Asian Low-Carbohydrate Diet with Increased Whole Egg Consumption Improves Metabolic Outcomes in Metabolic Syndrome: A 52-Week Intervention Study

Bonggochpass Pinsawas
Mahidol University
Pichanun Mongkolsucharitkul
Mahidol University
Tanyaporn Pongkunakorn
Mahidol University
Apinya Surawit
Mahidol University
Sophida Suta
Mahidol University
Thamonwan Manosan
Mahidol University
Suphawan Ophakas
Mahidol University
Sureeporn Pumeiam
Mahidol University
Kitti Sranacharoenpong
Mahidol University
Korapat Mayurasakorn (korapat.may@mahidol.ac.th)
Mahidol University

Research Article

Keywords: metabolic syndrome, Asian diet, low carbohydrate, long-term intervention

Posted Date: November 28th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3646877/v1

Additional Declarations: No competing interests reported.

Abstract

Background: The low-carbohydrate-ketogenic diet, an effective strategy to address metabolic syndrome (MetS) and obesity has been concerns about high fat consumption on atherogenic lipoproteins. This study aimed to compare the Asian ketogenic diet (AKD), which incorporates balanced protein and fat intake from Asian foods, with a balanced low-caloric diet (BLC) in individuals diagnosed with MetS.

Methods: A 52-week randomized clinical trial included three parallel groups: AKD with increased whole egg intake (Yolk-KD, aged 40.9 ± 1.7, n = 27), yolk-free ketogenic diet with egg white supplementation (White-KD, aged 41.5 ± 1.3, n = 26), and BLC diet (aged 38.5 ± 1.7, n = 22). Primary outcomes were anthropometric and metabolic changes.

Results: The AKD groups achieved significant reductions in weight and waist circumference ($P < 0.05$). Compared to the BLC group, the AKD groups demonstrated significant improvements in fasting blood glucose, insulin resistance, and lipid profile at weeks 12 and 35 ($P < 0.05$). All groups experienced improvements in insulin sensitivity, inflammation, and appetite-related hormones like leptin and peptide YY ($P < 0.05$). From weeks 35 to 52, the AKD consistently maintained reductions in anthropometric measurements, improved glucose tolerance, enhanced lipid profiles, and better liver function compared to the BLC.

Conclusion: The AKD proved safe and effective, yielding various metabolic improvements in individuals with Mets compared to the BLC. By emphasizing a low-saturated fat diet while disregarding dietary cholesterol, this approach holds promise for MetS and obesity management. Further studies are warranted.

Trial registration: ClinicalTrials.gov identifier: NCT04608136, registered on September 21, 2020.

INTRODUCTION

Obesity and type-2 diabetes (T2DM) are global public health challenges [1, 2], with T2DM affecting 10% of Southeast Asia adults, often undiagnosed [3]. These conditions are associated with cardiovascular disease, chronic kidney disease, and reduced quality of life. Amid strategies addressing these, dietary modification remains a cornerstone for sustainable disease management, focusing on weight loss, adopting a healthy lifestyle, and physical activity [4–7].

Two commonly practiced dietary approaches are low-fat, low-calorie diets (LFLC) and low-carbohydrate diets (LC) [6, 8, 9] ketogenic diets (KD) is a more extreme form of LC (typically < 20–50 g of carbohydrate/day), resulting in an elevation of ketone bodies in the blood or urine [10]. The majority of LC vs. LFLC studies have demonstrated short-to-intermediate term weight loss, improved lipoproteins, and glycemic control in overweight and obese individuals. However, long-term weight and metabolic maintenance differences are minimal [8, 11]. Notably, individual responses exhibited substantial variations across these studies, suggesting that specific strategies may yield better outcomes for

individuals based on their unique dietary patterns and both genomic and non-genomic responses. This emphasizes the fact that there is no universally applicable one-size-fits-all diet [12].

Expert Consensus advises against a very low carbohydrate diet (VLC) due to potential adverse events, including raised levels of low density lipoprotein [4], as well as long-term cardiovascular risk. Instead, they recommend tailored macronutrient distribution based on patient preferences and metabolic goals [7, 13]. Various eating patterns, including Mediterranean-style and LC eating plans, may also be appropriate for patients [5, 14]. Certain individuals may experience greater weight loss when assigned to LFLC diets compared to LC diets, and vice versa [12].

Insulin dynamics may influence success with LC diets, particularly for diabetes therapy and diabetes remission [4, 15] due to positive responses to a lower dietary carbohydrate amounts, higher protein intake, improved insulin sensitivity and macronutrient imbalance [16]. However, LC (+/-) high-fat diets (HF) originated in Western countries, with food recommendation based on Western ketogenic LC diets such as meats, butter, oils, nuts [9], while Asia has its unique dietary patterns and corresponding health responses. For instance, Thai cuisine typically includes rice, tropical oils, noodles, grilled meats, and local soups. Therefore, this study aims to explore whether baseline variations in anthropometries and glucose-insulin-metabolic homeostasis impact the differential success of individuals with metabolic syndrome (MetS) in achieving 12-month weight change when following a healthy balanced low-caloric diet (BLC) versus a healthy Asian ketogenic diet (AKD). We also seek to identify metabolic markers for a positive intervention response and potential barriers to successful weight loss.

RESEARCH DESIGN AND METHODS

The study protocol was approved by the Institutional Review Board of Siriraj Hospital, Mahidol University (COA: Si 286/2020). Written informed consent was obtained from all participants. The trial was registered in the ClinicalTrials.gov (NCT04608136).

Study design

This study utilized a controlled, open-label weight loss program to investigate the effects of different dietary interventions on individuals with MetS. Participants were randomly assigned to one of three groups 1) the healthy BLC group, 2) the healthy White-AKD group (egg white Asian ketogenic diet), and 3) the healthy Yolk-AKD group (egg yolk Asian ketogenic diet). Enrollment occurred between November 2020 to March 2021 with the final follow-up in December 2021. The study aimed to evaluate the impact of a 52-week experimental dietary intervention, comparing the BLC and AKD approaches, on metabolic markers in individuals with MetS. Secondary outcomes included changes in lipid profile, glycemic control, and metabolic hormone levels. The full study protocol was included in Supplementary Fig. 1.

Participants

Participants were invited to participate in clinical screening session where they provided written informed consent. In order to meet the inclusion criteria, participants had to be men or women between the aged of 18 and 60 years with body mass index (BMI) ≥ 25 kg/m^2, Additionally, participants were required to had MetS. The MetS and exclusion criteria were as defined in Supplementary Method 1.

Healthy weight loss intervention

Participants adhered to a comprehensive one-year food behavior modification program. The control group adhered to the BLC, a regimen tailored to their basal metabolic rate and the Thai food-based dietary guidelines [17]. The White-AKD and Yolk-AKD groups strictly adhered to a ketogenic diet, characterized by a marked reduction in carbohydrate intake to below 50 g/day and an emphasis on a low saturated fat diet. The Yolk-AKD group consumed a minimum of 3 whole eggs/day (20 g of protein), sourced from S.W. Food tech., Co., Ltd., Thailand. The White-AKD group, consumed a minimum of 200 g of white eggs/day (20 g of protein), and abstained from additional dietary cholesterol, sourced by Khaisook., Co., Ltd., Thailand. The 12-week intervention ensured single-blinding; data collection and lab staff were blinded to group assignments. Two staggered cohorts were used to optimize study efficiency.

Participants maintained their usual dietary habits for a four-week run-in period before the study. The 12-month intervention involved six instructional sessions led by a multidisciplinary team of nutritionists, doctors, and dietitians, both in-person and online, with each session accommodating 12–15 participants and led by two dietitians who were blinded to laboratory measures. At week 6, participants discussed food behavior modification during a meeting. Throughout the intervention, dietitians supported and motivated participants to adhere to the prescribed diets. After the 12-week intervention, individuals were encouraged to continue their diet intervention without strict guidance. All were advised to (1) maximize fiber and vegetable intake; (2) reduce added sugar intake, refined carbohydrate, and saturated fat; and (3) focus on whole and nutrient dense foods. Their dietary behavior was monitored for one year using an online communication platform. Dietary behavior was monitored for one year using an online platform. Data collection occurred at week 0, 6, 12, 35, and 52, at Siriraj Institute of Clinical Research and Siriraj Medical Research Center. Detailed information about the dietary intervention is provided in Supplementary Method 2.

