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PREVIEW: Prevention of diabetes through lifestyle intervention in a multicentre study in Europe in children (10-17y). Design, methods, and baseline results

Running title: PREVIEW children study: methods and baseline results

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ABSTRACT

Insulin resistance (IR) in adolescence is associated with T2DM. The PREVIEW study assesses the effectiveness of a high-protein, low-glycaemic index diet and moderate-protein, moderate-glycaemic index diet to decrease IR in insulin resistant children with overweight/obesity. Inclusion criteria were age 10-17y, HOMA-IR≥2.0 and overweight/obesity. In 126 children (13.6±2.2y, BMI z-score 3.04±0.66, HOMA-IR 3.48±2.28) anthropometrics, fat mass percentage (FM%), metabolic parameters, physical activity, food intake and sleep were measured. Baseline characteristics did not differ between the groups. IR was higher in pubertal children with morbid obesity than in prepubertal children with morbid obesity (5.41±1.86 vs. 3.23±1.86, p=0.007) and prepubertal and pubertal children with overweight/obesity (vs. 3.61±1.60, p=0.004 and vs. 3.40±1.50, p<0.001 respectively). IR was associated with sex, Tanner stage, BMI z-score, and FM%. Fasting glucose concentrations were negatively associated with Baecke Sport (r=-0.223, p=0.025) and positively with daytime sleepiness (r=0.280, p=0.016) independent of sex, Tanner stage, BMI z-score and FM%. In conclusion, IR was most severe in pubertal children with morbid obesity. The relations between fasting glucose concentration with Baecke Sport and sleepiness suggest these might be possible targets for diabetes prevention.

180 words

INTRODUCTION

Up to 44.0% of children with overweight present with insulin resistance (IR), a precursor of T2DM[i]. IR is defined as the inability of insulin to increase glucose uptake and utilization, leading to a compensatory increase in insulin secretion to maintain normal blood glucose values. IR is associated with metabolic disturbances, non-alcoholic fatty liver disease (NAFLD) and development of cardiovascular disorders. IR in children is further complicated by a physiological transient insulin resistance during puberty, which seems to be more severe in children with overweight and obesity[1-3]. Some children appear to have insufficient β-cell insulin secretion to compensate for the increased IR, which puts them at risk for β-cell exhaustion and, ultimately, T2DM[3]. Thus, puberty may be a critical time for diabetes prevention in insulin resistant children with overweight and obesity.

Previous studies have shown that weight loss improves IR in children with overweight and obesity[4]. Diets higher in protein, especially when combined with lower glycaemic index (GI), have shown to be protective for obesity in children[5]. However, it is not known which dietary strategy is most effective for IR reduction, independent of weight change, in high-risk insulin resistant children. The PREVention of diabetes through Lifestyle Intervention and population studies in Europe and around the World (PREVIEW) study aims to assess the effectiveness of two dietary strategies on reducing IR, independent of weight change, in insulin resistant children at high risk for T2DM. Participants were randomized into a moderate-protein, moderate-GI diet, following clinical standards for diabetes prevention, or a high-protein, low-GI diet in line with the most successful diet for children in the DiOGenes study[5]. In this paper the study design, methods and baseline results are presented.

MATERIALS AND METHODS

Here we present a concise version of the methods. More information on the study protocol is presented in the Supplement.

1. Participants

The PREVIEW children study is a randomized trial conducted at three study sites (Maastricht University, the Netherlands; University of Navarra, Spain; and Swansea University, United Kingdom). Inclusion criteria included age 10-17 years, overweight or (morbid) obesity, IR (HOMA-IR≥2.0 for children Tanner stages ≥3 or any HOMA-IR for children Tanner stages 1-2), and written informed consent by both parents and children aged ≥12 years. Children were excluded from participation in the presence of medical conditions or medication use that might

compromise study outcomes (e.g. T2DM, bariatric surgery or metformin use) and issues leading to difficulty in compliance with the protocol (e.g. severe food intolerances).

