Association between habitual diet and the postprandial glucose response - an enable study

Anna Reik, Beate Brandl, Gunther Schauberger, Nina Wawro, Jakob Linseisen, Thomas Skurk, Dorothee Volkert, Hans Hauner, Christina Holzapfel

Angaben zur Veröffentlichung / Publication details:

Reik, Anna, Beate Brandl, Gunther Schauberger, Nina Wawro, Jakob Linseisen, Thomas Skurk, Dorothee Volkert, Hans Hauner, and Christina Holzapfel. 2022. "Association between habitual diet and the postprandial glucose response - an enable study." *Molecular Nutrition and Food Research* 66 (16): 2200110. https://doi.org/10.1002/mnfr.202200110.

RESEARCH ARTICLE

Molecular Nutrition & Food Research
www.mnf-journal.com

Association between Habitual Diet and the Postprandial Glucose Response—An *Enable* Study

*Anna Reik, Beate Brandl, Gunther Schauberger, Nina Wawro, Jakob Linseisen, Thomas Skurk, Dorothee Volkert, Hans Hauner, and Christina Holzapfel**

Scope: It is inconclusive which factors influence inter-individual variations of postprandial glucose response (PPGR). This study investigates whether the habitual diet is associated with PPGR.

Methods and results: Data from healthy adults (young adults with 18–25 years, middle-aged adults with 40–65 years, and older adults with 75–85 years) is collected at baseline and during an oral glucose tolerance test (OGTT) collected. Habitual diet is assessed by a food frequency questionnaire and two 24-h food lists. Associations between habitual diet and glucose incremental area under the curve ($iAUC_{min}$) are examined by regression models. The intake of cereals and cereal products is negatively associated with glucose $iAUC_{min}$ ($p = 0.002$) in the total cohort ($N = 459$, 50% women, 55 ± 21 years, BMI 26 ± 5 kg m^{-2}). Up to 9% of the variance in the glycemic response is explained by the respective dietary parameters identified in the models of the specific age groups.

Conclusion: There are age-specific diet-related effects on PPGR. The usual intake of cereals and cereal products seems to play a greater role in PPGR in more than one age group. Further research is needed, to establish how diet can be optimized based on age and PPGR.

1. Introduction

People show inter-individual postprandial changes in metabolite circulation in the blood to standardized meals,[1–3] possibly providing crucial information on the metabolic resilience.[4] Changes in metabolite circulation are often referred to as postprandial response, whereas metabolic resilience describes how the postprandial response to an external stimulus is.[5] Research on which factors determine the variability of postprandial responses indicates that health status, phenotype, genotype, and lifestyle might be major contributors.[1–4]

Diet may affect postprandial response and metabolic resilience in two ways. Firstly, the high availability of energy shortly after meal intake puts the body into an anabolic state, in which the absorbed energy is stored.[6,7] Specific stress stimuli can in turn mobilize energy reserves, thereby changing substrate

A. Reik, H. Hauner, C. Holzapfel
Institute for Nutritional Medicine
School of Medicine
University Hospital Klinikum rechts der Isar
Technical University of Munich
Munich, Germany
E-mail: christina.holzapfel@tum.de

B. Brandl, T. Skurk
ZIEL - Institute for Food & Health
Technical University of Munich
Freising, Germany

G. Schauberger
Chair of Epidemiology
Department of Sport and Health Sciences
Technical University of Munich
Munich, Germany

N. Wawro, J. Linseisen
Independent Research Group Clinical Epidemiology
Helmholtz Zentrum München
German Research Center for Environmental Health (GmbH)
Neuherberg, Germany

N. Wawro, J. Linseisen
Chair of Epidemiology
University of Augsburg
University Hospital Augsburg
Augsburg, Germany

D. Volkert
Institute for Biomedicine of Aging
Friedrich-Alexander Universität Erlangen-Nürnberg
Nuremberg, Germany

H. Hauner
Else Kröner-Fresenius-Center for Nutritional Medicine
Chair of Nutritional Medicine
School of Life Sciences
Technical University of Munich
Freising, Germany

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/mnfr.202200110

DOI: 10.1002/mnfr.202200110

Table 1. Baseline characteristics of participants.

Variable	Total $N = 459$[a)]	Young adults $n = 94$[a)]	Middle-aged adults $n = 205$[a)]	Older adults $n = 160$[a)]	p[b)]
Age [years]	55 (±21)	22 (±2)	52 (±7)	78 (±3)	<0.001
Women	230/459 (50%)	48/94 (51%)	103/205 (50%)	79/160 (49%)	
Weight [kg]	76 (±16)	68 (±12)	82 (±16)	74 (±13)	<0.001
BMI [kg m^{-2}]	26.0 (±4.5)	22.1 (±2.5)	27.5 (±4.5)	26.5 (±4.0)	<0.001
Fat mass [%]	32 (±10)	21 (±8)	32 (±8)	37 (±8)	<0.001
WC [cm]	91 (±15)	78 (±8)	94 (±14)	96 (±14)	<0.001
HC [cm]	101 (±9)	96 (±6)	103 (±9)	103 (±9)	<0.001
Systolic BP [mmHg]	130 (±19)	114 (±12)	127 (±16)	143 (±18)	<0.001
Diastolic BP [mmHg]	83 (±10)	76 (±7)	85 (±9)	84 (±9)	<0.001
Glucose [mg dL^{-1}]	94 (±10)	91 (±8)	94 (±10)	95 (±11)	0.060
Total cholesterol [mg dL^{-1}]	213 (±43)	179 (±32)	223 (±39)	221 (±43)	<0.001
TAG [mg dL^{-1}]	111 (±55)	94 (±40)	121 (±65)	107 (±43)	0.001
HDL-C [mg dL^{-1}]	61 (±17)	61 (±16)	59 (±16)	64 (±17)	0.006
LDL-C [mg dL^{-1}]	132 (±39)	102 (±27)	140 (±37)	138 (±38)	<0.001

BMI, body mass index; BP, blood pressure; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; p, p-value; TAG, triacylglycerol; WC, waist circumference. [a)] Data are shown as mean (±SD) or n/N (%); [b)] Kruskal–Wallis rank sum test; Pearson's Chi-squared test.

utilization.[6] However, chronic stress can trigger adaptive mechanisms of postprandial response that negatively affect metabolic resilience in the long term, contributing to disease predisposition.[7,8] Secondly, food components play a role in various metabolic processes to maintain homeostasis. Therefore, inadequate intake of food compounds could disrupt metabolic processes, negatively impacting metabolic resilience.[7] As shown by Berry et al.,[1] diet-related modifiable factors, such as meal composition or meal context, seem to determine postprandial responses to a meal challenge to a larger extent than previously assumed. Further, it is well known that people following an unfavorable habitual diet show adverse metabolic characteristics and disease prevalence to a higher degree, in comparison to people following a healthier dietary pattern.[9] Therefore, it is of interest to identify diet-related factors that may be associated with the postprandial response, possibly altering the metabolic resilience in the long term.

It has been established that the macronutrient composition of a meal has a direct effect on the postprandial response after its consumption.[10a,b,11] However, knowledge about the effect of long-term diet composition and dietary habits on postprandial response and metabolic resilience is limited. Most studies focus on measures such as glucose tolerance or insulin sensitivity, both based on the 2-h glucose level after an oral glucose tolerance test (OGTT), serving as a proxy for the risk of type 2 diabetes mellitus (T2DM), rather than the postprandial glycemic response. Fiamoncini et al.[5] observed that less healthy dietary patterns were associated with dysfunctions in postprandial glycemic response after a mixed meal challenge, defined as a lower glucose clearance. Furthermore, studies have shown that a diet characterized by high consumption of red and processed meat, alcoholic beverages, refined grains, sugar-sweetened beverages, as well as a low intake of fruits is positively associated with a higher risk for diabetes, based on the glucose tolerance after an OGTT.[12,13] These findings indicate that there is an interplay between diet, the postprandial response, and health. However, there is limited knowledge on whether dietary patterns have long-term effects on the postprandial response and whether there are age-specific differences in the postprandial response.

Therefore, we performed an OGTT across three different age groups. Clinical and metabolic parameters were quantified, and the long-term habitual diet was estimated, to investigate the association between various nutritional parameters and postprandial glycemic response as incremental glucose area under the curve ($iAUC_{min}$) after a glucose load across different age groups. We assume possible associations of generation-specific dietary habits on the postprandial glucose response (PPGR).

2. Results

2.1. Characteristics of the Study Population

Baseline parameters significantly differ between age groups ($p < 0.010$), except for fasting glucose (**Table 1**).