Anthropometric assessment and blood pressure

Body weight (BW) was measured using a digital weight scale (HD-395, Tanita Corporation, Tokyo, Japan), height (Ht) was measured using a height measuring stand (The Institute of Nutrition, Mahidol University (INMU), Nakhon Pathom, Thailand). Waist circumference (WC) was measured at the umbilicus level (Diet & PA clinic, DPAC, Department of Health, Thailand). Blood pressure (BP) was measured using an automatic blood pressure monitor (HEM-7322, Omron healthcare Co., Ltd., Kyoto, Japan)

Specimen collection and analysis

Blood samples were collected for analysis, including fasting blood sugar (FBS), insulin, Hemoglobin A1C (HbA1C), total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), beta-

hydroxybutyric acid (βHB), aspartate transaminase (AST), alanine aminotransferase (ALT). A 75-gram oral glucose tolerance test (OGTT) was conducted at 6 time points (0, 30, 60, 90, 120, and 180 minutes) [18]. The biochemical analysis was performed by the Department of Clinical Pathology at Siriraj Hospital, Bangkok, Thailand. Insulin resistance was assessed using the homeostatic model assessment for insulin resistance (HOMA-IR)[19]. Plasma human metabolic hormones, including c-peptide, glucose-dependent insulinotropic polypeptide (GIP), interleukin-6 (IL-6), leptin, monocyte chemoattractant protein-1 (MCP-1), peptide YY (PYY), tumor necrosis factor alpha (TNF alpha). were measured using human metabolic hormone magnetic bead panel assay; HMHMAG-34K (Milliplex® MAP Kit, Millipore, Billerica, MA, USA) [20].

Food record

Participants submitted 3-day food records covering two weekdays and one weekend day. A total of 30 recalls were used to calculate dietary intake by using INMUCAL–Nutrient Software version 4.0 (INMU, Nakhon Pathom, Thailand).

PA assessment

PA was analyzed by using the Thai PA questionnaire (Thai-PAQ) [21]. The duration of PA at different intensities was converted to daily average of metabolic equivalent (MET) and was counted as MET-min/week. The Thai-PAQ was validated for Thai individuals at risk for T2DM and supported PA promotion in communities.

Statistical analysis

Data were analyzed using the intention-to-treat principle. Continuous variables were presented as mean ± standard deviation (SD), and discrete variables were reported as percentages. Group differences in trial outcomes were evaluated using one-way ANOVA with Bonferroni's post-test for continuous variables and the chi-squared test for categorical variables. Repeated measures ANOVA models adjusted for time, group, sex, age, and time x group interactions were employed to evaluate the effects of each diet program on trial outcome changes. Glucose and insulin levels were analyzed at 12 and 52 weeks using a linear mixed model, followed by pairwise comparisons of marginal linear predictions. The area under the curve (AUC) 0–180 min was calculated and compared between the three groups using one-way ANOVA and Bonferroni’s post-test. Statistical significance was defined as $P < 0.05$. STATA version 17.0 (Stata Corporation, College Station, TX, USA) was used for all statistical analyses.

RESULTS

Participants

All eligible participants (n = 75) were randomly assigned into three groups: BLC (n = 22), White-AKD (n = 26), and Yolk-AKD (n = 27) (Fig. 1). Table 1 presents the demographic characteristics of the included participants in the three groups at baseline. Out of the total, 64 participants completed the 12-week

primary endpoints, and 33 participants completed the 52-week secondary endpoints. The mean BW for the BLC, White-AKD and Yolk-AKD groups were 81.5 ± 2.01, 82.5 ± 2.44, and 83.0 ± 2.56 kg, respectively, corresponding to a BMI of approximately 32 kg/m^2. No significant differences were observed in BW, WC, comorbidity, lipid profile, FBS, insulin, HOMA-IR, and physical activities among the three groups (ns).

Table 1
Baseline demographics and anthropometric and metabolic variables

	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)
Age, years	38.5 ± 1.72	41.5 ± 1.32	40.9 ± 1.72
Comorbidity, (%)			
Diabetes	(0)	(3.8)	(7.4)
Hypertension	(4.5)	(15.4)	(25.9)
Dyslipidemia	(0)	(3.8)	(0)
Fatty liver	(4.5)	(0)	(3.7)
Gout	(9.1)	(0)	(0)
Anthropometries			
BW, kg	80.9 ± 0.31	83.3 ± 0.29	85.1 ± 0.28
BMI, kg/m^2	31.3 ± 0.12	31.7 ± 0.11	32.3 ± 0.11
WC, cm	97.6 ± 0.66	97.5 ± 0.60	99.7 ± 0.59
Blood pressure			
SBP, mmHg	129.8 ± 2.29	129.8 ± 2.08	131.7 ± 2.04
DBP, mmHg	89.5 ± 1.74	87.1 ± 1.58	89.9 ± 1.55
Biochemistries			
FBS, mg/dL	104.2 ± 1.28	106.1 ± 1.16	101.0 ± 1.13
Fasting insulin, μU/mL	21.1 ± 1.50	18.8 ± 1.36	20.3 ± 1.33
HbA1c, %	5.9 ± 0.05	6.1 ± 0.04	5.8 ± 0.04
HbA1c, mmol/mol	41 ± 2.68	43 ± 2.44	40 ± 2.37
HOMA-IR	5.7 ± 0.88	4.3 ± 0.81	4.7 ± 0.84
TC, mg/dL	194.7 ± 4.68	199.7 ± 4.25	188.2 ± 4.17
TG, mg/dL	157.1 ± 10.37	158.9 ± 9.43	157.7 ± 9.23
HDL-C, mg/dL	44.5 ± 0.83	45.2 ± 0.75	43.6 ± 0.74
LDL-C, mg/dL	142.1 ± 3.30	144.5 ± 3.00	132.8 ± 2.94
Ratio of TC to HDL-C	4.55 ± 0.47	4.65 ± 0.40	4.50 ± 0.43
AST, U/L	28.0 ± 2.67	22.4 ± 2.42	24.0 ± 2.37

	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)
ALT, U/L	25.3 ± 2.53	29.5 ± 2.30	27.7 ± 2.25
Metabolic hormones			
Leptin, mg/dL	20.7 ± 2.16	16.8 ± 1.99	18.5 ± 1.92
Creatinine, mg/dL	0.73 ± 0.01	0.75 ± 0.01	0.82 ± 0.01
Physical activities (MET-minutes/week)	7178.0 ± 796.5	7246.8 ± 804.6	7145.5 ± 826.5

Data are mean ± SEM. BLC, a healthy balanced low-caloric diet; White-AKD, a healthy egg white Asian ketogenic diet; Yolk-AKD, a healthy egg yolk Asian ketogenic diet; BW, body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment for insulin resistance; TC, total cholesterol; TG, triglyceride; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; AST, aspartate transaminase; ALT, alanine aminotransferase.

Dietary intake

Participants adhered to the general principles of all diet guidelines at baseline (Supplementary Table 1). There were no significant differences in average total energy intake between the AKD groups and time points (ns). The AKD groups met the macronutrient goals with average carbohydrate intake falling below the threshold of < 50 g/day during the KD experimental condition at 4 to 8 weeks (42.6 ± 8.14 to 49.7 ± 9.22 g/day; 12.5 to 14.9% of energy). In contrast, the BLC group did not show a significant decrease in daily caloric intake at all time points, and there were no significant differences in macronutrient intake at 4 to 8 weeks (ns).

Primary outcomes

The effect of time significantly influenced changes in BW across all groups, with a maximum weight loss phase from 1 to 9 months, followed by a subsequent maintenance phase lasting beyond 9 to 12 months. The AKD groups exhibited faster reductions in BW compared to the BLC group (the diet x time interaction, $P < 0.05$). At 12 weeks, weight changes from baseline were − 2.8 kg (95% CI, -7.1 to 2.7 kg) for BLC, -3.9 kg (95% CI, -5.8 to -1.3 kg) for White-AKD, and − 4.0 kg (95% CI, -7.5 to -0.9 kg) for Yolk-AKD, without significant differences among the groups (Fig. 2A). However, White-AKD showed a significant reduction in BW compared to BLC at week 12 ($P < 0.05$). Figure 2B-D displays the percentages of BW changes over 2% from baseline and individual BW changes at 12 weeks and 52 weeks.

All groups experienced significant decreases in WC ($P < 0.05$), without differences among the groups (Fig. 2E-F). At week 12, WC decreased by a mean of -1.5 cm (95% CI, -2.8 to 4.9 cm) in BLC, -3.3 cm (95% CI, -4.8 to 0.2 cm) in White-AKD, and − 3.8 cm (95% CI, -4.5 to 0.3) in Yolk-AKD. No significant effects on

BP changes were found between the groups ($P > 0.05$) (Table 2). However, a modest decrease in diastolic blood pressure was observed in all groups at week 12.

