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Impact of a 12-week personalized dietary intervention on vascular function and cardiovascular risk factors

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Abstract

Aims: Individuals with liver insulin-resistant (LIR) or muscle insulin-resistant (MIR) phenotypes may respond differently to dietary interventions. Given the interaction between insulin resistance and cardiovascular risk, this sub-analysis of the PERSON study examined whether a personalized diet according to MIR or LIR phenotypes improves vascular function and cardiovascular disease risk factors.

Materials and Methods: We randomized 119 participants to a 12-week low-fat, high-protein, high-fibre diet (LFHP; may be optimal for LIR) or Mediterranean diet (high in monounsaturated fat, HMUFA; may be optimal for MIR). Randomization linked the insulin-resistant (IR) phenotype to the proposed optimal diet, leading to PhenoDiet A (MIR-HMUFA and LIR-LFHP) and PhenoDiet B (MIR-LFHP and LIR-HMUFA). Before and after the intervention, vascular function (carotid artery reactivity) and cardiovascular risk factors (blood pressure, total cholesterol, HDL-cholesterol and Framingham risk score) were examined. A 7-point oral glucose tolerance test was performed to determine insulin resistance (Matsuda index and HOMA-IR) and disposition index.

Results: Following drop-out ($n = 18$), 101 participants finished the intervention (54 women, 61 ± 7 years, 27.6 [26.4;30.0] kg/m^2), with $n = 80$ available for the primary outcome of vascular function. Overall, the dietary interventions significantly decreased blood pressure, total cholesterol, HDL-cholesterol and the Framingham risk score (all $p < 0.05$), while vascular function was not affected ($p = 0.485$). Insulin resistance ($p \leq 0.001$), but not disposition index ($p = 0.362$), was significantly improved after intervention. The Matsuda index ($p = 0.078$) tended to increase more

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and total cholesterol ($p = 0.052$) tended to decrease more in PhenoDiet group B than A, but other changes in outcome parameters were not significantly different between PhenoDiet groups. The LFHP diet resulted in more pronounced improvements in cholesterol, diastolic blood pressure (DBP) and insulin resistance compared with the HMUFA diet (all $p < 0.05$).

Conclusion: A 12-week diet improves metabolic and cardiovascular outcomes, but not vascular function in insulin-resistant adults with overweight or obesity. Whilst the LFHP diet resulted in greater improvements in cardiometabolic risk markers than the HMUFA diet, we found no significant differences between the PhenoDiet groups.

KEYWORDS
cardiovascular, diet, insulin resistance, nutrition

1 | INTRODUCTION

Presence of insulin resistance (IR) is strongly related to the development of type 2 diabetes (T2D), but also to cardiovascular disease (CVD).[1–3] For example, IR is characterized by hyperglycaemia, hyperinsulinaemia, lipotoxicity, oxidative stress and inflammation.[4,5] These metabolic aberrations inhibit the production of nitric oxide, increase endothelin-1 release and increase the expression of vascular adhesion molecules in the endothelium, which subsequently contribute to endothelial dysfunction and the development of atherosclerosis.[6] In addition, these impairments in vascular function may also worsen perturbations in glucose homeostasis, possibly by reducing blood flow and the delivery of insulin and glucose to peripheral tissues that play a key role in glucose homeostasis.[4,7]

Dietary interventions have shown promising results for improving IR,[8] and possibly also vascular function.[9,10] Interestingly, the success of a diet in improving body weight and/or glucose homeostasis seems related to the metabolic phenotype of an individual.[11] Post hoc analyses in large intervention studies show that parameters associated with glucose metabolism and IR can serve as valuable predictors of the outcome of a dietary intervention.[12–14] The tissue-specific IR phenotype links to the predominant pathophysiological location of IR: the muscle (MIR) or liver (LIR).[15,16] Studies show that LIR- or MIR phenotypes are associated with distinct lipidome,[17] metabolome,[18] and adipose tissue inflammatory transcriptome and systemic inflammatory profiles.[19,20] Accordingly, the IR phenotype may respond differently to distinct dietary interventions. Indeed, post-hoc analyses of the CORDIOPREV-DIAB trial have shown long-term adherence to a Mediterranean diet (high in monounsaturated fat, HMUFA) to be more beneficial for those with MIR to improve glucose homeostasis, whilst a low-fat, high-protein, high-fibre diet (LFHP) seems optimal in those with LIR.[15] In addition, both high-protein[21–23] and high-fibre diets,[24] as well as the Mediterranean diet,[25,26] have been shown to reduce liver fat content and inflammation,[21] which in turn may improve hepatic insulin sensitivity.[27,28] Thus, an LFHP diet may be optimal for individuals with LIR, while a HMUFA-type diet may be more beneficial for individuals with MIR.

We have recently demonstrated, for the first time in a prospective setting, that modulation of macronutrient content according to MIR and LIR within the context of dietary guidelines further improved insulin sensitivity and cardiometabolic health.[29,30] Individuals with the MIR phenotype showed a more pronounced cardiometabolic health improvement on a LFHP diet, while individuals with the LIR phenotype had the greatest cardiometabolic health benefit from a HMUFA diet.[29,30] Although these observations may conflict with previous observations,[15] this may be explained by differences in study population, diet composition and/or methodological aspects. At least, these data highlight both the potential and the complexity of precision nutrition.

Due to the close relationship between IR and vascular dysfunction,[4,7] optimizing the diet to improve glucose homeostasis may also translate into superior effects on cardiovascular risk factors as well. The aim of this study was to explore if personalization of a 12-week dietary intervention through linking the IR phenotype (i.e., MIR or LIR) to the type of diet (i.e., LFHP and HMUFA) would optimize effects on vascular function and CVD risk factors in individuals with IR. To our knowledge, this is the first study to examine whether personalization of diet (through linking IR phenotype to the type of diet) translates to optimal effects on vascular function in individuals with IR.