The mean postprandial blood glucose trajectory of young adults during the OGTT differs from the other two age groups (**Figure 1**A). The peak of mean postprandial glucose concentration for middle-aged and older adults is reached 60 min after glucose drink consumption, 30 min later than in young adults. In all age groups, glucose reaches the lowest mean postprandial concentration 180 min after glucose drink consumption. In addition to age-specific differences, inter-individual variation within each age group (Figure 1B) can be observed, especially for middle-aged and older adults. The glucose $iAUC_{min}$ significantly differs between age groups (7490 ± 3166 mg*min dL^{-1} for young adults, 10197 ± 4489 mg*min dL^{-1} for middle-aged adults, and 10910 ± 4326 mg*min dL^{-1} for older adults; $p < 0.001$; data not shown).

Total energy intake, as well as the intake of dairy products, sugar and confectionery, and alcoholic beverages, does not

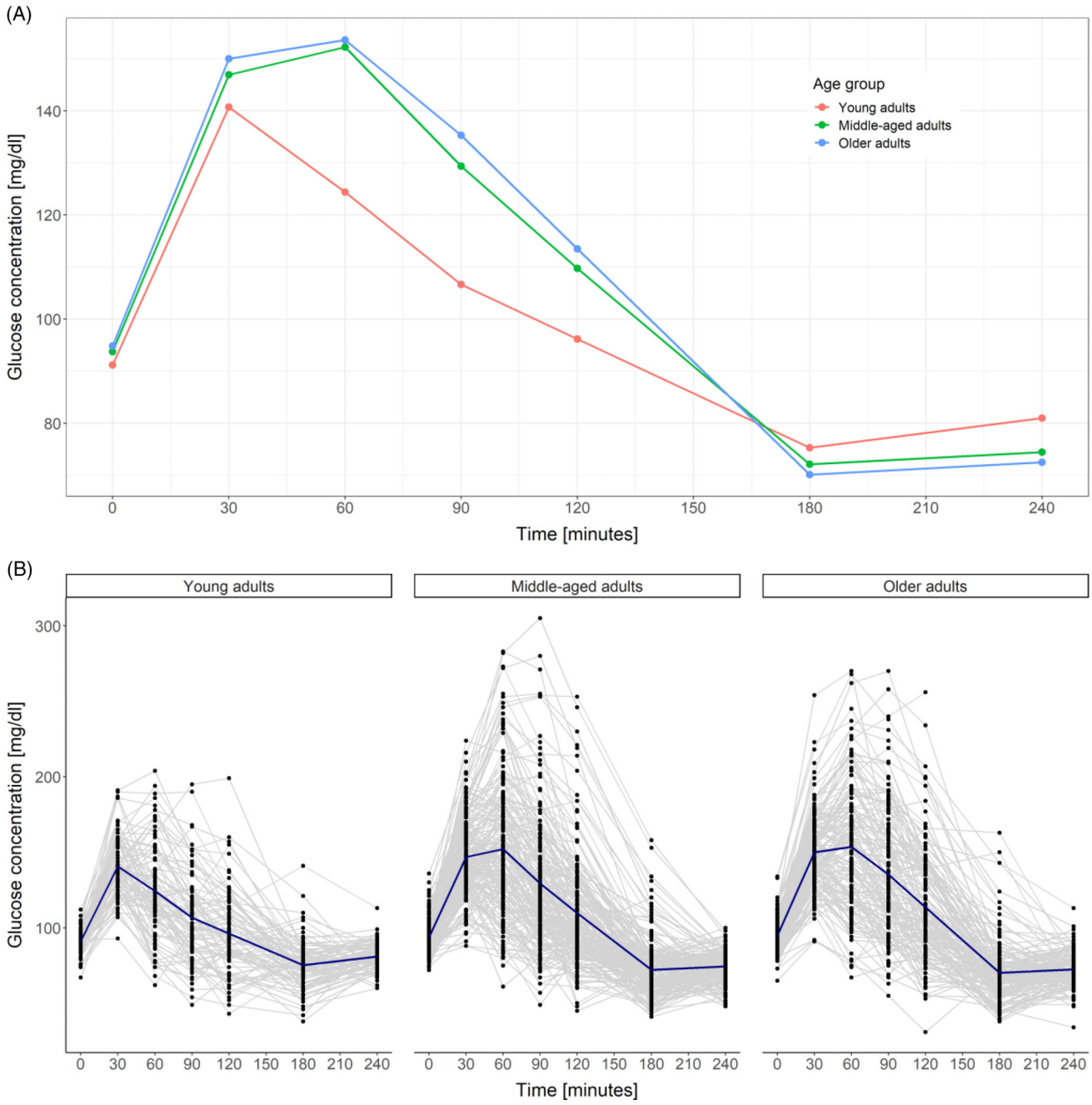

Figure 1. A) Mean postprandial glucose trajectories for each age group during the OGTT, B) with plotted dots for mean blood glucose levels at each time point. Individually fitted blood glucose trajectories (grey) with the mean blood glucose concentrations (blue) after OGTT-drink consumption.

significantly differ between age groups (**Table 2**). Older adults have the highest AHEI (51 ± 10) and show the highest intake of fruits and nuts (237 ± 100 g d^{-1}) and fish and shellfish (27 ± 15 g d^{-1}), as well as the lowest consumption of meat and meat products (101 ± 38 g d^{-1}) (Table 2). Young and middle-aged adults have a similar AHEI value (46 ± 10 and 46 ± 9, respectively) but show differences in the average intake of food groups, such as vegetables (259 ± 82 and 194 ± 56 g d^{-1}, respectively) or cereals and cereal products (218 ± 68 and 177 ± 54 g d^{-1}, respectively) (Table 2).

2.2. Associations of Diet-Related Parameters with the Glucose $iAUC_{min}$

For the total cohort, univariate linear regression models show a statistically significant negative association of the intake of cereals and cereal products with glucose $iAUC_{min}$ (**Table 3**), which remains statistically significant after Bonferroni correction. The intake of eggs and egg products, meat and meat products, and alcoholic beverages show positive associations with glucose $iAUC_{min}$ (Table 3). Multivariate prediction models based on the

Table 2. Dietary characteristics of participants at baseline.

Variable	Total $N = 459$[a]	Young adults $n = 94$[a]	Middle-aged adults $n = 205$[a]	Older adults $n = 160$[a]	p[b]
Total energy intake [kcal d^{-1}]	1934 (±388)	1941 (±387)	1906 (±365)	1972 (±421)	0.400
Protein intake [E%]	16.05 (±1.62)	16.22 (±1.54)	16.40 (±1.57)	15.40 (±1.56)	<0.001
Fat intake [E%]	40.2 (±3.5)	39.0 (±3.7)	40.8 (±3.2)	40.1 (±3.5)	<0.001
Carbohydrate intake [E%]	43.1 (±4.2)	44.4 (±4.5)	42.0 (±4.0)	43.9 (±4.0)	<0.001
Fiber intake [g d^{-1}]	20.8 (±6.2)	22.7 (±7.5)	19.0 (±5.0)	22.1 (±6.2)	<0.001
Potatoes, other tubers [g d^{-1}]	57 (±22)	41 (±15)	51 (±13)	77 (±24)	<0.001
Vegetables [g d^{-1}]	204 (±68)	259 (±82)	194 (±56)	181 (±53)	<0.001
Pulses, legumes [g d^{-1}]	6.45 (±4.86)	8.28 (±8.43)	5.89 (±3.29)	6.04 (±2.75)	0.014
Fruits, nuts [g d^{-1}]	190 (±97)	163 (±92)	171 (±85)	237 (±100)	<0.001
Dairy products [g d^{-1}]	236 (±126)	249 (±125)	234 (±129)	229 (±121)	0.400
Cereals, cereal products [g d^{-1}]	182 (±59)	218 (±68)	177 (±54)	165 (±49)	<0.001
Meat, meat products [g d^{-1}]	110 (±43)	104 (±40)	118 (±45)	101 (±38)	<0.001
Fish, shellfish [g d^{-1}]	22 (±14)	12 (±8)	23 (±14)	27 (±15)	<0.001
Eggs, egg products [g d^{-1}]	19 (±13)	15 (±12)	19 (±14)	21 (±13)	<0.001
Fats [g d^{-1}]	24 (±9)	18 (±7)	25 (±8)	29 (±8)	<0.001
Sugar, confectionery [g d^{-1}]	35 (±14)	34 (±12)	35 (±14)	36 (±15)	0.500
Cake [g d^{-1}]	51 (±23)	31 (±8)	48 (±18)	69 (±23)	<0.001
Non-alcoholic beverages [mL d^{-1}]	1638 (±264)	1625 (±218)	1671 (±252)	1597 (±302)	0.006
Alcoholic beverages [mL d^{-1}]	148 (±180)	138 (±164)	157 (±195)	141 (±166)	0.600
Condiments, sauces [g d^{-1}]	25 (±12)	39 (±15)	23 (±8)	17 (±4)	<0.001
Soups, bouillon [g d^{-1}]	32 (±30)	22 (±19)	29 (±22)	44 (±41)	<0.001
Miscellaneous [g d^{-1}]	15 (±18)	34 (±26)	13 (±9)	6 (±8)	<0.001
AHEI	47 (±10)	46 (±10)	46 (±9)	51 (±10)	<0.001

AHEI, alternate healthy eating index; p, p-value. [a] Data is shown as mean (±SD); [b] Kruskal-Wallis rank sum test.

stepwise regression method revealed that the intake of vegetables, cereals and cereal products, meat and meat products, fish and shellfish, eggs and egg products, and condiments and sauces (**Figure 2**A), as well as the carbohydrate and fat intake (Figure 2B) improved the model for the total cohort according to the AIC (see values in Tables S2, S3, Supporting Information). Increased consumption of cereals and cereal products, significantly predicts a reduced glucose $iAUC_{min}$, whereas a higher consumption of meat and meat products predicts a higher glucose $iAUC_{min}$ (Figure 2A). A higher carbohydrate intake significantly predicts a decrease in glucose $iAUC_{min}$ (Figure 2B).

