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## Genetic predisposition to adiposity is associated with increased objectively assessed sedentary time in young children

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### Abstract

Increased sedentariness has been linked to the growing prevalence of obesity in children, but some longitudinal studies suggest that sedentariness may be a consequence rather than a cause of increased adiposity. We used Mendelian randomization to examine the causal relations between body mass index (BMI) and objectively assessed sedentary time and physical activity in 3-8 year-old children from one Finnish and two Danish cohorts [ $N_{\text{TOTAL}}=679$ ]. A genetic risk score (GRS) comprised of 15 independent genetic variants associated with childhood BMI was used as the instrumental variable to test causal effects of BMI on sedentary time, total physical activity, and moderate-to-vigorous physical activity (MVPA). In fixed effects meta-analyses, the GRS was associated with 0.05 SD/allele increase in sedentary time ( $P=0.019$ ), but there was no significant association with total physical activity ( $\beta=0.011$  SD/allele,  $P=0.58$ ) or MVPA ( $\beta=0.001$  SD/allele,  $P=0.96$ ), adjusting for age, sex, monitor wear-time and first three genome-wide principal

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#### Conflict of interest

The authors declare no conflict of interest.

#### Data availability

Relevant data for the present study are within the paper and its Supporting Information files. If you wish to see additional data, the authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Data is available from the Novo Nordisk Foundation Center for Basic Metabolic Research, section of Metabolic Genetics whose authors may be contacted at [torben.hansen@sund.ku.dk](mailto:torben.hansen@sund.ku.dk).

components. In two-stage least squares regression analyses, each genetically instrumented one unit increase in BMI z-score increased sedentary time by 0.47 SD ( $P=0.072$ ). Childhood BMI may have a causal influence on sedentary time but not on total physical activity or MVPA in young children. Our results provide important insights into the regulation of movement behaviour in childhood.

## Keywords

Genetic risk score; childhood BMI; adiposity; sedentary time; mendelian randomization

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## Introduction

Increased sedentary time and decreased physical activity have been linked to the recent increase in the prevalence of overweight and obesity among children (1, 2). However, evidence from longitudinal studies suggests that decreased physical activity and increased sedentary time may be an outcome rather than a cause of increased adiposity in children (3, 4).

Genetic variants associated with body mass index (BMI) can be utilized as instrumental variables in Mendelian randomization to test for causal relationships between adiposity and physical activity or sedentary behaviour. In 2014, Richmond et al. performed instrumental variable analyses in 4296 children 11 years of age from the UK using a genetic risk score (GRS) for obesity (5), derived from 32 gene variants identified in a published genome-wide association study (GWAS) of adult BMI (6). Genetic predisposition to higher BMI was robustly associated with longer sedentary time and lower levels of physical activity (5), suggesting causality. However, these findings remain to be replicated in younger children in whom genetic determinants of movement behaviour may be particularly discernible due to higher tendency for voluntary and spontaneous, play-oriented activity (7, 8). Further, a recent GWAS in children identified 15 loci for childhood BMI (9), making it possible to generate a more specific instrumental variable for childhood adiposity than the GRS for adult BMI used by Richmond et al. (5).

The aim of the current study was to investigate whether a GRS of 15 loci for childhood BMI is associated with objectively assessed sedentary time and physical activity in young children.

## Methods

### Participants

The participants of the study include 287 Danish children 3 years of age from the Småbørns Kost Og Trivsel I and II (SKOT I and II) studies (10) and 400 Finnish children from the Physical Activity and Nutrition in Children (PANIC) study (11). Details on the recruitment, inclusion criteria and ethical approvals in SKOT I, SKOT II, and PANIC are provided in Supplementary Material 1.

## Measurement of body size and composition

In the SKOT I and II studies, body weight was measured by the Tanita WB-100MA digital scale (Tanita Corporation, Tokyo, Japan) and body height by the 235 Heightronic digital stadiometer (QuickMedical, Issaquah, WA, USA). The age and gender-specific BMI z-score was calculated using the WHO Anthro software, version 3.2.2 (12). In the PANIC study, body weight was measured using the InBody® 720 bioimpedance device (Biospace, Seoul, Korea) and body height using a wall-mounted stadiometer. Age and gender-specific BMI z-score was calculated based on Finnish reference data (13).