Table 2
Effect of diet programs on cardiometabolic parameters and metabolic hormone levels

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
BW, kg	6	-0.7 (-1.3 to 0.7)	-2.1 (-4.8 to -1.2)*	-1.9 (-2.3 to 0.6)	0.763
	12	-2.8 (-7.1 to 2.7)	-3.9 (-5.8 to -1.3)*†	-4.0 (-7.5 to -0.9)*	0.021
	35	-1.5 (-4.8 to 2.4)	-5.4 (-7.7 to -2.9)*	-6.4 (-8.4 to -1.5)*	0.870
	52	+ 0.8 (-0.7 to 1.3)	-2.0 (-2.6 to -0.9)*	-4.0 (-5.4 to -1.6)*	0.826
P-value by time[b]		0.534	0.024	0.045	
WC, cm	6	-0.3 (-1.3 to 2.9)	-1.6 (-2.9 to 0.8)	-3.1 (-5.7 to -2.0)*	0.509
	12	-1.5 (-2.8 to 4.9)	-3.3 (-4.8 to 0.2)	-3.8 (-4.5 to 0.3)	0.562
	35	-3.2 (-6.2 to -1.0)*	-4.8 (-6.7 to -2.9)*	-5.8 (-9.0 to -0.4)*	0.826
	52	-2.4 (-7.0 to -0.3)*	-3.4 (-6.3 to -0.4)*	-4.1 (-6.2 to 0.9)	0.443
P-value by time[b]		0.032	0.031	0.028	
SBP, mmHg	6	-5.2 (-10.1 to 0.5)	-3.7 (-5.3 to 5.2)	-2.4 (-6.4 to 3.3)	0.686
	12	-3.9 (-8.6 to 1.0)	-3.7 (-5.0 to 4.3)	-8.4 (-11.8 to -0.4)*	0.340
	35	-1.9 (-8.1 to 4.7)	-7.1 (-10.4 to 3.1)*	-6.1 (-9.9 to 0.9)	0.271
	52	-1.4 (-6.8 to 4.7)	-4.6 (-7.8 to -0.7)*	-4.2 (-7.7 to 2.1)	0.536
P-value by time[b]		0.439	0.001	0.031	
DBP, mmHg	6	-2.7 (-7.8 to 0.2)	-1.5 (-4.7 to 2.4)	-2.7 (-4.3 to 2.0)	0.184
	12	-7.0 (-10.2 to 2.8)	-4.7 (-8.9 to -2.9)*	-7.4 (-8.6 to 0.2)	0.065
	35	-2.2 (-6.2 to 2.0)	-4.5 (-6.7 to -0.6)*	-4.1 (-6.3 to 0.5)	0.878
	52	-1.4 (-4.3 to 3.4)	-2.0 (-6.0 to 0.9)	-2.9 (-5.4 to 1.0)	0.272
P-value by time[b]		0.575	0.009	0.089	
HbA1c, %	12	+ 0.1 (-0.4 to 0.2)	-0.1 (-0.3 to 0.1)	-0.2 (-0.4 to 0.2)‡§	0.033
	35	0.0 (-0.2 to 0.1)	-0.2 (-0.5 to 0.0)	-0.1 (-0.4 to 0.1)	0.492
	52	-0.2 (-0.4 to 0.1)	-0.3 (-0.4 to -0.1)*	-0.1 (-0.2 to 0.2)	0.978
P-value by time[b]		0.245	0.045	0.769	

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
HbA1c,	12	+ 1.0 (-4.2 to 2.1)	-1.0 (-3.0 to 1.2)	-2.0 (-4.1 to 2.2)‡§	0.049
mmol/mol	35	0.0 (-2.0 to 1.2)	-2.0 (-5.0 to 0.1)	-1.0 (-4.0 to 1.2)	0.326
	52	-2.0 (-4.0 to 1.0)	-3.0 (-4.0 to -1.1)*	-1.0 (-2.1 to 2.1)	0.897
P-value by time[b]		0.584	0.039	0.607	
FBS, mg/dl	6	+ 4.7 (-1.5 to 1.9)	-6.8 (-9.7 to -4.6)*†	-2.1 (-5.2 to 1.3)‡	0.032
	12	+ 0.1 (-1.6 to 2.2)	-4.9 (-9.8 to 2.4)	-1.8 (-9.2 to 0.9)	0.453
	35	-4.6 (-9.4 to 1.2)*	-9.3 (-14.8 to -5.0*	-6.5 (-10.1 to -1.2)*	0.136
	52	+ 2.9 (1.6 to 5.5)	+ 0.6 (-3.7 to 1.6)	+ 0.8 (-2.1 to 4.2)	0.789
P-value by time[b]		0.044	0.001	0.009	
Fasting insulin,	6	+ 6.1 (-8.8 to -1.2)*	-2.3 (-3.0 to 2.2)†	-2.2 (-4.9 to 1.0)‡	0.028
µU/ml	12	-2.0 (-4.0 to 2.5)	-4.4 (-5.2 to 1.0)†	-7.1 (-14.3 to -1.2)*‡	0.046
	35	-2.2 (-5.2 to 2.4)	-2.9 (-3.7 to 2.0)*	-4.6 (-5.1 to -1.3)*	0.169
	52	-1.2 (-2.6 to 3.8)	-3.8 (-5.0 to 1.7)	-2.9 (-4.1 to 2.3)	0.451
P-value by time[b]		0.020	0.089	0.001	
HOMA-IR	6	+ 0.4 (-0.3 to 3.0)	-0.3 (-1.6 to 1.5)†	-0.1 (-2.8 to 0.4)§	0.006
	12	-0.8 (-2.7 to -0.7)*	-0.2 (-1.7 to 1.4)	-1.6 (-2.3 to -1.2)*	0.089
	35	-0.8 (-2.9 to -0.4)*	-0.3 (-2.2 to 0.9)	-0.9 (-2.1 to -0.6)*	0.234
	52	-0.9 (-2.0 to -0.4)*	-0.8 (-1.5 to -0.3)*	-1.1 (-3.4 to -0.8)*	0.170
P-value by time[b]		0.005	0.027	0.019	
TC, mg/dl	6	+ 0.5 (-2.0 to 1.6)	-3.5 (-4.9 to -1.7)*	+ 1.8 (-8.0 to 6.8)	0.168
	12	+ 3.6 (1.3 to 9.3)*	+ 1.2 (-2.5 to 6.4)†	-4.7 (-9.0 to 1.8)‡	0.002
	35	+ 0.9 (0.2 to 6.0)	+ 0.2 (-3.4 to 1.4)	-1.7 (-2.4 to 1.5)	0.121
	52	+ 11.3 (5.5 to 26.6)*	+ 14.4 (3.2 to 25.2)*	+ 19.6 (8.8 to 30.0)*	0.317

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
P-value by time[b]		0.037	0.045	0.002	
TG, mg/dl	6	+ 1.7 (-2.4 to 4.2)	-12.7 (-18.1 to 5.0)	-11.7 (-21.9 to 2.1)	0.234
	12	+ 13.5 (-3.6 to 18.5)	-18.1 (-16.6 to -2.8)*†	-14.9 (-23.8 to -5.4)*‡	0.001
	35	-0.4 (-5.8 to 4.2)	-27.0 (-25.2 to -9.8)*†	-14.9 (-25.0 to -7.4)*	0.015
	52	-32.5 (-57.7 to -6.5)*	-24.3 (-21.1 to − 5.3)*	-31.8 (-59.5 to -8.3)*	0.170
P-value by time[b]		0.025	0.001	0.001	

Table 2
Effect of diet programs on cardiometabolic parameters (Count)

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
HDL-C, mg/dl	6	+ 2.1 (-0.6 to 6.1)	+ 0.1 (-1.9 to 2.6)	+ 1.0 (-2.2 to 2.6)	0.234
	12	-0.7 (-1.9 to 3.5)	-1.1 (-4.0 to 0.9)	+ 1.4 (-1.9 to 4.0)	0.170
	35	+ 2.8 (-6.4 to 0.5)	+ 4.9 (1.9 to 6.8)*	+ 3.4 (0.4 to 5.8)*	0.717
	52	+ 4.6 (-7.4 to -0.5)*	+ 5.1 (1.7 to 7.6)*	+ 5.2 (2.1 to 8.1)*	0.776
P-value by time[b]		0.027	0.001	0.001	
LDL-C, mg/dl	6	+ 0.5 (-2.7 to 4.8)	+ 3.3 (0.9 to 6.7)*	+ 0.5 (-3.0 to 10.8)	0.644
	12	+ 2.4 (-7.1 to 8.8)	+ 2.1 (-2.9 to 5.7)[†]	-2.6 (-4.8 to 1.0)[‡]	0.027
	35	+ 8.8 (2.9 to 13.2)*	+ 13.0 (6.9 to 21.4)*	+ 10.4 (7.5 to 24.6)*	0.204
	52	-4.2 (-15.5 to 6.8)	+ 0.3 (-2.2 to 3.9)	+ 1.4 (-4.2 to 13.0)	0.538
P-value by time[b]		0.049	0.001	0.035	
Ratio of	6	+ 0.12 (0.08 to 0.69)*	-0.01 (-0.31 to 0.18)	+ 0.15 (-0.15 to 0.51)	0.215
TC to HDL-C	12	-0.05 (-0.42 to 0.29)	+ 0.16 (-0.08 to 0.44)	-0.07 (-0.38 to 0.18)	0.381
	35	+ 0.01 (-0.40 to 0.42)	+ 0.09 (-0.32 to 0.50)	+ 0.03 (-0.48 to 0.41)	0.621
	52	+ 0.05 (-0.33 to 0.51)	+ 0.18 (-0.38 to 0.31)	+ 0.11 (-0.49 to 0.62)	0.478
P-value by time[b]		0.034	0.112	0.068	

Data of cardiometabolic parameters are mean change (95% CI). serum beta hydroxybutyrate (βHB) and data of metabolic hormone levels are mean ± SEM. [a]P-values are for time effects and time x group interactions (i.e., BLC, A healthy balanced low caloric diet; White-AKD, yolk-free ketogenic diet with egg white supplementation; Yolk-AKD) for all subjects analyzed by repeated measures ANOVA (p-value < 0.05). [b]Within a row, values with different superscript letters are significantly different using Bonferroni adjusted (p-value < 0.05). *Data were significant differences from baseline. Significant difference between diet groups: [†]BLC and White-AKD; [‡]BLC and Yolk-AKD; [§]White-AKD and Yolk-AKD. BW, body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-B, HOMA of b cell function; βHB, beta hydroxybutyrate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol; LDL-C, low-density lipoprotein cholesterol.