2 | METHODS

2.1 | Study population

This current study was executed within the framework of the PERSonalized glucose Optimization through Nutritional intervention (PERSON) study[29,30] and includes tissue-specific insulin resistant (MIR or LIR), weight stable (3 months ≤3 kg weight gain/loss) individuals (age 40–75), with a BMI between 25 and 40 kg/m^2. Main exclusion criteria were: pre-diagnosed diabetes types 1 and 2, glucose/lipid altering medications, uncontrolled hypertension, alcohol consumption >14 units/week, smoking and moderate-to-vigorous physical activity

(MVPA) >4 h/week. A table with all exclusion criteria can be found elsewhere in the design paper of the study.[29]

2.2 | Study design

As aforementioned, this research was part of the two-center PERSonalized glucose Optimization through Nutritional intervention (PERSON) study.[29,30] It involves two centers located in the Netherlands, Maastricht University Medical Center+ and Wageningen University & Research (WUR). The complete design and the CONSORT diagram, which were approved by the local Medical Ethical Committee (NL637680.068.17), are published elsewhere.[29] Following IR phenotyping, participants were randomly allocated to follow the proposed optimal Phenotype-based diet (PhenoDiet) group A (LFHP for LIR, HMUFA for MIR), or PhenoDiet group B (LFHP for MIR, HMUFA for LIR), as described previously.[29,30] We used center-specific minimization with randomization factors of 1.0 for the LIR/MIR phenotype and 0.8 for age and sex and a base probability of 0.7 by means of biased coin.[29] The PERSON study was registered at a clinical trial register (ClinicalTrials.gov, NCT03708419) and executed according to the Declaration of Helsinki.

The focus of the present sub-study is on vascular outcomes. Vascular measurements were performed at WUR ($n = 119$) only, thus in a subgroup of the total PERSON study population. Before and during week 12 of the intervention, vascular function, cardiovascular risk factors, IR and disposition index were assessed (Figure 1), as described in more detail below. Other results of the PERSON study have been recently published elsewhere.[30]

2.3 | Screening

During screening, glucose and insulin values measured during a 7-point OGTT (time points 0, 15, 30, 45, 60, 90 and 120) were used to calculate the muscle insulin sensitivity index (MISI) and hepatic insulin sensitivity index (HIRI). Calculations were based on Abdul-Ghani et al.[16] The modelling of MISI was optimized by O'Donovan et al.[31] HIRI and MISI have been validated against the gold standard hyperinsulinaemic-euglycaemic clamp.[16,31] The first blood sample ($t = 0$) was drawn fasted from an intravenous cannula (antecubital vein). The remaining samples were taken after ingestion of a 200-mL 75-g glucose solution (Novolab). Data from The Maastricht study,[32] from which a population with characteristics similar to the PERSON participants was selected, was used for MISI/HIRI tertile reference categories. Participants were classified as having MIR if their MISI was within the lowest tertile, and as LIR if their HIRI was within the highest tertile.[29] After inclusion of the first 163 participants of the PERSON study, LIR prevalence was found to be lower than expected when using the reference categories from The Maastricht Study. As a result, the median HIRI of the PERSON study was used as cutoff thereafter to classify individuals.

Education level, retirement status and alcohol consumption habits were assessed during screening with questionnaires. A food frequency questionnaire (FFQ, validated, 163-items) assessed habitual dietary intake.[33]

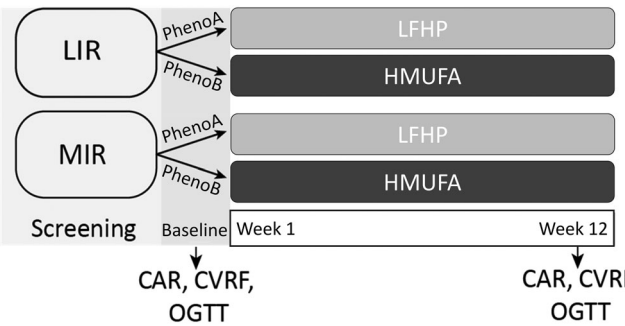

FIGURE 1 Study design. LIR, liver insulin resistance; MIR, muscle insulin resistance; LFHP, low-fat, high-protein diet; HMUFA, high-monounsaturated fatty acid diet; CAR, carotid artery reactivity; CVRF, cardiovascular risk factors; OGTT, oral glucose tolerance test. Light grey background indicates PhenoDiet group A, dark grey background indicates PhenoDiet group B.

2.4 | Diet intervention

During the 12-week intervention, measures were taken to attempt to maintain weight stability among the participants, in order to assess the effect of the diet rather than weight loss. Participants were instructed to maintain their habitual physical activity levels. The moderate-fat diet high in MUFA (HMUFA) reflected a targeted macronutrient composition of 38% of energy from fat (20% MUFA, 8% PUFA and 8% SFA), 48% of energy from carbohydrates (30% polysaccharides) and 14% of energy from protein. The dietary intervention 'low in fat, and high in protein' (LFHP) was composed of a similar amount of energy from carbohydrates as the HMUFA diet (i.e., 48%) and furthermore included 28% of energy from fat (10% MUFA, 8% PUFA and 8% SFA) and 24% of energy from protein (Table 1). A more detailed description of the diet, including the

TABLE 1 Macronutrient composition of the LFHP and HMUFA diets.

	LFHP	HMUFA
Fat (Energy %)	28	38
Monounsaturated	10	20
Polyunsaturated	8	8
Saturated	8	8
Protein (Energy %)	24	14
Carbohydrates (Energy %)	42	42
Fibre, g/MJ	>4	3

Note: Energy % of total energy intake.
Abbreviations: HMUFA, high-monounsaturated fats; LFHP, low-fat, high-protein. MJ, megajoule.

quantify and details of the foods, procedures of provision of the food, instructions given to participants and exceptions has been described elsewhere.[29]

Due to COVID-19 restrictions, some aspects of the intervention had to be adjusted, as the weekly visits were not possible anymore: on-site visits were substituted by phone/video calls and key products were delivered to participants at home.

2.5 | Vascular function

Carotid artery reactivity (CAR) was assessed after an overnight fast (>10 h) with ultrasound (Terason uSmart 3300, Burlington, MA, USA) at baseline and during the last week of the intervention. For assessments, additional exclusion criteria applied: angina pectoris, Raynaud disease, chronic pain syndrome affecting the upper extremities, arteriovenous shunt, scleroderma and heart infarction or heart failure within the last 3 months.

