Strengthening evidence for causal effects of physical activity and sedentary behaviors on type 2 diabetes risk in at-risk children from childhood to late adolescence using the QUALITY cohort

Type of manuscript: Original research

***Running head*:** Physical activity, sedentary behaviors and diabetes

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Word count: 4703/3500.

Number of tables and figures**:** 5.

Number of references*:* 38/30.

ABSTRACT (300/300 words)

Background. Uncertainty remains regarding the causal effect of physical activity and sedentary behaviors on type 2 diabetes (T2D) development in children. The objective of our study was to estimate average treatment effects (ATEs) of physical activity and sedentary behaviors on T2D risk in childhood and adolescence.

Methods. We used data from the QUebec Adipose and Lifestyle InvesTigation in Youth (QUALITY) cohort of children with a parental history of obesity evaluated at 8-10 years (n=630), 10-12 years (n=564) and 15-17 years (n=377), in Québec, Canada (2005-2015). We measured moderate-to-vigorous physical activity (MVPA) and sedentary time by accelerometry, and leisure screen time by questionnaire at each cycle. Outcomes included fasting and 2-h glycemia and validated indices of insulin sensitivity and insulin secretion. We estimated ATEs of MVPA, sedentary time, and screen time on markers of T2D using longitudinal marginal structural models with time-varying exposures, outcomes and confounders from 8-10 to 15-17 years and inverse probability of treatment and censoring weighting. We considered both the current and cumulative effects of exposures on outcomes.

Findings. Based on cumulative exposure results, estimated ATEs for MVPA were 5·6% (95% CI: 2·8; 8·5) on insulin sensitivity and -3·8% (-7·1; -0·5) on second-phase insulin secretion per 10-minute daily increment across 8-10 to 15-17 years. ATEs for sedentary time and reported screen time yielded reduced insulin sensitivity (-8·2% [-12·3; -3·9] and -6·4% [-10·1; -2·5], respectively), increased second-phase insulin secretion (5·9% [1·9; 10·1] and 7·0% [-0·1; 14·7], respectively), and higher fasting glycemia (0·03 mmol/L [0·003; 0·05] and 0·02 mmol/L [0·01; 0·03], respectively) per supplemental daily hour from 8-10 to 15-17 years.

Interpretation. Using modern causal inference approaches strengthened the evidence of MVPA and sedentary behaviors as key targets for prevention of T2D in children.

Funding. Canadian Institutes of Health Research, Canada Heart and Stroke Foundation, Fonds de Recherche du Québec-Santé.

KEY WORDS

Type 2 diabetes, insulin sensitivity, insulin secretion, physical activity, sedentary behaviors, children, longitudinal marginal structural models, cohort study

RESEARCH INTO CONTEXT

Evidence before this study

We searched observational studies in English in Pubmed/Medline between 2000 and 2022 using keywords (child or adolescent) and ("physical activity" or exercise or sport* or athletics) and ("type 2 diabetes" or "insulin resistance" or "impaired fasting glucose" or "impaired glucose tolerance" or "glucose intolerance"). We conducted the same search using keywords for sedentary behaviors instead of physical activity: screen* or sedentary or seated or stationary or "desk-bound" or "tv viewing" or "video game" or "computer" or reading. Randomized controlled trials (RCTs) intervening on physical activity in children with overweight or obesity have led to a reduction in insulin resistance, insulin secretory requirements, and postprandial glycemia. However, the limited duration and the controlled setting of findings from RCTs restrict their longer term, “real life” applicability. Findings from observational cohort studies of two to seven years duration suggest that higher physical activity levels and reduced screen time are positively associated with insulin sensitivity. Yet these associations are potentially distorted because important confounders are missing, and the time-varying nature of confounders not accounted for, which are key considerations for valid causal inferences. Thus, there is little robust evidence that physical activity and sedentary behaviors are independent causes of type 2 diabetes (T2D) in childhood.

Added value of this study

Our cohort study addresses shortcomings of existing evidence in the field of lifestyle habits and T2D in children. We investigated the roles of objectively-measured physical activity and sedentary time, as well as screen time, on markers of insulin sensitivity and secretion and fasting and

postprandial glycemia derived from an oral glucose tolerance test over a seven-year follow-up in children with parental obesity. We addressed confounding and informative censoring using longitudinal marginal structural models, a causal inference method that emulates RCTs conditional to explicit causal assumptions. The use of this method allowed us to account for the time-varying and interconnected nature of lifestyle habits, insulin sensitivity/secretion and adiposity across puberty, which is critical but has never been done to date in studies investigating pediatric T2D and lifestyle habits. We found that higher levels of moderate-to-vigorous physical activity and less time spent in sedentary behaviors improved insulin sensitivity and reduced insulin secretory requirements between 8-10 and 15-17 years of age. Children engaging in more sedentary behavior were more likely to have higher fasting glycemia levels during the same period. Importantly, we found that cumulative effects of physical activity levels and sedentary behaviors were greater on insulin sensitivity, insulin secretion, and glycemia than their effect at a single point in time.

Implications of all the available evidence

By using statistical methods that enable the identification of causal effects in an extensively phenotyped cohort of youth, our study provides critical evidence of the independent causal role of *specific* lifestyle habits on T2D risk from childhood to late adolescence. The findings of our study suggest that physical activity and sedentary behaviors are key targets for T2D prevention, whereby even small incremental changes in these behaviors during childhood and adolescence can improve insulin sensitivity, and reduce insulin secretory requirements and fasting glycemia among children with parental obesity. Increasing physical activity by 10 minutes daily and reducing screen time by 1 hour daily are both feasible and clinically applicable strategies for at-risk children and can also

be implemented in health promotion initiatives in the general pediatric population. Moreover, the fact that cumulative effects from pre-puberty to late adolescence were of greater magnitude than effects at a given time point conveys the importance of early (prior to 8 years) and sustained (across childhood and adolescence) lifestyle interventions to prevent T2D in at-risk populations. Finally, with this study, we demonstrate that well-designed prospective cohort studies with appropriate statistical methods can be used to identify causal effects of lifestyle habits on cardiometabolic health in children. Such evidence complements knowledge that stems from RCTs by studying lifestyle habits on a longer term and in natural contexts.

With 41 million children overweight or obese worldwide,[1] prevention of obesity and its associated consequences in the pediatric population is an important public health challenge. Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is on the rise in youth, affecting 18% of adolescents in the United States.[2] Considering the rapid progression from prediabetes to overt type 2 diabetes (T2D)[3] and the high prevalence of diabetes complications in youth with T2D,[4] identifying specific targets for prevention, such as lifestyle habits, is paramount.

Two key elements in the pathophysiology of T2D in youth are insulin sensitivity and insulin secretion by the pancreatic beta-cells. These two features follow a hyperbolic relationship: in healthy youth, for a given level of insulin sensitivity, insulin secretion is adjusted in order to maintain normoglycemia.[5] When insulin sensitivity declines (e.g., with overweight or obesity) insulin secretory requirements increase to keep glycemia in the normal range. However, when insulin secretory demands do not suffice, glycemia rises above normal levels, resulting in prediabetes, and with further beta-cell exhaustion, to T2D development.[6] Therefore, lower insulin sensitivity and altered beta-cell function herald future T2D development; equivalently, higher insulin sensitivity and a preserved beta-cell function reduce its risk.

Physical activity increases energy expenditure, improves insulin sensitivity and potentially preserves beta cell function.[7] In contrast, sedentary behaviors, such as watching television and passive transportation, are associated with reduced energy expenditure, with screen time additionally associated with higher energy intake and worsened diet quality.[8] Most randomized controlled trials of physical activity in children have shown a reduction in insulin resistance;

however, studies were conducted mostly among children with obesity, were limited to 12 months of follow-up and occurred in a controlled setting.[9] Given that declines in physical activity with concomitant increases in screen time are observed during adolescence,[10] conclusions on the role of physical activity on T2D risk from randomized controlled trials over a one year span have a restricted applicability in real life. Moreover, testing physical activity and sedentary behavior interventions with randomized controlled trials spanning childhood into adolescence would be unfeasible in terms of resources required and clinically impracticable.

Observational cohort studies, including work by our team and others have reported a positive association between physical activity and insulin sensitivity,[11-14] and a negative association between screen time and insulin sensitivity.[11] However, these studies had limited follow-up (2-4 years), except for Jago *et al* (6 years) and Metcalf *et al* (7 years).[12,13] Jago *et al*[12] did not consider pubertal stage and none[11-14] accounted for dietary habits, despite being potential confounders in the association between physical activity, sedentary behaviors, and T2D risk. Only Telford *et al*[14] and Metcalf *et al*[13] considered time-dependent confounding. Yet traditional regression models do not properly account for time-varying confounding that affects associations between lifestyle habits and the development of T2D in the longitudinal setting. Confounders can be affected by prior exposure (e.g., adiposity affected by prior physical activity levels) and outcome (e.g., children with prediabetes will be encouraged to improve their lifestyle habits). Given the interrelatedness and the time-varying nature of lifestyle habits, adiposity and insulin dynamics, there is little robust evidence of physical activity and sedentary behaviors as independent determinants of T2D in childhood. The use of appropriate methods to handle confounding in longitudinal studies is warranted.

Our objectives are to estimate the causal effects of objectively-measured physical activity levels, sedentary time, and reported screen time, on 1) dynamic measurements of insulin sensitivity and secretion and 2) glycemia from childhood to late adolescence, in a cohort of children with a family history of obesity, using longitudinal marginal structural models.[15] This method emulates repeated randomized controlled experiments from observational studies relative to measured confounders, potentiating the estimation of causal effects under explicit assumptions.

METHODS

Data were drawn from the Quebec Adipose and Lifestyle Investigation in Youth (QUALITY) prospective cohort of youth at risk of obesity in Québec, Canada.[16] The cohort's overarching objective is to better understand the natural history of obesity, its determinants, and cardiometabolic consequences starting in childhood.

Population

Children of Western European descent (White Non-Hispanic race/ethnicity) were recruited at 8-10 years of age if they had at least one biological parent with obesity, defined as a BMI $\geq$ 30 kg/m^2 or a waist circumference above 102 cm in men and 88 cm in women.[16] A school-based sampling within a 75-km radius of 3 major urban centers was undertaken through the distribution of information pamphlets in elementary schools. Children were not eligible if they had T2D at study entry, took medication interfering with glucose metabolism or were unable to participate in most study measurements.

Ethical procedures

Ethical approval was obtained from the Research Ethics Committee of Centre Hospitalier Universitaire Sainte-Justine (CHUSJ) and Institut Universitaire de Cardiologie et Pneumologie de Québec (IUCPQ). Written assent and consent were obtained from all the children and their parents.

Data collection

The QUALITY cohort comprises a total of 630 children evaluated at baseline (8-10 years, 2005-2008), 564 at first follow-up (10-12 years, 2008-2011) and 377 at second follow-up (15-17 years, 2012-2015). Clinical research evaluations took place at CHUSJ in Montréal, or at IUCPQ in Québec City. Unless specified, all variables were measured at each evaluation cycle.