## Assessment of sedentary time, total physical activity and MVPA

In the SKOT I and II studies the ActiGraph GT3X accelerometer (ActiGraph LLC, Pensacola, FL, USA), and in the PANIC study Actiheart (Actiheart, CamNTEch Ltd., Cambridge, UK) was used to assess sedentary time and physical activity. Details on the assessment of activity behaviours are provided in Supplementary Material 1.

## Genotyping, SNP selection, and genetic risk score construction

Children in SKOT I and II were genotyped using the Illumina Infinium HumanCoreExome Beadchip. Children in the PANIC study were genotyped using the Illumina Custom Infinium Cardio-Metabochip and the Illumina Infinium HumanCoreExome Beadchip (Illumina, San Diego, CA, USA) and the genotypes from the two arrays were combined (see Supplementary Material 1 for information on quality control). The SNPs included in the GRS were selected based on a previously published GWAS meta-analysis in children 2-10 years of age (9) that identified 15 independent loci associated with BMI at genome-wide significance ( $p < 5 \times 10^{-8}$ ). We constructed a weighted BMI-increasing GRS by summing the number of BMI-increasing alleles weighted by the effect sizes of the variants estimated in the GWAS discovery study (Supplementary Material 1, Supplementary Table 1).

## Statistical analysis

All association analyses were performed using R, version 3.3.1. Only children with valid physical activity and genotype data ( $n_{SKOT I}=208$ ;  $n_{SKOT II}=71$ ;  $n_{PANIC}=400$ ) were included in the present analyses. Sedentary time, total physical activity, and moderate-to-vigorous intensity physical activity (MVPA) variables were rank inverse normally transformed to approximate normal distribution with a mean of 0 and standard deviation (SD) of 1, and the effect sizes are thus reported in SD units of the inverse normally transformed trait.

The associations of the BMI z-score as well as the BMI-increasing GRS with sedentary time, physical activity and MVPA were analysed by linear regression adjusting for age, sex, and monitor wear-time. The association of the BMI-increasing GRS with the BMI z-score was analysed by linear regression adjusting only for monitor wear-time, because the BMI z-score is age and sex-specific. The BMI-increasing GRS did not show an association with additional potential confounders in PANIC, the largest cohort included in the meta-analysis (sleep, socioeconomic status;  $p > 0.05$ , data not shown). The causal relationships between BMI and activity behaviours were tested using two-stage least squares regression analyses implemented in the 'AER' package in R (version 3.3.3). We used the Durbin-Wu-Hausman (DWH) test for endogeneity and calculated the F-statistic for the PANIC cohort (F-

statistic<sub>PANIC</sub>) to compare effect estimates between the instrumental and observational analyses (14). To test for potential directional pleiotropy in the genetic instrument, we used Egger regression, implemented in the ‘MendelianRandomization’ package in R (version 3.3.3), where the deviation of the intercept from zero provides evidence of pleiotropy (15). The associations of the BMI-increasing GRS, two-stage least squares regression and Egger regression analyses were additionally adjusted for the first three genome-wide principal components of the respective study. We pooled the results from the SKOT I, SKOT II and PANIC studies by fixed effects meta-analyses using the ‘meta’ package in R (version 4.6.0).

## Results

The characteristics of children from the SKOT I, SKOT II and PANIC studies are summarized in Supplementary Table 2. The average age of the children was 3.0 years (range 2.9-3.3 years) in SKOT I; 3.0 years (range 2.9-3.2 years) in SKOT II; and 7.6 years (range 6.6-9.0 years) in PANIC. The GRS was normally distributed in all three cohorts, with a mean (range) of 8.6 (3.8-14.7), 9.0 (5.0-17.8) and 9.3 (3.7-16.1) BMI-increasing alleles in SKOT I, SKOT II and PANIC, respectively.