The CAR test was performed after a minimum of 10 min of supine rest. CAR measures the diameter change of the right common carotid artery in response to a 3-min cold pressor test (CPT) (sympathetic stimulus). During CPT, the left hand of the participant was immersed in cold water (≤4°C) up to the wrist. The average diameter of a 1-min baseline recording was compared with the maximum diameter response (in 10 second intervals) during the 3-min CPT. Carotid artery diameter was evaluated continuously (25–30 frames per second), using semi-automated wall-tracking and edge-detection software to evaluate the diameter. Details of the software and assessment procedures can be found elsewhere.[34] Data were filtered manually for major artefacts, caused, for example, by swallowing, breathing or probe movement. Analysis was done blinded, and an independent assessor reviewed the analyses. In response to the CPT, the carotid artery can dilate or constrict. The direction of reactivity was determined by a positive (dilation) or negative (constriction) area under the curve (CAR_{AUC}). CAR% was then defined as the maximum dilation or constriction from baseline, divided by the baseline diameter.

2.6 | Cardiovascular disease risk factors

CVD risk factors measured before the start of the intervention and during week 12 of the intervention include fasting levels of total cholesterol and high-density lipoprotein (HDL) cholesterol (Cobas Pentra C400 with ABX Pentra Cholesterol CP reagens or ABX Pentra HDL Direct, respectively). Blood pressure was measured in a sitting position after 5-min rest (dominant arm, automated sphygmomanometer, average of two measurements). The Framingham risk score for cardiovascular disease was calculated as described by D'Agostino et al.,[35] based on age, total cholesterol, HDL-cholesterol, treated/untreated systolic blood pressure, diabetes and smoking status. Two measurements of height, weight and waist–hip circumference were taken and averaged at each point of assessment.

2.7 | Glucose homeostasis

A 7-point OGTT was performed at baseline and repeated during week 12 of the dietary intervention. MISI and HIRI[16,31] were calculated as follows: MISI = (dGlucose/dt)/insulin [mean during OGTT in pmol/L], with dGlucose/dt being the rate of decay of plasma glucose concentration (mmol/L) during the OGTT. HIRI = $glucose_{0\text{-}30}$ [AUC in mmol/L × h] × $insulin_{0\text{-}30}$ [AUC in pmol/L × h].

Matsuda index was calculated as: 10000 ÷ square root of (fasting plasma glucose (mmol/L) × fasting insulin (pmol/L)) × (mean glucose T0, T30, T60, T90, T120 (mmol/L) × mean insulin T0, T30, T60, T90, T120 (pmol/L)).[36] Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as: HOMA-IR: fasting glucose (mmol/L) × (fasting insulin (mU/L)/22.5). In case of a missing timepoint value ($N = 2$), mean glucose/insulin were calculated with the remaining timepoints.[37]

Disposition index was calculated as: Matsuda index × AUC30 insulin (pmol/L)/AUC30 glucose (mmol/L). AUC30 was calculated as the CAR from 0 to 30 min with the trapezoid method.

2.8 | Physical activity

Physical activity was measured with the activPAL$_3$ micro (PAL Technologies Ltd., Glasgow, UK), starting during the baseline measurements and continuing for ~1 week during the first week of the dietary intervention. At the end of the intervention, physical activity was reassessed starting in week 11, continuing until the end of week 12 (Figure 1). During this measurement period, we excluded days when participants visited the university or had to fill in extensive questionnaires. A valid measurement period included a minimum of 1 weekend +3 week days. ActivPAL data were analysed with an adapted script based on Winkler et al.[38] Adaptations were made to include sleep/wake diaries filled in by participants.

2.9 | Statistical analysis

The present paper reflects a sub-study of the original PERSON study[30] and focused on vascular function as the primary outcome parameter. This assessment was performed in one of the two measurement sites (WUR), meaning an anticipated sample size of $n = 101$. Based on previous work on vascular function, demonstrating an effect size of 2 ± 2% following a lifestyle intervention,[39,40] and assuming a power of 90%, a sample size of 101 would allow detecting an effect size of 0.65%.

Normally distributed data are presented as mean ± SD, non-normal data as median [IQR]. To examine the overall effects of diet, changes in the outcome variables for the total study population were assessed with a paired t-test or Wilcoxon signed-rank test in the case of a non-normal distribution of the delta score (Week 12—baseline). Our central aim was to assess whether personalization of a 12-week dietary intervention would optimize effects. For this purpose, we first examined the effects of linking the IR phenotype to the type of diet (i.e., PhenoDietA versus PhenoDietB), followed by comparing the

TABLE 2 Participant characteristics.

		Total N = 101	LFHP-PhenoDiet A N = 17	LFHP- PhenoDiet B N = 31	HMUFA- PhenoDiet A N = 36	HMUFA- PhenoDiet B N = 17	p-value
Age, years		61 ± 7	61 ± 4	62 ± 8	60 ± 8	60 ± 8	0.671
Sex, female		54 (53.5%)	9 (52.9%)	18 (58.1%)	19 (52.8%)	8 (47.1%)	0.907
BMI, kg/m^2		27.6 [26.4; 30.0]	26.7 [26.2; 27.6]	27.4 [26.3; 29.9]	27.6 [26.4; 29.7]	29.6 [28.4; 31.4]	0.061
Statins, yes		5 (5.0%)	1 (5.9%)	3 (9.7%)	1 (2.8%)	0 (0.0%)	0.569
Antihypertensives, yes		9 (8.9%)	1 (5.9%)	4 (12.9%)	3 (8.3%)	1 (5.9%)	0.892
Retired, yes		32 (31.7%)	3 (17.6%)	13 (41.9%)	11 (30.6%)	5 (29.4%)	0.374
Education level[a]	Low	4 (4.0%)	2 (11.8%)	2 (6.5%)	0 (0.0%)	0 (0.0%)	0.327
	Int	39 (39.0%)	8 (47.1%)	12 (38.7%)	14 (40.0%)	5 (29.4%)	
	High	57 (57.0%)	7 (41.2%)	17 (54.8%)	21 (60.0%)	12 (70.6%)	
Total energy, kcal		2178.0 ± 589.5	1994.1 [1749.0; 2368.1]	1955.5 [1839.2; 2229.0]	2251.3 [1721.8; 2524.4]	2491.4 [1858.8; 3114.2]	0.257
Carbohydrates, energy%		42.3 [39.4; 45.7]	41.2 [37.8; 47.3]	42.1 [40.6; 45.7]	42.6 [37.1; 45.9]	42.5 [40.0; 43.3]	0.690
Protein, energy%		15.4 [14.4; 16.6]	15.6 ± 1.8	15.9 ± 2.0	15.6 ± 2.5	15.2 ± 1.9	0.801
Fat, energy%		36.5 [34.1; 40.5]	35.4 [33.0; 43.9]	36.5 [34.4; 38.2]	36.5 [33.2; 40.2]	36.4 [34.9; 42.2]	0.868
Saturated fat, energy %		13.9 [12.0; 15.3]	13.6 [11.3; 15.1]	13.9 [11.9; 15.7]	14.2 [12.3; 15.2]	13.9 [12.3; 16.6]	0.927
Fibre, g/MJ		2.5 ± 0.6	2.5 [2.1; 2.9]	2.5 [2.1; 2.9]	2.5 [2.0; 3.1]	2.4 [2.0; 2.9]	0.946
Alcohol, glasses/ week		3.5 [0.9; 6.0]	4.0 [0.0; 9.0]	3.0 [0.5; 6.0]	3.0 [2.0; 5.0]	4.0 [0.5; 6.0]	0.960