Outcomes

Children underwent a 2-h oral glucose tolerance test (OGTT) following a 12-h fast with blood samples retrieved at 0, 30, 60, 90 and 120 minutes after ingesting 1·75g glucose/kg (max 75g). Presence of IFG, IGT or T2D was determined using American Diabetes Association criteria: IFG if fasting glucose ≥ 5·6 but < 7 mmol/L; IGT if 2-h glucose ≥ 7·8 but < 11·1 mmol/L and T2D if fasting glucose ≥ 7 mmol/L or 2-h glucose ≥ 11·1 mmol/L.[17] To reflect dysglycemia while optimizing statistical power, we used continuous values of fasting plasma glucose and 2-h post load glucose as outcomes. Insulin sensitivity was estimated using the Matsuda Insulin Sensitivity Index (Matsuda-ISI): 10 000 / square root (fasting glucose (mg/dL) x fasting insulin (µU/mL) x mean glucose over 2-h OGTT x mean insulin over 2-h OGTT).[18] The first phase of insulin secretion

was calculated as the ratio of the area under the curve of insulin (pmol/L) to glucose (mmol/L) during the first 30 minutes of the OGTT and the second phase of insulin secretion during the 120 minutes of the OGTT.

Exposures

Moderate-to-vigorous physical activity (MVPA) and sedentary time were measured by accelerometry (Actigraph LS 7164 and GT3X, Actigraph LLC, Pensacola, Florida) which allow objective measurement of physical activity intensity, frequency, and duration. The accelerometer was worn during the seven days following the research visit. Children were asked to maintain their habitual daily routines and activities during that period, such that physical activity and sedentary time should reflect their usual levels. Based on valid accelerometry data (minimally worn ten hours/day for four days), time spent at sedentary and MVPA intensity levels was determined using pediatric cut points (sedentary time: 0-100 counts per minute; MVPA: > 2296 counts per minute).[19] Information on accelerometer data reduction and scoring procedures can be found elsewhere.[11] In the first two evaluation cycles, children were asked to remove the accelerometer before going to bed. In the third cycle, children kept the accelerometer overnight and a validated algorithm[20] was used to discriminate between sedentary time and sleep.

Leisure screen time was reported by the children by interviewer-administered questions on the usual number of hours the child watched television, used computer for leisure and played video game consoles on weekdays and weekends.[21] The weighted average of time spent during week and weekend days was calculated. In the third evaluation cycle, we integrated a question on social media use and added this screen-based activity to the total screen time. For greater accuracy, we

subtracted 29% from total screen time at 15-17 years in adolescents who reported media multitasking, based on the frequency of multiple screen use reported in a survey among adolescents.[22] Different thresholds (-15% and -20%) were also tested in sensitivity analyses. We also capped screen time so as not to exceed 24 hours with sleep duration.

Covariates

A trained research nurse measured children's height and weight following standardized protocols.[16] Body mass index (BMI, kg/m^2) z-scores were computed based on the World Health Organization normative data.[23] Percentage of body fat (%BF) was measured by dual-energy x-ray absorptiometry (GE Lunar Corporation, Madison, USA). Children's pubertal stage based on Tanner criteria was assessed by a trained nurse. Sleep duration was estimated using accelerometer removal time in the first two evaluation cycles, and questionnaires on habitual bedtime and wake up time in the third evaluation cycle. Cardiorespiratory fitness was measured at each cycle with peak oxygen consumption (VO_2 peak, ml/kg of lean body mass/minute) during an adapted incremental exercise test on ergocycle. Dietary intake was measured in the first and third cycles using 3 non-consecutive 24-h dietary recalls by a research dietitian. Children and their parents were provided instructions and given a disposable portions kit to estimate portions of food at home. Nutrient analysis was performed with the CANDAT Nutrient Analysis Software (Godin and associates, 2007) based on the Canadian Nutrient File. Dietary variables used included energy intake (kcal/day) and the Diet Quality Index-International as an overall measure of diet quality.[24] As 24-h dietary recalls were not measured at the second evaluation cycle, we carried energy intake and Diet Quality Index-International values forward from the first to the second evaluation cycle. An implicit assumption was that energy intake and diet quality did not change substantially

between 8-10 and 10-12 years. Parents self-reported their household income, history of diabetes and living context at home (living together/shared custody/single parent) at baseline. Parents' weight and height were measured at baseline only following the same protocols as in children.[16]

Statistical analysis

Descriptive statistics are reported at each evaluation cycle using means and standard deviations (SD) for normally distributed variables, medians (interquartile range) for non-normally distributed variables and proportions for categorical variables.

Definition of causal effects

We estimated average treatment effect (ATEs) of MVPA, sedentary time, and screen time, on insulin sensitivity, insulin secretion and glycemia from childhood to late adolescence. The exposure and outcome variables are continuous. We define ATEs as the difference in average outcome levels by increments of ten minutes per day for MVPA, and one hour per day for sedentary time or screen time from 8-10 to 15-17 years of age. We conceptualize the effect of exposures in two ways: 1) Point-in-time: effect of the exposure level at a given time *t* on the outcome variable at time *t*; 2) Cumulative: effect of the average of the exposure levels up to time *t* on the outcome variable at time *t.* Physiological plausibility of both effects is supported by evidence.[7]

Longitudinal relations between exposures, outcomes, and confounders are portrayed in the directed acyclic graph (DAG) in **Figure 1.** The exposure, the outcome and the potential confounders are time-varying across all three evaluation cycles (8-10, 10-12, and 15-17 years). Consequently, each

variable is affected by its previous level. Moreover, potential confounders, such as adiposity, other lifestyle habits, and fitness, could be influenced by prior physical activity levels and be on the causal pathway between the exposure and outcome. In this context, using traditional multivariable regression models adjusting for confounders affected by prior exposures would underestimate the associations. Finally, we assume that prior outcome levels influence the exposure, in that a child with elevated glycemia may be advised by their physician to change lifestyle habits in order to improve glucose homeostasis. Consequently**,** we used longitudinal marginal structural models (LMSM) to estimate ATEs, a method developed to account for confounders appropriately in such contexts.[15] To build the LMSM, we performed inverse probability of treatment weighting (IPTW) and inverse probability of censoring weighting (IPCW) to address confounding and informative censoring, respectively.

Inverse probability of treatment weighting (IPTW)

IPTW recreates a pseudopopulation of children with balanced covariates for any observed level of an exposure (MVPA or sedentary time or screen time) at each evaluation cycle. Weights were estimated for each continuous exposure at each evaluation cycle using the continuous covariate balancing propensity score (CBPS) method.[25] The weights were calculated for each child using the predicted density of the exposure conditional on the confounders and prior exposure and outcome levels in the denominator, and stabilized using the predicted marginal density of the exposure in the numerator. Confounding factors were selected based on theoretical knowledge and included sex and history of diabetes in parents (fixed in time), and age, pubertal stage, %BF, screen time, VO_2 peak, sleep duration, energy intake, Diet Quality Index-International, and familial income (time-varying). See **Figure S1** in **Supplementary Material** for a DAG on the relation between

variables at one time point. When the outcome was first- or second-phase insulin secretion, we additionally included Matsuda-ISI at the corresponding time in the propensity score model using penalized regression splines, via a generalized additive model, to account for the non-linear association between insulin sensitivity and insulin secretion. In sensitivity analyses, we performed IPTW using BMI z-score instead of %BF and using mother's and father's BMI instead of parental history of diabetes.

Inverse probability of censoring weighting (IPCW)

IPCW recreates a pseudopopulation where children present at follow-up are weighted to represent the censored children based on their pre-censoring characteristics. Weights were estimated with a logistic regression model (also using the CBPS) on the censored status at each cycle based on variables associated with the outcome and/or probability of censoring: age, sex, child's BMI z-score, valid accelerometry data (yes/no), distance from the research center of home, familial income, parents living together (yes/no) and the parents' age, BMI and physical activity levels. **Table S1 (Supplementary Material)** details the variables included in the treatment and censoring weights models.

Computation of LMSMs

LMSMs were estimated by computing a regression model weighted by the product of the treatment and censoring weights at each time point using generalized estimation equations (GEEs), following LMSM methodology.[15] The ATE is derived from the estimated regression coefficient of MVPA (or sedentary time or screen time) in the LMSM. An "independence" correlation structure was

specified in the GEE[15], with standard errors estimated through a robust variance estimator to account for intra-individual correlation.[26] We used the identity link for fasting and 2-h glycemia, and the log link for insulin sensitivity and insulin secretion indices because of their skewed distribution. Regression coefficients for the log link models were exponentiated and multiplied by 100% to represent the percent change in the outcome per unit increment in the exposure. LMSMs were estimated with both point-in-time and cumulative definitions of exposure. The following equation shows parameters included in the MVPA and fasting glycemia point-in-time model, as an example:

$$FG_t = \beta_0 + \beta_{A,t}A_{PA,t} + \varepsilon, weight = sw_{PA,t} * cw_t,$$

where *t* corresponds to the time points {0 = 8-10 years, 1 = 10-12 years, 2 = 15-17 years), FG_t to fasting glucose at time *t*, β_0 to the intercept, $\beta_{A,t}$ to the ATE, $A_{PA,t}$ to MVPA at time *t*, ε to the error term, $sw_{PA,t}$ to the treatment weight for MVPA at time *t*, and cw_t to the censoring weight at time *t*. For the cumulative exposure model, we substituted the value of MVPA at time t with the cumulative version of MVPA.

Causal assumptions

Causal presuppositions, namely consistency, exchangeability (i.e., absence of confounding), positivity, and temporality were proposed for the causal interpretation of the ATE in observational studies. We provide a summary assessment of the causal presuppositions in the **Supplementary Material**.

Assuming data followed a missing at random (MAR) pattern, we performed multiple imputation with Amelia II which relies on a bootstrap-based expectation-maximization algorithm and generated ten imputed datasets. ATEs and their variance were estimated for each imputed dataset. We then pooled the ATEs over the ten imputed datasets and calculated corresponding confidence intervals using Rubin's rule. Because IPCW was already being used to mitigate data missing due to attrition, we only imputed missing data in children who completed their research visit. Variables in the imputation model included exposures, outcomes, and confounding factors. Analyses were conducted using R 4·1·1 (© 2021 The R Foundation for Statistical Computing, Vienna, Austria) with packages *geepack, cbps* and *amelia*.

Role of the funding source

Funders played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; nor in preparation, review, or approval of the manuscript; nor the decision to submit the manuscript for publication.

RESULTS

Characteristics of participants

Characteristics of participants are presented by evaluation cycle in **Table 1**. At baseline, the mean age of participants was 9·6 years (SD: 0·9). Girls comprised 46% (n = 287) of the sample. Half of the children presented overweight or obesity at baseline (49%, n = 310). Diet quality, based on the Diet Quality Index-International, was 60·4 units (SD: 7·3) out of 100, and median daily energy intake was 1674 kilocalories (25^{th}-75^{th} perc.: 1421-1953). During the 7 years of follow-up, MVPA

decreased by 23 minutes/day on average while sedentary time increased by 4·6 h/day and screen time increased by 1·8 h/day **(Figure 2)**.