Regarding the age groups, after Bonferroni correction, univariate linear regression models revealed that despite the intake of pulses and legumes as well as meat and meat products being positively associated with glucose $iAUC_{min}$ in middle-aged adults, no other diet-related parameters showed to be associated with the glucose $iAUC_{min}$ in the age groups (Table 3). Multivariate prediction models based on the stepwise regression method revealed a different set of predictors for glucose $iAUC_{min}$ in each age group (Figure 2). Increased consumption of cereals and cereal products, predicts a lower glucose $iAUC_{min}$ in young and older adults (Figure 2A). A higher intake of vegetables, meat and meat products, and eggs and egg products, predict a higher glucose $iAUC_{min}$ in middle-aged adults (Figure 2A). Overall, no dietary parameter was included as a predictor for the glucose $iAUC_{min}$ through all three age groups.

The proportions of variance of the glucose $iAUC_{min}$ explained by dietary parameters are shown in Table S4, Supporting Information. Food groups or nutrients explained up to 9% of the observed variation in glucose $iAUC_{min}$, whereas age-specific differences are apparent.

Cross-validation demonstrated that the addition of the food groups selected by stepwise regression improves the multivariate prediction models since all values of the cross-validated R^2 and the cross-validated RMSE improve compared to the basic model which only contains the mandatory variables. The addition of the macronutrients hardly improves the respective measures (Table S4, Supporting Information).

2.3. Cluster Analysis

Cluster analysis according to postprandial blood glucose trajectories revealed three clusters (**Figure 3**). Cluster A is the group with the largest share of participants (47.9%) and shows the lowest rise in mean postprandial blood glucose. The glucose peak of cluster A is reached after 30 min, and the glucose curve returns to its mean baseline value around 120 min. Cluster B is the second largest cluster with 40.9% of the participants and shows a higher rise in mean postprandial blood glucose. The mean glucose level reaches its peak around 60 min and returns to baseline values around 150 min. Cluster C represents 11.2% of the participants. The mean postprandial blood glucose of this

Table 3. Associations between diet-related parameters and glucose $iAUC_{min}$ during an OGTT.

Variable[b]	Total ($N = 412$)[a]			Young adults ($n = 87$)[a]			Middle-aged adults ($n = 196$)[a]			Older adults ($n = 129$)[a]		
	β	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
Total calorie intake	59.80	−453.94; 573.55	0.819	−204.11	−1138.52; 730.30	0.665	−119.10	−935.16; 696.96	0.774	355.92	−547.30; 1259.14	0.437
Carbohydrate intake	−324.67	−764.00; 114.67	0.147	32.07	−330.72; 394.86	0.861	116.60	30.82; 202.38	0.008	−120.17	−395.50; 155.16	0.389
Fat intake	−10.99	−437.77; 415.79	0.960	55.85	−307.67; 419.38	0.761	121.19	35.29; 207.08	0.006	−126.88	−401.79; 148.03	0.363
Protein intake	158.59	−286.38; 603.57	0.484	65.32	−293.80; 424.44	0.718	125.50	39.14; 211.87	0.005	−108.98	−391.34; 173.38	0.446
Fiber intake	−409.21	−1034.41; 216.00	0.199	45.95	−307.15; 399.05	0.796	121.92	35.98; 207.87	0.006	−122.49	−396.40; 151.43	0.378
Potatoes, other tubers	40.57	−472.08; 553.23	0.876	68.12	−293.18; 429.42	0.709	113.76	27.00; 200.52	0.010	−125.76	−401.52; 149.99	0.368
Vegetables	300.47	−230.03; 830.96	0.266	62.99	−295.34; 421.33	0.727	130.68	44.26; 217.09	0.003	−138.41	−413.86; 137.04	0.322
Pulses and legumes	162.50	−329.55; 654.55	0.517	78.16	−282.15; 438.46	0.667	134.82	48.37; 221.26	0.002	−125.01	−401.59; 151.58	0.373
Fruits and nuts	−20.37	−516.84; 476.09	0.936	76.91	−276.62; 430.44	0.666	119.60	32.35; 206.86	0.007	−131.98	−407.58; 143.61	0.345
Dairy products	−217.17	−690.90; 256.55	0.368	74.58	−285.21; 434.38	0.681	127.74	42.17; 213.32	0.004	−119.06	−394.77; 156.65	0.394
Cereals, cereals products	−1009.28	−1659.73; −358.84	0.002	−58.02	−421.53; 305.49	0.752	116.12	26.70; 205.54	0.011	−174.54	−444.59; 95.52	0.203
Meat, meat products	646.04	−1.91; 1293.98	0.051	37.28	−319.28; 393.85	0.836	135.27	48.81; 221.72	0.002	−118.53	−394.94; 157.89	0.398
Fish, shellfish	−193.06	−673.96; 287.84	0.430	66.79	−289.25; 422.83	0.710	129.75	43.80; 215.70	0.003	−126.8	−401.24; 147.64	0.362
Eggs, egg products	507.79	74.50; 941.08	0.022	63.20	−297.15; 423.55	0.728	102.08	14.51; 189.66	0.023	−133.5	−405.88; 138.89	0.334
Fats	−150.03	−706.49; 406.44	0.596	62.73	−301.94; 427.41	0.733	120.93	34.06; 207.80	0.007	−126.03	−400.11; 148.05	0.365
Sugar, confectionery	−103.23	−530.31; 323.85	0.635	69.28	−292.65; 431.21	0.704	121.09	34.33; 207.85	0.006	−113.97	−389.22; 161.29	0.414
Cake	−1.16	−567.25; 564.93	0.997	63.91	−295.25; 423.08	0.724	126.79	35.74; 217.83	0.007	−127.56	−404.30; 149.17	0.363
Non-alcoholic beverages	−229.04	−691.46; 233.39	0.331	60.38	−299.34; 420.09	0.739	121.63	36.36; 206.91	0.005	−124.82	−400.53; 150.90	0.372
Alcoholic beverages	519.13	23.46; 1014.79	0.040	32.43	−324.20; 389.06	0.857	112.96	25.78; 200.15	0.011	−131.39	−405.76; 142.98	0.345
Condiments, sauces	−513.63	−1119.25; 91.98	0.096	75.28	−282.73; 433.29	0.677	120.78	28.55; 213.00	0.011	−133.89	−410.28; 142.50	0.340
Soups, bouillon	17.21	−476.18; 510.59	0.945	35.09	−329.08; 399.26	0.848	119.52	32.35; 206.69	0.007	−122.08	−399.38; 155.22	0.385
Miscellaneous	−137.65	−744.26; 468.97	0.656	48.90	−313.32; 411.11	0.789	128.11	35.96; 220.25	0.007	−120.58	−396.39; 155.24	0.389
AHEI	−266.63	−723.35; 190.10	0.252	35.83	−309.57; 381.23	0.837	121.98	34.34; 209.62	0.007	−122.89	−398.01; 152.22	0.378

AHEI, alternate healthy eating index; β, beta coefficient; CI, confidence interval; p, p-value. [a] Linear regression adjusted for total energy intake, BMI, sex, and age; [b] Variables are scaled and winsorized.

