1.52âŁ“5.34). 121 participants (60%) were assessed at 24 months ($n = 53$ control, $n = 68$ intervention). The reduction in BMI SDS at 12 months from baseline was lost in both groups at 24 months (âˆ'0.03 control [95% CI: âˆ'0.14 to 0.09] and âˆ'0.02 intervention [âˆ'0.12 to 0.08]). However, participants who attended â‰¥70% of intense intervention sessions had a reduction in BMI SDS of âˆ'0.22 compared to a return to baseline levels for those attending < 70% ($p = 0.002$). Intervention participants were faster on the 550m walk/run test (âˆ'0.57mins, $p < 0.0001$), and both groups reported improvements in quality of life ($p < 0.05$), and reduction in sweet drink intake ($p < 0.001$).

Conclusion: High adherence to the intense intervention resulted in sustained reductions in BMI SDS at two years. Futher, even with home-based assessments only, improvements in quality of life and reduction in sweet drink intake were achieved. Obesity programmes incorporating assessments and an intense intervention can result in improvements, with attendance being key to long-term outcome.

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Improved vascular structure and function following intermittent energy restriction in adolescents with obesity

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Background: In adults, intermittent energy restriction (IER), popularised as the 5:2 diet, is as effective for weight loss and improved cardiovascular risk as continuous energy restriction. We investigated the impact of IER on vascular structure and function in adolescents with obesity.

Methods: During weeks 1–12, participants followed an IER plan consisting of a Very Low Energy Diet (VLED) 3 days/week (500–600 kcal/day) and a standard healthy diet 4 days/week. For weeks 13–26, participants were given a choice to continue with 1–3 days of VLED/week or follow a standard healthy diet. Outcomes measured at 0, 12 and 26 weeks were BMI expressed as a percentage of the 95th percentile (BMI%95th), blood pressure, fasting lipids, pulse wave velocity (PWV), carotid intima-media thickness (CIMT), and flow meditated dilation (FMD).

Results: 30 participants, aged 12–17 years (median 15.2 years, female $n = 25$) with a median BMI 34.9 kg/m^2 (range: 27.7–52.4), were recruited. Compared with baseline, BMI%95th was significantly reduced at 12 weeks (mean difference [SD], $n = 23$, −5.4 [2.2], $p < 0.0001$) and 26 weeks ($n = 21$, −5.0 [9.3], $p = 0.02$). Triglycerides and brachial systolic blood pressure were also reduced at 26 weeks compared with baseline ($n = 21$, −0.22 mmol/L [0.31], $p = 0.008$ and $n = 13$, −5.6 mmHg [8.9], $p = 0.042$, respectively). CIMT ($n = 16$, −0.06 μm [0.05], $p = 0.001$) and FMD ($n = 15$, absolute increase of 0.51% [0.5], $p = 0.001$) improved between baseline and 12 weeks. The improvement was maintained at 26 weeks. Reduced BMI%95th was associated with improved PWV (rho = 0.63, $p = 0.022$) and FMD ($r^2 = 0.80$, $p < 0.0001$) at 26 weeks.

Conclusion: IER is an effective dietary intervention in adolescents with obesity, resulting in reduced BMI%95th and cardiovascular risk in the short term. Findings demonstrate a potential benefit to cardiovascular health if maintained. A 12-month RCT is underway comparing IER with continuous energy restriction.

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Systems genetics as a tool to probe hepatic lipid and energy metabolism

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Dysregulation of lipid homeostasis is a precipitating event in the pathogenesis and progression of hepatosteatosis and metabolic syndrome. However, defining the molecular mechanisms that underpin lipid dysregulation in humans has proven challenging due to complex gene and environment interactions. Nevertheless, genome-wide association studies (GWAS) have indicated there to be an approximately 30% heritability for hepatosteatosis, however only ∼10% has been directly attributable to genetic variants. This highlights a discrepancy that likely exists because most linear GWAS models do not account for features such as structural variation, rare variants and complex epistatic or gene-by-environment interactions. More recently, systems biology approaches utilizing genetic reference panels (GRPs) in model organisms have increased our ability in this regard, because they allow for integration of multiple layers of biological information (trans-omics), and for the control of environmental influence. Accordingly, we undertook a systems genetics analysis of mammalian lipid metabolism. Here we quantify 311 individual lipid species in the liver and plasma of replicate animals from 107 strains of an inbred mouse GRP (>300 individual mice), and integrated these data with matched hepatic proteomics performed on the same set of mice. Subsequent analysis of correlation networks and QTL mapping incorporating strain-specific phenotype and genotype data facilitated the generation of a powerful resource that expands our understanding of mammalian lipid metabolism, identifies *bona fide* effectors of lipid abundance, and provides several targets of interest for disease intervention.