2. Design and intervention

The first 8 weeks of the study were aimed at weight stabilization in spite of growth. Children received a personalized menu following the recommended guidelines of 15/55/30 energy percentage (En%) protein/carbohydrate/fat. In the 96-weeks intervention phase children were randomized into a moderate-protein moderate-GI arm (MPMGI) consisting of a target macronutrient composition of 15/55/30En% protein/carbohydrate/fat, and a GI≥56, or a high-protein, low-GI arm (HPLGI) consisting of 25/45/30En% protein/carbohydrate/fat and a GI≤50 *(Supplementary Table 1)*. Children received personalized menus and recipes in line with their randomization arm and energy needs. All children received instructions on both high-intensity and moderate-intensity physical activity (PA) and exercise in general was encouraged. Nutritional and PA counselling was provided at each visit to improve compliance. The study protocol was approved by local Medical Ethics Committees and was compliant with the Declaration of Helsinki and the ICH-GCP. The trial was registered on ClinicalTrials.gov (number NCT01777893).

3. Measurements

Measurements were performed during standardized clinical investigation days (CIDs) *(Supplementary Table 2)*.

3.1 Anthropometric measurements and body composition

Height and weight were measured while children were in fasted state, barefoot, and wearing only underwear. Subsequently body mass index (BMI), age- and sex-specific BMI z-scores and overweight classifications were calculated[6]. Body composition was measured using air-displacement plethysmography or bio-impedance measurements. Children were classified as prepubertal (Tanner genital/mammae stages 1-2) or pubertal (Tanner stages 3-5)[7,8].

3.2 Parameters of glucose metabolism, lipids, inflammation, and liver parameters and blood pressure

After an overnight fast, a blood sample was taken to assess glucose metabolism parameters, lipids, markers of inflammation and liver parameters *(Table 1 & Supplementary Table 2)*. Insulin sensitivity was assessed by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; *glucose (mmol/L) * insulin (mU/L) / 22,5*)[9]. Children were defined as insulin resistant when HOMA-IR≥2.0 or any HOMA-IR for prepubertal children due to a physiologically lower HOMA-IR in early puberty[2]. An average of three blood pressure measurements was used for analyses.

3.3 Lifestyle factors: food intake behaviour, physical activity and sleep

Children completed a 4-day food record to assess energy intake, macronutrient composition, glycaemic index and glycaemic load (GL). The three Factor Eating Questionnaire (TFEQ) adapted for children was used to assess food intake behaviour[10]. In a subcohort at UM 24h urinary nitrogen was obtained to calculate protein intake. PA was measured by 7-day accelerometry using an Actigraph (Actigraph GT3X accelerometer) and by the Baecke questionnaire adapted for children[11]. The Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) were used to assess self-reported sleep parameters[12,13]. In a subcohort sleep was measured using polysomnography.

4. Statistical analyses

In future analyses, effects of the two dietary arms will be compared using ANOVA repeated measures with diet as a factor. Multiple regression analyses will be used to identify the contribution of different variables to HOMA-IR change. Baseline analyses in this paper were performed using the Statistical Package for the Social Sciences (SPSS) 24.0 (SPSS Inc, New York). ANOVA or Mann-Whitney-U test were used for assessing differences between the two intervention groups, depending on normality of data. Associations between parameters were assessed using Pearson's or Spearman's correlation coefficients, which were corrected for relevant variables. A p-value <0.05 was considered statistically significant.

RESULTS

126 children that completed screening and body composition measurement were included in baseline analyses (58.7% girls, age 13.6±2.2y, BMI z-score 3.04±0.66, HOMA-IR 3.35±1.80, 31.0/46.0/23.0% overweight/obesity/morbid obesity, *Figure 1 and Table 1*). Participant characteristics were not significantly different between the HPLGI and MPMGI groups.

HOMA-IR distribution in high-risk children (HOMA-IR≥2.0) did not differ between children in different Tanner stages or between the sexes (*Supplementary Figure 1*). IR was higher in pubertal children with morbid obesity than in prepubertal children with morbid obesity (5.41±1.86 vs. 3.23±1.86, p=0.007), and prepubertal and pubertal children with overweight/obesity (vs. 3.61±1.60, p=0.004 and 3.40±1.50, p<0.001 respectively).