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
AST, U/L	12	-4.0 (-4.4 to 3.5)	+ 2.9 (-2.9 to 3.4)†	-7.2 (-10.6 to -0.1)*‡	0.049
	35	-7.9 (-8.7 to -0.3)*	-1.3 (-3.1 to 1.1)	-4.1 (-7.3 to -0.3)*	0.783
	52	-4.9 (-5.3 to 4.0)	-2.2 (-5.8 to 1.5)	-3.3 (-6.9 to -0.2)*	0.569
P-value by time[b]		0.026	0.231	0.002	
ALT, U/L	12	+ 3.8 (-0.9 to 6.6)	+ 1.4 (-4.8 to 5.3)	-7.6 (-9.9 to 1.8)	0.059
	35	-4.3 (-8.6 to 4.3)	-7.2 (-8.5 to 3.8)	-7.2 (-12.5 to -1.5)*	0.192
	52	-1.0 (-2.7 to 7.7)	-7.7 (-9.0 to 2.2)	-5.4 (-9.7 to -0.9)*	0.306
P-value by time[b]		0.349	0.212	0.011	
Serum βHB,	0	0.13 ± 0.03	0.15 ± 0.21	0.16 ± 0.03	0.869
(mmol/L)	6	0.10 ± 0.03	0.20 ± 0.11*†	0.19 ± 0.01*‡	0.007
	12	0.12 ± 0.04	0.26 ± 0.05*†	0.22 ± 0.04*‡	0.013
	35	0.12 ± 0.03	0.17 ± 0.03	0.21 ± 0.03*‡§	0.011
	52	0.13 ± 0.02	0.16 ± 0.01	0.18 ± 0.01‡	0.022
P-value by time[b]		0.596	0.008	0.001	
Metabolic	12	-55 (-69 to -33)*	-65 (-89 to -45)*†	-79 (-101 to 60)*‡	0.004
syndrome, %	35	-62 (-98 to -45)*	-69 (-71 to 40)*†	-64 (-34 to 76)*	0.032
	52	-80 (-105 to -67)*	-92 (-125 to -57)*†	-75 (-95 to -45)*§	0.048

Data of cardiometabolic parameters are mean change (95% CI). serum beta hydroxybutyrate (βHB) and data of metabolic hormone levels are mean ± SEM. [a]P-values are for time effects and time x group interactions (i.e., BLC, A healthy balanced low caloric diet; White-AKD, yolk-free ketogenic diet with egg white supplementation; Yolk-AKD) for all subjects analyzed by repeated measures ANOVA (p-value < 0.05). [b]Within a row, values with different superscript letters are significantly different using Bonferroni adjusted (p-value < 0.05). *Data were significant differences from baseline. Significant difference between diet groups: †BLC and White-AKD; ‡BLC and Yolk-AKD; §White-AKD and Yolk-AKD. BW, body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-B, HOMA of b cell function; βHB, beta hydroxybutyrate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol; LDL-C, low-density lipoprotein cholesterol.

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
P-value by time[b]		0.001	0.001	0.044	

Data of cardiometabolic parameters are mean change (95% CI). serum beta hydroxybutyrate (βHB) and data of metabolic hormone levels are mean ± SEM. [a]P-values are for time effects and time x group interactions (i.e., BLC, A healthy balanced low caloric diet; White-AKD, yolk-free ketogenic diet with egg white supplementation; Yolk-AKD) for all subjects analyzed by repeated measures ANOVA (p-value < 0.05). [b]Within a row, values with different superscript letters are significantly different using Bonferroni adjusted (p-value < 0.05). *Data were significant differences from baseline. Significant difference between diet groups: [†]BLC and White-AKD; [‡]BLC and Yolk-AKD; [§]White-AKD and Yolk-AKD. BW, body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-B, HOMA of b cell function; βHB, beta hydroxybutyrate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein–cholesterol; LDL-C, low-density lipoprotein cholesterol.

Relative to BLC, AKD groups demonstrated modest and sustained reductions in BW, WC, and BP at week 35 (Fig. 2A-B, 2E-F. Table 2). Overall, BW changes at 52 weeks (1 year) were + 0.8 kg (95% CI, -0.7 to -1.3.kg) for BLC, -2.0 kg (95% CI, -2.6 to -0.9.kg) for White-AKD, and − 4.0 kg (95% CI, -5.4 to -1.6.kg) for Yolk-AKD. This suggests superior adherence to both AKD interventions over the short-to-long terms as compared with the conventional BLC. However, there was no significant difference in these anthropometries among all groups at week 52.

Secondary outcomes

The AKD exerted a favorable impact upon glucose tolerance and metabolic outcomes.

The time to reach maximum glucose concentration (Tmax) during GTT was 60 minutes for the BLC (black line), White-AKD (blue line), and Yolk-AKD (red line) individuals (Fig. 3A-B). During the 12-week intervention, participants in the AKD groups showed enhanced glucose tolerance compared to the BLC groups, as evidenced by decreased in Tmax at 60–90 minutes and lower circulating glucose levels as well as reduced AUC for glucose and insulin responses (Fig. 3B-D). Specifically, the Yolk-AKD group exhibited 0.4X reduction in AUC compared to the BLC group ($p < 0.01$), while the White-AKD group demonstrated a 1.2X decrease in the AUC compared to the BLC group ($p < 0.01$) (Fig. 3B). At 52 weeks, Tmax was 60 minutes for the Yolk-AKD group and 90 minutes for the White-AKD and BLC groups (Fig. 3E). The Yolk-AKD group exhibited remarkable reductions in the AUC differences of insulin response compared to the other groups, suggesting enhanced insulin responsiveness in the long run (Fig. 3G-H).

Effect of Asian KD on metabolic outcomes

The KD impacts not only upon carbohydrate intake but also upon individual protein and fat intake, thus potentially affecting circulating glucose and lipid homeostasis. As compared with the BLC, White-AKD, and Yolk-AKD groups displayed an expected marked decrease in FBS beginning at 6 weeks after the

intervention ($P < 0.05$). As shown in Table 2, FBS, insulin, and HOMA-IR in The AKD groups were either significantly or modestly lower than those in the BLC group, consistent with the results obtained during GTT (Fig. 3A-H). These improvements were observed from week 6 and continued until 1 year after the intervention. (Table 2).

Significant changes were observed in the lipid panel (Table 2), indicating improvements in lipid metabolism after AKD intervention. The lipid panel showed a notable decrease in triglyceride levels in the AKD groups, while total cholesterol, HDL cholesterol, and LDL cholesterol remained relatively unchanged (Supplementary Fig. 2). Additionally, there was a trend of decreased levels of AST and ALT, indicating potential liver function improvement. Fasting blood βHB concentrations averaged 0.26 ± 0.05 mmol/L for the White-AKD group and 0.22 ± 0.04 mmol/L for the Yolk-AKD group throughout the twelve-week KD condition. A subset of participants met the nutritional ketosis threshold of βHB > 0.5 mmol/L (11%), whereas others met borderline criteria (4%) or remained below this level (85%).

At the beginning of the study, all participants had MetS (100%). The AKD groups exhibited a significant decrease in the prevalence of Mets compared to the BLC group at both the 12-week and 52-week follow-up assessments (Table 2). After 12 weeks, reductions of 55% (BLC), 65% (White-AKD), and 79% (Yolk-AKD) were observed. Similarly, after 52 weeks, reductions of 25% (BLC) and 27% (White-AKD), along with a modest increase of 4% (Yolk-AKD), were noted. Notably, the reduction of MetS was significantly greater in the White-AKD group compared to both the BLC and Yolk-AKD groups ($P < 0.05$) (Table 2).

Table 3 presents the changes in metabolic hormones in response to the BLC and AKD diets. Both the BLC and AKD diets results in significant reductions in plasma levels of C-peptide, insulin, HOMA-IR, leptin, IL-6, MCP-1 and PYY ($P < 0.05$). Notably, there were slightly greater reductions in plasma IL-6, insulin, leptin and PYY in the Yolk-AKD group compared to the other two groups. The Yolk-AKD group also showed a significant decreases in IL6 levels between baseline and week 35 ($P < 0.05$).