Missing data

Among children, 15% (n = 95), 26% (n = 146) and 14% (n = 53) had missing accelerometry data at the first, second, and third evaluation cycles, respectively. Details on the proportion of missing data per cycle can be found in **Table S2** in **Supplementary Material**. Accelerometry data were more likely to be missing in children with lower insulin sensitivity and diet quality and higher %BF, pubertal stage, and sleep duration; children with missing OGTT data were on average younger with a higher %BF (**Supplementary Material Table S3**).

Causal estimates

Information on IPTW and IPCW weights estimation (distribution, empirical positivity assessment, covariate balancing) appear in the **Supplementary Material**. **Table 2** presents estimated ATEs and 95% CI for point-in-time and cumulative effects of MVPA, sedentary time and screen time on insulin sensitivity and insulin secretion from complete case and imputed data analyses. Based on cumulative exposure results, estimated ATEs for MVPA were 5·6% (95% CI: 2·8; 8·5) on insulin sensitivity and -3·8% (-7·1; -0·5) on second-phase insulin secretion per 10-minute daily increment across 8-10 to 15-17 years. ATEs for sedentary time and reported screen time yielded reduced insulin sensitivity (-8·2% [-12·3; -3·9] and -6·4% [-10·1; -2·5], respectively) and increased second-phase insulin secretion (5·9% [1·9; 10·1] and 7·0% [-0·1; 14·7], respectively). Overall, MVPA appeared beneficial, and sedentary time and screen time deleterious, to insulin sensitivity and

insulin secretory requirements from 8-10 to 15-17 years. ATEs for fasting and 2-h glycemia are shown in **Table 3.** Likewise, based on cumulative exposure results, ATEs for sedentary time and screen time indicated higher fasting glycemia (0·03 mmol/L [0·003; 0·05] and 0·02 mmol/L [0·01; 0·03], respectively) per supplementary daily hour from 8-10 to 15-17 years. The magnitude of ATEs suggested a greater effect of cumulative exposures compared to point-in-time exposures (e.g., for MVPA and insulin sensitivity: 5·6% [2·8; 8·5] vs. 3·9% [1·6; 6·2]).

Sensitivity analyses

Sensitivity analyses with varying proportions of total screen time at the third evaluation cycle adjusted for multitasking of screens (-15% and -20%), or using BMI z-score instead of %BF as a measure of adiposity, or using parental BMI instead of parental history of diabetes, did not modify conclusions. For instance, ATEs for cumulative exposures on insulin sensitivity, using complete case data, varied between 4·8% and 5·1% per 10-minute increase in MVPA, between -8·5% and -10·9% per 1-hour increase in sedentary time, and between -2·6% and -4·1% per 1-hour increase in screen time across scenarios. Overall, the direction of the ATEs and the precision of the CIs from complete case analyses were similar to those from multiple imputation, with slight variations in the amplitude of effect.

DISCUSSION

Our study contributes to the current evidence provided by observational and interventional studies, in that objectively-measured MVPA and sedentary time, as well as reported screen time, influence

insulin dynamics and glycemia in a cohort of at-risk children. Our results suggest that greater physical activity levels and less sedentary behavior during childhood and adolescence are linked to improved insulin sensitivity and lower insulin secretory requirements. Both point-in-time and cumulative exposures were associated with insulin sensitivity and secretion, with cumulative exposures generally resulting in effects of greater amplitude.

In the scant available longitudinal research, an inverse association between MVPA and insulin resistance (i.e., the inverse of insulin sensitivity) assessed with the homeostatic model of insulin resistance (HOMA-IR) was reported in children.[12,14] We previously reported that MVPA at 8-10 years was associated with higher peripheral insulin sensitivity two years later.[11] In keeping with our previous findings, in the current study, every 10-minute daily increment in MVPA was associated with greater insulin sensitivity from childhood to late adolescence, irrespective of adiposity, diet quality, pubertal stage and other confounders. That even small increments in daily MVPA influence insulin sensitivity, and that this effect be cumulative from childhood to late adolescence, argue for early intervention.

Insulin sensitivity informs on the ability of the liver, peripheral muscle and adipose tissues to absorb glucose into cells to produce energy, and occupies a central role in glucose homeostasis. Among youth with obesity, those living with T2D display reduced insulin sensitivity compared to those with normal glucose tolerance.[27] Yet impaired beta-cell function (insulin secretion adjusted for insulin sensitivity) remains the most distinguishing factor between youth with normal glucose tolerance, prediabetes and T2D, with the most impaired beta-cell function noted in youth with

T2D.[27] Alterations in beta-cell function precede the development of T2D and are apparent even in normal glucose tolerance states.[28] Physical activity contributes to beta-cell mass preservation and proliferation, upregulates signaling pathways and reduces inflammation and oxidative stress.[7] We observed that higher levels of MVPA were associated with lower insulin secretory requirements independently of cardiorespiratory fitness. MVPA appears as a relevant and practical intervention target to protect against beta-cell exhaustion in late adolescence, in contrast to fitness which is less directly modifiable. In addition, we observed that the estimated ATE for MVPA was greater in reducing second-phase than first-phase insulin secretion, which we previously observed cross-sectionally in our cohort.[29] Likewise, in a previous RCT, twelve months of exercise training in male adolescents with overweight or obesity reduced total insulin secretion but not early-phase insulin secretion.[30] Thus, higher physical activity levels appear more beneficial in reducing the total insulin response in contrast to the first phase in at-risk adolescents.

Screen time was cross-sectionally associated with higher HOMA-IR in British children[31]. More time watching television, but not computer/video game use, was linked to greater fasting insulin and HOMA-IR in Canadian adolescents living with overweight or obesity.[32] We previously observed that leisure screen time was associated with lower insulin sensitivity two years later in our cohort, but no association was noted with insulin secretion.[11] In line with our and others' findings, we observed that objectively measured sedentary time, as well as reported screen time were associated with lower insulin sensitivity during childhood and early adolescence. In contrast to our previous study[11], we observed that these measures were also associated with increased insulin secretory requirements. Thus, the deleterious effects of sedentary behaviors on insulin secretion might be more perceptible over a longer period of follow-up into late adolescence.

Finally, our findings align with the literature pointing to sedentariness as a determinant of cardiometabolic disease[33], independent of MVPA levels, and on the distinct impacts of screen time on cardiometabolic risk in children compared with total sedentary time, the latter including a broader range of sedentary pursuits including reading and school work.

More sedentary time and screen time during childhood and adolescence were associated with higher fasting glycemia. In both cases, ATEs did not appear clinically meaningful (0·03 and 0·02 mmol/L higher glycemia per 1-hour daily increment). ATEs for MVPA suggested lower 2-h glycemia, but with large CIs around the estimate. Most observational[13,32] studies in the general pediatric population did not report effects of physical activity and sedentary behaviors on fasting glycemia. In children and adolescents with overweight or obesity, intensive physical activity interventions achieved a reduction in 2-h post load glucose,[34,35] but not in fasting glucose.[9] Thus, while post-load glycemia seems responsive to physical activity interventions in at-risk youth, the extant literature suggests that fasting glucose is highly regulated, and that it can be affected only in the long term.

Strengths of this study include the objective assessment of physical activity and total sedentary time with accelerometry. We used dynamic measurements of peripheral insulin sensitivity and beta-cell function during an OGTT to estimate T2D risk[36], instead of HOMA-IR, which only provides information on hepatic insulin resistance, being based on fasting levels of insulin and glucose.[37] Moreover, we applied LMSM in a comprehensively phenotyped cohort, allowing us to account for a rich set of confounders and overcome shortcomings of previous studies in this field.

Most variables were measured with tools of excellent validity (e.g., accelerometry, 24-h dietary recalls, VO_2 peak), thus limiting measurement error in our study.

Although we used IPCW, high attrition at the third evaluation cycle (40%) remains an important limitation of the study. Next, it was not possible to distinguish between the specific type of activity measured by accelerometry. For instance, aerobic exercise might be more favorable to insulin sensitivity than resistance training. For this study, we chose MVPA, sedentary time, and screen time as exposure variables of interest given prior evidence of their relationships with glucose homeostasis in youth.[11-13] Physical activity includes activities at light, moderate and vigorous intensity. Because we examined only MVPA, and not light-intensity physical activity (LPA) explicitly, our findings relating to physical activity do not necessarily extend to the effect of light-intensity activities, such as casual walking and light weight training, on future T2D risk. Moreover, we did not include LPA as a confounder in the models because it is a linear combination of other model variables (MVPA, sedentary time and sleep) and would induce multi-collinearity. Because the correlation between LPA and sedentary time is relatively high (r = -0.53 to -0.75), we acknowledge that any estimate of the effect of decreasing sedentary time could be capturing in part the effect of increasing LPA. From a practical standpoint, increasing LPA may be an effective method to decrease sedentary time. Future studies should examine the impact of various intensities of physical activity on T2D risk, while accounting for all other movement behaviors in a 24-hour period.

We considered causal presuppositions and did not identify major threats. However, we cannot confirm whether the presuppositions are truly met, notably for exchangeability, where unknown confounders and residual confounding remain possible even if we accounted for a large number of potential confounders. Moreover, a limitation of our DAG is that we set confounders at the same time point as the exposure instead of the prior time point because of the small number of evaluation cycles. Adjusting for prior confounders would have required that we restrict the outcome models to the 10-12 to 15-17 year periods only. Another issue is that by definition, point-in-time estimates evaluated the relationship between exposures and outcomes at the same time point. Physical activity and sedentary time were measured by accelerometry after the blood sampling for glucose and insulin. Causal interpretation of the results relies on the assumption that MVPA and sedentary time measurements reflect the usual levels of participants. Hence, although MVPA and sedentary time were measured shortly after outcomes, reverse causation is unlikely because participants were not informed of their glycemia until well after the period of accelerometer wear. If that assumption does not hold, point-in-time estimates for MVPA and sedentary time should be interpreted as contemporaneous associations. Finally, multiple imputation relies on the assumption that data were MAR. While this assumption cannot be verified, we included a rich set of variables in our imputation model, which increases the likelihood that the MAR assumption holds.[38]

To conclude, our findings suggest that promoting physical activity and limiting sedentary behaviors, in particular screen time, enhance insulin sensitivity, and reduce insulin secretory requirements and fasting glycemia during childhood and adolescence, which could ultimately contribute to the prevention of T2D later in life among children with a parental history of obesity. By using modern statistical methods that helped disentangle the interrelations between physical

activity, sedentary behaviors and other lifestyle habits from childhood to late adolescence on insulin sensitivity and secretion, we strengthened the evidence that these behaviors are critical targets for T2D prevention in the pediatric population. Importantly, cumulative exposures were strongly associated with insulin sensitivity and insulin secretory requirements, underscoring the importance of early intervention to prevent T2D risk.

DECLARATION OF INTEREST

Mélanie Henderson is recipient of the 2019 Canadian Society of Endocrinology and Metabolism's Young Investigator Award. The other authors have no conflicts of interest relevant to this article to disclose.

ACKNOWLEDGMENTS

We thank Dr. Marie Lambert (1952 - 2012), pediatric geneticist and researcher, who initiated the QUALITY cohort. Her leadership and devotion to QUALITY will always be remembered and appreciated. We wish to also thank the dedicated QUALITY Cohort staff, including Catherine Pelletier and Ginette Lagacé, and all families participating in the QUALITY cohort, without whom this research would not be possible.