Parameters of glucose metabolism were positively associated with sex, Tanner stage, BMI z-score, fat mass index, fat free mass index and FM%. Independently of sex, Tanner stage, BMI z-score and FM%, Baecke Sport score was inversely (r= -0.223, p=0.025) and ESS daytime sleepiness positively (r=0.280, p=0.016) associated with fasting blood glucose concentrations (*Supplementary Table 3*).

Drop-out analyses showed no differences between children that completed the PA and food intake questionnaires and children that did not. Children that completed sleep questionnaires had a higher FFMI (19.0±2.6 vs. 17.3±2.4kg/m2, p=0.001), lower FM% (37.1±9.3 vs. 40.4±7.1%, p=0.027) and higher fasting blood glucose concentration (4.8±0.7 vs. 4.4±0.7mmol/L, p=0.007) than children that did not complete these questionnaires (*Supplementary Table 4*).

DISCUSSION

This paper describes the methods and baseline analyses of the PREVIEW children study. PREVIEW is the first international randomized trial to assess the effects of a high-protein, low-GI and moderate-protein, moderate-GI diet on IR in insulin resistant children, independent of weight changes and puberty. In addition, the longitudinal follow-up (2y) in the PREVIEW study will help fill a gap in the knowledge of HOMA-IR development during puberty in at risk children.

It has been shown that a reduction in BMI is associated with IR reduction in children with overweight and obesity[4]. The DiOGenes study showed that a diet with a higher protein content, especially when combined with a lower GI, significantly decreased the percentage of overweight and obesity in children of all ages[5]. This study also found that the HP-LGI diet improved glucose metabolism even in the absence of BMI z-score changes[14]. Other studies focussing on IR in children often included metformin prescription, which hinders evaluation of the independent effects of diet and physical activity on IR[15]. Unique about the PREVIEW study is that it studies the impact of a dietary intervention on IR, independent of weight changes, in an at-risk group of insulin resistant children with overweight/obesity during puberty, without providing metformin.

Baseline subject characteristics were not significantly different between the two intervention groups, demonstrating good randomization. No differences were found in HOMA-IR between children in different Tanners stages or between the sexes, which is probably due to including only high-risk children (HOMA-IR≥2.0) in these analyses.

As expected, pubertal children with morbid obesity had a significantly higher HOMA-IR than prepubertal children or children with overweight. High HOMA-IR in children with morbid obesity in this and previous studies indicates that these children especially are at high risk for β-cell exhaustion, which can result in decreased and insufficient β-cell secretion and T2DM[2,3,16]. The PREVIEW study aims to provide more insight in longitudinal insulin resistance development during puberty in a 2y follow-up design.

We confirmed that in insulin resistant children with overweight and obesity, parameters of glucose metabolism are associated with increasing puberty stages and markers of adiposity (BMI z-score, FFMI, FMI and FM%)[1]. Physical

activity, measured as Baecke Sport score, appeared to be inversely associated with fasting blood glucose concentrations, independent of sex, Tanner stage, BMI z-score and FM%. However, glucose concentrations and accelerometry counts were not related, and Baecke scores were not associated with accelerometry counts. Fasting blood glucose concentrations were positively related to ESS daytime sleepiness.

Strengths of the PREVIEW study are the assessment and monitoring of a wide range of targets associated with reduction of IR, i.e. diet, PA and sleep in pubertal children at risk, and the international setting. Limitations are the absence of a normal weight control group due to ethical considerations of research in children. Since the research was set in free-living conditions, compliance with the protocol may vary. Response to some lifestyle assessments using questionnaires was quite low due to refusal to answer questionnaires or incomplete questionnaires, limiting interpretation of lifestyle-related outcomes of the intervention. Drop-out analyses revealed some differences between children that did and did not complete all assessments, which will be taken into account in future analyses (*Supplementary Table 4*).