Table 3
Effect of diet programs on metabolic hormone levels

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
C-Peptide	12	1.8 ± 0.10	1.8 ± 0.10	1.9 ± 0.09	0.556
(ng/ml)	35	1.3 ± 0.08*	1.4 ± 0.08*	1.4 ± 0.07*	0.857
	52	1.4 ± 0.06*	1.5 ± 0.06*	1.4 ± 0.05*	0.707
P-value by time[b]		< 0.001	< 0.001	< 0.001	
GIP	12	0.07 ± 0.01	0.06 ± 0.01	0.07 ± 0.01	0.720
(ng/ml)	35	0.08 ± 0.01	0.06 ± 0.01	0.07 ± 0.01	0.714
	52	0.09 ± 0.01*	0.08 ± 0.01*	0.08 ± 0.00	0.770
P-value by time[b]		0.045	0.032	0.379	
IL-6	12	25.5 ± 9.54	26.0 ± 8.77	39.8 ± 8.45	0.743
(pg/ml)	35	24.2 ± 6.62	14.4 ± 6.09	29.8 ± 5.87	0.701
	52	30.2 ± 7.44	30.7 ± 6.84	22.4 ± 6.59*	0.612
P-value by time[b]		0.483	0.096	0.013	
Leptin	12	20.7 ± 2.16	16.8 ± 1.99	18.5 ± 1.92	0.749
(ng/ml)	35	16.0 ± 1.60*	12.1 ± 1.47*	12.6 ± 1.42*	0.249
	52	16.4 ± 1.34*	15.0 ± 1.23	15.3 ± 1.19	0.968
P-value by time[b]		< 0.001	< 0.001	< 0.001	< 0.001
MCP-1	12	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.139
(ng/ml)	35	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.286
	52	0.07 ± 0.01*	0.07 ± 0.01*	0.07 ± 0.01*	0.391
P-value by time[b]		< 0.001	< 0.001	< 0.001	< 0.001

Data of cardiometabolic parameters are mean ± SEM. [a]P-values are for time effects and time x group interactions (i.e., BLC, A healthy balanced low caloric diet; White-AKD, yolk-free ketogenic diet with egg white supplementation; Yolk-AKD) for all subjects analyzed by repeated measures ANOVA (p-value < 0.05). [b]Within a row, values with different superscript letters are significantly different using Bonferroni adjusted (p-value < 0.05). *Data were significant differences from baseline. Significant difference between diet groups: [†]BLC and White-AKD; [‡]BLC and Yolk-AKD; [§]White-AKD and Yolk-AKD. GIP, glucose-dependent insulinotropic polypeptide; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; PYY, peptide YY; TNF alpha, tumor necrosis factor alpha.

Variables	Time (weeks)	BLC (n = 22)	White-AKD (n = 26)	Yolk-AKD (n = 27)	P-value[a]
PYY	12	73.1 ± 15.01	59.5 ± 13.81	63.3 ± 13.31	0.580
(pg/ml)	35	62.1 ± 11.50	56.8 ± 10.58	51.4 ± 10.20	0.420
	52	34.7 ± 6.68*	36.6 ± 6.14	25.4 ± 5.92*	0.605
P-value by time[b]		< 0.001	< 0.001	< 0.001	
TNF alpha	12	3.9 ± 0.27	3.7 ± 0.24	3.6 ± 0.24	0.468
(pg/ml)	35	3.4 ± 0.22*	3.4 ± 0.20	3.5 ± 0.20	0.699
	52	3.9 ± 0.18	3.6 ± 0.16	3.5 ± 0.16	0.917
P-value by time[b]		< 0.001	0.459	0.986	

Data of cardiometabolic parameters are mean ± SEM. [a]P-values are for time effects and time x group interactions (i.e., BLC, A healthy balanced low caloric diet; White-AKD, yolk-free ketogenic diet with egg white supplementation; Yolk-AKD) for all subjects analyzed by repeated measures ANOVA (p-value < 0.05). [b]Within a row, values with different superscript letters are significantly different using Bonferroni adjusted (p-value < 0.05). *Data were significant differences from baseline. Significant difference between diet groups: [†]BLC and White-AKD; [‡]BLC and Yolk-AKD; [§]White-AKD and Yolk-AKD. GIP, glucose-dependent insulinotropic polypeptide; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; PYY, peptide YY; TNF alpha, tumor necrosis factor alpha.

DISCUSSION

In this randomized clinical trial, a dietary intervention focused on a healthy low-carbohydrate, balanced protein, and fat, utilizing locally available Asian foods, yielded significant improvements in anthropometric and metabolic outcomes. The intervention successfully maintained weight loss for up to 9 months and improved glucose-insulin homeostasis for at least 12 months, despite participants consuming an average carbohydrate intake of 12–14% and a relatively higher fat intake of 45–59% (Supplementary Table 1). The AKD groups demonstrated better insulin responsiveness, although the mean reduction in HbA1c between groups was modest. Furthermore, at 12-month follow up, the AKD group exhibited a comparatively lower increase in BW and WC than the BLC group, indicating superior adherence to the AKD intervention. This findings align with meta-analyses [4, 22] which underscore the potential of the AKD intervention in ameliorating MetS and improving body weight, glucose tolerance, and lipid profile, surpassing other dietary approaches [5, 9]. This study also identified changes in macronutrient proportions within the AKD groups, but no significant difference in energy intake were observed. These finding suggest that beneficial outcomes are associated with modification in macronutrient composition rather than a reduction in energy intake. However, due to the study design, the effects of reducing carbohydrate intake independently of caloric restriction and weight loss on metabolic outcomes could not be determined.

In contrast to prior work [4, 5] on LCD interventions and HbA1c, a majority of participants in the current study (81%) was in an unaware prediabetes categories [HbA1c < 6.5% (48 mmol/mol)], Therefore, the marked improvement in HbA1c in all groups was not clearly observed. However, in individuals with diabetes, a LCD intervention led to improvements BW, resulting in improved glycemia and HbA1c [5]. Recently studies have shown that very-low-carbohydrate diet was associated with reductions of visceral fat and liver fat [23, 24]. Notably, the average difference in weight loss between low-carb and low-fat diets at 3–9 months from this trial (-4.9 to -3.9 kg; Table 2) were substantially better than other LCD trials at 3–6 months from the meta-analysis (-1.7 kg; 95% CI -3.85 to 0.92; 13 studies) [4]. The BW changes were maximized at 35 weeks in the AKD groups but not the BLC groups ($P < 0.05$). In line with a prior work, The AKD groups also showed lower fasting blood sugar, reduced glucose levels during glucose tolerance testing, and a shortened time to reach the maximum glucose level, indicating positive effects on glucose control [5, 25]. Additionally, Yolk-AKD group exhibited lower AUC differences in insulin response compared to the other two groups. Previous studies comparing the KD to the low-fat and energy-controlled diets have reported similar outcomes across different age groups, including children, teenagers, and adults [5, 26–28]. However, due to the more detailed control required in the BLC group and its slower rate of weight loss compared to the AKD groups, it may be a challenge for participants in this group to control their food intake. These results suggest that adherence to the AKD interventions led to superior short-to-long-term weight loss and glucose-insulin homeostasis outcomes compared to the conventional BLC.

The term “VLCD or “KD” generally refers to a diet that is very low in carbohydrates, modest in protein, and high in fat, including saturated fat. However, our preliminary data and several of reports [4, 29, 30] showed that this variant of KD was associated with increased LDL-C compared with individuals on a low-fat diet, suggesting a possible long-term risk for cardiovascular disease. A previous study by Dorans et al [5] used a healthy LCD with low in saturated fats and foods high in unsaturated fats and oils which resulted in stable lipoprotein profiles and reduced 10-year atherosclerotic risk score. Therefore, our study adopted this food pattern and modified into our Asian eating pattern. At 35 week, we noted an increase in LDL-C and HDL-C in all groups, but no changes were seen in the ratio of TC to LDL-C. This difference was no longer significant at 12 months. Recently research suggested that the association of LDL-C to cardiovascular risk varies based on particle size, and LCD and KD tend to increase LDL-C particle size [31, 32], indicating that the increase in LDL-C alone may not be accompanied by an increased cardiovascular risk [25]. In addition, no participants experienced severe ketosis symptoms, a condition that can be harmful when ketone production is unregulated. This suggests that weight loss can be effectively achieved while nutritional ketosis were unnecessary, and ketosis was unlikely to account for the findings [33].

Several studies have found that the KD could reduce TG and increase HDL-C [4, 5, 25]. Our study showed similar results, with a greater decrease in TG and increase in HDL-C in the AKD groups than the BLC group. Interestingly, the Yolk-AKD group, which consumed more than 3 eggs/day, showed a tendency for increased HDL-C without affecting TC levels. This is consistent with a previous study in adults who supplemented with 1 egg/ day for 12 weeks [34] and in school-age children who supplemented with 3

eggs/day for 35 weeks [35]. It implies that egg can be a part of healthy KD as long as the diet contains is low in saturated fat and follow a good overall dietary pattern in addition to egg intake [36].

The changes in metabolic hormone levels among the different groups were relatively similar, and no significant differences were observed between the groups. Leptin and PYY are relevant to satiety [33]. Leptin acts as a measure of energy reserves, guiding the regulation of energy homeostasis, neuroendocrine processes, and metabolism [37]. Some studies have found that macronutrient composition does not affect the secretion of appetite-related hormones, but changes in weight and body composition do impact the levels of these hormones [33, 38]. Both the AKD and BLC groups reduced leptin and PYY significantly. This study confirm previous studies [39] that after weight loss from KD decreased leptin and PYY levels in long-term following various KD regiments. While our study did not identify differences in change in self-reported appetite between the diet groups, we confirmed that AKD did reduce overall body weight more than a BLC. Notably, most dietary effects on peptide YY are explained by differences in the macronutrient content of the diet, not weight loss [33]. Furthermore, it has been found that each group exhibited improvements in hormones associated with inflammation. The study identified a decreasing trend in IL-6, MCP-1, and TNF-alpha, which are associated with inflammatory cytokines. A study of a scoping review of neurological and inflammatory outcomes in humans reported that KD reduces inflammatory loading [40].