The QUALITY (QUebec Adipose and Lifestyle InvesTigation in Youth) Cohort Collaborative Group is an inter-university research team from Université de Montréal, Concordia University, Université Laval, McGill University, and University of Toronto including (alphabetical): Tracie A. Barnett, Arnaud Chiolero, Vicky Drapeau, Josée Dubois, Katherine Gray-Donald, Mélanie Henderson (PI), Marie Lambert (posthumous), Émile Lévy, Marie-Ève Mathieu, Katerina Maximova, Jennifer J. McGrath, Belinda Nicolau, Jennifer O'Loughlin, Gilles Paradis, Paul Poirier, Catherine M. Sabiston, Angelo Tremblay, and Michael Zappitelli.

FUNDING

The QUALITY cohort is funded by the Canadian Institutes of Health Research (#OHF-69442, #NMD-94067, #MOP-97853, #MOP-119512), the Heart and Stroke Foundation of Canada (#PG-040291) and the Fonds de Recherche du Québec - Santé. Soren Harnois-Leblanc is supported by a doctoral bursary for health professionals from the Fonds de Recherche du Québec – Santé. Andraea Van Hulst holds a Junior 1 salary award from the Fonds de recherche du Québec – Santé. Tracie A. Barnett is supported by a Fonds de Recherche du Québec - Santé senior salary award. Marie-Ève Mathieu holds a Fonds de Recherche du Québec – Santé Junior 1 salary award. Miceline Mésidor is recipient of doctoral bursary from the Fonds de Recherche du Québec – Santé. Jennifer J. McGrath is supported by the Canadian Institutes of Health Research and the Fonds de recherche du Québec – Sante (senior salary award). Angelo Tremblay holds the Canada Research Chair in Environment and Energy Balance. Marie-Pierre Sylvestre holds a Junior 2 salary award from the Fonds de recherche du Québec – Santé. Mélanie Henderson holds a Young Investigator Award from the Canadian Society of Endocrinology and Metabolism and a Fonds de Recherche du Québec - Santé Junior 2 salary award. Funders played no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

DATA SHARING

Will individual participant data be available (including data dictionaries)?	Yes
What data in particular will be shared?	Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices)
What other documents will be available?	Study protocol, analytic code
When will data be available (start and end dates)?	Beginning 3 months and ending 6 months following article publication
With whom?	Investigators whose proposed use of the data has been approved by the executive committee of the QUALITY cohort
For what types of analyses?	To replicate findings from the current project
By what mechanism will data be made available?	Requests should be directed to melanie.henderson.hsj@gmail.com; to gain access, data requestors will need to sign a data access agreement

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1 **TABLES**

2 **Table 1. Characteristics of the children in the QUALITY cohort at each evaluation cycle**

	Baseline (n=630)	1st follow-up (n=564)	2nd follow-up (n=377)
Age, years	9.6 (0.9)	11.7 (0.9)	16.8 (1.0)
Girls, % (n)	46 (287)	45 (251)	46 (173)
Pubertal stage, % (n)			
Prepubertal (1)	79 (494)	33 (186)	0.3 (1)
Peripubertal (2-4)	21 (135)	65 (364)	10 (31)
Post-pubertal (5)	0 (0)	2 (10)	90 (274)
zBMI	1.04 (1.36)	0.97 (1.33)	0.76 (1.28)
BMI category, %			
Underweight	0.2 (1)	1 (5)	1 (5)
Normal weight	51 (319)	50 (281)	59 (222)
Overweight	23 (146)	24 (135)	23 (86)
Obese	26 (164)	25 (143)	17 (64)
Body fat percentage, %	25.3 (17.4 – 35.2)	27.8 (19.4 – 36.4)	29.3 (18.2 – 36.2)
Dysglycemia, % (n)[a]			
IFG	4 (22)	6 (35)	10 (37)
IGT	8 (47)	11 (57)	12 (44)
Type 2 diabetes	0.3 (2)	1 (3)	1 (2)
Fasting glucose, mmol/L	4.9 (0.4)	5.1 (0.4)	5.1 (0.4)
2-h post-load glucose, mmol/L	6.4 (1.1)	6.5 (1.2)	6.4 (1.4)
Matsuda-ISI	8.8 (5.8 – 12.3)	6.2 (4.2 – 9.3)	6.3 (4.5 – 8.9)
First-phase insulin secretion	26.4 (17.8 – 41.0)	35.7 (24.3 – 53.4)	30.3 (21.1 – 43.6)

Second-phase insulin secretion	32.3 (22.9 – 47.7)	44.5 (30.8 – 63.2)	41.8 (29.5 – 58.5)
MVPA, min/day	48 (31 – 65)	39 (27 – 56)	24 (14 – 37)
Sedentary time, min/day	366 (73)	428 (77)	639 (118)
Screen time, hour/day	2.2 (1.3 – 3.7)	2.9 (1.9 – 4.4)	3.9 (2.6 – 5.5)
Sleep duration, hour/day	10.4 (0.7)	9.9 (0.7)	8.8 (0.9)
VO_2 peak, ml/min/kg lean mass	57.8 (6.8)	59.3 (7.3)	50.2 (6.5)
Diet Quality Index-International[b]	60.4 (7.3)	-	60.1 (8.3)
Energy intake, kcal/day	1674 (1421 - 1953)	-	1889 (1508 - 2250)
Familial income, CAD[c]	42 K (19)	49 K (22)	57 K (24)
Parent with type 2 diabetes, % (n)	12 (75)	-	-
Mother's BMI	28.9 (24.5 – 33.0)	29.0 (25.1 – 33.2)	29.3 (25.0 – 33.6)
Father's BMI	30.0 (27.1 – 33.3)	30.6 (27.4 – 33.9)	31.0 (27.8 – 34.7)

Legend. CAD: Canadian dollars; BMI: body mass index; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; Matsuda-ISI: Matsuda insulin sensitivity index; MVPA: moderate-to-vigorous physical activity; VO_2 peak: peak oxygen consumption (cardiorespiratory fitness). Continuous variables presented as mean (SD) if normally distributed or as median (25^{th} – 75^{th} p.) otherwise. Categorical variables are presented as the percentage (number of observations).

[a]Some children had both IFG and IGT: 5 at baseline, 11 at 1^{st} follow-up and 5 at 2^{nd} follow-up.

[b]The Diet Quality Index-International ranges from 0 to 100, with higher scores indicative of better diet quality.

[c]The familial income is divided by the square root of the number of persons living in the home.

Table 2. Estimated average treatment effects of MVPA, sedentary time and screen time during childhood and adolescence on insulin sensitivity and secretion from 8-10 to 15-17 years

	Insulin sensitivity, % $\widehat{ATE}$ (95% CI)		First-phase insulin secretion, adjusted for insulin sensitivity, % $\widehat{ATE}$ (95% CI)		Second-phase insulin secretion, adjusted for insulin sensitivity, % $\widehat{ATE}$ (95% CI)	
	Complete case	Multiply imputed	Complete case	Multiply imputed	Complete case	Multiply imputed
MVPA, 10 min daily increment	n = 890[a]	n = 1571				
Point-in-time	**4.4 (1.5 ; 7.4)**	**3.9 (1.6 ; 6.2)**	-1.4 (-4.7 ; 2.1)	-0.9 (-3.9 ; 2.1)	-0.5 (-5.3 ; 4.6)	-1.1 (-4.2 ; 2.1)
Cumulative	**5.1 (2.7 ; 7.5)**	**5.6 (2.8 ; 8.5)**	-2.4 (-6.0 ; 1.3)	-3.7 (-7.2 ; 0.03)	-2.1 (-6.9 ; 2.9)	**-3.8 (-7.1 ; -0.5)**
Sedentary time, 1 hour daily increment	n = 896					
Point-in-time	-3.4 (-8.0 ; 1.3)	**-4.2 (-6.9 ; -1.3)**	1.0 (-1.2 ; 3.2)	-0.2 (-2.1 ; 1.7)	**3.0 (0.7 ; 5.3)**	**1.9 (0.1 ; 3.7)**
Cumulative	**-8.5 (-13.2 ; -3.5)**	**-8.2 (-12.3 ; -3.9)**	**5.8 (1.2 ; 10.6)**	2.5 (-1.8 ; 7.1)	**8.6 (4.8 ; 12.5)**	**5.9 (1.9 ; 10.1)**
Screen time, 1 hour daily increment	n = 970					
Point-in-time	-2.1 (-4.8 ; 0.7)	**-3.4 (-5.6 ; -1.0)**	**2.3 (0.4 ; 4.3)**	1.1 (-1.1 ; 3.4)	**2.2 (0.2 ; 4.2)**	1.3 (-2.1 ; 4.7)
Cumulative	-2.6 (-5.6 ; 0.5)	**-6.4 (-10.1 ; -2.5)**	2.0 (-0.7 ; 4.9)	**6.6 (0.2 ; 13.5)**	2.0 (-1.0 ; 5.2)	7.0 (-0.1 ; 14.7)

Legend. ATE: average treatment effect; MVPA: moderate-to-vigorous physical activity. Results in bold indicate statistical significance at 5% level (two-sided).

[a]Indicates the total number of observations, not the number of participants in the cohort. For example, the 890 observations here include 433, 305 and 152 participants at the first, second and third evaluation cycle, respectively.

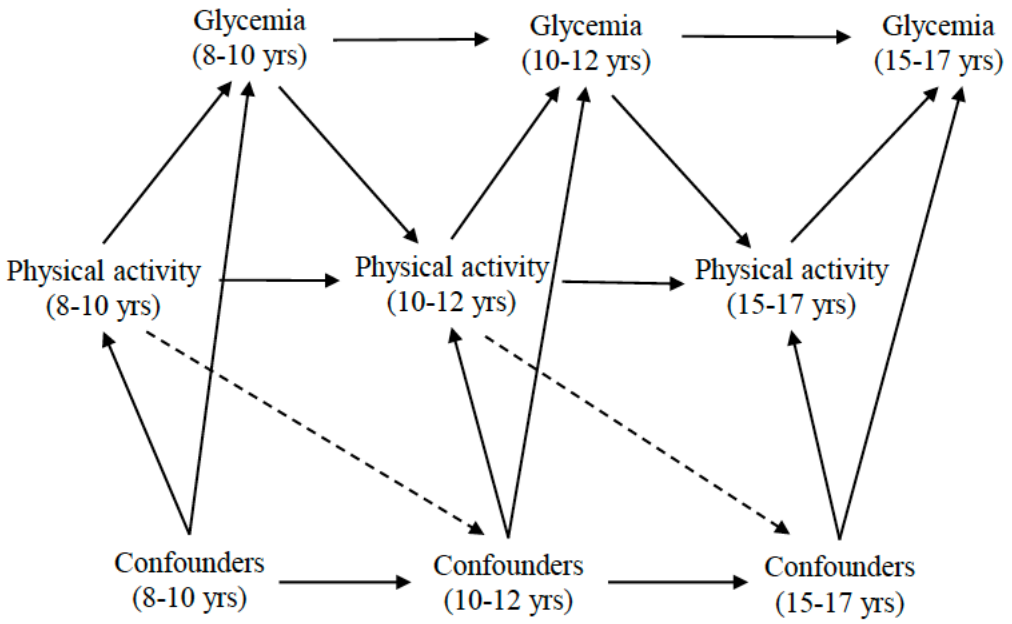
Table 3. Estimated average treatment effects of MVPA, sedentary time and screen time during childhood and adolescence on fasting and 2-h post load glucose levels from 8-10 to 15-17 years