Abbreviations: BMI, body mass index; HMUFA, high-monounsaturated fatty acid diet; LFHP, low-fat high-protein diet.
[a]Low: no education, primary education, lower/preparatory vocational education, lower general secondary education; medium: int., intermediate vocational education, higher general senior secondary education, pre-university secondary education; high: higher vocational education, university. For education level and glasses of alcohol: total N = 100. Normally distributed data are presented as mean ± SD, non-normal data as median [IQR].

effect of the type of diet alone (i.e., LFHP versus HMUFA). Analysis of intervention effects with repeated measures linear mixed models revealed a substantial violation of homoscedasticity for our primary outcome (vascular function). Therefore, differences in delta scores (week 12—baseline) between interventions (PhenoDiet group A versus PhenoDiet group B; LFHP versus HMUFA) were analysed with linear regression models, corrected for baseline values. In a second model, we corrected additionally for age and sex. As participants lost weight during the intervention, which was not intended, we adjusted for weight change in model 3 (Tables S1 and S2). In a fourth model, we corrected for changes in physical activity (Tables S1 and S2). To this end, physical activity expressed as % of awake timetakes into account the interconnectedness between physical activity and sedentary behaviour, meaning that a higher percentage of the day spent in physical activity results in a lower percentage spent in sedentary behaviour. Analyses were done in R studio, R version 3.6.2.[41]

3 | RESULTS

In total, 119 participants were included. During the intervention, 7 participants dropped out, resulting in a sample size of 112. Assessments of cardiovascular risk and the OGTT could not be completed for 11 participants due to local COVID-19 lockdowns. This resulted in data that were available for analysis of those endpoints in 101 participants. Baseline characteristics for the whole group and per intervention arm are shown in Table 2. Regarding the vascular function assessment, a total of 105 out of 119 participants were eligible for vascular function assessment, with 83 participants completing week-12 measurements (6 dropouts, 16 local COVID-19 lockdown). An additional three ultrasound recordings were excluded due to measurement problems, resulting in a total population for vascular function assessments of 80 (representing a subgroup of the n = 101).

On average, participants (53.5% female) were 61 ± 7 years old, with a median BMI of 27.6 [IQR: 26.4;30.0] kg/m^2. Participant characteristics of the total group (n = 101) and per intervention arm can be found in Table 2. Total physical activity, sedentary time, LIPA and MVPA time did not significantly change during the intervention (Table 3). There was no significant difference between PhenoDiet group A versus group B or LFHP versus HMUFA diets for any of these physical (in)activity outcomes (Tables 4 and 5).

Vascular function. In the total study population (n = 80), vascular function did not change during the intervention (Table 3). ΔCAR% and ΔCAR_{AUC} were not different between PhenoDiet group A and

TABLE 3 Outcomes at baseline and week 12: Total study population.

Outcome		Total group	*p*-value
CAR%, % *N* = 80	Baseline	2.39 [1.37; 3.34]	0.485
	Week 12	2.23 [1.25; 3.00]	
	Delta	−0.18 [−1.40; 1.08]	
CAR_{AUC}, cm*s *N* = 80	Baseline	1.57 [0.55; 2.33]	0.783
	Week 12	1.42 [0.52; 1.99]	
	Delta	−0.15 [−0.90; 0.88]	
SBP, mmHg *N* = 100	Baseline	124 [114; 136]	<0.001
	Week 12	118 [110; 128]	
	Delta	−5 ± 10	
DBP, mmHg *N* = 100	Baseline	73 ± 10	0.004
	Week 12	71 ± 10.0	
	Delta	−2 ± 7	
TC, mmol/L *N* = 97	Baseline	5.45 ± 1.04	<0.001
	Week 12	4.83 ± 0.93	
	Delta	−0.62 [−0.89; −0.36]	
HDL-C, mmol/L *N* = 97	Baseline	1.30 [1.11; 1.48]	<0.001
	Week 12	1.22 [1.06; 1.36]	
	Delta	−0.09 ± 0.11	
TC/HDL-C, ratio *N* = 97	Baseline	4.31 ± 1.09	<0.001
	Week 12	4.08 ± 1.02	
	Delta	−0.23 ± 0.38	
FRS *N* = 96	Baseline	11.6 ± 3.8	<0.001
	Week 12	10.4 ± 3.8	
	Delta	−1.0 [−2.0; 0.0]	
Weight, kg *N* = 101	Baseline	85.6 ± 10.8	<0.001
	Week 12	83.5 ± 10.8	
	Delta	−2.1 ± 2.3	
WHR *N* = 101	Baseline	0.960 [0.910; 1.010]	0.159
	Week 12	0.950 [0.890; 1.010]	
	Delta	−0.006 ± 0.042	
Matsuda *N* = 101	Baseline	13.1 [9.7; 17.4]	<0.001
	Week 12	14.0 [11.1; 20.1]	
	Delta	1.3 [−0.8; 4.4]	
HOMA-IR *N* = 101	Baseline	1.6 [1.3; 2.1]	0.001
	Week 12	1.4 [1.1; 2.0]	
	Delta	−0.1 [−0.4; 0.1]	
Disposition index *N* = 101	Baseline	420.1 [293.8; 647.6]	0.362
	Week 12	438.2 [298.4; 627.3]	
	Delta	16.1 ± 177.0	
Sitting, h *N* = 93	Baseline	9.5 ± 1.4	0.586
	Week 12	9.5 ± 1.5	
	Delta	0.1 ± 1.3	
PA, h *N* = 93	Baseline	6.2 ± 1.6	0.315
	Week 12	6.1 ± 1.7	
	Delta	−0.1 ± 1.2	
LIPA, h *N* = 93	Baseline	5.0 ± 1.3	0.111
	Week 12	4.9 ± 1.4	
	Delta	−0.2 ± 1.0	
MVPA, h *N* = 93	Baseline	1.2 [0.9; 1.4]	0.338
	Week 12	1.2 [0.8; 1.5]	
	Delta	0.0 [−0.2; 0.3]	

Note: Normally distributed data are presented as mean ± SD, and non-normal data as median [IQR]. P-value for differences between baseline and week 12.