This study has notable strengths. It comprehensively examines multiple metabolic outcomes, including body weight, waist circumference, glucose tolerance, lipid profile, metabolic hormone levels, and the prevalence of MetS. This comprehensive assessment enhances our understanding of the dietary intervention's effects. Another strength is the emphasis on utilizing locally available foods, allowing individuals to make informed choices with guidance from nutritional doctors and dietitians. The study's meticulous reporting of adherence and monitoring of dietary intake and macronutrient composition strengthen the validity of the findings. However, there are limitations to consider. The study focuses on a specific group with MetS, limiting generalizability. Further research with diverse populations is needed. Additionally, due to the inherent nature of the dietary interventions, blinding of participants was not possible, introducing potential bias. The study did not investigate certain aspects such as body composition and LDL-C particle size, which could provide additional insights.

CONCLUSION

This study presents compelling evidence regarding the efficacy of the AKD as we classified as VLC, balanced protein, and low in saturated fat, in ameliorating various metabolic outcomes in individuals with MetS. The AKD, which prioritizes a low-saturated fat diet while disregarding dietary cholesterol, demonstrates its effectiveness in improving atherogenic lipoproteins. Notably, the AKD leads to modest and sustained reductions in body weight and waist circumference, enhances glucose tolerance, improves lipid profile and liver function, and diminishes the prevalence of MetS. These findings underscore the potential of the AKD as a valuable dietary intervention for individuals with MetS who aspire to optimize

their metabolic well-being. However, further research is imperative to elucidate the long-term implications, underlying mechanisms, and viability of the AKD as a sustainable lifestyle intervention.

Abbreviations

T2DM	Type-2 diabetes
LFLC	Low-fat, low-calorie diets
LC	Low-carbohydrate diets
KD	Ketogenic diets
VLC	Very low carbohydrate diet
HF	High-fat diets
MetS	Metabolic syndrome
BLC	Balanced low-caloric diet
AKD	Asian ketogenic diet
White-AKD	Egg white Asian ketogenic diet
Yolk-AKD	Egg yolk Asian ketogenic diet
BMI	Body mass index
BW	Body weight
Ht	Height
INMU	The Institute of Nutrition, Mahidol University
DPAC	Department of Health, Thailand
WC	Waist circumference
BP	Blood pressure
FBS	Fasting blood sugar
HbA1c	Hemoglobin A1C
TC	Total cholesterol

TG	Triglyceride
HDL-C	HDL-cholesterol
LDL-C	LDL-cholesterol
βHB	Beta-hydroxybutyric acid
AST	Aspartate transaminase
ALT	Alanine aminotransferase
OGTT	Oral glucose tolerance test
HOMA-IR	Homeostatic model assessment for insulin resistance
GIP	Glucose-dependent insulinotropic polypeptide
IL-6	Interleukin-6
MCP-1	Monocyte chemoattractant protein-1
PYY	Peptide YY
TNF alpha	Tumor necrosis factor alpha
Thai-PAQ	Thai PA questionnaire
MET	Metabolic equivalent
SD	Standard deviation
AUC	Area under the curve
Tmax	Time to reach maximum glucose concentration

Declarations

Acknowledgments: The authors are grateful to the participants in this study. We also would like to acknowledge all support from the Siriraj Institute of Clinical Research to help this project successful. K.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors: Conceptualization, K.M.; methodology, K.M.; formal analysis, B.P., A.S.; investigation, B.P., T.P., S.S., T.M., S.O.; data curation, A.S.; writing—original draft preparation, B.P., K.M.; writing—review and

editing., B.P., K.M., K.S.; supervision, K.M., K.S.; project administration, S.P.; funding acquisition, K.M., S.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Mahidol University, grant number 10493.

Availability of data and materials

There are restrictions on the availability of these data because participants were informed in the consent form that their personal data will not be made publicly available.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Faculty of Medicine Siriraj Hospital, Mahidol University (COA: Si 286/2020). All participants provided written informed consent before beginning the study.

Consent for publication

All authors approved the final version of the manuscript for publication.

Competing interests

The authors declare no conflicts of interest.

References

1. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism*. 2022;133:155217. doi:10.1016/j.metabol.2022.155217
2. Mayurasakorn K, Hasanah N, Homma T, et al. Caloric restriction improves glucose homeostasis, yet increases cardiometabolic risk in caveolin-1-deficient mice. *Metabolism*. 2018;83:92-101. doi:https://doi.org/10.1016/j.metabol.2018.01.012
3. IDF diabetes atlas, South-East Asia region diabetes data. [Internet]. International Diabetes Federation. 2021. Available from: https://diabetesatlas.org/data/en/region/7/sea.html [cited 30 July, 2023]
4. Chawla S, Silva FT, Medeiros SA, et al. The effect of low-fat and low-carbohydrate diets on weight loss and lipid levels: a systematic review and meta-analysis. *Nutrients*. 2020;12(12):3774.
5. Dorans KS, Bazzano LA, Qi L, et al. Effects of a low-carbohydrate dietary intervention on hemoglobin A1c: a randomized clinical trial. *JAMA Netw Open*. 2022;5(10):e2238645. doi:10.1001/jamanetworkopen.2022.38645
6. Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391(10120):541-51. doi:10.1016/S0140-6736(17)33102-1

7. Rosenfeld RM, Kelly JH, Agarwal M, et al. Dietary interventions to treat type 2 diabetes in adults with a goal of remission: an expert consensus statement from the American College of Lifestyle Medicine. *Am J Lifestyle Med*. 2022;16(3):342-62. doi:10.1177/15598276221087624
8. Gardner CD, Trepanowski JF, Del Gobbo LC, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA*. 2018;319(7):667-79. doi:10.1001/jama.2018.0245
9. Westman EC, Yancy WSJ. Using a low-carbohydrate diet to treat obesity and type 2 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. 2020;27(5):255-60. doi:10.1097/med.0000000000000565
10. Ludwig DS. The ketogenic diet: evidence for optimism but high-quality research needed. *J Nutr*. 2020;150(6):1354-9. doi:10.1093/jn/nxz308
11. Naude CE, Brand A, Schoonees A, et al. Low-carbohydrate versus balanced-carbohydrate diets for reducing weight and cardiovascular risk. *Cochrane Database Syst Rev*. 2022;1(1):Cd013334. doi:10.1002/14651858.CD013334.pub2
12. Stanton MV, Robinson JL, Kirkpatrick SM, et al. DIETFITS study (diet intervention examining the factors interacting with treatment success) - study design and methods. *Contemp Clin Trials*. 2017;53:151-61. doi:10.1016/j.cct.2016.12.021
13. Riddle MC, Cefalu WT, Evans PH, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. *Diabetes Care*. 2021;44(10):2438-44. doi:10.2337/dci21-0034
14. Stentz FB, Brewer A, Wan J, et al. Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet: randomized control trial. *BMJ Open Diabetes Res Care*. 2016;4(1):e000258. doi:10.1136/bmjdrc-2016-000258
15. Cucuzzella M, Riley K, Isaacs D. Adapting medication for type 2 diabetes to a low carbohydrate diet. *Front Nutr*. 2021;8:688540. doi:10.3389/fnut.2021.688540
16. Grech A, Sui Z, Rangan A, et al. Macronutrient (im)balance drives energy intake in an obesogenic food environment: an ecological analysis. *Obesity (Silver Spring)*. 2022;30(11):2156-66. doi:https://doi.org/10.1002/oby.23578
17. Sirichakwal PP, Sranacharoenpong K, Tontisirin K. Food based dietary guidelines (FBDGs) development and promotion in Thailand. *Asia Pac J Clin Nutr*. 2011;20(3):477-83.
18. Chotwanvirat P, Thewjitcharoen Y, Parksook W, et al. Development of new lemon-lime flavored beverage for OGTT: acceptability and reproducibility. *J Med Assoc Thai*. 2016;99(5):497-504.
19. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-9. doi:10.1007/bf00280883
20. Human metabolic hormone magnetic bead panel assay (HMHMAG-34K) overview [Internet]. Milliplex. 2021. Available from: https://www.merckmillipore.com/TH/en/product/MILLIPLEX-MAP-Human-Metabolic-Hormone-Magnetic-Bead-Panel-Metabolism-Multiplex-Assay,MM_NF-HMHEMAG-34K?ReferrerURL=https%3A%2F%2Fwww.google.com%2F&bd=1 [cited 26 November, 2022