	Fasting glucose, mmol/L $\widehat{ATE}$ (95% CI)		2-h post load glucose, mmol/L $\widehat{ATE}$ (95% CI)	
	Complete case	Multiply imputed	Complete case	Multiply imputed
MVPA, 10 min daily increment	n = 961	n = 1571		
Point-in-time	0.002 (-0.02 ; 0.02)	-0.005 (-0.02 ; 0.01)	-0.05 (-0.11 ; 0.02)	-0.04 (-0.09 ; 0.01)
Cumulative	0.004 (-0.01 ; 0.02)	0.01 (-0.02 ; 0.03)	**-0.05 (-0.11 ; -0.001)**	-0.03 (-0.08 ; 0.02)
Sedentary time, 1 hour daily increment	n = 967			
Point-in-time	**0.01 (0.001 ; 0.03)**	**0.01 (0.001 ; 0.03)**	0.02 (-0.02 ; 0.07)	0.02 (-0.01 ; 0.06)
Cumulative	**0.04 (0.01 ; 0.07)**	**0.03 (0.003 ; 0.05)**	0.05 (-0.03 ; 0.12)	0.04 (-0.03 ; 0.11)
Screen time, 1 hour daily increment	n = 1053			
Point-in-time	0.003 (-0.01 ; 0.02)	0.005 (-0.01 ; 0.02)	-0.02 (-0.07 ; 0.03)	-0.02 (-0.07 ; 0.03)
Cumulative	0.01 (-0.003 ; 0.03)	**0.02 (0.01 ; 0.03)**	-0.01 (-0.08 ; 0.06)	-0.01 (-0.06 ; 0.05)

Legend. ATE: average treatment effect; MVPA: moderate-to-vigorous physical activity. Results in bold indicate statistical significance at 5% level (two-sided).

FIGURE PANELS

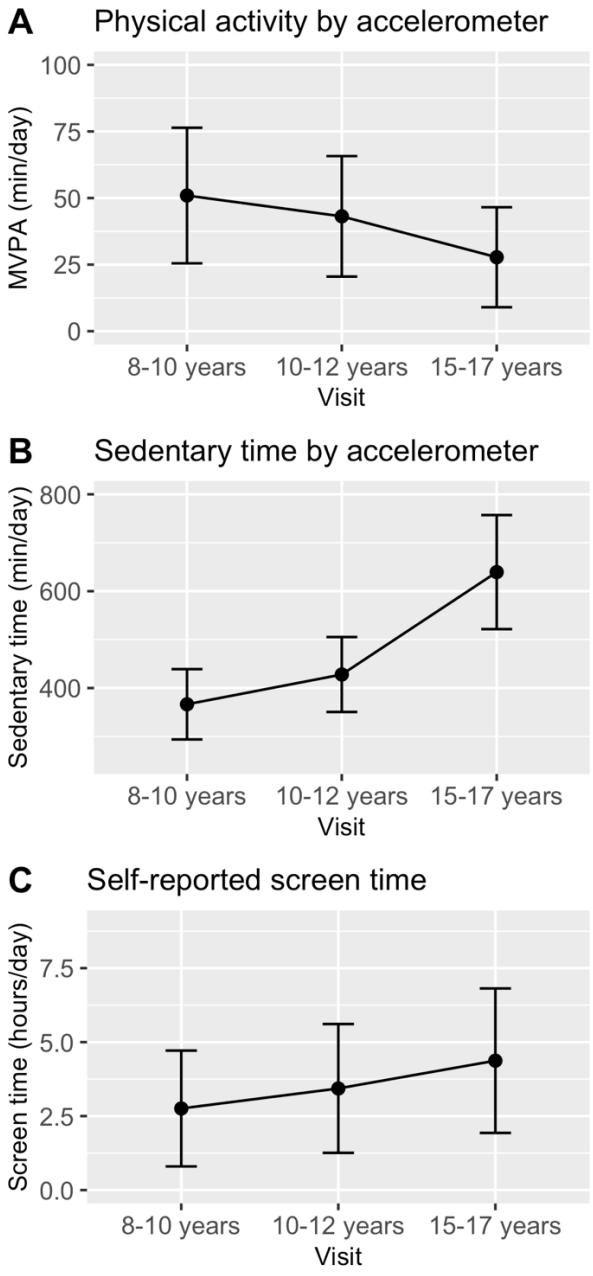
Figure 1. Directed acyclic graph on the longitudinal relationship between physical activity and glycemia, illustrating time-varying relations between variables



Legend. The figure shows the longitudinal association between physical activity and glycemia from 8-10 to 15-17 years of age. Confounders included sex and history of diabetes in parents (fixed in time), and age, pubertal stage, %BF, screen time, VO_2 peak, sleep duration, energy intake, Diet Quality Index-International, and familial income (time-varying). We assume a similar DAG for the other exposure-outcome model combinations. According to the DAG, we assume that physical activity (PA) at an earlier age influences PA at later time points (e.g., PA at 8-10 years influences PA at 10-12 years). Similarly, glycemia at an earlier age influences glycemia at later time points (e.g., glycemia at 8-10 years influences glycemia at 10-12 years), and likewise for confounders (e.g., confounders at 8-10 years influences confounders at 10-12 years). Next, we assume that at each age, PA influences glycemia at the corresponding time point. Moreover, glycemia at an earlier

time point may affect PA at the subsequent time point (e.g., glycemia at 8-10 years influences PA at 10-12 years, etc.). We also assume that confounders influence PA and glycemia at the corresponding time points (e.g., confounders at 8-10 years influences PA and glycemia at 8-10 years). Finally, we assume that PA at an earlier age influences confounders at a later time point (e.g., PA at 8-10 years influences confounders at 10-12 years).

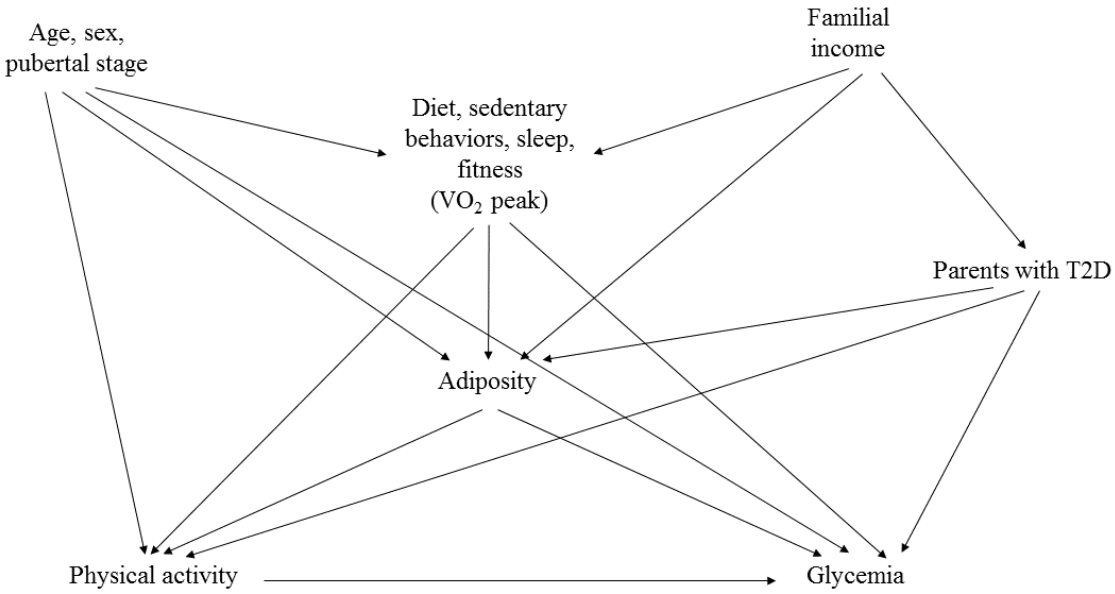
Figure 2. Trajectories of MVPA, sedentary time, and screen time from 8-10 to 15-17 years



Legend. MPVA: moderate-to-vigorous physical activity. Trajectories of observed data from 8-10 to 15-17 years of age are presented for MVPA, sedentary time and screen time using means and one standard deviation for the error bars.

SUPPLEMENTARY MATERIAL

Figure S1. Directed acyclic graph displaying the relation between physical activity, and glycemia



Legend. The directed acyclic graph represents the relation between physical activity and glycemia at a given time point. The covariates were selected based on theoretical knowledge, and the relations between the variables were validated by experts in the field. We assume a similar relation between variables for the associations pertaining to the other exposure (sedentary time, screen time) and outcome (glycemia 2-h, insulin sensitivity, insulin secretion) combinations.

Table S1. Variables included in inverse probability of treatment and inverse probability of censoring weighting models

	Probability of treatment (propensity score)	**Probability of censoring**
Fixed in time		
	Sex and history of type 2 diabetes in parents *at 8-10 years*	
Time-varying		
1st evaluation cycle (8-10 years old)	Age, pubertal stage, %BF, familial income, screen time[a], VO_2 peak, sleep, energy intake, and DQI-I *at 8-10 years*	-
2nd evaluation cycle (10-12 years old)	Energy intake, DQI-I[b], exposure level, and outcome level *at 8-10 years* Age, pubertal stage, %BF, familial income, screen time, VO_2 peak, and sleep *at 10-12 years*	Age, sex, BMI z-score, familial income, parents living together (yes/no), parental levels of physical activity, father's age *at 8-10 years*
3rd evaluation cycle (15-17 years old)	Exposure level and outcome level *at 10-12 years* Age, pubertal stage, %BF, familial income, screen time, VO_2 peak, sleep, energy intake, and DQI-I *at 15-17 years*	Age, sex, BMI z-score, familial income, parents living together (yes/no), parental levels of physical activity, father's age, mother's BMI, valid accelerometer data (yes/no), and distance from research center[c] *at 10-12 years*

Legend. BMI: body mass index, DQI-I: diet quality index-international, MVPA: moderate-to-vigorous physical activity, VO_2 peak: peak oxygen consumption (cardiorespiratory fitness), %BF: percentage of body fat. When the outcome was first- or second-phase insulin secretion, we additionally included insulin sensitivity at the corresponding time in the propensity score model.

[a]We provide the variables selected when the exposure of interest was MVPA. In the setting where sedentary time or screen time were the exposure of interest, MVPA was considered in the propensity scores models.

[b]Because 24-h dietary recalls were only performed at the 1st and 3rd evaluation cycle, we carried energy intake and DQI-I values forward from the 1st to the 2nd evaluation cycle. The implicit assumption was that energy intake and DQI-I did not change substantially between 8-10 to 10-12 years.

