with larger, more diverse populations and longer durations are needed to fully understand the implications of these findings for glycemic control and metabolic health.

Ethical approval, consent to participate

The study protocol was approved by the Institutional Review Board of Madras Diabetes Research Foundation and was registered in the Clinical Trials Registry of India (*CTRI/2022/02/040661 [Registered on: 28/02/2022]*). Written informed consent was obtained from all participants before enrollment in the study.

CRediT authorship contribution statement

Xianyu Zhu: Conceptualization, Methodology, Formal analysis, Validation, Investigation, Writing - Original Draft, Writing – Review & Editing. Rajagopal Gayathri: Formal analysis, Investigation, Writing - Review & Editing. **Valangaiman Sriram Manasa:** Formal analysis, Investigation. **Kuzhanthaivelu Abirami:** Formal analysis, Investigation. **Shilpa N. Bhupathiraju:** Writing - Review & Editing. **Ranjit Mohan Anjana:** Writing - Review & Editing. **D Ian Givens:** Methodology, Writing – Review & Editing. **Anisha Wijeyesekera:** Methodology, Formal analysis, Supervision, Writing – Review & Editing. **Vasudevan Sudha:** Investigation, Methodology, Project administration, Supervision, Writing – Review & Editing. **Viswanathan Mohan:** Writing - Review & Editing. **Karani S. Vimaleswaran:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – Review & Editing.

Data availability

The data that support the findings of this study are available from the corresponding author, Karani S. Vimaleswaran (v.karani@reading.ac.uk), upon reasonable request.

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Conflict of interest

D.I.G has received travel expenses and honoraria in connection with lectures and meetings from the Dairy Council (now Dairy UK), Dutch Dairy Association, European Dairy Association, and the International Dairy Federation. He has also been a consultant to the Estonian Biocompetence Centre of Healthy Dairy Products (BioCC) and to the Dairy Council on fats in dairy products and cardiometabolic disease.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.04.018.

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