21. Chirdkiatisak M, Sranacharoenpong K, Churak P, et al. Thai diabetes prevention education program: development and validation of the Thai physical activity questionnaire for at-risk people. *J Public Health*. 2019;27(5):659-67. doi:10.1007/s10389-018-0989-2
22. Mansoor N, Vinknes KJ, Veierød MB, et al. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2016;115(3):466-79. doi:10.1017/s0007114515004699
23. Cunha GM, Correa de Mello LL, Hasenstab KA, et al. MRI estimated changes in visceral adipose tissue and liver fat fraction in patients with obesity during a very low-calorie-ketogenic diet compared to a standard low-calorie diet. *Clin Radiol*. 2020;75(7):526-32. doi:10.1016/j.crad.2020.02.014
24. Kong Z, Sun S, Shi Q, et al. Short-term ketogenic diet improves abdominal obesity in overweight/obese Chinese young females. *Front Physiol*. 2020;11:856. doi:10.3389/fphys.2020.00856
25. Saslow LR, Daubenmier JJ, Moskowitz JT, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. *Nutr Diabetes*. 2017;7(12):304. doi:10.1038/s41387-017-0006-9
26. Partsalaki I, Karvela A, Spiliotis BE. Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents. *J Pediatr Endocrinol Metab*. 2012;25(7-8):697-704. doi:doi:10.1515/jpem-2012-0131
27. Al Aamri KS, Alrawahi AH, Al Busaidi N, et al. The effect of low-carbohydrate ketogenic diet in the management of obesity compared with low caloric, low-fat diet. *Clin Nutr ESPEN*. 2022;49:522-8. doi:https://doi.org/10.1016/j.clnesp.2022.02.110
28. Brehm BJ, Seeley RJ, Daniels SR, et al. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab*. 2003;88(4):1617-23. doi:10.1210/jc.2002-021480
29. Burén J, Ericsson M, Damasceno NRT, et al. A ketogenic low-carbohydrate high-fat diet increases LDL cholesterol in healthy, young, normal-weight women: a randomized controlled feeding trial. *Nutrients*. 2021;13(3):814. doi:10.3390/nu13030814
30. Homma T, Homma M, Huang Y, et al. Combined salt and caloric restrictions: potential adverse outcomes. *J Am Heart Assoc*. 2017;6(10). doi:10.1161/jaha.116.005374
31. Gerber PA, Berneis K. Regulation of low-density lipoprotein subfractions by carbohydrates. *Curr Opin Clin Nutr Metab Care*. 2012;15(4):381-5. doi:10.1097/MCO.0b013e3283545a6d
32. Salas Noain J, Minupuri A, Kulkarni A, et al. Significant impact of the ketogenic diet on low-density lipoprotein cholesterol levels. *Cureus*. 2020;12(7):e9418. doi:10.7759/cureus.9418
33. Hu T, Yao L, Reynolds K, et al. The effects of a low-carbohydrate diet on appetite: a randomized controlled trial. *Nutr Metab Cardiovasc Dis*. 2016;26(6):476-88. doi:10.1016/j.numecd.2015.11.011
34. Mayurasakorn K, Srisura W, Sitphahul P, et al. High-density lipoprotein cholesterol changes after continuous egg consumption in healthy adults. *J Med Assoc Thai*. 2008;91(3):400-7.

35. Suta S, Surawit A, Mongkolsucharitkul P, et al. Prolonged egg supplement advances growing child's growth and gut microbiota. *Nutrients*. 2023;15(5):1143.
36. Czekajło-Kozłowska A, Różańska D, Zatońska K, et al. Association between egg consumption and elevated fasting glucose prevalence in relation to dietary patterns in selected group of Polish adults. *Nutr J*. 2019;18(1):90. doi:10.1186/s12937-019-0516-5
37. Mendoza-Herrera K, Florio AA, Moore M, et al. The leptin system and siet: a mini review of the current evidence. *Front Endocrinol (Lausanne)*. 2021;12:749050. doi:10.3389/fendo.2021.749050
38. De Amicis R, Leone A, Lessa C, et al. Long-term effects of a classic ketogenic diet on ghrelin and leptin concentration: a12-month prospective study in a cohort of Italian children and adults with GLUT1-deficiency syndrome and drug resistant epilepsy. *Nutrients*. 2019;11(8). doi:10.3390/nu11081716
39. Lambrechts DA, Brandt-Wouters E, Verschuure P, et al. A prospective study on changes in blood levels of cholecystokinin-8 and leptin in patients with refractory epilepsy treated with the ketogenic diet. *Epilepsy Res*. 2016;127:87-92. doi:10.1016/j.eplepsyres.2016.08.014
40. Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin*. 2007;45(2):27-37. doi:10.1097/AIA.0b013e318034194e

Figures

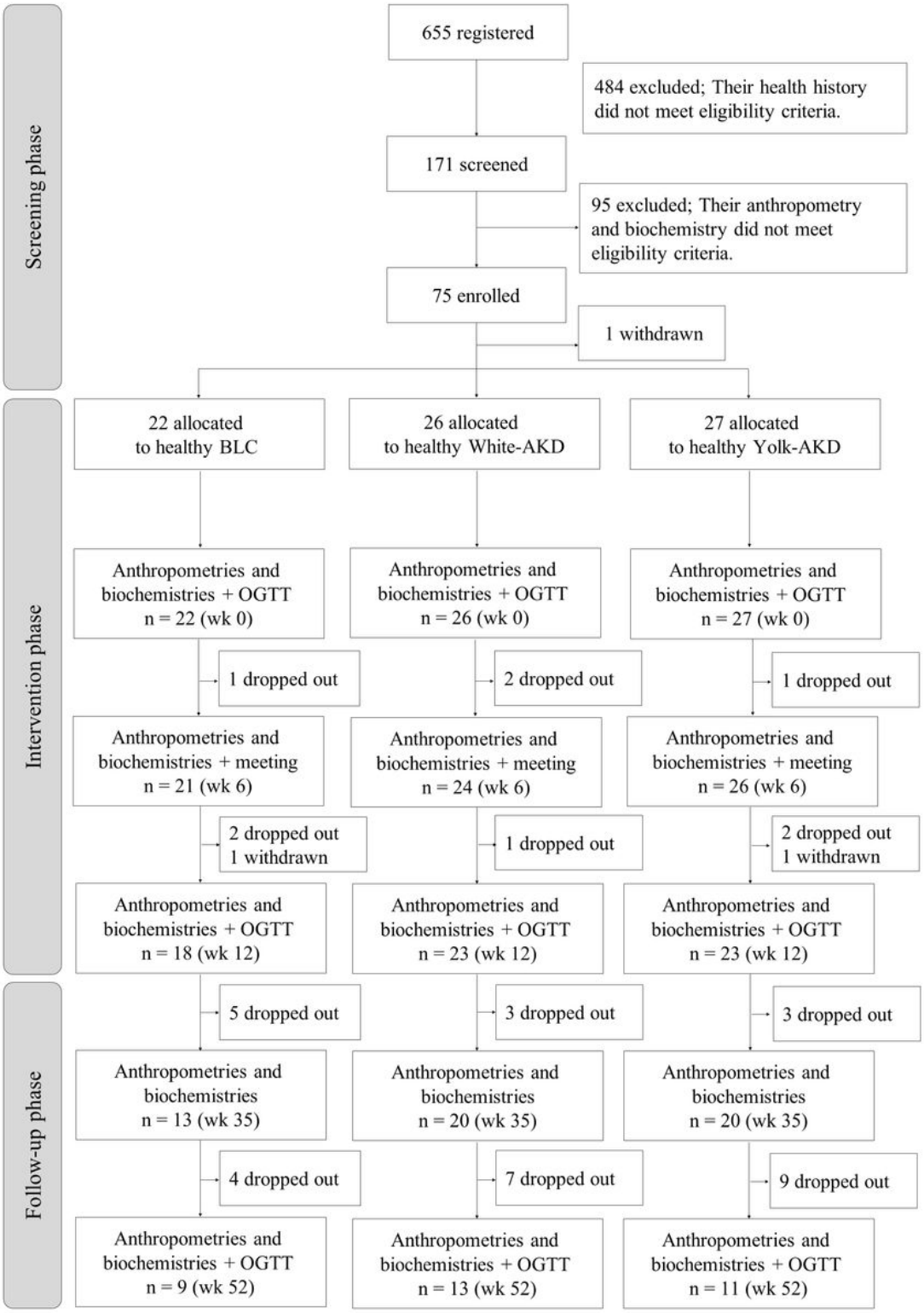

Figure 1

The flow of participants throughout the trial

OGTT, oral glucose tolerance test; BLC, a healthy balanced low-caloric diet; White-AKD, a healthy egg white Asian ketogenic diet; Yolk-AKD, a healthy egg yolk Asian ketogenic diet; wk, week.