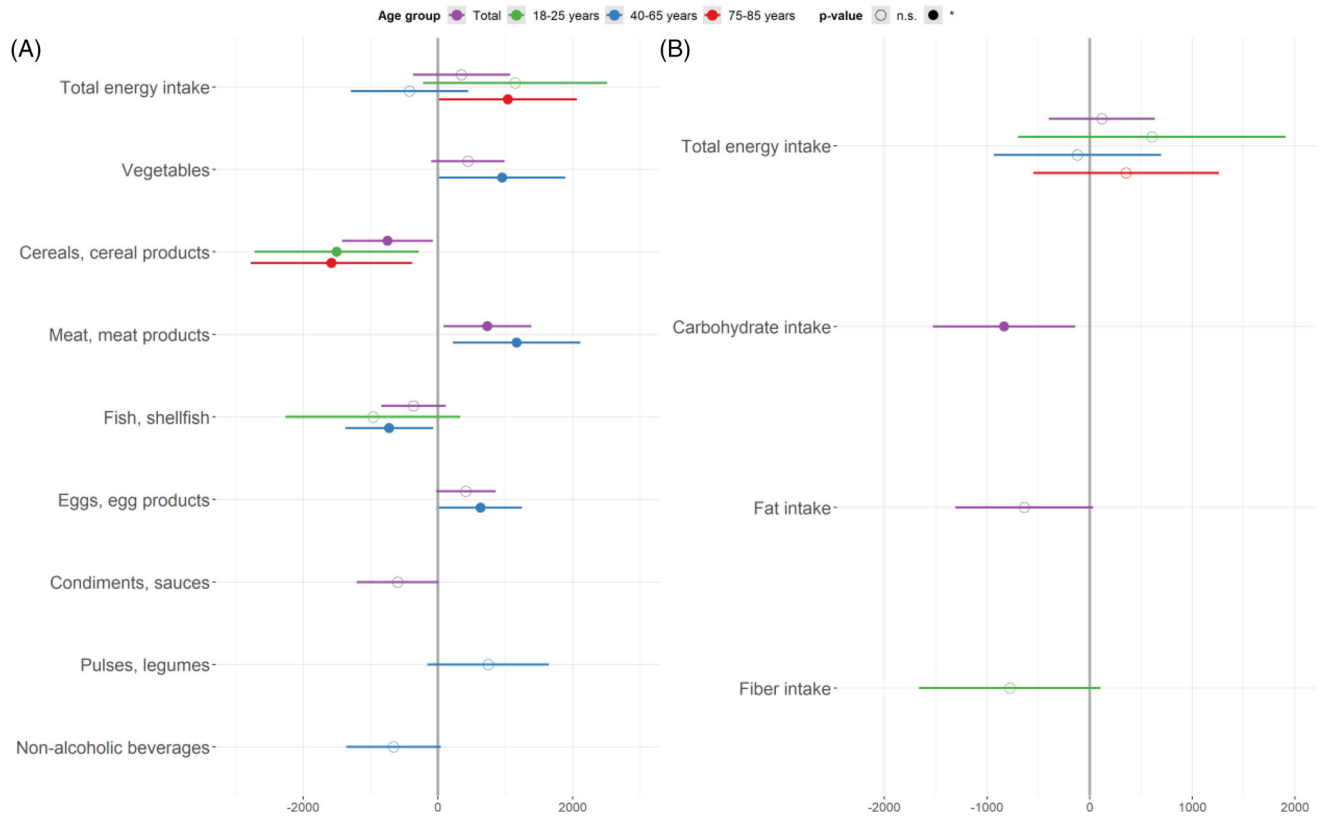

Figure 2. Forest plot. A) Food groups B) and nutrients as predictors for glycemic response (glucose $iAUC_{min}$) during an OGTT based on the stepwise multivariate linear regression model. Different colors refer to age groups and shape refers to significance level (n.s., not significant; *, $p < 0.005$). Predictors were scaled, under-, or overreporters were limited from analysis by winsorization.

cluster rises the highest, reaches its peak around 60 min, and decreases to the baseline value around 180 min (Figure 3). The mean glucose $iAUC_{min}$ increases continuously from cluster A to C (6615 ± 2167, 11632 ± 2474, 17726 ± 3163 mg*min dL^{-1}, respectively; data not shown).

Table 4 summarizes the baseline characteristics of each cluster. Sex is equally distributed in clusters A and B, whereas male participants are overrepresented (76%) in cluster C. Almost all baseline parameters significantly differ between clusters, with exception of diastolic blood pressure, and total and LDL-cholesterol. Overall, cluster A is characterized by the lowest mean age (51 ± 22 years), BMI (25.0 ± 4.1 kg m^{-2}), fat mass (30 ± 11%), and waist circumferences (87 ± 14 cm). Further, health-related parameters such as blood pressure (127/82 ± 20/10 mmHg), fasting blood glucose (90 ± 8 mg dL^{-1}), or triacylglycerol levels (102 ± 48 mg dL^{-1}) are significantly lower in cluster A. The AHEI does not significantly differ between clusters. There are characteristic differences in the consumption of nutrients and food groups (Table 4).

Table 5 displays the results of the multinomial logistic regression models. Overall, a higher intake of carbohydrates, dairy products, cereals and cereal products, and condiments and sauces lead to a higher odds ratio for assignment to cluster A or B in comparison to cluster C. With a higher intake of pulses and legumes, eggs and egg products, and alcoholic beverages, the odds ratio for assignment to cluster C is higher in comparison to cluster A or B.

Figure 4 visualizes the stepwise regression model, which was applied to evaluate which dietary predictors best explain the variability of the cluster assignment (Table S5, Supporting Information). Overall, food groups such as cereals and cereal products, and non-alcoholic beverages lead to an improvement of the model according to the AIC (Figure 4A). Higher consumption of cereals and cereal products, for example, indicates a higher likelihood of assignment to cluster A (OR 3.79, 95% CI 1.90–7.53, $p < 0.001$) and B (OR 2.33, 95% CI 1.19–4.56, $p = 0.014$) compared to cluster C. For the nutrient intake, only carbohydrate intake entered the model as a predictor for cluster assignment (Figure 4B). A higher intake of carbohydrates, predicts that participants are less likely to be assigned to cluster C in comparison to clusters A or B (OR 1.60, 95% CI 1.07–2.41, $p = 0.023$ and OR 1.35, 95% CI 0.91–2.01, $p = 0.137$, respectively).

3. Discussion

Our findings demonstrate that the investigated anthropometric, blood, and vital parameters change with age. There is a shift in body composition and other health-related parameters, such as blood pressure or lipid profile. Mean fasting blood glucose levels were not significantly different between age groups. This might

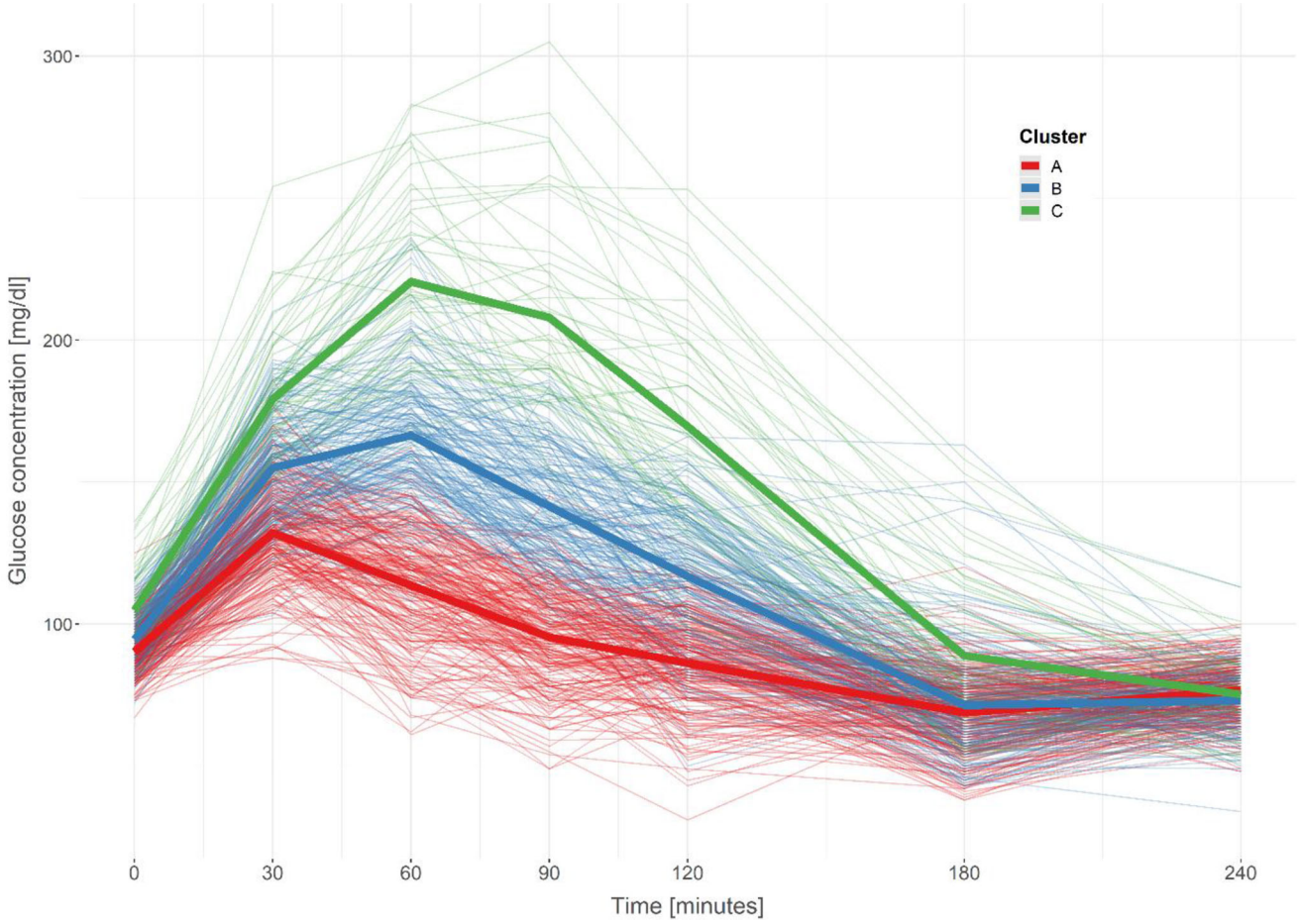

Figure 3. Individually fitted blood glucose trajectories with color-coded cluster assignment (cluster A = red; cluster B = blue B; cluster C = green). Means of blood glucose trajectories of each cluster are represented by the bold line of the corresponding color.

be due to adaptation mechanisms of insulin secretion to maintain a normal glucose level in the fasting state.