In conclusion, the PREVIEW study is a randomized trial aiming to assess the most effective diet for preventing IR increase, independent of weight change, and corrected for puberty stage, in at risk children with overweight and obesity. Baseline characteristics did not differ between the HPLGI and the MPMGI intervention arms. In children with overweight and obesity at risk for T2DM development, IR was most severe in pubertal children with morbid obesity. IR was associated with sex, adiposity and Tanner stage. Fasting glucose concentrations were independently inversely related to Baecke sport and positively to sleepiness, indicating these might be possible tools for diabetes prevention.
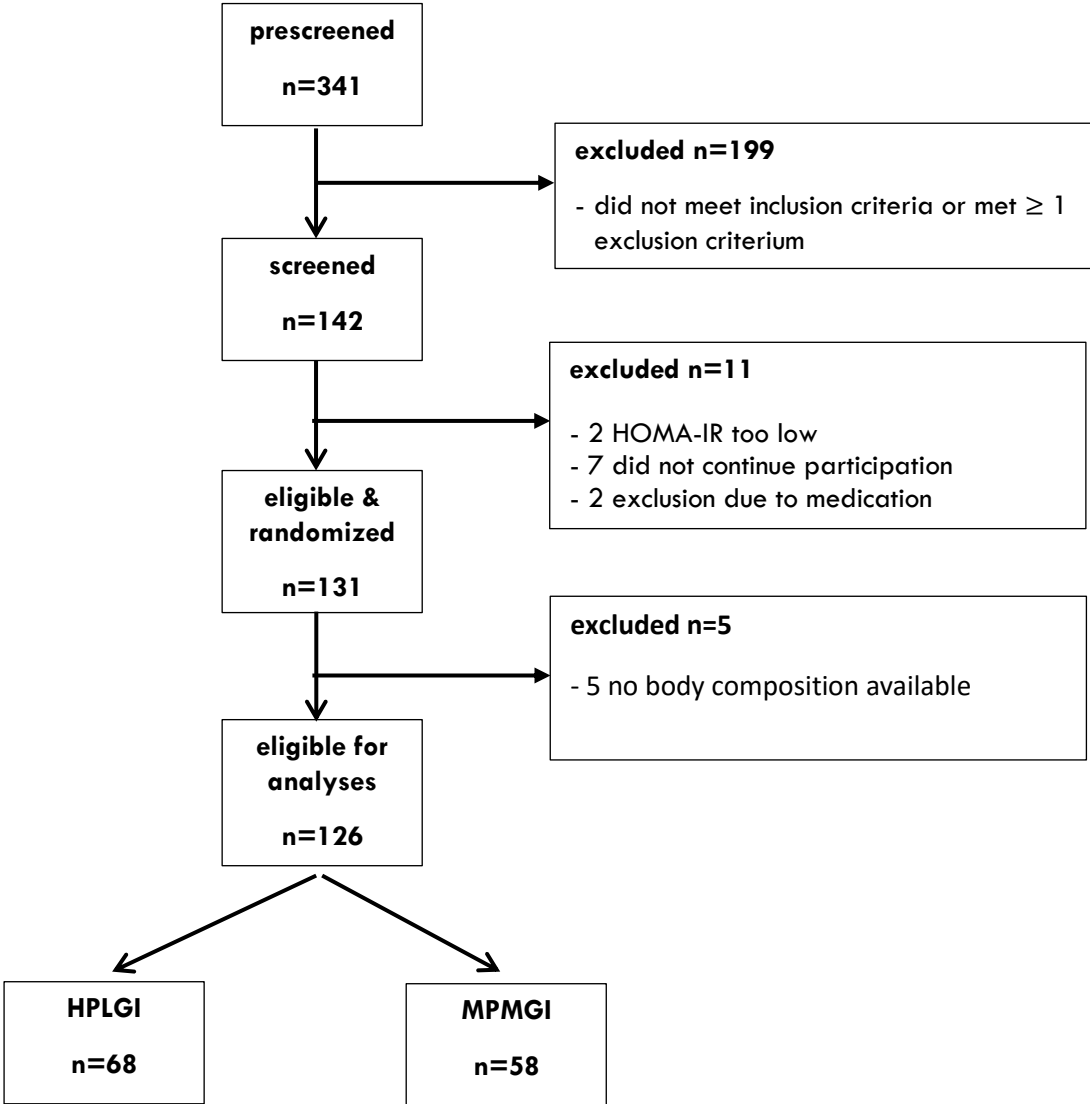
FIGURES

