Abstract book

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Abstracts

Inhoud

Title:	**Improving the estimation of visceral adipose tissue using metabolite biomarkers**
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Abstract:	**Introduction:** Visceral adipose tissue (VAT) is strongly related to cardiometabolic disease and therefore an important target to identify individuals at high cardiometabolic risk. There is a need for clinically applicable prediction tools to estimate visceral fat. We developed a prediction model for VAT using simple clinical variables and evaluated the added value of metabolomics measurements. **Methods:** We analyzed cross-sectional data of 2,501 middle-aged individuals from the Netherlands Epidemiology of Obesity study with MRI-quantified abdominal VAT and Nightingale metabolomics. We used ridge regression to create a basic prediction model for VAT using thirteen clinical variables including age, sex, BMI, waist circumference, glucose, and lipid profile. This model was expanded by adding 145 metabolites using ridge and LASSO regression. We developed models for the total sample as well as men and women separately and internally validated all models through bootstrapping. **Results:** The included participants (52.4% men) had a mean (SD) BMI of 29.5 (4.2) kg/m^2 and VAT of 144 (64) cm^2. The optimism corrected explained variance (R^2) of the basic model after bootstrapping was 0.66 in the total sample (0.52 in men, 0.66 in women), with calibration slopes of 1.00 in the total sample (0.99 in men and women). Optimism corrected c-statistics for a VAT cut-off of 100 cm^2 were 0.89 in the total sample, 0.86 in men and 0.88 in women. Adding metabolites resulted in only minor improvements: for LASSO (mean retained metabolites: 50) the R^2 in the total sample was 0.68 and 0.67 for ridge, while the c-statistics and calibration slopes were nearly identical to the basic model. **Conclusion:** A model using standard clinical predictors including age, sex, BMI, waist circumference, glucose, and lipid profile was able to make reliable estimates of VAT. Adding metabolites from the Nightingale platform did not substantially improve the model's performance **1. Conflict of interest:** Dennis Mook-Kanamori is a part-time clinical research consultant for Metabolon, Inc. All other co- authors have no conflicts of interest to declare. **2. Funding:** The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Centre, and by the Leiden University, Research Profile Area 'Vascular and Regenerative Medicine'. We acknowledge support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation (CVON2014-02 ENERGISE).

Title:	**The impact of Personalized Lifestyle Advice on type 2 diabetes remission as compared to usual care in newly diagnosed type 2 diabetics in the primary care setting in Hillegom, the Netherlands**
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****	**Introduction:** The core pathophysiological defects of type 2 diabetes (T2D) are insulin resistance (IR) in the organs (e.g. muscle and liver) and reduced β-cell function (BCF). As a result of differences in pathophysiology between patients, specific phenotypes exist within the (pre)-T2D population. These specific phenotypes may require a more tailored treatment instead of a "one-size-fits all" solution. We describe an innovative personalized lifestyle approach and tested its effectiveness, in comparison to usual care, in a primary care setting. **Methods:** An oral glucose tolerance test (OGTT) was performed to assess the subtypes of 82 (pre)T2D subjects according to BCF and/or presence of hepatic IR, muscle IR or both. Subjects were then allocated to one of seven personalized lifestyle treatments, consisting of 13 weeks of a dietary, exercise or combined intervention. Fasting plasma glucose (FPG), HbA1c, body weight (BW) and waist circumference were measured at baseline, after 13 weeks and at 6, 12 and 24 months. As a control, retrospective data from 58 T2D patients was used to compare the effect of the intervention with usual care provided by the general practitioner. **Results:** Only the intervention group had a significant reduction in BW, HbA1c, and FPG after 13 weeks, compared to both baseline and controls. Additionally, 55% of the subjects shifted to a less complex T2D subtype and 32% of the subjects were found to be fully normalized after 13 weeks of intervention. After two years of follow-up, BW, HbA1c and FPG remained significantly lower as compared to baseline. In the control group, only a reduction in body weight was observed. **Conclusion:** The personalized lifestyle treatment more effectively addressed the core defects of T2D and thereby significantly improved the health status of T2D patients, in comparison to usual care even after two years follow-up. **1. Conflict of interest:** None **2. Funding:** TNO

The role of birth generation and gender in the age trajectories of obesity and its risk factors in the Doetinchem study.