[c]Distance calculated in kilometers between the participant's civic address and the research center visited (CHU Sainte-Justine in Montréal or Institut Universitaire de Cardiologie et Pneumologie in Québec city).

Causal assumptions

We examined the consistency, exchangeability, and positivity causal presuppositions (Hernan and Robins, Causal Inference: What If, Boca Raton: Chapman & Hall/CRC, 2020). For consistency, values of the exposure should correspond to a well-defined intervention, and the counterfactuals should link to the observed data. Given the definition of exposure in the study, the assumed intervention group is one in which children do 10 minutes more of MVPA daily (treated group), and the other group keep their usual levels of MVPA (non-treated group) from 8-10 to 15-17 years. A similar intervention is applicable to sedentary time and screen time: the treated group engages in one hour less daily, and the non-treated group keeps usual levels. Also, the definition of the intervention must be precise enough that the effects of all versions of treatment are identical. In our study, for example, we are interested in the effect of doing an additional 10 minutes of MVPA, regardless of the activity (cycling, jogging, etc.). It is assumed that, as long as the activity is within the defined intensity and duration, the exposed children will have a value of the observed outcome that matches the value of the counterfactual if they had been treated.

Exchangeability requires independence between the counterfactual and the exposure conditional on the predictors of the outcome for any level of the exposure, which refers to no unmeasured confounders. We selected confounders based on theoretical and clinical knowledge, and the relations between the variables were validated by experts in the field. However, because this study is nonrandomized, differences in the distribution of unknown confounders may remain across exposure levels.

The probability of a level of exposure conditional on the covariates should be greater than zero based on the positivity assumption. In our study, no matter the child's characteristics (age, sex, adiposity, income, etc.), we assume that every child has the opportunity to engage in a given observed level of MVPA, sedentary time or screen time. We assessed positivity empirically, with propensity scores evenly distributed across tertiles of MVPA, sedentary time, and screen time for the three evaluation cycles.

Temporality also merits discussion. In the study, physical activity and sedentary time were measured with an accelerometer worn during the seven days following the research visit, thus measured after blood sampling for glucose and insulin. Causal interpretation of the results relies on the assumption that MVPA and sedentary time measurements reflect the usual levels for participants. In the context of this study, the temporal sequence would not be respected if the participants changed their physical activity and sedentary time levels because of their outcome values. This situation is however highly unlikely, because blood samples needed to be processed and the participant and their parents were subsequently notified of abnormal glucose values only (insulin sensitivity and secretion indices being used in research predominantly were not sent to participants) through a mailed letter. They would not have received said letter before physical activity and sedentary time were measured.

IPTW weight estimation

Handling extreme weights

When recreating the balanced pseudopopulation, we must ensure that some participants are not extremely over- or under-represented (e.g., a weight of 100 signifies that the child accounts for 100 copies of himself in the pseudo-population). Most treatment weights had an acceptable range, that we defined as ≥ 0.033 to ≤ 30. We truncated the extreme weights at the 1st percentile (or 2nd if necessary) and the 99th percentile when they exceeded the acceptable range. Boxplots for the distribution of the treatment weights at each visit are presented below **(Figures S2-S6).** For simplicity, we show the distribution of the weights in the original dataset, before multiple imputation.

Empirical assessment of positivity

If there was only one variable in the set of confounders L (e.g., sex), we could verify whether children have a non null probability of engaging in the different levels of moderate-to-vigorous physical activity, sedentary time, and screen time for each level of this variable (e.g., in girls and boys) at every time point. However, L is multidimensional and comprises several continuous variables, such that the number of different scenarios of characteristics L is undefinable. We cannot verify if the probability of treatment is non null in all possible combinations of L. A way to verify positivity in this case is to compare the distribution of the propensity score (denominator of the treatment weights) across the levels of the treatment. To do so, we divided the treatment level in tertiles and verified whether the distribution of treatment weights was comparable across each tertile of treatment. Histograms of the propensity scores for moderate-to-vigorous physical activity, sedentary time, and screen time per evaluation cycle are shown below in **Figures S7-S9**. For parsimony, we present only the propensity score for the insulin sensitivity outcome model.

Balancing the covariates

Covariates in the IPTW estimation were well balanced with most correlations between every exposure and every confounder, as determined by Pearson correlation coefficients, generally below 0.1 at each time point, with some exceptions below 0.2. For illustrative purposes, love plots below present the correlation between each confounder and the exposure before and after weighting for propensity score models for physical activity, sedentary time and screen time at baseline, 1st follow-up and 2nd follow-up (**Figures S10-S18**). Similarly, most variables after IPCW estimation were well balanced with a standardized mean difference below 0.1 for each variable between the censored children and the non-censored children, shown with love plots in **Figures S19-S20**. These statistical diagnostics indicate that the weighting was successful in balancing the measured confounders across the different levels of exposure and censoring status at every time point.

Table S2. Proportion of missing data (%), per visit

	1st evaluation cycle (n=630)	2nd evaluation cycle (n=564)	3rd evaluation cycle (n=377)
MVPA	15.1	25.9	14.1
Accelerometry-derived sedentary time	15.1	25.9	14.1
Screen time	0.3	0.5	1.3
Matsuda-ISI	5.4	5.3	13.8
First-phase insulin secretion	5.4	4.3	10.1
Second-phase insulin secretion	5.4	5.3	13.8
Fasting glucose	0.8	2.8	1.1
2-h post load glucose	1.6	3.9	1.3
Body fat percentage	1.0	0.4	0.5
Pubertal stage	0.2	0.7	19.1
History of type 2 diabetes in the parents	0.0	-	-
Familial income	0.8	0.9	2.1
Sleep duration	22.3	0.4	0.0
Cardiorespiratory fitness	4.0	5.1	6.4
DQI-I	2.7	-	2.1
Energy intake	2.7	-	2.1

Legend. DQI-I: diet quality index-international, Matsuda- ISI: Matsuda insulin sensitivity index, MVPA: moderate-to-vigorous physical activity.

Table S3. Associations between baseline variables and missingness of accelerometry and oral glucose tolerance test data, OR (95% CI)

	Missingness of accelerometry (MVPA)		
	1st evaluation cycle	**2nd evaluation cycle**	**3rd evaluation cycle**
MVPA		1.06 (0.98 ; 1.15)	1.09 (0.95 ; 1.22)
Screen time	1.02 (0.91 ; 1.14)	1.01 (0.92 ; 1.11)	0.96 (0.81 ; 1.12)
Matsuda-ISI	1.00 (0.99 ; 1.00)	**0.99 (0.991 ; 0.998)**	1.003 (0.998 ; 1.01)
Age	0.96 (0.76 ; 1.22)	1.20 (0.98 ; 1.48)	1.07 (0.79 ; 1.46)
Sex	0.85 (0.54 ; 1.32)	1.04 (0.71 ; 1.52)	0.81 (0.45 ; 1.46)
Body fat percentage	1.01 (0.99 ; 1.03)	**1.02 (1.0004 ; 1.04)**	0.998 (0.97 ; 1.03)
Pubertal stage	1.06 (0.61 ; 1.77)	**1.79 (1.15 ; 2.76)**	1.41 (0.71 ; 2.66)
History of type 2 diabetes in the parents	0.74 (0.34 ; 1.48)	1.08 (0.59 ; 1.90)	0.68 (0.23 ; 1.66)
Familial income	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)
Sleep duration		1.16 (0.85 ; 1.59)	**1.66 (1.04 ; 2.65)**
Cardiorespiratory fitness	0.98 (0.95 ; 1.02)	0.99 (0.96 ; 1.02)	1.04 (0.99 ; 1.09)
DQI-I	1.03 (0.99 ; 1.06)	0.98 (0.96 ; 1.01)	**0.96 (0.92 ; 0.998)**
Energy intake	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)
	Missingness of OGTT (Matsuda-ISI)		
	1st evaluation cycle	**2nd evaluation cycle**	**3rd evaluation cycle**
MVPA	0.87 (0.72 ; 1.02)	**1.19 (1.03 ; 1.36)**	0.94 (0.81 ; 1.07)
Screen time	0.99 (0.81 ; 1.17)	0.89 (0.71 ; 1.09)	0.88 (0.73 ; 1.04)
Matsuda-ISI		1.01 (0.999 ; 1.01)	0.999 (0.993 ; 1.004)
Age	1.29 (0.88 ; 1.91)	**0.58 (0.38 ; 0.88)**	1.07 (0.78 ; 1.46)
Sex	1.55 (0.78 ; 3.16)	0.82 (0.38 ; 1.73)	0.77 (0.42 ; 1.39)
Body fat percentage	**1.05 (1.02 ; 1.08)**	0.98 (0.94 ; 1.02)	**1.03 (1.001 ; 1.06)**
Pubertal stage	1.40 (0.60 ; 2.99)	0.41 (0.10 ; 1.20)	1.29 (0.65 ; 2.47)
History of type 2 diabetes in the parents	1.30 (0.43 ; 3.19)	1.17 (0.34 ; 3.13)	0.70 (0.23 ; 1.70)
Familial income	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)
Sleep duration	0.79 (0.43 ; 1.43)	1.29 (0.71 ; 2.29)	1.13 (0.69 ; 1.81)
Cardiorespiratory fitness	0.99 (0.94 ; 1.04)	1.02 (0.97 ; 1.08)	1.02 (0.98 ; 1.07)
DQI-I	0.998 (0.95 ; 1.05)	0.98 (0.94 ; 1.04)	0.99 (0.95 ; 1.03)
Energy intake	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)	1.00 (0.999 ; 1.000)

Legend. CI: confidence interval, DQI-I: diet quality index-international, Matsuda-ISI: Matsuda insulin sensitivity index, MVPA: moderate-to-vigorous physical activity, OGTT: oral glucose tolerance test, OR: odds ratio. OR were estimated with a logistic regression, with an indicator of missingness for accelerometry and for the OGTT data as the response variable (R, 1=missing, 0=observed), and the baseline variable as the explanatory variable. For accelerometry, we computed the missingness indicator based on missing MVPA data. For the OGTT, we coded the missingness indicator based on missing Matsuda-ISI values, because this index integrates the greatest proportion of glucose and insulin data derived from the OGTT in its computation. Results in **bold** indicate statistically significant OR at the 5% level.