Figure 1. Flowchart of participants in the PREVIEW children study

Table 1. Anthropometric characteristics, parameters of glucose metabolism, lipids, inflammation, liver parameters and cardiovascular risk at baseline

	All participants (n=126)			HPLGI (n=68)			MPMGI (n=58)			p-value
	mean	±	SD	mean	±	SD	mean	±	SD	
Female (n; %)	74 (58.7%)			39 (57.4%)			35 (60.3%)			0.856
Age (yr)	13.6	±	2.2	13.7	±	2.4	13.4		2.0	0.512
Tanner G/M stage (median (IQR))	3 (2 - 4)			3 (2 - 5)			3 (2 - 4)			0.440
Anthropometric characteristics										
Height (m)	1.61	±	0.11	1.61	±	0.11	1.60	±	0.10	0.695
Weight (kg)	78.0	±	19.7	80.0	±	20.9	75.7	±	18.2	0.472
BMI (kg/m2)	29.8	±	4.9	30.1	±	5.1	29.3	±	4.6	0.536
BMI z-score	3.04	±	0.66	3.10	±	0.69	2.97	±	0.63	0.543
IOTF class (median (IQR))	2 (1 - 2)			2 (1 - 3)			2 (1 - 2)			0.205
Body composition										
Fat free mass index (kg/m2)	17.9	±	2.6	18.0	±	2.8	17.9	±	2.4	0.985
Fat mass index (kg/m2)	11.8	±	3.9	12.3	±	3.9	11.4	±	3.9	0.297
Fat mass (%)	39.2	±	8.1	40.0	±	7.4	38.2	±	8.9	0.379
Parameters of glucose metabolism										
Glucose (mmol/L)	4.6	±	0.7	4.6	±	0.68	4.5	±	0.7	0.132
Insulin (pmol/L)	109.6	±	74.2	107.2	±	51.5	112.4	±	94.6	0.482
HOMA-IR	3.35	±	1.80	3.44	±	1.66	3.24	±	1.96	0.294
HbA1c (mmol/l)	32.7	±	2.7	32.7	±	2.9	32.8	±	2.5	0.800
C-peptide (nmol/L)	0.9	±	0.3	0.9	±	0.3	0.9	±	0.3	0.844
Lipids										
Total cholesterol (mmol/L)	4.1	±	0.8	4.1	±	0.7	4.2	±	0.8	0.894
HDL (mmol/L)	1.3	±	0.3	1.3	±	0.3	1.3	±	0.3	0.763
LDL (mmol/L)	2.4	±	0.6	2.4	±	0.6	2.4	±	0.7	0.650
TAG (mmol/L)	1.1	±	0.5	1.1	±	0.5	1.1	±	0.6	0.562
FFA (mmol/L)	0.7	±	0.2	0.7	±	0.3	0.6	±	0.2	0.321
Inflammation										
CRP (mg/L)	2.9	±	3.1	2.9	±	2.7	3.0	±	3.5	0.393
Liver parameters										
ASAT (U/L)	25.1	±	8.1	23.9	±	7.4	26.6	±	8.8	0.063
ALAT (U/L)	24.7	±	14.6	23.5	±	13.8	26.2	±	15.5	0.182
Cardiovascular parameters										
Systolic blood pressure (mmHg)	116	±	12	117	±	13	116	±	12	0.949
Diastolic blood pressure (mmHg)	67	±	8	67	±	8	66	±	7	0.316
Heart rate (beats per minute)	75	±	12	76	±	13	74	±	10	0.432
Physical activity (n=107)										
Baecke Work	2.5	±	0.4	2,4	±	0,3	2,6	±	0,4	0.053
Baecke Sport	2.8	±	0.5	2,7	±	0,5	2,8	±	0,5	0.657
Baecke Leisure	2.8	±	0.7	2,9	±	0,6	2,8	±	0,7	0.740
Baecke total	8.1	±	1.0	8,0	±	1,0	8,2	±	1,1	0.451
Counts (counts per minute)[a]	306.7	±	108.5	316,6	±	101,9	291,0	±	118,7	0.352