In agreement with previous studies,[1,3] we observed high inter-individual variability of glycemic response to an OGTT, even within each age group. Glucose trajectories of people with impaired metabolic resilience, do not return to baseline values within 2 h.[8] In our study, we observed that baseline glucose was similar in each age group, but the postprandial glucose trajectories of middle-aged and older adults were biphasic and reached their peak 30 min later compared with young adults. These observations suggest that age-depended differences in PPGR during an OGTT are attributable to age-dependent changes in metabolic resilience.[6] Differences in the PPGR despite similar fasting glucose levels were also observed elsewhere.[5,11] Overall, carbohydrate metabolism deteriorates with age,[14] which is further confirmed by the here observed higher glucose $iAUC_{min}$ to an OGTT.

The distribution of the intake of macronutrients or fiber, the intake of almost all main food groups, and the AHEI significantly differ between each age group, illustrating generation-specific food preferences. Young adults follow an overall less healthy dietary pattern in comparison to older adults, supporting previous findings.[15] As stated elsewhere,[16] we observed that older adults have the highest AHEI score, describing a greater adherence to a healthier diet. Some publications on German cohorts have equally demonstrated, that older adults are more likely to follow a healthier diet, characterized by lower consumption of meat or soft drinks and the highest intake of fish, vegetables, fruits, or whole grains in comparison with younger participants.[17,12]

Results based on nutrient intake indicate that the usual carbohydrate intake might be a significant predictor of a decrease in the glycemic response in the total cohort (Table 2). Since carbohydrates are absorbed as glucose in the bloodstream, leading to the release of insulin from the pancreatic β-cells and triggering several pathways of glucose metabolism,[7] it is assumed that if this process is frequently activated by stress stimuli, more adaptive mechanisms are likely to occur, possibly cumulatively affecting metabolic resilience in the long term.[7,8] However, Zeevi et al.[3] described that the PPGR to different meals varies, although the total amount of consumed carbohydrates was similar. This was confirmed by another publication, showing that carbohydrate intake explains less than 25% of postprandial variability.[18] It has to be mentioned that these results are not fully comparable with our findings, since these studies evaluated what effect a specific amount of carbohydrate has on the postprandial response, instead of looking at the long-term effects of the habitual diet as a whole.

Table 4. Baseline characteristics of the three clusters.

	Variable	Cluster A $n = 210$[a)]	Cluster B $n = 179$[a)]	Cluster C $n = 49$[a)]	p[b)]
	Age [years]	51 (±22)	58 (±19)	65 (±15)	<0.001
	Women	118/210 (±56%)	90/179 (±50%)	12/49 (±24%)	
Anthropometry	Weight [kg]	73 (±14)	78 (±16)	85 (±16)	<0.001
	BMI [kg m^{-2}]	25.0 (±4.1)	26.5 (±4.5)	28.4 (±4.3)	<0.001
	Fat mass [%]	30 (±11)	32 (±9)	33 (±8)	0.023
	WC [cm]	87 (±14)	94 (±14)	102 (±14)	<0.001
	HC [cm]	100 (±9)	102 (±9)	103 (±9)	0.002
Health status	Systolic BP [mmHg]	127 (±20)	133 (±20)	136 (±15)	<0.001
	Diastolic BP [mmHg]	82 (±10)	84 (±10)	84 (±9)	0.056
	Glucose [mg dL^{-1}]	90 (±8)	95 (±9)	105 (±14)	<0.001
	Total cholesterol [mg dL^{-1}]	215 (±44)	214 (±41)	208 (±43)	0.600
	TAG [mg dL^{-1}]	102 (±48)	113 (±53)	135 (±68)	<0.001
	HDL-C [mg dL^{-1}]	64 (±17)	60 (±16)	56 (±17)	0.002
	LDL-C [mg dL^{-1}]	131 (±40)	134 (±38)	131 (±38)	0.600
Diet	Total energy intake [kcal d^{-1}]	1913 (±388)	1940 (±399)	2048 (±343)	0.016
	Protein intake [E%]	15.97 (±1.57)	16.14 (±1.62)	15.84 (±1.60)	0.300
	Fat intake [E%]	39.9 (±3.2)	40.3 (±3.7)	40.7 (±3.9)	0.300
	Carbohydrate intake [E%]	43.8 (±3.9)	42.9 (±4.5)	41.5 (±4.5)	<0.001
	Fiber intake [g d^{-1}]	21.3 (±6.2)	20.7 (±6.6)	20.0 (±5.1)	0.300
	Potatoes, other tubers [g d^{-1}]	55 (±23)	58 (±21)	63 (±24)	0.011
	Vegetables [g d^{-1}]	210 (±63)	202 (±72)	179 (±71)	<0.001
	Pulses, legumes [g d^{-1}]	6.66 (±5.39)	6.39 (±4.76)	6.11 (±3.33)	0.400
	Fruits, nuts [g d^{-1}]	186 (±93)	195 (±102)	202 (±99)	0.600
	Dairy products [g d^{-1}]	241 (±134)	237 (±116)	202 (±129)	0.046
	Cereals, cereal products [g d^{-1}]	189 (±62)	177 (±57)	169 (±43)	0.120
	Meat, meat products [g d^{-1}]	102 (±39)	113 (±42)	132 (±47)	<0.001
	Fish, shellfish [g d^{-1}]	20 (±13)	22 (±15)	25 (±14)	0.039
	Eggs, egg products [g d^{-1}]	17 (±11)	20 (±14)	25 (±18)	<0.001
	Fats [g d^{-}]	23 (±8)	26 (±10)	28 (±9)	0.007
	Sugar, confectionery [g d^{-1}]	35 (±14)	35 (±14)	36 (±16)	0.900
	Cake [g d^{-1}]	48 (±23)	52 (±22)	60 (±26)	0.004
	Non-alcoholic beverages [mL d^{-1}]	1663 (±254)	1624 (±273)	1581 (±252)	0.048
	Alcoholic beverages [mL d^{-1}]	121 (±135)	150 (±188)	252 (±263)	0.030
	Condiments, sauces [g d^{-1}]	26 (±13)	24 (±11)	21 (±6)	0.016
	Soups, bouillon [g d^{-1}]	31 (±31)	33 (±29)	39 (±35)	0.042
	Miscellaneous [g d^{-1}]	18 (±19)	13 (±17)	12 (±11)	<0.001
	AHEI	48 (±10)	47 (±10)	47 (±11)	0.600

AHEI, alternate healthy eating index; BMI, body mass index; BP, blood pressure; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; p, p-value; TAG, triacylglycerol; WC, waist circumference. [a)] Data are shown as mean (SD) or n/N(%); [b)] Kruskal–Wallis rank sum test; Pearson's Chi-squared test.

We observed that the AHEI is not associated with $iAUC_{min}$. Similarly, it has been reported that the habitual diet, measured by a food frequency questionnaire, has only a small effect (<2%) on an individual's PPGR (iAUC 0–2 h).[1] It has to be mentioned, that there is no universally valid definition for the term "habitual diet" and the dietary data of this publication is not fully comparable with our dietary dataset.

Results based on food groups indicate that cereals and cereal products have a decreasing effect on the glycemic response for the total cohort and two age groups. As reviewed by Desmarchelier et al.,[19] dietary fiber such as β-glucan found in oats can decrease postprandial lipemia. Several mechanisms, including slowed gastric emptying and modified insulin secretion, are discussed to be involved,[19] whereby one can assume that such mechanisms might also influence glucose metabolism. In this work, only the main food group "cereals and cereal products" was evaluated. Therefore, no assumptions can be made regarding which subcategory of cereals might be possibly responsible for the observed effects, especially since dietary fiber alone did not show any associations with PPGR. All other investigated food

Table 5. Associations between diet-related parameters and cluster assignment.