Figures S2-S6. Distribution of the treatment weights per evaluation cycle, after truncation

Figure S2

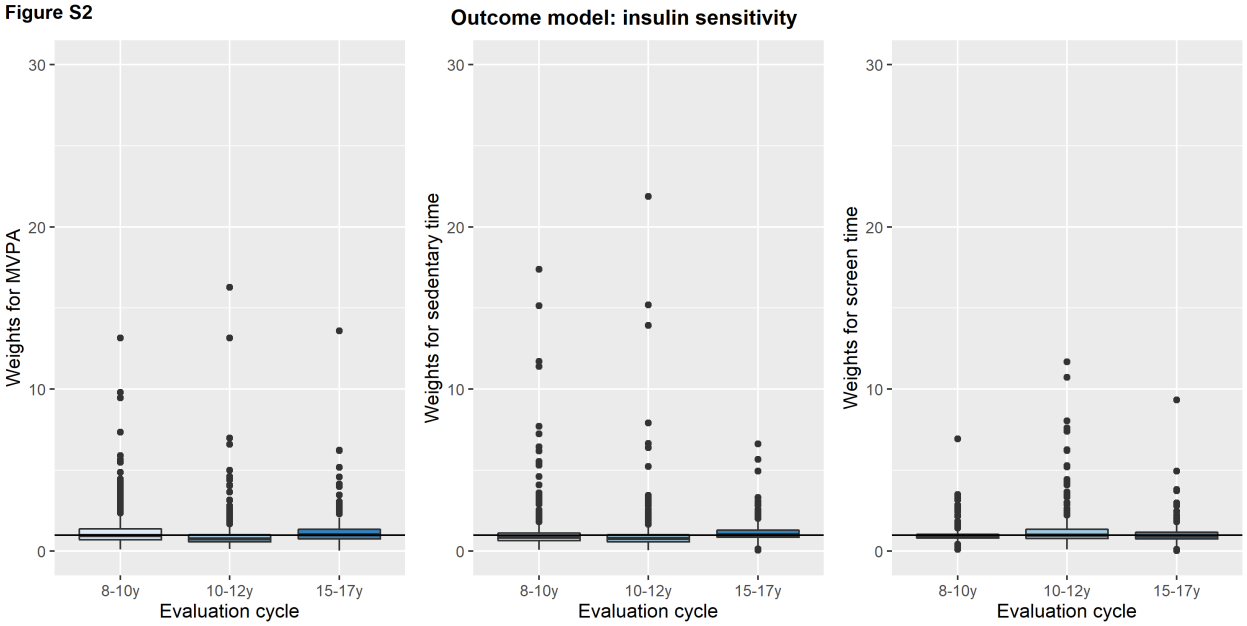


Figure S3

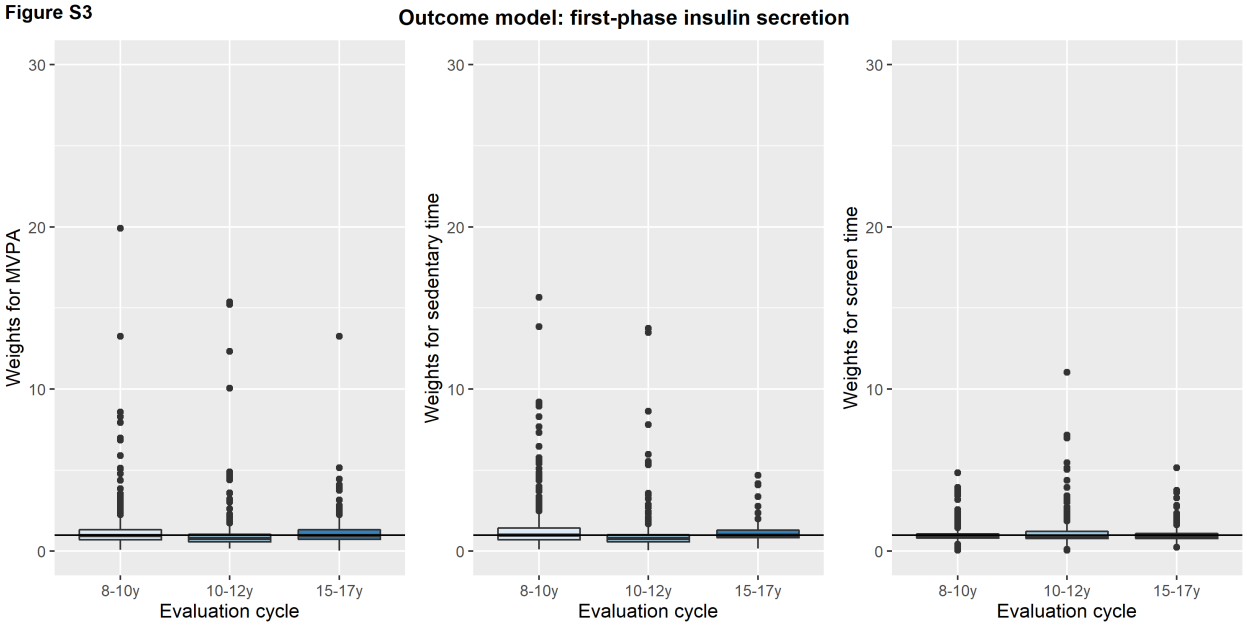


Figure S4

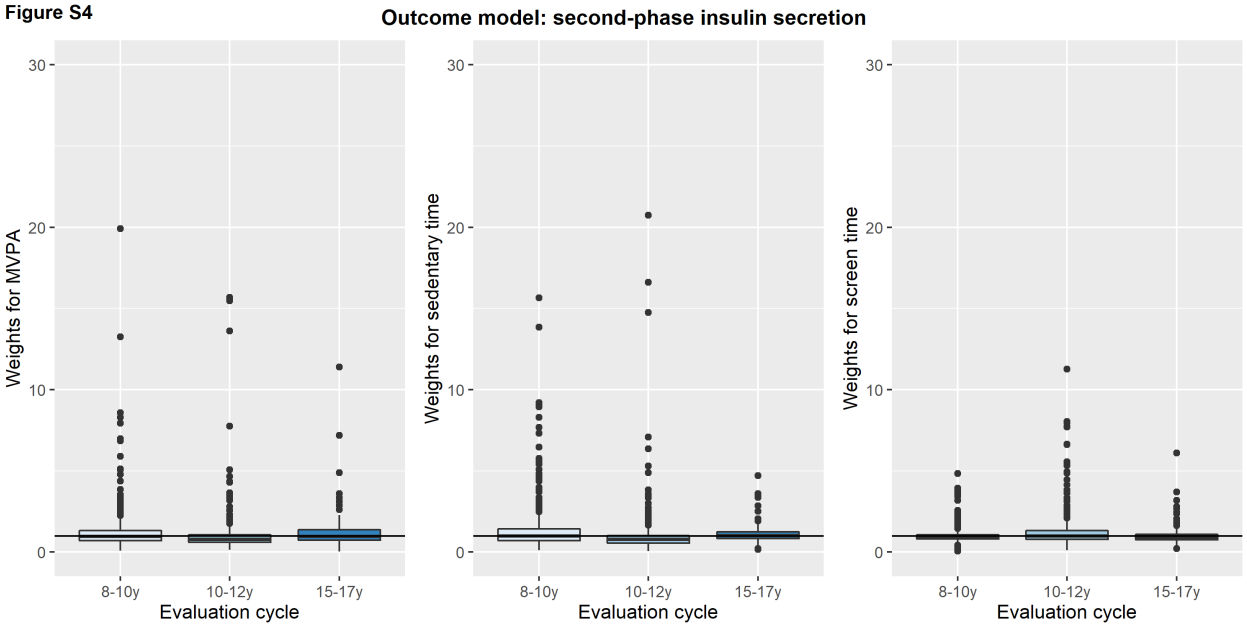


Figure S5

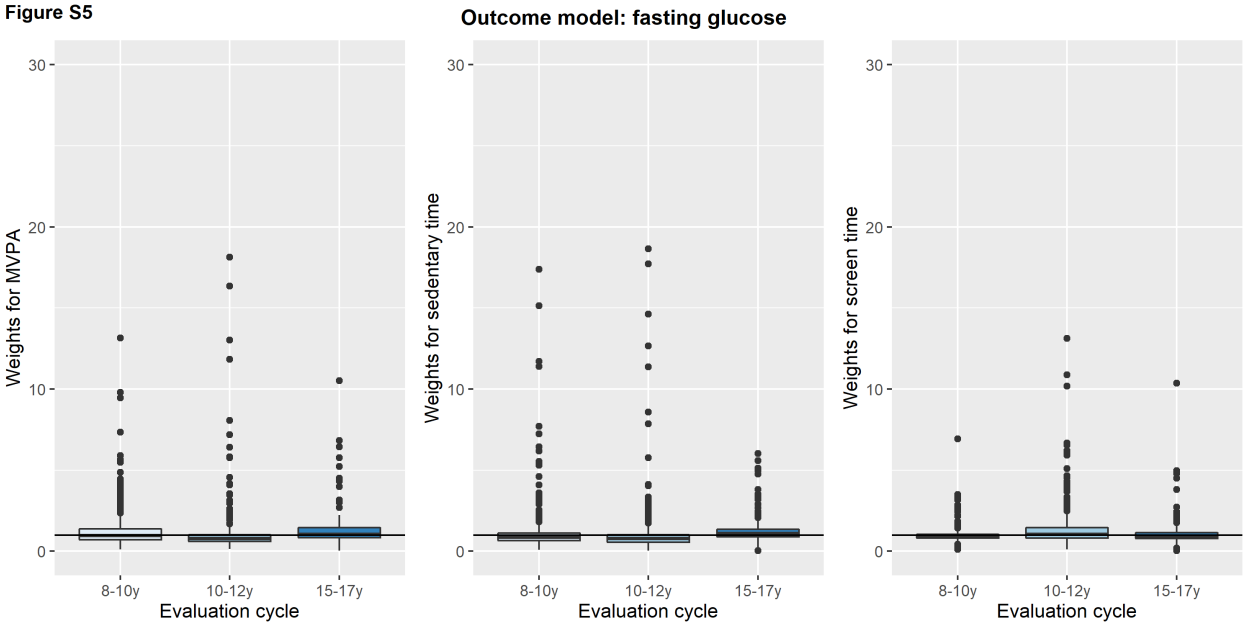
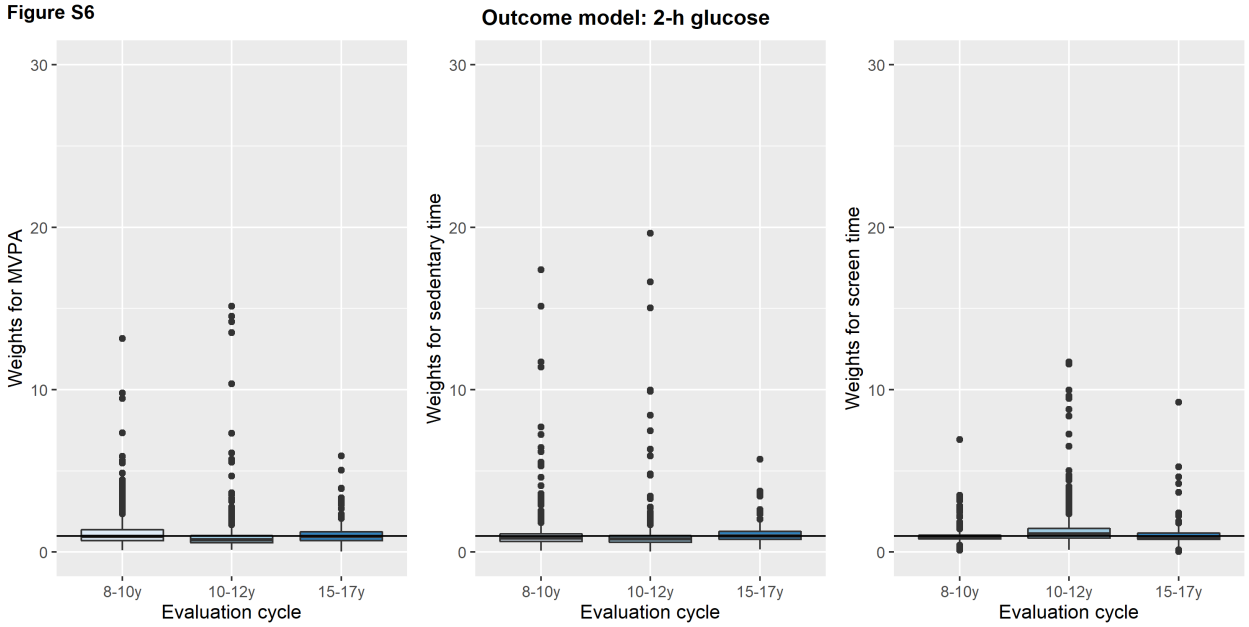


Figure S6



Legend. MVPA: moderate-to-vigorous physical activity. The boxplots show that the medians of the treatment weights are close to 1, indicating that the pseudopopulation is proportionally representative of the sample population. As specified above, weights under 0.033 or above 30 were truncated.