Food intake behaviour (n=73)										
TFEQ cognitive restraint of eating	11,0	±	3,8	10,6	±	3,6	11,5	±	4,1	0.307
TFEQ disinhibition	6,2	±	3,3	6,7	±	3,5	5,4	±	3,0	0.092
TFEQ hunger	5,4	±	3,3	5,8	±	3,7	4,9	±	2,5	0.414
GI [b]	52.4	±	8.2	50.9	±	7.7	54.3	±	8.7	0.140
GL [b]	97.9	±	35.4	93.4	±	30.9	103.0	±	32.8	0.193
Energy intake (kJ/day) [b]	6958	±	1957	6674	±	1613	7341	±	2326	0.219
Fat (En%) [b]	25.7	±	7.4	35.9	±	7.8	35.4	±	6.9	0.909
Carbohydrates (En%) [b]	45.1	±	7.1	44.7	±	7.8	45.6	±	6.1	0.643
Protein (En%) [b]	17.2	±	3.0	17.5	±	2.4	16.9	±	3.7	0.496
Fibre (g) [b]	14.0	±	5.5	13.9	±	5.0	14.1	±	6.2	0.897
Estimated protein intake (g/kg/d)[c]	0.48	±	0.38	0.52	±	0.49	0.44	±	0.21	0.458
Sleep assessment (n=68)										
TST (min)	466	±	70	463	±	61	469	±	79	0.521
REM (min)	107	±	59	110	±	78	102	±	30	0.309
SWS (min)	135	±	65	141	±	83	128	±	39	0.803
WASO (min)	45	±	70	50	±	92	40	±	37	0.637
QS (%)	50.5	±	10.1	51	±	10	50	±	10	0.934
Sleep questionnaires (n=48)										
ESS	5.7	±	4.0	6.3	±	4.3	4.9	±	3.4	0.249
PSQI Total score	3.7	±	2.1	3.9	±	2.2	3.4	±	2.0	0.438
PSQI Sleep quality	0.7	±	0.6	0.9	±	0.6	0.5	±	0.6	0.061
PSQI Sleep latency	0.7	±	1.0	0.8	±	1.0	0.6	±	0.8	0.575
PSQI Sleep duration	0.4	±	0.7	0.5	±	0.7	0.3	±	0.6	0.556
PSQI Sleep efficiency	0.2	±	0.6	0.5	±	0.7	0.3	±	0.6	0.765
PSQI Sleep disturbances	1.0	±	0.6	1.0	±	0.6	1.1	±	0.7	0.437
PSQI Sleeping medications	0.1	±	0.5	0.1	±	0.6	0.2	±	0.5	0.732
PSQI Daytime dysfunction	0.4	±	0.6	0.4	±	0.6	0.4	±	0.6	0.804

Data presented as mean $\pm$ SD or median (interquartile range). Tanner G/M stage = Tanner stage for genitals (boys[8]) or mammae (girls[7]); BMI = Body Mass Index; IOTF = International Obesity Task Force overweight class[6]; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance[9]; HDL-cholesterol = high density lipoprotein-cholesterol; LDL-cholesterol = low density lipoprotein-cholesterol; TAG = triacylglycerides; CRP = c-reactive protein; AST = aspartate transaminase; ALT = alanine transaminase ; TFEQ = Three Factor Eating Questionnaire[10]; PSQI = Pittsburgh Sleep Quality Index[12]; ESS = Epworth Sleep Scale questionnaire[13]; TST = total sleep time; REM = Rapid Eye Movement Sleep; SWS = Slow Wave Sleep; WASO = Wake after Sleep Onset; QS = Quality of Sleep ((REM + SWS) / TST). [a] n=67. [b] n=54. [c] n=27.

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