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Abstract

Introduction: Obesity is a global public health problem due to its alarming increase and strong associations with its risk factors and comorbidities, including type 2 diabetes (T2D) and cardiovascular disease (CVD). Obesity increases with age, follows a sex-specific course and is affected by birth generation, which determines the extent of exposure to the recent obesogenic environment. Our aim was to study the role of birth generation and gender in the age trajectories of anthropometric measures of obesity and its outcomes in a representative sample of the Dutch population.

Methods: We used data from the longitudinal Doetinchem Cohort Study, that started in 1987–1991 and had 5 follow-up examinations after 6, 11, 16, 21 and 26 years (n =4470). The analyses were stratified by sex and birth generation, i.e. 10-year age groups (20–29, 30–39, 40–49, and 50–59 years) at baseline. Generalized estimation equations were used to test whether a generation had, at a similar age, a significantly different obesity risk factor compared to a generation born 10 years earlier (i.e. generation shift).

Results: Unfavorable generation shifts (p-value<0.05) for BMI, weight, waist circumference, overweight and obesity were pronounced in men between every generation while in women were especially present between the most recently born generations. Surprisingly, this was associated with a higher prevalence of T2D only among men (p-value<0.05). From age 50–59 years on, all generations of women converged with respect to BMI, weight and waist circumference. No generation shifts were observed for hypertension, hypercholesterolemia and low HDL-C.

Conclusion: Our results show that the younger generations are overweight and obese at a younger age. For men and not women, this is associated with an increased prevalence of T2D.

Conflict of interest:

None

Funding

Ministry of Health, Welfare and Sport of the Netherlands and the National Institute for Public Health and the Environment.

Title:	**Chromosomal microarray analysis as a diagnostic test for genetic obesity disorders – Yield in a pediatric cohort and identification of novel obesity candidate genes**
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Abstract:	**Introduction:** Obesity is a complex multifactorial disease. One of the genetic factors contributing to obesity is copy number variation (CNV): deletions or duplications of parts of chromosomes. Chromosomal microarray analysis is a widely used technique to identify CNVs. It is a first-tier diagnostic test for patients with intellectual disability, but it can also be valuable to explain isolated early-onset obesity. We present the results of microarray testing in our tertiary pediatric obesity center. **Methods:** In this prospective observational study, all included patients underwent an extensive diagnostic workup including SNP-microarray analysis. Identified CNVs were classified according to the current international guidelines and evaluated for their obesity association. **Results:** In total, 344 patients were included, median age 10.8 years (IQR 7.7-14.1); median BMI-SDS +3.7 (IQR+3.3-+4.3). We identified (potentially) clinically relevant CNVs in 34 individuals (9.9%). In 10 patients, a known genetic obesity syndrome was diagnosed; 16p11.2 deletion syndrome was the most frequently diagnosed. Interestingly, we identified 15q13.3 duplications including the *CHRNA7* gene in 5 patients. This is a known risk-allele for learning and behavioural problems, but has not yet been associated with a childhood obesity phenotype. In 8 patients, an unknown CNV was identified in which novel possible obesity-associated genes were present. In an additional 2 cases, a region of homozygosity (ROH) was found in which the *LEPR* gene was present, which is associated with autosomal recessive genetic obesity. After this, we could indeed diagnose homozygous *LEPR* mutations in these patients. **Conclusion:** A variety of underlying genetic causes of obesity can be found by using microarray analysis in cohorts with severe early-onset obesity. We identified known genetic obesity syndromes and several CNVs containing candidate genes that have not been previously described in association with obesity. SNP-array analysis also allows detection of ROHs which facilitates diagnosis of recessive genetic obesity disorders. **1. Conflict of interest:** None **2. Funding:** None