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Metabolomic analysis of insulin resistance across different mouse strains and diets

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Insulin resistance is a major risk factor for many diseases. However, its underlying mechanism remains unclear in part because

it is triggered by a complex relationship between multiple factors including genes and the environment. Here we used metabolomics combined with computational methods to identify factors that classified insulin resistance across individual mice derived from three different mouse strains fed two different diets. Three inbred ILSXISS strains were fed high fat or chow diets and subjected to metabolic phenotyping and metabolomics analysis of skeletal muscle. There was significant metabolic heterogeneity between strains, diet and individual animals. Distinct metabolites were changed with insulin resistance, diet and between strains. Computational analysis revealed 113 metabolites that were correlated with metabolic phenotypes. Using these 113 metabolites, combined with machine learning to segregate mice based on insulin sensitivity we identified C22:1-CoA, C2-carnitine and C16-ceramide as the best classifiers. Strikingly, when these three metabolites were combined into one signature, they classified mice based on insulin sensitivity more accurately than each metabolite on its own or other published metabolic signatures. Furthermore, C22:1-CoA, was 2.3-fold higher in insulin resistant mice and correlated significantly with insulin resistance. We have identified a metabolomic signature comprised of three functionally unrelated metabolites that accurately predicts whole body insulin sensitivity across three mouse strains. These data indicate the power of simultaneous analysis of individual, genetic and environmental variance in mice for identifying novel factors that accurately predict metabolic phenotypes like whole body insulin sensitivity.

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Diet and environment: some "Inconvenient Truths" about obesity-related insulin resistance

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Recent studies using different strains of mice have highlighted that genetic makeup has a significant impact on how animals respond to dietary interventions important for understanding the development of obesity, insulin resistance and type 2 diabetes in humans. However, variations in environmental conditions (diet, temperature, diurnal rhythm) can also have a major influence on the outcome, and interpretation, of experiments, although not necessarily in the way expected. Our recent investigations in chow and high fat fed mice have determined that housing temperature significantly alters metabolic rate as well as glucose and lipid metabolism in certain tissues, but this appears to have little impact on whole body glucose homeostasis and fat deposition. Obesity in humans is not always associated with reduced insulin action (Diabetologia 2013, 56:875). A similar dissociation between obesity and insulin resistance can also be demonstrated in mice made obese by feeding a high-starch diet compared to mice made obese by feeding a high-fat diet suggesting that insulin resistance is not a simple correlate of excess adipose tissue. Assessing the insulin signalling pathway and glucose uptake in muscle over the diurnal cycle of feeding and fasting revealed that the compensatory hyperinsulinemia seen in insulin resistant fat-fed rats resulted in similar phosphorylation levels of key insulin signalling proteins in muscle as chow-fed insulin sensitive animals. Despite this similar phosphorylation state, glucose uptake remained lower in muscle of fat-fed rats across the feeding period. These observations suggest that obesity-related insulin resistance is more complex than a simple relationship with excess fat deposition or reduced insulin signalling in insulin sensitive tissues. A more holistic rather than candidate approach may be required to fully understand all the mechanisms involved in this importance predictor of metabolic disease.

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The role of Ap2a2 in PPARα-mediated regulation of lipolysis in adipose tissue

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Adipose tissue plays a major role in the regulation of systemic metabolic homeostasis, and defects in insulin action and lipolysis have the capacity to impact systemic glycaemic control. In this respect, the AP2 adaptor complex plays an important role in clathrin-mediated endocytosis of various cell surface receptors in adipose tissue, including the glucose transporter GLUT4, the insulin receptor and beta-adrenergic receptors. The AP2 complex is a hetero-tetramer (α, β, μ and σ subunits), with the alpha-subunit being important for attachment of the AP2 complex to the membrane and for cargo internalization. The alpha-subunit exists in two isoforms, Ap2a1 and Ap2a2. Of interest, Ap2a2 (but not Ap2a1) has recently been identified as a peroxisome proliferator-activated receptor alpha (PPARα) target gene. The effects of PPARα on the AP2 adaptor complex and clathrin-mediated endocytosis in adipose tissue are not well described.

We have generated adipose tissue-specific Ap2a2 knockout mice and investigated metabolic alterations on a standard chow diet, in the presence of lipid overload (8 weeks high-fat feeding) as well as with dietary supplementation with the PPARα-agonist pirinixic acid (WY-14643). Supplementation with WY was required to drive expression of Ap2a2 in adipose tissue of wild-type mice and produce genotype-specific effects. Deletion of Ap2a2 led to minor improvements on systemic level, and did not affect basal or insulin-stimulated glucose uptake, or fatty acid metabolism. However, deletion of Ap2a2 had a substantial impact on beta-adrenergic activation of lipolysis. Adipose tissue of Ap2a2-KO mice lost its ability to respond to beta-adrenergic stimuli, as evidenced by a lack in increases in cAMP, PKA activation and glycerol release. These differences were not due to differential expression of beta-adrenergic receptors, but more likely to defects in AP2-mediated receptor endocytosis and recycling.

This study indicates a novel role for PPARα in beta-adrenergic regulation of lipolysis in adipose tissue.

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