A higher BMI z-score was associated with increased sedentary time ( $\beta=0.22$  SD,  $P=7.6 \times 10^{-9}$ ) and reduced MVPA ( $\beta=-0.17$  SD,  $P=1.1 \times 10^{-5}$ ), but not with total physical activity ( $\beta=0.003$  SD,  $P=0.94$ ) (Figure 1). Heterogeneity was observed in the association of BMI z-score with sedentary time and MVPA ( $p_{\text{het}} < 0.05$ ).

A higher BMI-increasing GRS was associated with a higher BMI z-score ( $\beta=0.056$  SD/allele,  $P=0.003$ ) and longer sedentary time ( $\beta=0.040$  SD/allele,  $P=0.019$ ), suggesting a causal effect of BMI z-score on sedentary behavior (Figure 2). In two-stage least squares analyses, each genetically instrumented one unit increase in BMI z-score increased sedentary time by 0.47 SD ( $P=0.072$ ,  $F\text{-statistic}_{\text{PANIC}}=8.2$ ), and no difference was found between the observational and genetically instrumented estimates in the DWH test ( $P > 0.05$ ). We found no evidence of directional pleiotropy in the genetic instrument using the Egger intercept test ( $P_{\text{INTERCEPT}}=0.28$ ), and the causal estimate from Egger regression was directionally consistent with that derived from the two-stage least squares method.

There was no significant association between the BMI-increasing GRS and MVPA ( $\beta=0.001$ ,  $P=0.96$ ) or total physical activity ( $\beta=0.011$ ,  $P=0.58$ ), and two-stage least squares analyses were not suggestive of a causal effect of BMI on MVPA ( $\beta=-0.026$ ,  $P=0.94$ ,  $F\text{-statistic}_{\text{PANIC}}=7.5$ ) or physical activity ( $\beta=0.22$ ,  $P=0.55$ ,  $F\text{-statistic}_{\text{PANIC}}=7.5$ ) (Figure 1).

## Discussion

In the present study, a GRS for childhood BMI was nominally significantly associated with BMI and sedentary time, but not with total physical activity or MVPA. Our results may suggest that higher adiposity is causally associated with longer sedentary time but not with decreased physical activity in young children.

Consistent with our findings, Richmond et al. (5) found that a higher GRS for BMI was positively associated with longer daily sedentary time in 11-year old children from the UK.

However, they also reported that a higher GRS was associated with lower levels of total physical activity and MVPA, whereas we found no association between the GRS and total physical activity or MVPA. While the sample sizes for the present analyses were smaller than in the study by Richmond et al., we observed an effect close to zero for the association of the GRS with physical activity and MVPA, and with confidence intervals suggesting that little or no effect is present in 3-8 year old children. Nevertheless, our findings should ideally be validated in further studies including large samples of young children with objectively measured activity behaviour.

The age of the children and country-specific differences in the education system may partly explain the observed differences in the results of the study by Richmond et al (5) and our study. In our study, we also found heterogeneity in the association of the BMI z-score with sedentary time and MVPA, and visual observation of the forest plots indicated that the two SKOT cohorts show consistent results which differ from those seen for the PANIC cohort, which may be due to the different age range of children included in these cohorts. Most 3-year-old Danish children attend kindergarten where physical activity typically consists of play-oriented activities (16) and the children are free to choose whether to play passively or actively. The Finnish children 6-8 years of age were first graders in primary schools when they were invited to participate in the PANIC study. They were thus more likely to engage in play-oriented physical activity because of their recent pre-school times than the 11-year-old children from the UK, although they also spent longer periods of time in sedentary and non-sedentary activities during school hours. The tendency to engage in voluntary and play-oriented activities in younger children could explain the lack of association between the GRS for childhood BMI and physical activity in the present study.

While our results are suggestive of an effect of adiposity on sedentary behaviour, we could not investigate whether a genetic predisposition to sedentary behaviour reciprocally results in higher BMI, because no genetic variants associated with sedentary behaviour have yet been robustly identified (17). Similarly, we could not examine whether MVPA has a causal effect on BMI in young children, and whether such an effect explains the observed association between higher BMI and lower MVPA. Furthermore, we cannot fully exclude the possibility of residual pleiotropy, i.e. that the selected genetic variants act not only on BMI but also on other phenotypes related to sedentary time.