Title:	**Oral butyrate induces satiety and improves insulin resistance via gut microbiota**
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Abstract:	**Introduction:** The prevalence of obesity has been increasing steadily over the past two decades, and personalized therapeutic strategies to induce a negative energy balance are still required. We recently showed that dietary butyrate reduces food intake and activates brown adipose tissue as dependent on the gut-brain neural circuit, and also alters the gut microbiota composition (Li, Gut 2018). In the present study, we aimed to evaluate the causal role of gut microbiota in the beneficial effects of butyrate on host metabolic health. **Methods:** Donor APOE*3-Leiden.CETP mice, a well-established translational model for developing diet-induced human-like metabolic syndrome, received a high-fat diet with or without sodium butyrate for 6 weeks. Fecal microbiota was collected and transplanted into the gut microbiota-depleted recipient APOE*3-Leiden.CETP mice for 6 weeks, during which recipients were fed the high-fat diet. **Results:** 16S sequencing revealed that fecal microbiota transplantation (FMT) alters the gut microbiota composition in recipients. A persistent decrease in bodyweight gain was observed in the butyrate-FMT group, accompanied with a marked decrease in body fat. In addition, butyrate-FMT recipient mice displayed a significant reduction in the average food intake as compared with the control-FMT group. Moreover, butyrate-FMT reduced the homeostatic model assessment of insulin resistance as compared with controls. **Conclusions:** We revealed a causal role of gut microbiota in the beneficial metabolic effects of butyrate by persistently reducing food intake and improving insulin resistance, collectively preventing high-fat diet-induced metabolic disorders. **1. Conflict of interest:** None **2. Funding:** YW is supported by a VENI grant from NWO-ZonMW (91617027). PCNR is Established Investigator of the Dutch Heart Foundation (2009T038).

Title:	**Pharmacological treatment with FGF21 activates adipose tissue thermogenesis to protect against adiposity and atherosclerosis in APOE*3-Leiden.CETP mice**
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Abstract:	**Introduction:** Fibroblast growth factor 21 (FGF21), a key regulator of energy metabolism, is currently evaluated in humans for the treatment of obesity and its related cardiometabolic disorders. In the present study we aimed to elucidate the mechanisms underlying the anti-obesity effects of FGF21 and the consequences for atherosclerosis development in a well-established mouse model for human-like lipoprotein metabolism. **Methods:** Female APOE*3-Leiden.CETP mice were fed a cholesterol-enriched Western-type diet for 3 weeks, randomized and subcutaneously injected with either vehicle or long-circulating recombinant FGF21 at a pharmacological dose (1 mg/kg body weight) 3 times per week for 16 weeks. At the end of the study, kinetic studies were performed to study lipid clearance, and adipose tissue and liver histology were assessed. Atherosclerotic lesion area, severity and composition were measured in the aortic root. **Results:** FGF21 reduced body fat mass gain and markedly reduced hepatic steatosis. In addition, FGF21 decreased plasma total cholesterol, as explained by a reduction of non-HDL-cholesterol. Mechanistically, FGF21 promoted brown adipose tissue (BAT) activation and white adipose tissue (WAT) browning, thereby enhancing the selective uptake of fatty acids from triglyceride-rich lipoproteins into BAT and into browned WAT, consequently accelerating the clearance of the cholesterol-enriched remnants by the liver. Ultimately, FGF21 attenuated atherosclerosis development as evidenced by largely decreased atherosclerotic lesion area, improved lesion severity and increased atherosclerotic plaque stability index. **Conclusion:** FGF21 reduces body fat by activating BAT and browning WAT, thereby accelerating triglyceride-rich lipoprotein turnover to improve hypercholesterolemia and reduce atherosclerosis development. We have thus provided additional support for the clinical use of FGF21 in the treatment of cardiometabolic diseases. **1. Conflict of interest:** Larsson M, Wallenius K, Dekker N, Peng XR are employees of AstraZeneca. **2. Funding:** This work was supported by the Netherlands Organization for Scientific Research-NWO (VENI grant 91617027 to YW); the Netherlands Organization for Health Research and Development-ZonMW (Early Career Scientist Hotel grant 435004007 to YW); the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation (CVON-GENIUS-2); and the Netherlands Heart Foundation (grant 2009T038 to PCNR).