Abbreviations: AUC, area under the curve; CAR, carotid artery reactivity; DBP, diastolic blood pressure; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LIPA, light-intensity PA; MVPA, moderate-to-vigorous PA; PA, physical activity; SBP, systolic blood pressure; TC, total cholesterol; WHR, waist-to-hip ratio.

group B (Table 4), and we found no significant difference between both diets (LFHP/HMUFA) on CAR (Table 5). Adjustment for weight change or changes in physical activity did not change these results (Tables S1 and S2).

Cardiovascular risk factors. Overall, dietary intervention decreased CVD risk factors (SBP, total cholesterol, HDL-cholesterol, total cholesterol/HDL-cholesterol ratio, Table 3). The Framingham risk score also decreased significantly (Table 3). Despite the goal of keeping participants weight stable, body weight decreased by 2.1 ± 2.3 kg ($p < 0.001$), while waist-to-hip ratio did not change significantly ($p = 0.159$). Total cholesterol ($p = 0.052$) tended to decrease more in PhenoDiet group B than in A, but changes in other CVD risk factors were not different between PhenoDiet group A and B (Table 4). LFHP resulted in a greater decrease in total cholesterol, HDL-cholesterol and DBP compared with MUFA (Table 5). Adjustment for weight change or physical activity change did not alter study outcomes (Tables S1 and S2), except for the change in DBP, which was not significantly different between LFHP and HMUFA ($p = 0.05$, $p = 0.079$, respectively). The decrease in SBP, Framingham risk score and weight was not different between LFHP versus HMUFA (Table 5).

Glucose homeostasis. Overall, dietary intervention improved insulin sensitivity, indicated by increased Matsuda index and decreased HOMA-IR, while the disposition index remained unchanged (Table 3). The Matsuda index ($p = 0.078$) tended to increase more in PhenoDiet group B than in A, while HOMA-IR and the disposition index were not significantly different between PhenoDiet groups (Table 4). The LFHP diet resulted in a greater changes in Matsuda index and HOMA-IR compared with HMUFA (Table 5), while changes in disposition index were not different between these diets (Tables 4 and 5). Adjustment for weight change or physical activity change did not alter results for HOMA-IR, Matsuda index or disposition index (Tables S1 and S2).

TABLE 4 Changes in vascular function, cardiovascular risk factors, glucose homeostasis and physical activity: PhenoDiet group A ($N = 53$) versus PhenoDiet group B ($N = 48$).