Variable[b]	Cluster A → C[a]			Cluster B → C[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
Total energy intake	0.89	−0.54; 0.3	0.576	0.92	−0.49; 0.33	0.703
Carbohydrate intake	1.60	0.07; 0.88	0.023	1.35	−0.1; 0.7	0.137
Fat intake	0.83	−0.57; 0.19	0.321	0.89	−0.49; 0.25	0.530
Protein intake	1.01	−0.4; 0.42	0.958	1.17	−0.25; 0.56	0.442
Fiber intake	1.18	−0.43; 0.76	0.581	1.10	−0.49; 0.68	0.745
Potatoes, other tubers	1.10	−0.32; 0.52	0.644	1.04	−0.37; 0.45	0.837
Vegetables	0.78	−0.8; 0.29	0.366	1.00	−0.54; 0.54	0.988
Pulses, legumes	0.72	−0.79; 0.15	0.176	0.79	−0.71; 0.23	0.320
Fruits, nuts	0.80	−0.67; 0.21	0.314	0.88	−0.56; 0.31	0.571
Dairy products	1.40	−0.14; 0.82	0.169	1.45	−0.1; 0.85	0.127
Cereals, cereal products	3.22	0.51; 1.83	0.001	2.07	0.08; 1.38	0.028
Meat, meat products	0.76	−0.83; 0.28	0.327	1.03	−0.51; 0.58	0.901
Fish, shellfish	1.12	−0.29; 0.51	0.577	1.01	−0.39; 0.4	0.975
Eggs, egg products	0.74	−0.63; 0.02	0.067	0.85	−0.46; 0.14	0.291
Fats	0.97	−0.48; 0.41	0.889	1.09	−0.35; 0.52	0.699
Sugar, confectionery	1.05	−0.31; 0.41	0.802	0.97	−0.39; 0.33	0.865
Cake	0.87	−0.58; 0.3	0.535	0.83	−0.62; 0.24	0.396
Non-alcoholic beverages	1.24	−0.2; 0.63	0.310	1.00	−0.41; 0.41	0.994
Alcoholic beverages	0.71	−0.7; 0.01	0.057	0.80	−0.55; 0.11	0.193
Condiments, sauces	1.68	−0.22; 1.26	0.169	1.56	−0.29; 1.19	0.236
Soups, bouillon	0.90	−0.47; 0.26	0.575	0.91	−0.44; 0.26	0.616
Miscellaneous	0.81	−0.76; 0.35	0.459	0.59	−1.12; 0.07	0.086
AHEI	0.85	−0.58; 0.25	0.430	0.78	−0.66; 0.17	0.242

AHEI, alternate healthy eating index; CI, confidence interval; OR, odds ratio; *p*, *p*-value. [a] Multinominal logistic regression ($N = 412$) adjusted for total energy intake, BMI, sex, and age; [b] Variables are scaled and winsorized.

groups showed either no association or rather sporadic associations through age groups, with no discernible pattern. Although a previous work does suggest that meal composition plays a significant role in the glycemic response,[18] we cannot conclude that the here observed associations between the intake of food groups with the glucose $iAUC_{min}$ are due to the age-specific differences in dietary preferences or whether other determinants influenced these results.

There is no single diet-related parameter that predicts glucose $iAUC_{min}$ in all three age groups, rather each age group has shown a specific set of predictors. Finally, it should be mentioned that food groups are not consumed individually and do not reflect an individual's food choices.[12] Consequently, a breakdown of the main food groups into their subcategories would give more insights into which food components have higher health implications and are possibly associated with changes in the glycemic response.

We were able to identify three clusters of postprandial blood glucose excursions, that are characterized by distinct metabolic phenotypes. Cluster A shows the lowest metabolic risk for chronic diseases and the healthiest dietary pattern. Riedl et al.[13] described that unfavorable food choices (low intake of fruits, and a high intake of meat and sugar-sweetened beverages) are significantly associated with T2DM, which was assessed through an OGTT. This finding implies, that the habitual diet might have a long-term effect on postprandial glucose metabolism, increasing the risk for later metabolic diseases, such as T2DM. Morris et al.[20] clustered their study population based on metabolic traits as well as characteristics of their PPGR to an OGTT and were able to identify four different metabotypes, with one cluster being at "metabolic risk" and having the most differential response to an OGTT. Another publication described that a metabotype in which the majority of participants showed a healthier dietary pattern, had a reduced glycemic response.[5]

Overall, univariate and multivariate regression confirmed that carbohydrate intake and the consumption of cereals and cereal products show an association with cluster assignment, and can significantly predict cluster assignment based on the shape of postprandial glycemic trajectories.

We acknowledge that the sample size for each age group is limited, possibly affecting statistical power due to stratification. However, since age group stratification was already considered in the recruitment of participants, we were able to evaluate age-specific differences in the association between diet and glucose $iAUC_{min}$.

In addition, it should be noted that with the applied diet assessment tools, recall bias or misreporting cannot be ruled out. However, we had substantial dietary data available, which enabled us to investigate not only the effect of specific food items on postprandial metabolic response but also the effect of the habitual diet.

We acknowledge that the postprandial response to an OGTT does not correspond to "real-life" postprandial metabolism, since it only reflects the ingestion of a sugary drink.[21] Further, there is no available data regarding food consumption the day prior to the OGTT in this work. Without this information, we cannot verify whether participants adhered to standardization specifications before the OGTT and how the food consumption of the previous day might influence the postprandial glycemic response. Nevertheless, the OGTT provides valuable insights into glucose metabolism, since it was carried out based on a standardized protocol by trained staff, enabling us to precisely control the glycemic stimulus and measure different rates of glucose absorption.

Due to the high complexity of the available data on habitual diet, we limited our primary outcome to the glucose $iAUC_{min}$. However, several metabolic pathways are synergistically activated through a homeostasis-changing stimulus. Therefore, metabolomics data could better help to unravel the complexity of metabolic resilience.

The AUC as an outcome gives insights into the overall size of the glycemic response.[4] We should keep in mind, that the AUC is estimated based on the integrated function between specific time points and is, therefore, only a simplified proxy to evaluate blood glucose variations in a time frame. However, we were able to collect blood samples covering 4 h of the postprandial state, which we consider well-suited to characterize the glycemic response to an OGTT.

Finally, due to the cross-sectional design of this study, we cannot make assumptions about causal effects of diet on postprandial glycemic response. In this context, it is conceivable that people with a healthier lifestyle show better metabolic resilience

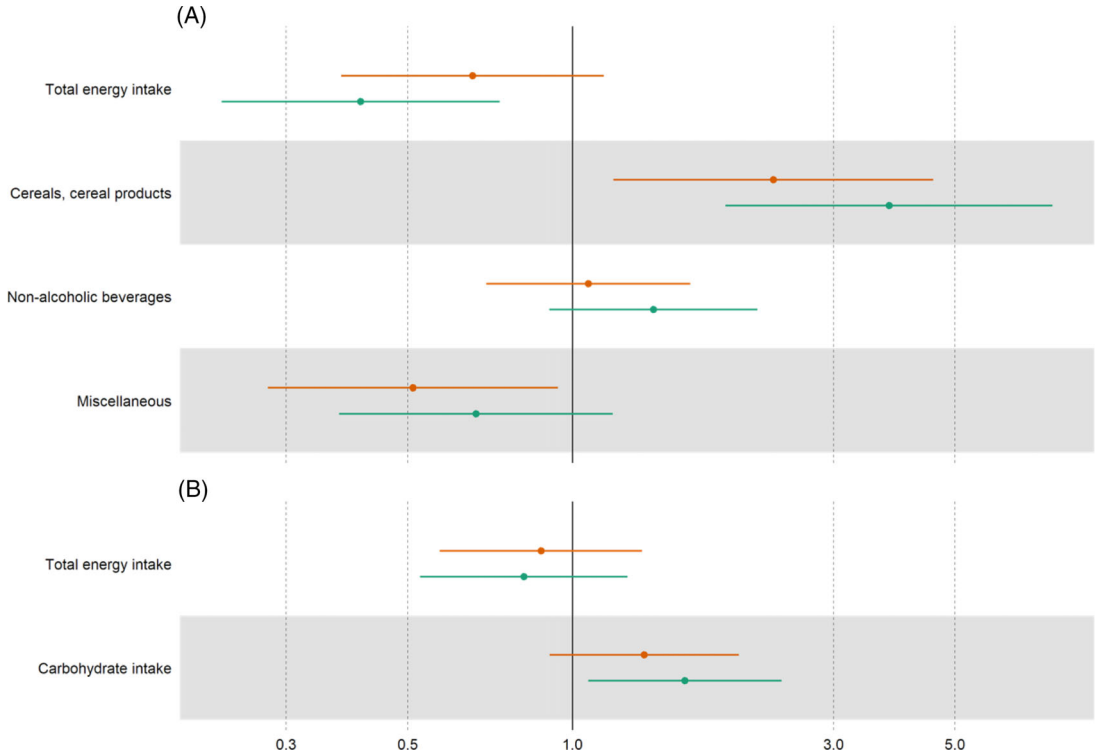

Figure 4. Forest plot. A) Food groups B) and nutrients as predictors for cluster assignment based on the stepwise multivariate linear model. Odds ratio for assignment to cluster A in comparison to cluster C (green) and odds ratio for assignment to cluster B in comparison to cluster C (orange). Predictors were scaled, under-, or overreporters were limited from analysis by winsorization.

to metabolic perturbations. In contrast, it is also possible that people with a higher risk for chronic disease follow a healthier lifestyle, to reverse unfavorable metabolic responses or slow down their long-term consequences. Therefore, both longitudinal and intervention studies considering habitual diet as a predicting factor for PPGR in different life stages are needed.