Title:	**Synergistic effect of feeding time and diet on hepatic steatosis and gene expression in male Wistar rats**
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Abstract:	**Introduction:** Eating out of phase with the endogenous biological clock alters clock- and metabolic gene expression in rodents and can induce obesity and type 2 diabetes mellitus. Diet composition can also affect clock gene expression. Here, we assessed the combined effect of diet composition and feeding time on (i) body composition, (ii) energy balance and (iii) circadian expression of hepatic clock and metabolic genes. **Methods:** Male Wistar rats were fed a chow or a free-choice high-fat, high-sugar (fcHFHS) diet, either *ad libitum* or with food access restricted to either the light or dark period. Body weight, adiposity, and hepatic fat accumulation, as well as hepatic clock- and metabolic mRNA expression were measured after 5 weeks of diet. Energy expenditure was measured using calorimetric cages. **Results:** Animals with access to the fcHFHS diet only during the light period showed more hepatic fat accumulation than fcHFHS dark-fed animals, despite less calories consumed. In contrast, within the chow-fed groups, light-fed animals showed the lowest hepatic fat content. Locomotor activity and heat production followed feeding times, except in the fcHFHS light-fed group. Hepatic clock- and metabolic gene expression rhythms also followed timing of food intake. Yet, in the fcHFHS light-fed animals, clock gene expression was 3h advanced compared to chow light-fed animals, an effect not observed in the fcHFHS dark-fed animals. **Conclusion:** A fcHFHS-diet consumed in the light period promotes hepatic fat accumulation and advances clock gene expression in male Wistar rats, likely due to a mismatch between energy intake and expenditure. Similar mechanisms may contribute to metabolic derangements observed in, e.g., shift workers. 1. **Conflict of interest:** none disclosed 2. **Funding:** JEO was supported by an Academic Medical Center PhD scholarship.

SEX DIFFERENCES IN BEHAVIOUR AND METABOLISM IN A BINGE-EATING MOUSE MODEL

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Introduction: Binge-eating disorder (BED) is currently the most prevalent eating disorder diagnosed. During binge-eating episodes, patients eat large amounts of food in a short period of time despite already being full. The caloric intake during these episodes, however, is not compensated for, leading to obesity and related diseases. BED has a higher prevalence in women than in men, however, the aetiology for this sex difference is unknown.

Methods: C57BL/6 mice of both sexes were housed individually in a metabolic cage system. This allows automatic food access regulation, and continuous monitoring of food intake, activity, and respirometry. After one week of habituation, we induced binge eating by giving mice continuous access to regular chow but restricted access to a Western-style diet (WD). Mice had access to the WD three times per week, during a two-hour period in the inactive (light) phase. The control group had continuous access to both diets. Body composition was monitored every two weeks. Results are shown as mean ± SEM.

Results: Preliminary analysis of data during the access period on binge days in week four suggests that binge mice of both sexes ate more WD (499±62 mg) than control mice (119±18 mg, $p<0.001$). Interestingly, in the same timespan on non-binge days, the binge mice increased their chow intake compared to binge days: from 19±9 mg to 88±11 mg ($p=0.001$). During the access period on binge days, the binge mice spent more energy (345±8 kcal/h) than on non-binge days (270±7 kcal/h, $p=0.001$), which can only in part be explained by increased locomotor activity. Upon sacrifice, control females had gained 42.7±3.1% body weight over baseline, which was more than control males (29.2±2.3%, $p=0.005$). In binge mice, both sexes gained about 16.7±1.4% body weight compared to baseline. The weight gain corresponded with a higher fat percentage in control females than in control males (16.1±0.4%, $p=0.015$), and binge animals of both sexes (12.0±0.5%, $p<0.001$).

Conclusion: We successfully induced binge-like feeding in mice of both sexes by restricting their access to WD. Surprisingly, sex differences were only found in the body weight and composition of control mice, but not in binge mice. Using the metabolic cages, we identified differences in energy expenditure and activity between access and non-access days in the binge mice. This extensive phenotyping lays the groundwork for tissue analysis and further interventional studies with the aim of suppressing binge-eating behaviour.