					Model 1*		Model 2*	
Outcome	Diet group	Baseline	Week 12	Δ	β [95% CI]	*p*-value	β [95% CI]	*p*-value
CAR%, % $N = 80$	B	2.48 [1.35; 3.91]	2.24 [1.32; 2.74]	−0.27 [−1.43; 0.73]	REF	–	REF	–
	A	2.33 [1.38; 2.96]	2.07 [1.21; 3.16]	−0.17 [−1.29; 1.31]	0.03 [−0.84–0.89]	0.952	−0.06 [−0.92–0.81]	0.899
CAR_{AUC}, cm*s $N = 80$	B	1.67 [0.48; 2.91]	1.79 [0.53; 2.20]	0.19 [−0.78; 1.10]	REF	–	REF	–
	A	1.54 [0.79; 2.17]	1.05 [0.53; 1.86]	−0.34 [−0.98; 0.80]	−0.30 [−0.98–0.38]	0.376	−0.37 [−1.04–0.31]	0.287
SBP, mmHg $N = 100$	B	128 ± 16	120 ± 12	−8 ± 11	REF	–	REF	-
	A	122 ± 16	119 ± 15	−3 ± 10	2.84 [−0.60–6.28]	0.105	2.76 [−0.7–6.23]	0.117
DBP, mmHg $N = 100$	B	74 ± 10	71 ± 9	−3 ± 7	REF	–	REF	–
	A	73 ± 11	71 ± 11	−1 ± 6	1.32 [−1.13–3.76]	0.287	1.06 [−1.38–3.50]	0.392
TC, mmol/L $N = 97$	B	5.44 ± 1.06	4.72 ± 0.92	−0.66 [−0.95; −0.39]	REF	–	REF	–
	A	5.47 ± 1.03	4.92 ± 0.94	−0.59 [−0.85; −0.27]	0.18 [−0.00–0.37]	0.052	0.18 [−0.01–0.37]	0.059
HDL-C, mmol/L $N = 97$	B	1.30 [1.10; 1.47]	1.18 [0.99; 1.33]	−0.10 ± 0.12	REF	–	REF	–
	A	1.30 [1.16; 1.49]	1.23 [1.07; 1.38]	−0.07 ± 0.11	0.04 [−0.01–0.08]	0.103	0.04 [−0.01–0.08]	0.094
TC/HDL-C, ratio $N = 97$	B	4.34 ± 1.10	4.10 ± 1.07	−0.25 ± 0.40				
	A	4.28 ± 1.09	4.06 ± 0.97	−0.21 ± 0.36	0.03 [−0.12–0.17]	0.723	0.02 [−0.12–0.16]	0.813
FRS $N = 96$	B	11.8 ± 4.0	10.3 ± 3.8	−1.5 [−3.0; 0.0]	REF	–	REF	–
	A	11.3 ± 3.7	10.5 ± 3.9	−1.0 [−1.0; 0.0]	0.60 [−0.17–1.37]	0.124	0.48 [−0.22–1.18]	0.179
Weight, kg $N = 101$	B	86.6 ± 9.2	84.1 ± 9.0	−2.5 ± 2.2	REF	–	REF	–
	A	84.7 ± 12.1	83.0 ± 12.3	−1.7 ± 2.4	0.74 [−0.17–1.66]	0.110	0.63 [−0.28–1.55]	0.173
WHR $N = 101$	B	0.965 [0.910; 1.010]	0.945 [0.898; 1.002]	−0.004 ± 0.046	REF	–	REF	–
	A	0.960 [0.910; 1.000]	0.950 [0.880; 1.010]	−0.007 ± 0.038	−0.00 [−0.02–0.01]	0.563	−0.01 [−0.02–0.01]	0.336
Matsuda $N = 101$	B	12.2 [9.2; 15.2]	14.8 [11.2; 20.7]	2.1 [0.0; 4.8]	REF	–	REF	–
	A	13.4 [10.1; 18.3]	13.5 [11.1; 19.8]	0.4 [−1.3; 4.1]	−1.69 [−3.58–0.20]	0.078	−1.58 [−3.48–0.31]	0.101
HOMA-IR $N = 101$	B	1.7 [1.4; 2.2]	1.4 [1.1; 2.0]	−0.2 [−0.6; 0.1]	REF	–	REF	–
	A	1.5 [1.1; 2.0]	1.6 [1.1; 1.9]	−0.1 [−0.4; 0.2]	0.09 [−0.15–0.32]	0.465	0.07 [−0.16–0.30]	0.560
Disposition index $N = 101$	B	416.4 [253.5; 566.1]	432.1 [280.9; 589.0]	22.2 ± 169.7	REF	–	REF	–
	A	431.7 [320.3; 685.2]	443.1 [299.8; 655.1]	10.6 ± 184.8	1.46 [−64.68–67.61]	0.965	4.21 [−62.81–71.22]	0.901
Sitting, h $N = 93$	B	9.3 ± 1.4	9.3 ± 1.5	0.0 [−0.7; 0.9]	REF	–	REF	–
	A	9.6 ± 1.4	9.7 ± 1.6	−0.1 [−0.9; 0.9]	0.19 [−0.30–0.68]	0.442	0.18 [−0.31–0.67]	0.467
PA, h $N = 93$	B	6.3 ± 1.6	6.4 ± 1.7	0.2 [−0.8; 0.7]	REF	–	REF	–
	A	6.1 ± 1.6	5.9 ± 1.6	−0.1 [−0.8; 0.5]	−0.31 [−0.79–0.18]	0.213	−0.29 [−0.77–0.20]	0.241
LIPA, h $N = 93$	B	5.1 [4.3; 6.0]	4.9 [4.1; 5.8]	−0.0 [−0.6; 0.5]	REF	–	REF	–
	A	4.9 [4.1; 5.6]	4.8 [3.9; 5.7]	−0.2 [−0.6; 0.3]	−0.25 [−0.66–0.15]	0.220	−0.24 [−0.64–0.17]	0.252
MVPA, h $N = 93$	B	1.2 [0.9; 1.5]	1.2 [1.0; 1.6]	−0.0 [−0.2; 0.2]	REF	–	REF	–
	A	1.2 [0.9; 1.4]	1.1 [0.8; 1.5]	−0.0 [−0.2; 0.3]	−0.05 [−0.20–0.10]	0.491	−0.05 [−0.20–0.10]	0.523

Note: Normally distributed data are presented as mean ± SD, non-normally distributed data as median [IQR]. *Linear regression models testing differences in the change (week 12 minus baseline) in the outcome variable between PhenoDiet group A and group B. Model 1: corrected for baseline values; Model 2: corrected for baseline values, age, sex.
Abbreviations: AUC, area under the curve; CAR, carotid artery reactivity; DBP, diastolic blood pressure; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LIPA, light-intensity physical activity; MVPA, moderate-to-vigorous physical activity; PA, total physical activity; SBP, systolic blood pressure; TC, total cholesterol; WHR, waist-to-hip ratio.

4 | DISCUSSION

The primary objective of the present study was to explore whether a personalized diet, designed to optimize glucose homeostasis through linking the IR phenotype (i.e., MIR or LIR) to the type of diet (i.e., LFHP and HMUFA), has superior effects on vascular function and cardiovascular risk factors in individuals with a predominant MIR or LIR phenotype. First, we found that the consumption of both diets for 12 weeks improved cardiovascular risk factors and IR, but did not significantly affect vascular function and disposition index in the total study population. Second, phenotype-based allocation of the diets showed no superiority for vascular function, cardiovascular risk or glucose homeostasis, although a trend was present for larger improvements in total cholesterol and insulin sensitivity in PhenoDiet group B

TABLE 5 Changes in vascular function, cardiovascular risk factors, glucose homeostasis and physical activity: LFHP ($N = 48$) versus HMUFA ($N = 53$) diet.