This study provides insights into diet-related metabolic consequences of an OGTT in defined age groups. We were able to demonstrate that diet-related factors such as the usual intake of cereals and cereal products are associated with postprandial glycemic response. Moreover, these observations are confirmed if the cohort is clustered by the shape of their postprandial glucose trajectories. Intervention studies including deep phenotyping of participants are needed to better understand interactions involved in postprandial metabolism and to elucidate how diet can influence metabolic resilience. Such data might be of importance for the development of personalized prevention strategies for people at risk. The vision is, that diet can be optimized based on age and the postprandial phenotype, to counteract dysfunctions in the postprandial metabolism.

4. Experimental Section

Study Design and Setting: A study cohort with cross-sectional data of defined age groups was established within the *enable* cluster, an interdisciplinary consortium of nutrition research. Data collection of the *enable* cohort took place between 2016 and 2018 in Freising and Nuremberg, Germany. Enrolled participants attended two face-to-face visits. Clinical examinations (e.g., anthropometry, blood samples, and nutritional behavior) were assessed in visit 1. During visit 2, an OGTT was performed and questionnaires from various disciplines were completed. Further details on the study design were described elsewhere.[22]

The study protocol had been approved by the local Ethics Review Committee of the School of Medicine, Technical University of Munich (approval no. 452/15) and of the Friedrich-Alexander-University Erlangen-Nuremberg (approval no. 291/15B). The trial had been registered in the German Clinical Trials Register (DRKS00009797). All participants provided written informed consent.

Study Population and Eligibility Criteria: Healthy adults of Caucasian ancestry with a BMI between 18.5 and 35.0 kg m^{-2} of different age groups were recruited: young adults aged 18–25 years ($n = 94$), middle-aged adults (40–65 years) ($n = 205$), and older adults aged 75–85 years ($n = 160$).

Exclusion criteria included severe health conditions (such as chronic infections, endocrine diseases such as T2DM, untreated hypertension, history of myocardial infarction or stroke, heart failure, cancer, autoimmune diseases, stomach ulcer, psychological or neurological disease, or severe lung, liver, and kidney diseases), blood transfusion within the past 3 months, immobility, active smokers, weight loss >5% in the previous 3 months and participation in intervention studies.

Oral Glucose Tolerance Test: After a 12-h overnight fast, the OGTT was carried out. The OGTT-drink was prepared with 82.5 g glucose monohydrate (≥99.5% α-D (+)-glucose monohydrate Ph. Eur., Carl Roth GmbH + Co. KG, Germany), providing an equivalent to 75 g glucose, and filled up to 300 mL with boiled tap water. Blood was drawn at baseline and 30, 60, 90, 120, 180, and 240 min after consuming the OGTT drink. For the measurement of plasma glucose, a plasma-calibrated rapid tester (HemoCue Glucose 201+ System, HemoCue AB, Sweden) was used.

Dietary Assessment: Habitual diet was recorded by a web-based food frequency questionnaire (FFQ)[23] and two repeated 24-h food lists,[24] applied during visit 2. To account for seasonal changes in food intake, the second 24-h food list was repeated 3 months later. The 24-h food lists

are similar to 24-h recalls but are intended for repeated applications to assess the probable consumption of food groups instead of the portion size.[24] Based on these data, the usual food intake was derived by a two-part statistical model via mixed models as described elsewhere.[25] For nutrient intake calculation, food items were further linked to the German food composition table (Bundeslebensmittelschlüssel, version 3.02). Table S1, Supporting Information, gives a detailed overview of all main food groups and their corresponding subcategories. Data were used to estimate the modified alternate healthy eating index (AHEI).[26] The AHEI score can reach a maximum of 100 points, meaning that one of the 10 available food components is assigned to a value ranging from 0 to 10; data on trans fatty acids were not available. The higher the score, the healthier the dietary pattern is considered.

Assessment of Clinical Parameters: Anthropometric measurements were conducted in underwear, without shoes, and with an empty bladder. Body composition was assessed by bioelectrical impedance analysis (Seca mBCA 515; Seca GmbH + Co KG, Germany). Height was assessed using a stadiometer. Waist and hip circumferences were measured in a standing position, with a non-stretch measuring tape.

Systolic and diastolic blood pressure were assessed using the Omron M8 comfort (OMRON, Germany) blood pressure monitor with a cuff around the upper arm.

Blood was drawn from all participants in the fasted state by venipuncture. Collected blood was stored at room temperature until sent to an external lab (SYNLAB Medizinisches Versorgungszentrum Labor München Zentrum GbR, Munich, Germany) for the analysis of routine parameters.

Statistical Analysis: Statistical analysis was performed using the RStudio programming environment version 1.3.959 that uses R version 4.0.0 (R Core Team, 2020, http://www.r-project.org). *P*-values ≤0.05 were regarded as statistically significant.

The $iAUC_{min}$ was calculated using the trapezoidal rule, taking the lowest glucose concentration as a baseline value into account.

To evaluate the association of habitual diet with glucose $iAUC_{min}$, linear regression models were fitted. Models were adjusted for total energy intake, BMI, sex, and age. After Bonferroni correction for the total number of individual dietary parameters, a *p*-value ≤0.002 was considered statistically significant.

To get a simplified and interpretable prediction model, a stepwise regression method with both forward and backward selection was applied to estimate a multivariate regression model. Total energy intake, BMI, sex, and age were chosen as mandatory predictors necessary to adjust for their respective effects. Macronutrient and fiber intake, as well as the intake of the main food groups, were chosen as facultative predictors which were only included in the model if their inclusion leads to an improved model. Potential models were compared using the Akaike information criteria (AIC).[27] The predictive power of the multivariate models was evaluated via 10-fold cross-validation, comparing the selected models to the basic models only containing the mandatory predictors. Cross-validated R^2 and cross-validated root mean squared error (RMSE) were used as predictive performance measures.

All predictor variables were scaled before running the regression models so that all parameter estimates referred to the average change of the response variable (glucose $iAUC_{min}$) if the corresponding variable was increased by one standard deviation. Furthermore, under- and overreporters were winsorized with a percentile limit set at 0.01.

Cluster analysis was performed to identify homogenous subgroups, based on their postprandial glucose trajectories. Longitudinal *k*-means clustering was used as proposed by Genolini et al.,[28] using the classification criteria by Calinski and Harabasz.[29] Multinominal logistic regression was performed to assess the association between diet-related factors and the glucose $iAUC_{min}$ to an OGTT. Finally, the stepwise regression method was applied to receive multivariate models.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The authors acknowledge all participants of the *enable* study. They further thank Margot Maier, Sandra Eckardt, Rebecca Cruiz-Aguilar, and Karin Lietzau for the support with phenotyping, data collection, and monitoring; Irmgard Sperrer and Manuela Hubersberger for technical assistance; Johanna Thalhuber and Dr. Kerstin Dressel for support in the recruitment; Dr. Alfred Zollner and Adrian Balteanu (Munich Study Center) for support in data management; and Lucia Ciesielska for her support in the assessment of dietary data. This work was funded by a grant from the German Federal Ministry of Education and Research (grant no. 01EA1409H, 01EA1807H, 01EA1409C, 01EA1807C, 01EA1409E, 01EA1807E, and 01EA1709) within the framework of the *enable* Nutrition Cluster. This work is cataloged by the Steering Committee as *enable* publication number 90 (www.enable-cluster.de).

Conflict of Interest

The authorC.H. is a member of the scientific advisory board of 4 sigma GmbH (Oberhaching). The remaining authors declare no conflict of interest.

Author Contributions

A.R., G.S., C.H. conceived and designed the analysis; B.B., T.S., D.V. were responsible for data collection and management; B.B., T.S., D.V., H.H. were responsible for study management; A.R. and G.S. performed data analysis; N.W., J.L. estimated the habitual intake of food and nutrients, and supported the statistical analysis; A.R. wrote the first draft of the manuscript. All authors reviewed the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

food groups, nutrients, nutrition, oral glucose tolerance test, postprandial metabolism

Received: February 21, 2022
Revised: May 13, 2022
Published online: July 1, 2022

[1] S. E. Berry, A. M. Valdes, D. A. Drew, F. Asnicar, M. Mazidi, J. Wolf, J. Capdevila, G. Hadjigeorgiou, R. Davies, H. Al Khatib, C. Bonnett, S. Ganesh, E. Bakker, D. Hart, M. Mangino, J. Merino, I. Linenberg, P. Wyatt, J. M. Ordovas, C. D. Gardner, L. M. Delahanty, A. T. Chan, N. Segata, P. W. Franks, T. D. Spector, *Nat. Med.* **2020**, *26*, 964.