Conflicts of interest: none

Title:	**Anthropometrics in relation to endogenous and exogenous glucocorticoids during combined lifestyle intervention with cognitive behavioral therapy in obesity.**
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Abstract:	**Introduction**: Obesity shows striking similarities with a hypercortisolistic state and is associated with elevated cortisol levels. Here, we evaluated changes in and associations between anthropometrics, body composition, and long-term glucocorticoids during lifestyle intervention in obesity. We additionally assessed the role of systemic corticosteroid use on the effect on anthropometric changes. **Methods**: In this prospective longitudinal study we evaluated 118 subjects with obesity (mean age 41.8 years, BMI 40.2 kg/m²) who participated in a combined lifestyle intervention aimed at healthy nutrition and exercising with cognitive behavioral therapy. Anthropometrics, body composition, and scalp hair cortisol and cortisone concentrations (as a measure of chronic glucocorticoid exposure) were evaluated at baseline, after the intensive phase (week 10), and at end of intervention (week 75). **Results**: Participants initially lost significant weight (-5.3 kg [SE, ±0.4]), waist circumference (-6.7 cm [±0.6]), and BMI (-1.8 kg/m² [±0.1], all P<.001) and maintained this till end of the intervention. Weight change was mainly due to loss of fat mass and resulted in a relative increase in lean mass. Systemic corticosteroids were used by 19.5% (17/87) of the completers and was associated with different weight loss in comparison to nonusers ($P_{interaction}$=.041). Proportion of participants who lost ≥5% total body weight at end of intervention in nonusers and users was respectively 47.1% and 35.3%. Hair cortisol concentrations significantly decreased after 75 weeks (-0.23 log pg/mg [SE±0.06], P=.002) whereas cortisone levels initially increased and subsequently returned to baseline value. No significant associations were observed between changes in hair glucocorticoids and anthropometrics. **Conclusions**: Combined lifestyle intervention with cognitive behavioral therapy decreases long-term cortisol concentrations and improves anthropometrics and body composition in obesity. Association between these changes cannot fully explain these outcomes, suggesting mediation by other factors. Use of systemic corticosteroids should be considered as an important hindering factor in weight-loss attempts. **1. Conflict of interest:** None. **2. Funding:** EFCvR is funded by a Vidi grant from the Netherlands Organization of Scientific Research NWO / ZONMW (grant number: 91716453). EFCvR and ELTvdA are financially supported by the Elisabeth Foundation.

Title:	**Men lose more weight and improve more in metabolic parameters following a low-calorie diet but are less able to maintain the improvements after 6 months of follow up compared to women**
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Abstract:	**Introduction**: There may be sex differences in metabolic outcomes following a low-calorie diet (LCD) and a subsequent period aimed at weight maintenance. Understanding sex-specific differences in weight loss and weight maintenance may contribute to more targeted dietary interventions. **Methods**: 782 overweight or obese participants (35% men) were included in the large-scale multicenter DIOGenes trial (ClinicalTrials.gov Identifier: NCT00390637). Participants followed an 8-week low calorie diet (LCD) (800-1000 kcal/day), with a follow up weight maintenance period of 6 months on ad libitum diets varying in protein content and glycemic index. Body weight and several metabolic parameters were determined before and after the LCD diet, and after 6 months of follow-up. Multiple linear regression was performed to test the associations between sex and metabolic outcome parameters. **Results**: Men lost relatively more body weight compared to women during the LCD period (-11.7±3.0 vs. -10.6±2.5%, respectively, p<0.001), but regained more body weight during the follow-up period compared to women (1.67±5.72 vs. 0.15±6.16%, respectively, p=0.005). Although beneficial metabolic effects were found for both sexes following the LCD, the improvements in muscle insulin sensitivity index (MISI), total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), free fatty acids (FFA), triacylglycerol (TAG) and diastolic blood pressure (DBP) concentrations were more pronounced in men than in women (std. ß range: 0.073-0.164, p-values all <0.05). During the weight maintenance period, women demonstrated a lower rebound in fasting glucose, HIRI, HDL-cholesterol, FFA, TAG, SBP, and CRP (std. ß range: 0.099-0.183, p-values all <0.05). **Conclusion**: Men lost more body weight and improved more in several metabolic parameters following a LCD, whereas women were more successful in maintaining the improvements after an ad libitum 6-month weight maintenance period. These data suggest that sexual dimorphism in diet-induced changes in body weight and metabolic parameters should be taken into account when developing dietary interventions. **1. Conflict of interest:** The authors declare no conflict of interest **2. Funding:** No funding to declare