					Model 1*		Model 2*	
Outcome	**Diet**	**Baseline**	**Week 12**	**Δ**	**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**
CAR%, % $N = 80$	LFHP	2.40 [1.30; 3.79]	1.89 [1.25; 2.59]	−0.28 [−1.45; 1.03]	REF	–	REF	–
	HMUFA	2.36 [1.40; 3.00]	2.52 [1.32; 3.34]	0.10 [−1.13; 1.20]	0.40 [−0.46–1.26]	0.362	0.36 [−0.51–1.23]	0.410
CAR_{AUC}, cm*s $N = 80$	LFHP	1.48 [0.48; 2.90]	1.00 [0.36; 1.89]	0.08 [−0.81; 0.56]	REF	–	REF	–
	HMUFA	1.68 [0.78; 2.25]	1.68 [0.67; 2.06]	−0.20 [−0.91; 0.95]	0.34 [−0.34–1.02]	0.324	0.35 [−0.34–1.03]	0.315
SBP, mmHg $N = 100$	LFHP	123 [111; 134]	117 [108; 124]	−6 ± 11	REF	–	REF	–
	HMUFA	125 [117; 136]	121 [114; 132]	−4 ± 10	3.28 [−0.12–6.67]	0.058	3.30 [−0.15–6.75]	0.061
DBP, mmHg $N = 100$	LFHP	72 ± 9	69 ± 9	−3 ± 7	REF	–	REF	–
	HMUFA	74 ± 12	73 ± 10	−1 ± 7	2.73 [0.34–5.13]	0.026	2.48 [0.07–4.89]	0.044
TC, mmol/L $N = 97$	LFHP	5.49 ± 1.04	4.73 ± 0.94	−0.68 [−1.00; −0.44]	REF	–	REF	–
	HMUFA	5.42 ± 1.04	4.91 ± 0.93	−0.57 [−0.82; −0.20]	0.24 [0.06–0.42]	0.011	0.23 [0.05–0.42]	0.014
HDL-C, mmol/L $N = 97$	LFHP	1.33 [1.13; 1.48]	1.23 [1.04; 1.35]	−0.11 ± 0.10	REF	–	REF	–
	HMUFA	1.30 [1.08; 1.48]	1.22 [1.07; 1.37]	−0.06 ± 0.12	0.05 [0.01–0.09]	0.018	0.05 [0.01–0.10]	0.013
TC/HDL-C, ratio $N = 97$	LFHP	4.32 ± 1.12	4.09 ± 1.11	−0.23 ± 0.42	REF	–	REF	–
	HMUFA	4.30 ± 1.08	4.07 ± 0.93	−0.23 ± 0.34	−0.00 [−0.15–0.14]	0.968	−0.02 [−0.16–0.12]	0.800
FRS $N = 96$	LFHP	11.5 ± 3.7	10.1 ± 3.5	−1.0 [−2.0; 0.0]	REF	–	REF	–
	HMUFA	11.7 ± 4.0	10.6 ± 4.1	−0.5 [−2.0; 0.0]	0.32 [−0.46–1.09]	0.420	0.32 [−0.39–1.03]	0.374
Weight, kg $N = 101$	LFHP	83.6 ± 10.3	81.3 ± 10.0	−2.5 [−3.6; −0.5]	REF	–	REF	–
	HMUFA	87.4 ± 11.1	85.5 ± 11.3	−1.6 [−3.6; 0.1]	0.41 [−0.52–1.35]	0.383	0.37 [−0.56–1.30]	0.429
WHR $N = 101$	LFHP	0.950 [0.910; 1.010]	0.935 [0.880; 1.002]	−0.007 ± 0.045	REF	–	REF	–
	HMUFA	0.970 [0.910; 1.010]	0.960 [0.910; 1.010]	−0.005 ± 0.039	0.00 [−0.01–0.02]	0.743	0.00 [−0.01–0.02]	0.883
Matsuda $N = 101$	LFHP	13.3 [10.1; 17.9]	17.0 [11.9; 22.6]	2.1 [0.5; 6.5]	REF	–	REF	–
	HMUFA	13.0 [9.7; 16.2]	12.7 [10.5; 17.5]	0.2 [−1.3; 3.3]	−2.73 [−4.56–(−0.90)]	0.004	−2.60 [−4.45–(−0.75)]	0.006
HOMA-IR $N = 101$	LFHP	1.5 [1.2; 2.1]	1.2 [0.9; 1.7]	−0.3 [−0.5; 0.1]	REF	–	REF	–
	HMUFA	1.8 [1.3; 2.3]	1.7 [1.3; 2.0]	−0.0 [−0.4; 0.1]	0.26 [0.04–0.49]	0.021	0.24 [0.01–0.47]	0.038[#]
Disposition index $N = 101$	LFHP	433.4 [257.2; 732.1]	436.0 [284.6; 654.5]	26.0 [−80.4; 94.9]	REF	–	REF	–
	HMUFA	397.0 [309.5; 574.7]	443.1 [299.8; 597.3]	23.0 [−85.5; 105.2]	−2.71 [−68.78–63.36]	0.935	0.89 [−66.31–68.09]	0.979
Sitting, h $N = 93$	LFHP	9.4 ± 1.4	9.2 ± 1.5	−0.0 [−1.0; 0.6]	REF	–	REF	–
	HMUFA	9.6 ± 1.4	9.8 ± 1.5	−0.0 [−0.6; 1.0]	0.44 [−0.04–0.92]	0.071	0.42 [−0.06–0.90]	0.088
PA, h $N = 93$	LFHP	6.2 ± 1.6	6.3 ± 1.5	0.3 [−0.7; 0.7]	REF	–	REF	–
	HMUFA	6.2 ± 1.5	5.9 ± 1.7	−0.1 [−0.8; 0.4]	−0.35 [−0.82–0.13]	0.155	−0.31 [−0.80–0.17]	0.204
LIPA, h $N = 93$	LFHP	5.0 ± 1.4	5.0 ± 1.3	0.1 [−0.6; 0.5]	REF	–	REF	–
	HMUFA	5.0 ± 1.3	4.7 ± 1.4	−0.2 [−0.6; 0.3]	−0.30 [−0.70–0.10]	0.145	−0.27 [−0.68–0.14]	0.196
MVPA, h $N = 93$	LFHP	1.2 [0.9; 1.4]	1.2 [0.9; 1.6]	0.1 ± 0.3	REF	–	REF	–
	HMUFA	1.2 [0.9; 1.5]	1.1 [0.8; 1.5]	0.0 ± 0.4	−0.06 [−0.21–0.09]	0.457	−0.05 [−0.21–0.10]	0.498

Note: Normally distributed data are presented as mean ± SD, non-normal data as median [IQR]. *Linear regression models testing differences in the change (week 12 minus baseline) in the outcome variable between LFHP and HMUFA diets. Model 1: corrected for baseline values; Model 2: corrected for baseline values, age, sex. [#]For HOMA-IR, significance was driven by two participants. Exclusion resulted in non-significant differences ($p = 0.158$).

Abbreviations: AUC, area under the curve; CAR, carotid artery reactivity; DBP, diastolic blood pressure; FRS, Framingham risk score; HDL, high-density lipoprotein; HMUFA, high-monounsaturated fatty acid diet; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LFHP, low-fat, high-protein diet; LIPA, light-intensity physical activity; MVPA, moderate-to-vigorous physical activity; PA, total physical activity; SBP, systolic blood pressure; TC, total cholesterol.

versus A. Third, the LFHP diet resulted in greater improvements in several cardiovascular risk factors and measures of IR compared with HMUFA.

At group level, the 12-week diet intervention improved cardiovascular risk factors and IR. The Framingham risk score, which is linked to the 10-year risk of CVD,[35] also decreased. Both diets represent healthy diets, in line with dietary guidelines,[42] with the observation of improvements in cardiovascular and metabolic health being in line with previous findings.[15,43–45] In the present study, pre-intervention habitual dietary intake of saturated fat (14% of energy intake) and fibre intake (2.5 g/MJ) did not meet the recommendations (saturated fat <10% of energy intake, 3.4 g/MJ fibre). Through either

diet (HMUFA and LFHP), the dietary intake of the participants improved and may have contributed to these health improvements.