[2] S. Krug, G. Kastenmüller, F. Stückler, M. J. Rist, T. Skurk, M. Sailer, J. Raffler, W. Römisch-Margl, J. Adamski, C. Prehn, T. Frank, K.-H. Engel, T. Hofmann, B. Luy, R. Zimmermann, F. Moritz, P. Schmitt-Kopplin, J. Krumsiek, W. Kremer, F. Huber, U. Oeh, F. J. Theis, W. Szymczak, H. Hauner, K. Suhre, H. Daniel, *FASEB J.* **2012**, *26*, 2607.

[3] D. Zeevi, T. Korem, N. Zmora, D. Israeli, D. Rothschild, A. Weinberger, O. Ben-Yacov, D. Lador, T. Avnit-Sagi, M. Lotan-Pompan, J. Suez, J. A. Mahdi, E. Matot, G. Malka, N. Kosower, M. Rein, G. Zilberman-Schapira, L. Dohnalová, M. Pevsner-Fischer, R. Bikovsky, Z. Halpern, E. Elinav, E. Segal, *Cell* **2015**, *163*, 1079.

[4] D. J. Vis, J. A. Westerhuis, D. M. Jacobs, J. P. M. van Duynhoven, S. Wopereis, B. van Ommen, M. M. W. B. Hendriks, A. K. Smilde, *Metabolomics* **2015**, *11*, 50.
[5] J. Fiamoncini, M. Rundle, H. Gibbons, E. L. Thomas, K. Geillinger-Kästle, D. Bunzel, J.-P. Trezzi, Y. Kiselova-Kaneva, S. Wopereis, J. Wahrheit, S. E. Kulling, K. Hiller, D. Sonntag, D. Ivanova, B. van Ommen, G. Frost, L. Brennan, J. Bell, H. Daniel, *FASEB J.* **2018**, *32*, 5447.
[6] B. H. Goodpaster, L. M. Sparks, *Cell Metab.* **2017**, *25*, 1027.
[7] B. van Ommen, J. van der Greef, J. M. Ordovas, H. Daniel, *Genes Nutr.* **2014**, *9*, 423.
[8] A. F. M. Kardinaal, M. J. van Erk, A. E. Dutman, J. H. M. Stroeve, E. van de Steeg, S. Bijlsma, T. Kooistra, B. van Ommen, S. Wopereis, *FASEB J.* **2015**, *29*, 4600.
[9] A. Riedl, E. Hillesheim, N. Wawro, C. Meisinger, A. Peters, M. Roden, F. Kronenberg, C. Herder, W. Rathmann, H. Völzke, M. Reincke, W. Koenig, H. Wallaschofski, H. Daniel, H. Hauner, L. Brennan, J. Linseisen, *Mol. Nutr. Food Res.* **2020**, *64*, 1900918.
[10] a) H. Meng, N. R. Matthan, L. M. Ausman, A. H. Lichtenstein, *Am. J. Clin. Nutr.* **2017**, *105*, 842; b) S. Sato, E. B. Parr, B. L. Devlin, J. A. Hawley, P. Sassone-Corsi, *Mol. Metab.* **2018**, *16*, 1.
[11] A. Matone, C. M. O'Grada, E. T. Dillon, C. Morris, M. F. Ryan, M. Walsh, E. R. Gibney, L. Brennan, M. J. Gibney, M. J. Morine, H. M. Roche, *Mol. Nutr. Food Res.* **2015**, *59*, 2279.
[12] G. Pestoni, A. Riedl, T. A. Breuninger, N. Wawro, J.-P. Krieger, C. Meisinger, W. Rathmann, B. Thorand, C. Harris, A. Peters, S. Rohrmann, J. Linseisen, *Eur. J. Nutr.* **2021**, *60*, 2331.
[13] A. Riedl, N. Wawro, C. Gieger, C. Meisinger, A. Peters, W. Rathmann, W. Koenig, K. Strauch, A. S. Quante, B. Thorand, C. Huth, H. Daniel, H. Hauner, J. Linseisen, *Eur. J. Nutr.* **2020**, *59*, 1357.
[14] a) R. Basu, C. Dalla Man, M. Campioni, A. Basu, G. Klee, G. Toffolo, C. Cobelli, R. A. Rizza, *Diabetes* **2006**, *55*, 2001; b) S. Ravera, M. Podestà, F. Sabatini, M. Dagnino, D. Cilloni, S. Fiorini, A. Barla, F. Frassoni, *Sci. Rep.* **2019**, *9*, 10347.
[15] A. Afshin, P. J. Sur, K. A. Fay, L. Cornaby, G. Ferrara, J. S. Salama, E. C. Mullany, K. H. Abate, C. Abbafati, Z. Abebe, M. Afarideh, A. Aggarwal, S. Agrawal, T. Akinyemiju, F. Alahdab, U. Bacha, V. F. Bachman, H. Badali, A. Badawi, I. M. Bensenor, E. Bernabe, S. K. K. Biadgilign, S. H. Biryukov, L. E. Cahill, J. J. Carrero, K. M. Cercy, L. Dandona, R. Dandona, A. K. Dang, M. G. Degefa, et al., *Lancet* **2019**, *393*, 1958.
[16] Z. Shan, Y. Li, M. Y. Baden, S. N. Bhupathiraju, D. D. Wang, Q. Sun, K. M. Rexrode, E. B. Rimm, L. Qi, W. C. Willett, J. E. Manson, Q. Qi, F. B. Hu, *JAMA Intern. Med.* **2020**, *180*, 1090.
[17] T. Heuer, C. Krems, K. Moon, C. Brombach, I. Hoffmann, *Br. J. Nutr.* **2015**, *113*, 1603.
[18] O. Ben-Yacov, A. Godneva, M. Rein, S. Shilo, D. Kolobkov, N. Koren, N. Cohen Dolev, T. Travinsky Shmul, B. C. Wolf, N. Kosower, K. Sagiv, M. Lotan-Pompan, N. Zmora, A. Weinberger, E. Elinav, E. Segal, *Diabetes Care* **2021**, *44*, 1980.
[19] C. Desmarchelier, P. Borel, D. Lairon, M. Maraninchi, R. Valéro, *Nutrients* **2019**, *11*, 1299.
[20] C. Morris, C. O'Grada, M. Ryan, H. M. Roche, M. J. Gibney, E. R. Gibney, L. Brennan, *PLoS One* **2013**, *8*, e72890.
[21] Q. Wang, J. Jokelainen, J. Auvinen, K. Puukka, S. Keinänen-Kiukaanniemi, M.-R. Järvelin, J. Kettunen, V.-P. Mäkinen, M. Ala-Korpela, *BMC Med.* **2019**, *17*, 217.
[22] B. Brandl, T. Skurk, R. Rennekamp, A. Hannink, E. Kiesswetter, J. Freiherr, S. Ihsen, J. Roosen, M. Klingenspor, D. Haller, D. Krautwurst, T. Hofmann, J. Linseisen, D. Volkert, H. Hauner, *Front. Nutr.* **2020**, *7*, 582387.
[23] U. Nöthlings, K. Hoffmann, M. M. Bergmann, H. Boeing, *J. Nutr.* **2007**, *137*, 2781.
[24] J. Freese, S. Feller, U. Harttig, C. Kleiser, J. Linseisen, B. Fischer, M. F. Leitzmann, J. Six-Merker, K. B. Michels, K. Nimptsch, A. Steinbrecher, T. Pischon, T. Heuer, I. Hoffmann, G. Jacobs, H. Boeing, U. Nöthlings, *Eur. J. Clin. Nutr.* **2014**, *68*, 324.
[25] P. Mitry, N. Wawro, J. Six-Merker, D. Zoller, C. Jourdan, C. Meisinger, S. Thierry, U. Nöthlings, S. Knüppel, H. Boeing, J. Linseisen, *Front. Nutr.* **2019**, *6*, 145.
[26] N. Wawro, G. Pestoni, A. Riedl, T. A. Breuninger, A. Peters, W. Rathmann, W. Koenig, C. Huth, C. Meisinger, S. Rohrmann, J. Linseisen, *Nutrients* **2020**, *12*, 1684.
[27] H. Akaike, *IEEE Trans. Autom. Control* **1974**, *19*, 716.
[28] C. Genolini, X. Alacoque, M. Sentenac, C. Arnaud, *J. Stat. Soft.* **2015**, *65*, 1.
[29] T. Calinski, J. Harabasz, *Comm. Stats. Theory Methods* **1974**, *3*, 1.