

# Insulin resistance in adolescents with overweight and obesity

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# Valorisation

A recent report estimated that, without proven effective interventions, in 2025 a total of 268 million children will be overweight, of which 91 million will have obesity. Even in childhood obesity is already associated with a myriad of comorbidities affecting nearly every organ system, including but not limited to type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), as well as psychological consequences such as reduced quality of life. This thesis particularly focusses on the prevention of T2DM in adolescents. T2DM was typically considered to be an adult-onset disease, but in recent years 45% of new diabetes cases in adolescents were attributable to type 2. Moreover, up to 52% of adolescents with overweight present with IR, a known precursor of T2DM, and it is known that adolescents can convert from IR to T2DM much faster than adults. It is therefore important to gain more insight in IR in adolescence – and that research in this field is relevant, available and can be used for translation so that new strategies to prevent T2DM in youth can be developed.

The PREVIEW study was designed to assess the feasibility and effects of a lifestyle intervention, consisting of increasing protein intake, on IR and BMI z-score in adolescents with overweight and obesity at high risk for developing T2DM. Adolescents (aged 10-17y) with overweight/obesity and IR from the Netherlands, Spain and United Kingdom were randomized into two groups: a high-protein low-glycaemic-index (HP) group that was advised to increase protein intake to 25% of daily energy intake (En%), and a moderate-protein moderate-glycaemic-index (MP) group that increased protein to 15En%. Adolescents were also encouraged to increase physical activity. The second aim of the PREVIEW study was to gain more knowledge about the relationship with possible modifiable risk factors, specifically sleep duration and architecture and NAFLD, with pubertal IR and intervention-mediated changes herein.

Previous studies have shown that adolescents that have overweight/obesity and are also insulin resistant, are at risk for less or no BMI z-score reduction during lifestyle intervention compared to adolescents with overweight/obesity but without IR. In the PREVIEW study only adolescents with overweight/obesity and IR were selected, and mean BMI z-score decreased with -0.17 SD after one year and -0.19 SD after two years of intervention. This reduction is not only statistically significant, but also clinically relevant as BMI z-score reductions  $>-0.15$  have been related to improvement in glucose metabolism and cardiovascular risk markers. This shows that the advice to increase protein intake (in combination with instructions to increase physical activity) and personalized approach of the PREVIEW study are targets for successful treatment of adolescents with overweight/obesity – which is especially beneficial for those with IR as that were until now at risk for less intervention response.

Furthermore, the personalized instructions of the PREVIEW study rendered an overall increase in physical activity, especially moderate-to-vigorous activity and decrease in sedentary time, suggesting favourable changes in lifestyle parameters. After one year cognitive restraint of eating scores were significantly higher - indicating a more conscious attitude towards food intake - and this was directly associated with BMI z-score decrease. Thus, the results of this study indicated that increasing dietary restraint is a target for successful BMI z-score reduction in adolescents with overweight and obesity, which might be of benefit for patients as well as for clinicians and scientists aiming to improve current childhood obesity therapies.

It was also observed that NAFLD, which was present in 1/3<sup>rd</sup> of the adolescents in this cohort, was a risk factor for less BMI z-score decrease after one year of intervention. As screening for NAFLD at treatment onset is a relatively easy, cheap and non-invasive procedure, we would recommend to incorporate this in treatment strategies as this will effectively identify individuals that might be in need of additional support to achieve successful BMI z-score decrease.

None of the adolescents progressed to T2DM during the two years of study participation. After one year IR stabilization could be achieved despite progression of puberty, and this was related to decrease in BMI z-score. After two years HOMA-IR increased, suggesting that adolescents with overweight and obesity are at risk for persistence of high IR at the end of puberty, which is in line with cross-sectional observations from this and other studies. Thus, these results indicate the importance of preventing further IR exacerbation during puberty, especially in those with overweight/obesity as they are at risk for persistent high IR, but also demonstrate that it is possible to counteract IR increase and T2DM progression by decreasing BMI z-score. The results of the PREVIEW study are relevant to the society, because it provides a novel therapeutic strategy that successfully prevented IR increase and yielded BMI z-score decrease in a population that was previously at risk for less successful therapy outcomes. The PREVIEW study also identified several targets, e.g. increasing cognitive restraint of eating and screening for NAFLD, that are associated with BMI z-score decrease after one year of intervention and might thus aid clinicians and scientists aiming to improve current childhood obesity therapies. These results were shared with the scientific community and presented at several national and international conferences.

Apart from the medical and societal relevance, the outcomes of this study also have an economical relevance. The costs of diabetes are rising rapidly and are estimated to be a \$327mil per year in the USA alone. For children it has been shown that overweight and obesity lead to an incremental lifetime health costs of \$19.000,- per individual (data of 2012), resulting in considerable economical burden considering the estimated number of T2DM

globally as reported at the beginning of this chapter. At this moment a cost-benefit analysis of PREVIEW is being performed. A similar lifestyle intervention in children with overweight and obesity estimated a lifetime economic benefit of €11384,- to €19120,- per individual, and estimated that the economic benefit of an intervention in childhood were 4 to 7 times higher than the costs. As the PREVIEW study was particularly successful in those adolescents with high risk for T2DM development (and thus higher lifetime healthcare costs), it is expected that this lifestyle intervention contributes to reduced healthcare costs for the treatment of childhood obesity and diabetes.

Not only positive research results are valuable for the scientific and medical community. PREVIEW adds to a limited number of studies that aimed to increase protein intake in adolescents with overweight and obesity, and similar to our study most other studies observed that higher protein intake targets could not be achieved and maintained long-term in free living settings. However, when higher protein targets were met (as was the case in studies with an in-centre or in-centre-supermarket design) this resulted in significant BMI z-score decrease and reduction in HOMA-IR. These results indicate that achieving high protein targets with advice alone were not feasible in adolescents in free living settings, and future studies assessing the benefits of high-protein diets in adolescents should consider the incorporation of meal replacement, vouchers for protein-rich meals or protein supplements in their design.

Taken together, the PREVIEW intervention yielded a significant BMI z-score decrease in adolescents with overweight/obesity and IR, that were until now known to show significantly less BMI z-score decrease in conventional therapeutic strategies compared to peers without IR. In this group, that is at particularly high risk of developing T2DM, IR stabilized after one year of treatment which was associated to the reduction in BMI z-score. Increased dietary restraint scores were identified as targets for BMI z-score decrease, while NAFLD at study onset was related to less BMI z-score decrease after one year of study participation. A major strength of the study is that it was set in real-life settings, and the principles used in the PREVIEW study can therefore be very easily incorporated in other lifestyle interventions for adolescents with overweight and obesity.