Despite significant improvements in IR and cardiovascular risk factors during the intervention, we observed no significant changes in vascular function. This was unexpected, especially since our measure of vascular function (i.e., CAR) is associated with cardiovascular risk factors[46] and disease progression,[46,47] but also because vascular function is closely linked to IR.[4] Indeed, flow-mediated dilation (FMD), another measure of vascular function, has been repeatedly shown to improve following diet interventions.[48,49] Possibly, FMD may be more responsive than CAR to a diet as both measures reflect a different part of the vascular system (peripheral versus central) and are mediated through distinct pathways (shear stress versus sympathetic nervous system).[50,51] These observations may explain differences in outcomes between studies when examining the impact of dietary interventions on measures of vascular function. Alternatively, a longer diet intervention may be required for improvements in cardiovascular risk factors and IR to translate to improvements in vascular function.

Personalization of the dietary intervention by linking the tissue-specific IR phenotype to the proposed optimal diet represents a central concept in our study. We recently published the main outcomes of the PERSON study, which included 242 participants, demonstrating significantly greater improvements in glucose homeostasis and (peripheral) insulin sensitivity, C-reactive protein and fasting triglycerides in the PhenoDiet group B versus A.[30] Although the present sub-study was not powered to detect such changes in glucose homeostasis between groups, observations in the present sub-study are largely in line with the findings from the main analysis of the PERSON study.

While a healthy diet improved cardiovascular risk factors in the total study population, we found a more pronounced decrease in total cholesterol and DBP in individuals who followed the LFHP diet. Moreover, both diets reduced HDL-cholesterol concentration. Previous studies show conflicting results regarding the effects of diet on HDL-cholesterol, with increased or unchanged HDL-cholesterol levels reported after a Mediterranean diet[43,44] and decreased to increased HDL-cholesterol levels after a low-fat diet.[43,44,52–54] The restriction of alcohol consumption during the dietary intervention to ≤1 glass/day might have contributed to reductions in HDL-cholesterol, as alcohol consumption can increase HDL-cholesterol levels.[55] However, the decrease in HDL-cholesterol was not significantly different between participants with low (≤3.5 glasses/week) versus high (≥3.5 glasses/week) baseline alcohol consumption (split at median, $p = 0.986$, data not shown). Despite a reduction in HDL-cholesterol, the total cholesterol/HDL ratio decreased significantly, suggesting a relatively larger decline in total cholesterol than the change in HDL-cholesterol, with no difference between the diets. These changes in blood lipids may have a beneficial impact on CVD risk, as a lower total cholesterol/HDL ratio is associated with lower risk for CVD.[56,57] A greater improvement in DBP has previously been reported with a LFHP diet, compared with a Mediterranean diet, in individuals with type 2 diabetes.[43] A more pronounced though modest (nonsignificant) weight reduction (−2.5 kg [−3.6;-0.5] versus − 1.6 kg [−3.6;0.1]), and (non-significant) increase in physical activity (15.8 min [−44.3;43.8] versus −7.7 min [−50.4;26.0]) in individuals following the LFHP diet may, at least partially, contribute to the differences in ΔDBP observed between the LFHP and HMUFA diets. Adjustment for changes in weight or changes in physical activity resulted in a non-significant trend for the difference in blood pressure.

5 | STRENGTHS AND LIMITATIONS

A strength of this study is the objective assessment of physical activity before and after the intervention. Although total physical activity did not change significantly, even small increases in physical activity have previously been shown to be beneficial for blood pressure.[58] Since adjusting for changes in physical activity did not alter our results substantially, our results can primarily be related to the diet intervention rather than (subconscious) changes in physical activity.

A few limitations of this study need also to be acknowledged. This study was designed to keep participants weight stable, to be able to attribute outcomes to diet composition rather than weight loss. Despite our efforts to keep participants weight stable by adjusting energy groups when participants lost weight, participants lost an average of 2 kg during the 12-week intervention. Nevertheless, the present results were largely unaltered after adjustment for weight change. In addition, some of our secondary outcomes (CVD risk, IR) represent a subgroup analysis of the PERSON study and may therefore be underpowered. The present study was, however, sufficiently powered to detect differences in our primary outcome: vascular function. However, in previous work, we found that the effects of a lifestyle intervention on vascular function have previously been reported in a much smaller study population ($N = 19$).[39] A final limitation relates to the duration of the study, as some dietary intervention may require administration of >6 months to achieve significant effects.[59]

6 | CONCLUSION

In individuals with IR, a healthy diet can improve cardiovascular risk factors and IR within 12 weeks, with LFHP resulting in greater improvements than HMUFA in some markers of CVD risk (i.e., cholesterol, HDL-cholesterol and diastolic blood pressure) and IR (i.e., Matsuda index and HOMA-IR). In contrast, we found no adaptations in the common carotid artery vascular function. Importantly, assigning individuals based on their IR phenotype (LIR or MIR) to a distinct diet tended to further improve insulin sensitivity (Matsuda index) and total cholesterol but did not alter other cardiovascular risk factors or vascular function. Taken together, these results highlight the benefits of diet to improve cardiovascular risk and IR, with our data suggesting that the diet type per se (LFHP) has larger effects on some cardiovascular risk factors and IR compared with the personalization of the diet based on the IR phenotype.

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AUTHOR CONTRIBUTIONS

LW participated in data collection, performed the data analysis and drafted the manuscript. AG was responsible for execution of the study. GBH was responsible for data management. EEB was project leader and obtained funding for the project. DHJT also obtained funding for the project. EEB, LAA, GHG, EJMF and DHJT co-designed the study. LAA, MTEH, GHG and DHJT supervised the research activities. All authors participated in the discussion of results and revision of the article. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Aggregated and individual participant data and associated supporting documents will be made available from the corresponding author upon reasonable request. Individual participant data that underlie the results reported in this article, after deidentification, will be shared upon reasonable request after publication and ending 36 months following provision of the data to researchers who provide a methologically sound proposal. Proposals should be directed to the corresponding author, Dick Thijssen. All remaining data can be found in the Article and Supplementary.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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