Title:	**Effect of dexamphetamine on weight and satiety in Temple syndrome**
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Abstract:	**Rationale** Temple syndrome is a rare genetic obesity disorder caused by maternal uniparental disomy of chromosome 14. This disorder is characterized by hyperphagia and obesity which are challenging to treat. Dexamphetamine is a centrally-acting drug with weight loss and reduced appetite as side effects. Case reports have shown an effect of dexamphetamine on weight loss in hypothalamic obesity. This is a case report of the use of dexamphetamine in the treatment of hyperphagia in Temple syndrome. **Case presentation** The girl was born at 40w of gestation with a birthweight of 2200gr (<p3). From the age of 4y she developed hyperphagia and severe obesity. Genetic testing led to the diagnosis of Temple syndrome. The girl was referred at the age 14.5y because of therapy resistant obesity. Her height was 162.4cm(-0.4SDS), her weight was progressively increasing to 93.5kg(+3.5SDS), and BMI was 35.7(+3.6SDS). Laboratory tests showed prediabetes and signs of liver steatosis. Intensive supportive treatment was initiated by a pediatric dietician, lifestyle coach, and physiotherapist. Treatment with dexamphetamine was initiated twice daily 5mg. This was weekly increased with 5mg/day, depending on her wellbeing and side effects, to a maximum of 0.5mg/kg/day. She achieved an optimum dose of 0.4mg/kg/day. At follow-up at 13m, she reported improved satiety and lost -14% weight. At 20m, she lost 9.3% weight and she reported sustained satiety feelings. She experienced no side-effects. Laboratory tests were normalized. **Discussion** This patient with Temple syndrome was treated with dexamphetamine due to therapy resistant obesity. Her maximal weight loss was -14% and stabilized at -9.3%. This is a considerable effect, especially since anti-obesity treatment is stated clinically relevant in guidelines when a >-5% weight loss is achieved. Consistent satiety feelings and no side-effects were experienced. This case report suggests a promising role for dexamphetamine in selected patients with genetic obesity disorders and hyperphagia. **1. Conflict of interest:** none **2. Funding:** none

Title:	**A prospective analysis of children's lifestyle clusters and weight status, and the influence of their neighbourhood**
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Abstract:	**Introduction:** Knowledge about the relative contribution of different lifestyle factors to the development of childhood overweight is scarce. Therefore, we aimed to examine the association between children's lifestyle clusters and the development of childhood overweight. Additionally, we explored the influence of children's neighbourhood (i.e. spatial clustering) on these associations. **Methods:** We included 1818 children participating in the GECKO Drenthe cohort, with information on at least one lifestyle factor between ages 3-6 and data on measured weight and height at the age of 10. Diet was assessed by a Food Frequency Questionnaire, physical activity (PA) by accelerometry (Actigraph GT3X), and other lifestyle factors by questionnaires. Lifestyle patterns were defined using principal component analysis. The spatial clustering of children's lifestyle at neighbourhood level was quantified using the Global Moran's I spatial statistic. **Results:** Three lifestyle patterns were identified: 1) 'activity pattern' (low sedentary time and high moderate-to-vigorous PA), 2) 'high sleep/low screen time' and 3) 'healthy diet and high outdoor play'. These patterns explained 65.1% of the variance in children's lifestyle behaviour. Regression models revealed no effect of the 'activity pattern' on childhood overweight (all p>0.05). In contrast, the 'high sleep and low screen time' pattern was associated with a lower BMI (B[95%CI] = -0.07[-0.11; -0.03] SD) and lower odds to become overweight (OR[95%CI] = 0.77[0.65; 0.91]). Additionally, the 'healthy diet and outdoor play' pattern was associated with a lower BMI (B[95%CI] = -0.04[-0.08; -0.001] SD), but not with overweight (p>0.05). The spatial analyses showed significant spatial clustering in childhood overweight, in the presence of lifestyle factors. **Conclusion:** These preliminary results show that the lifestyle clusters of 'low screen time and high sleep' and 'healthy diet and high outdoor play' seem favourable in the prevention of childhood overweight. The spatial clustering suggests that there are additional factors in the child's neighbourhood that influence the development of childhood overweight. **1. Conflict of interest:** The authors declare that they have no competing interests. **2. Funding:** This study was performed within the Groningen Expert Center for Kids with Obesity, funded by an unrestricted grant from Hutchison Whampoa Ltd, Hong Kong and supported by the University of Groningen, Well Baby Clinic Foundation Icare, Noordlease, Paediatric Association Of The Netherlands and Youth Health Care Drenthe. Funding was unrestricted.