In conclusion, we showed that young children with higher genetic risk for obesity have increased objectively measured sedentary time but not decreased physical activity, suggesting that obesity may be causally associated with longer time spent in sedentary pursuits at this age. Reducing BMI may thus be an effective strategy to reduce sedentariness in overweight children. While the mechanisms underlying the potential causal relationship between BMI and sedentary time remain unclear, they are likely to involve both physiological factors and factors related to the family environment (18). Our findings provide novel insights into the regulation of movement behaviour in childhood and suggest that more attention should be given to the sedentary-time increasing effect of obesity in young children.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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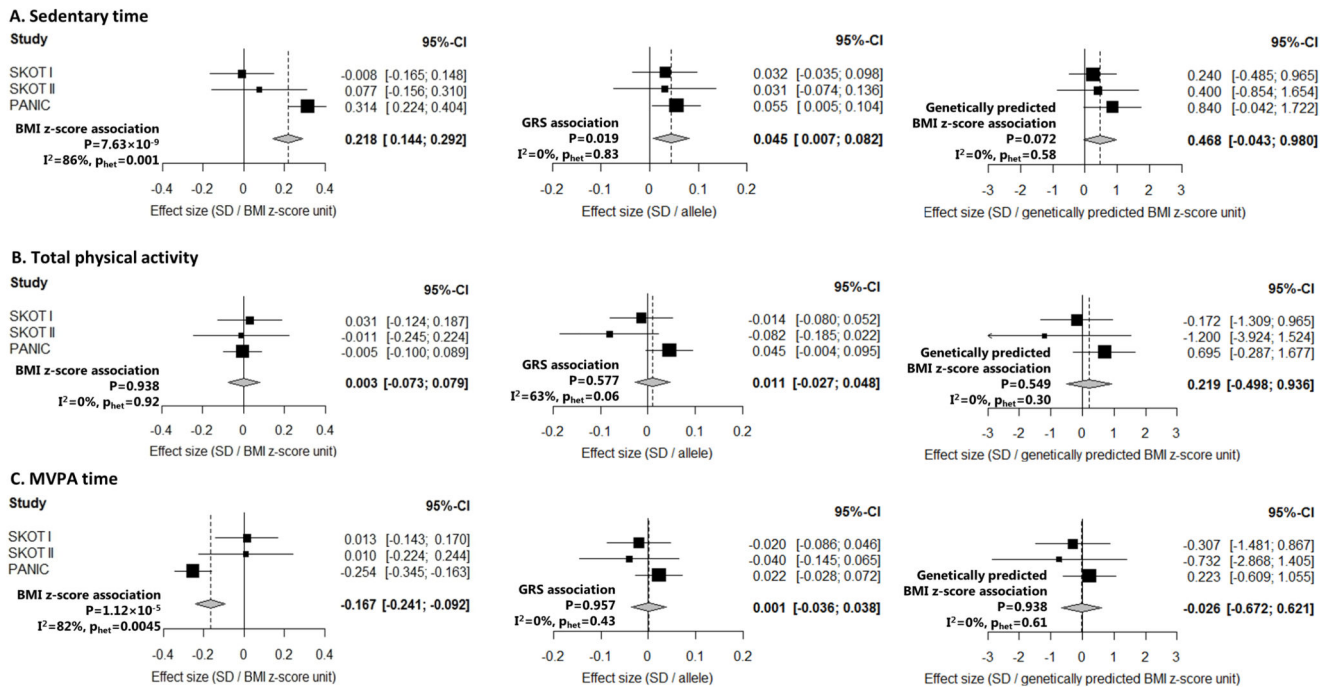
## Abbreviations

<b>GRS</b>	Genetic Risk Score
<b>BMI</b>	Body mass index
<b>MVPA</b>	moderate-to-vigorous physical activity
<b>GWAS</b>	Genome-wide association study