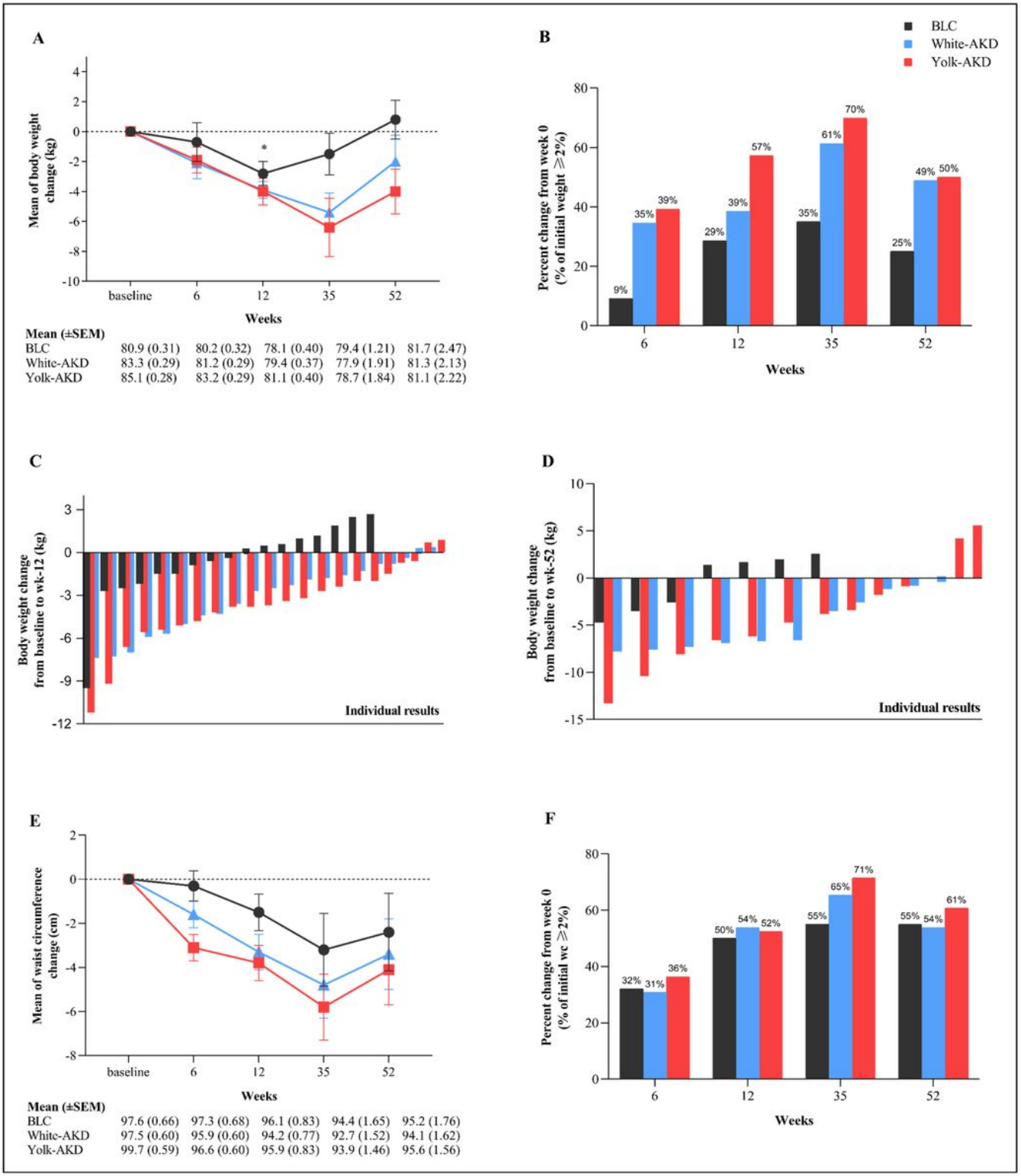

Figure 2

Changes in body weight (BW) and waist circumference (WC) over 1 year across different diet groups.

Panel A and B present the mean changes in BW and a bar chart of the percentages of participants in each trial group who achieved a total weight loss at least 2% of the initial BW from baseline to the end of the trial (week 52). Panel C and D present the mean changes in BW of observed data from the in-trial period,

involving individuals who underwent randomization and completed a 52-week assessment. Panel E and F present the mean changes in WC and a bar chart of the percentages of participants in each trial group who achieved a total WC loss at least 2% of the initial WC from baseline to the end of the trial (week 52). All the means were estimated from a repeated measures ANOVA model and significantly different using Bonferroni adjusted with time, group, sex, age, and a time x group interactions as explanatory variables in the intention-to-treat population. Asterisks indicate a significant difference (*$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$) between the groups. BLC, a healthy balanced low-caloric diet; White-AKD, a healthy egg white Asian ketogenic diet; Yolk-AKD, a healthy egg yolk Asian ketogenic diet.

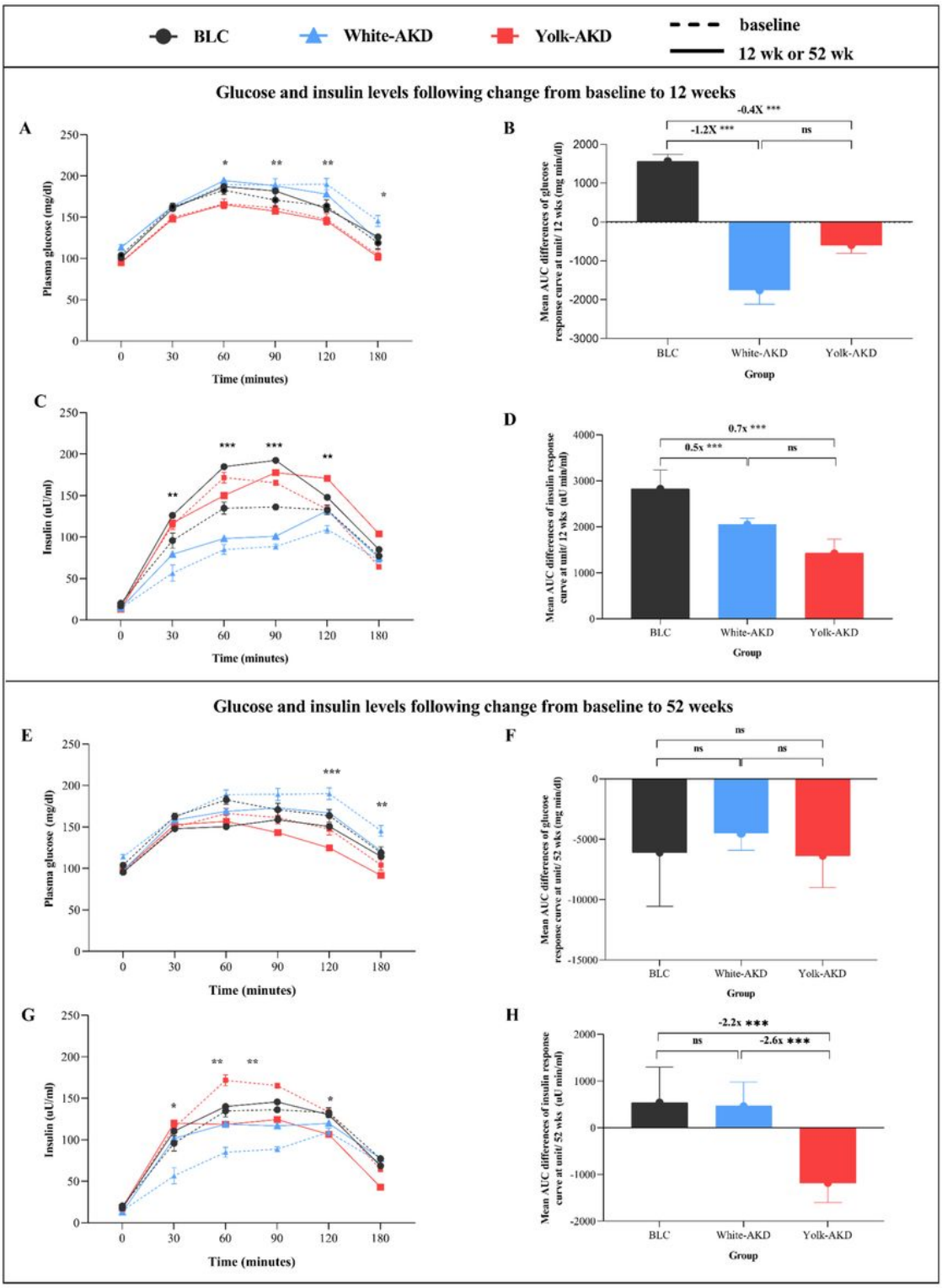

Figure 3

Changes from baseline in glucose and insulin levels over 1 year across different diet groups.

Glucose and insulin levels were monitored at 12- and 52-–weeks in a healthy balanced low-caloric diet (BLC), a healthy egg white Asian ketogenic diet (White-AKD), and a healthy egg yolk Asian ketogenic diet (Yolk-AKD) using a linear mixed model, followed by pairwise comparisons of marginal linear predictions.

Comparisons were made between Yolk-AKD and BLC, White-AKD and BLC, as well as Yolk-AKD and White-AKD. Significance levels were indicated as follows: *p < 0.05, **p < 0.01, ***p < 0.001 in the time course of blood glucose (A) and insulin (C) at 12-week, and the time course of blood glucose (E) and insulin (G) at 52-week, adjusted for multiple comparisons. The area under the curve (AUC) for the 0-180 min was calculated and compared among the three groups using one-way ANOVA followed by Bonferroni's post-test. Differences in AUC were evaluated for glucose (B) and insulin (D) at unit/12 weeks, as well as for glucose (F) and insulin (H) at unit/52 weeks.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GraphicalabstractNutrJBMC.tif
- SupplementNutrJBMC.docx