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Lifestyle intervention modify DNA methylation of adipose tissue in overweight and obese men with insomnia symptoms

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Objective To study whether diet and exercise intervention affect sleep and obesity-related genes' DNA methylation in overweight and obese men with insomnia symptoms
Methods The study participants were a subgroup of a large intervention and consisted of 10 overweight or obesity men aged 34-65 years with insomnia symptoms. They participated in a 6-month progressive aerobic exercise training and individualized dietary consoling program and were randomly selected from diet (n=4), exercise (n=3) and control (n=3) groups. Body composition included fat mass and lean mass in the whole body and abdominal android region were assessed by dual-energy X-ray densitometry. The fitness level (VO2max) was determined by 2-km walk test using a standard protocol. Blood samples from venous were taken at fasted state in the morning. Total cholesterol, high density lipid cholesterol, low density lipid cholesterol, triglycerides, glucose, insulin, non-esterified fatty acid, alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase were assessed by conventional methods. Subcutaneous adipose tissue was taken from abdominal region before and after the intervention. DNA was extracted from subcutaneous adipose tissue using a QIAamp DNeasy Tissue Kit. Whole genome-wide DNA methylation was obtained using MethylRAD-Seq. MethylRAD library preparation started from DNA digestion by FspEI, then digested products were run on agarose gel to verify digestion and DNA ligase was added to the digestion solution. After ligation products amplication, PCR was conducted by MyCycler thermal cycler (Bio-Rad). The target fragment was excised from polyacrylamide gel and DNA was diffused from the gel in nuclease-free water. For relative quantification of MethylRAD data, DNA methylation levels were determined using the normalized read depth (reads per million, RPM) for each site. For each restriction site, its methylation level was estimated by dividing the log-transformed depth of each site by the log-transformed maximum depth (representing 100% methylation; i.e. M-index ¼ log(depth site)/ log(depth max)), where depth max was summarized from the top 2% of sites (approx. 500 for the standard library) with the highest sequencing coverage. Heat map images are generated with Matlab 7.0 software and pathways are analysed by WEB-based Gene SeT AnaLysis Toolket. A statistical significance for methylated CpGs and pathways were set to p=0.001 and p=0.05, respectively.
Results No significant group differences by time were found in sleep-related variables, body composition, lifestyle factors nor with measured lipid and glucose biomarkers. However, whole genome-wide DNA methylation was decreased after dietary intervention, but was increased after exercise intervention, respectively. Correspondingly, 1253 and 708 differentially methylated loci were found in diet and exercise groups by contrast to the control group. Among them, the overlap genes between diet and exercise had multiple differentially methylated CpGs, including e.g. MYT1L (4 CpGs), CAMTA1 (3 CpGs), NRXN1 (3 CpGs), RPS6KA2 (3 CpGs), SEMA4D (3 CpGs). DNA methylation

in PCDH8 was negatively correlated with wake after sleep onset after exercise intervention and MYRIP associated with sleep duration showed lower methylation after the dietary intervention. Further, 13 (DIO1, GCK, GYS1,
LMNA, LY86, PNMT, PPARA, PPARD, SERPINE1, TH, TMEM18, TNFRSF1B and UBL5) and 2 (SDCCAG8 and TNF) obesity-related genes' DNA methylation profile changed in response to diet and exercise, respectively. Percentage changes of CpGs within KLHDC8A, ANKS1A, FGFRL1 and KDM3B were correlated with energy yield fat and carbohydrate, HOMA-IR and VO2max, respectively.
Conclusions We found that both exercise and dietary interventions have impacts on these genes related to sleep indicating by DNA methylation in PCDH8 and MYRIP, respectively. Further diet may be more effective than aerobic exercise intervention since greater number of modified obesity-related genes observed after dietary intervention. Our results indicate that reduce insomnia symptoms may need to more focus on control obesity.