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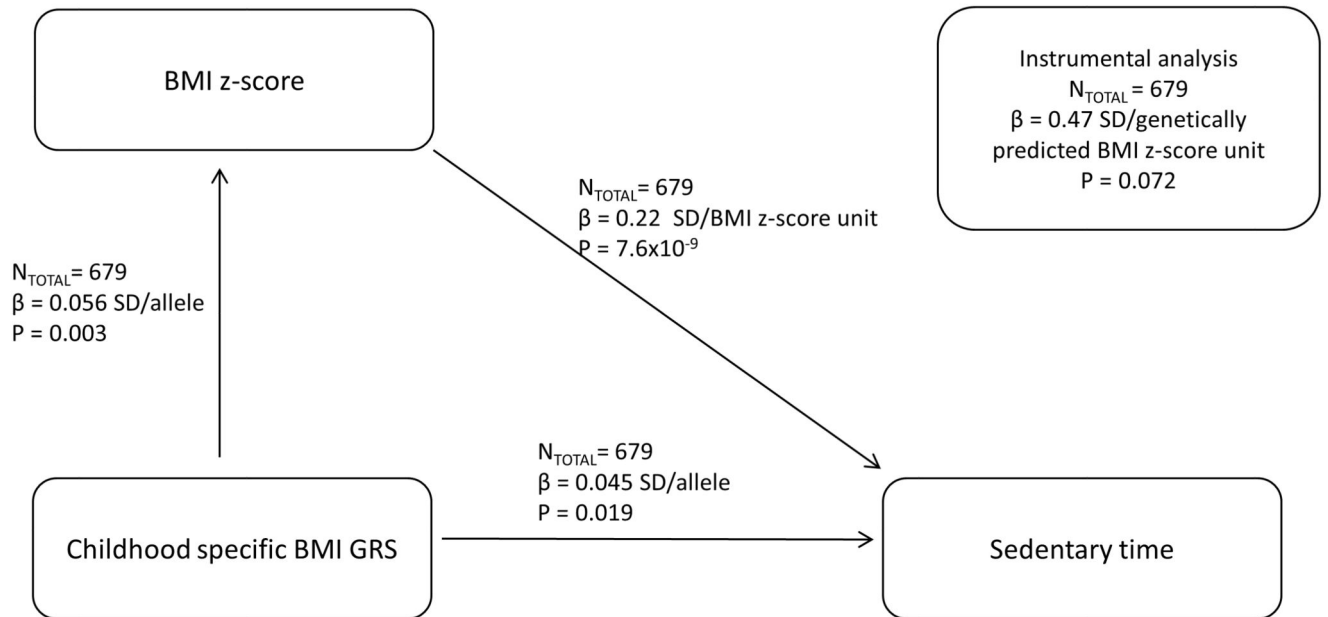
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**Figure 1.** Forest plots showing the associations of BMI z-score (left column), childhood BMI-increasing GRS (middle column) and genetically predicted BMI z-score (right column) with **A.** sedentary time, **B.** total physical activity, and **C.** moderate-to-vigorous physical activity (MVPA). For the GRS associations, the results are aligned according to the BMI-increasing allele of the GRS. All analyses are adjusted for age, gender, monitor wear-time and first three principal components. The effects were pooled using fixed effects models. The estimated per-BMI z-score, per-allele and per-genetically predicted BMI z-score effect sizes are reported in SD units based on inverse normally transformed outcome trait. Heterogeneity statistics include the  $I^2$  value that describes the percentage of variation across the meta-analysis that is due to heterogeneity, and  $p_{het}$ , the p-value for the  $\chi^2$  test of heterogeneity.





**Figure 2.** Mendelian randomization analysis to test the causal effect of childhood BMI on sedentary time. Beta values are expressed in units of standard deviation (SD) of the inverse-normally transformed traits. GRS = Genetic risk score, BMI z-score = age- and sex-specific BMI standard deviation score,  $N_{TOTAL}$  = number of individuals included in meta-analysis.