Figures S7-S9. Empirical assessment of the positivity assumption

Figure S7

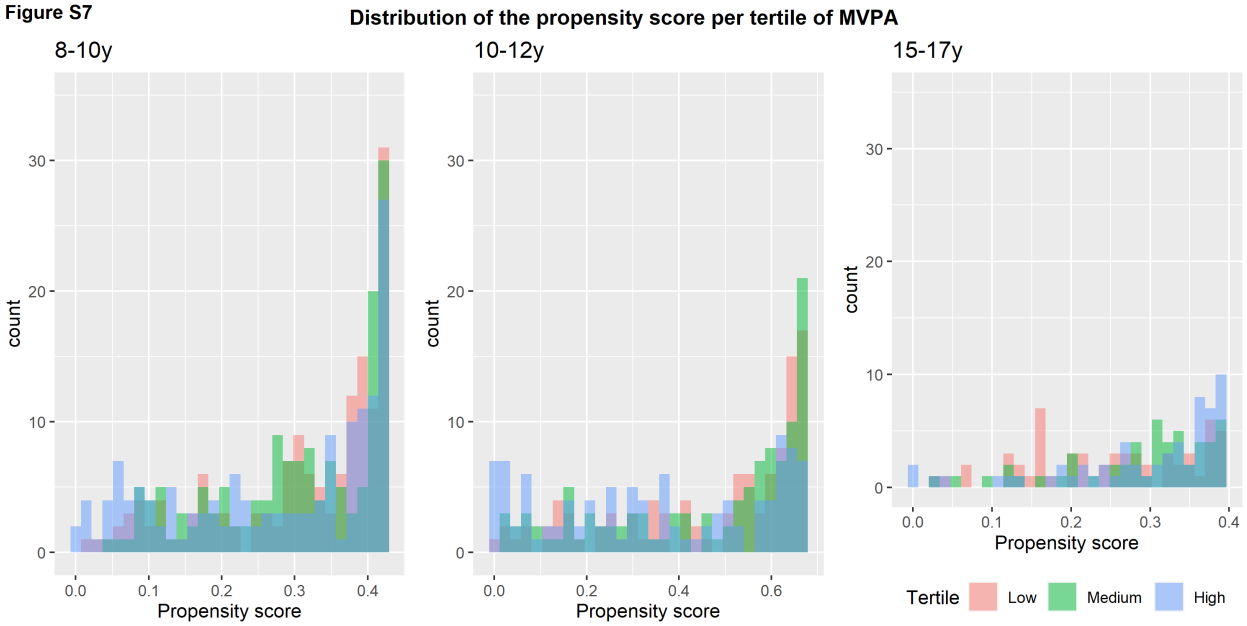


Figure S8

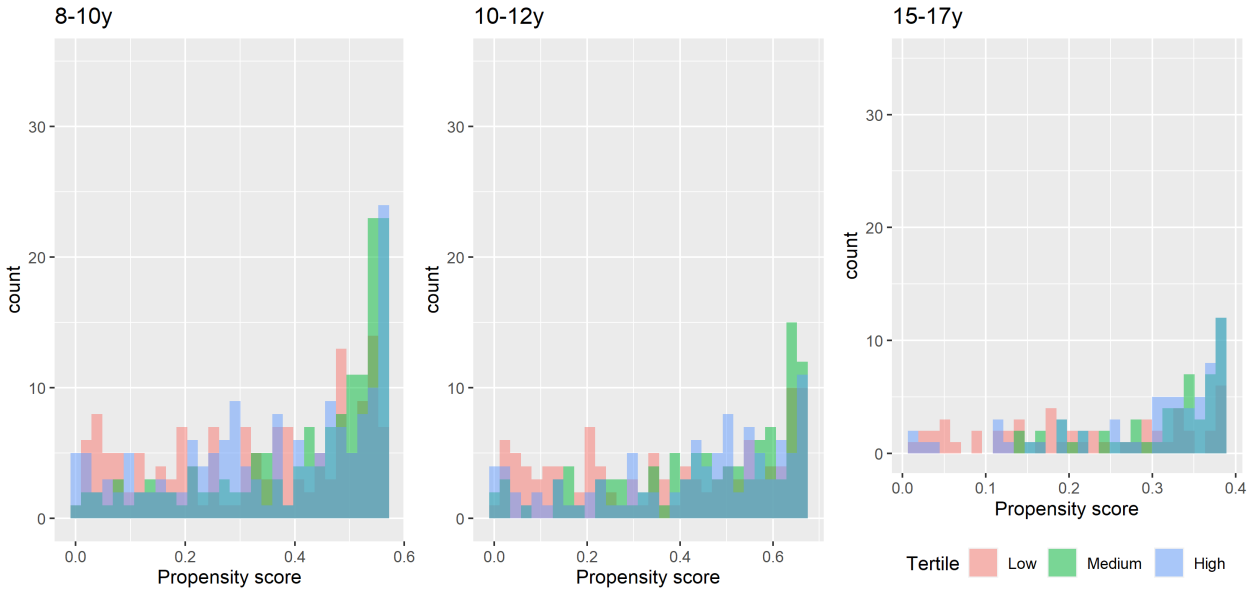
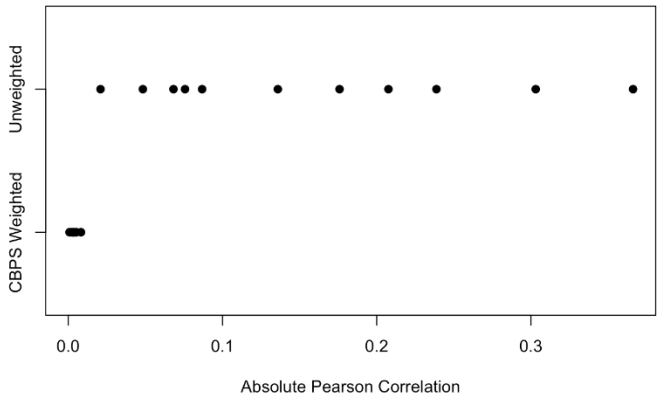


Figure S9

Legend. MVPA: moderate-to-vigorous physical activity. The histograms show that overall, the propensity scores are evenly distributed across tertiles of MVPA, sedentary time, and screen time for the three evaluation cycles in models adjusted for the covariates, the previous exposure and previous insulin sensitivity levels. We note a lesser overlap of the propensity score distribution on the left-hand side for children in the highest tertile of screen time (Figure S9).

Figures S10-S18. Examination of covariate balance for propensity score models with Love plots

Figure S10. Propensity score for moderate-to-vigorous physical activity, baseline



Legend. Each dot represents a covariate. Dots beside "Unweighted" indicate the correlation between the covariates and the exposure before weighting with the propensity score. Dots beside "CBPS Weighted" represent the correlation between the covariates and the exposure after weighting with the propensity score. The lower the correlation after weighting, the more the pseudopopulation has balanced characteristics across exposure levels. A general consensus is that a correlation below 0.1 after weighting is ideal. Correlations coefficients before and after weighting can be obtained with the balance() function in the CBPS package in R.

Figure S11. Propensity score for sedentary time, baseline

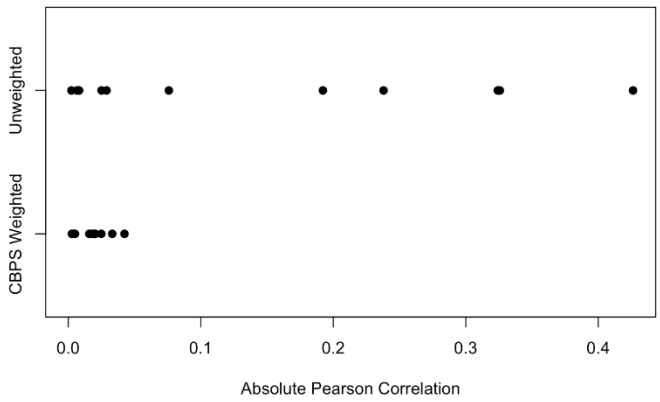


Figure S12. Propensity score for screen time, baseline

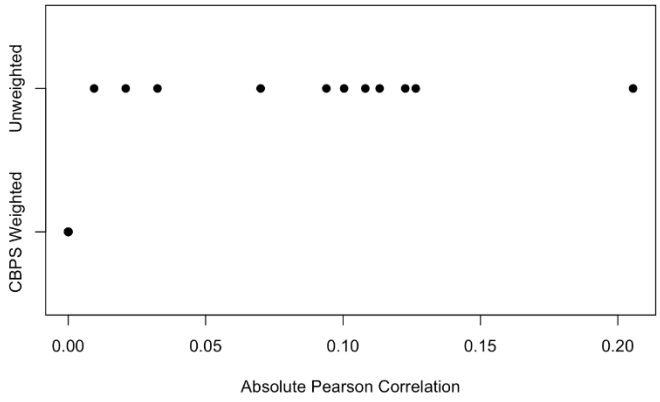


Figure S13. Propensity score for moderate-to-vigorous physical activity, 1st follow-up

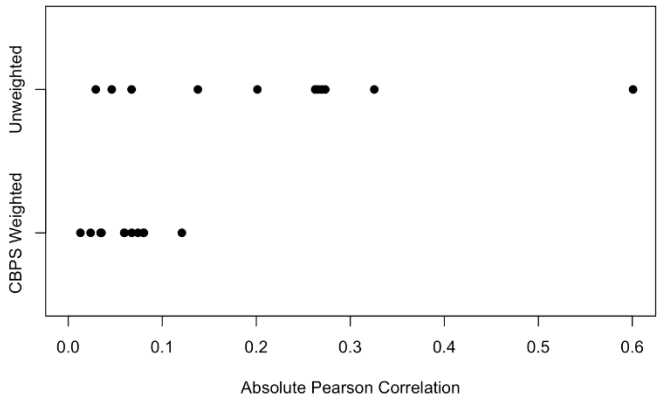


Figure S14. Propensity score for sedentary time, 1st follow-up

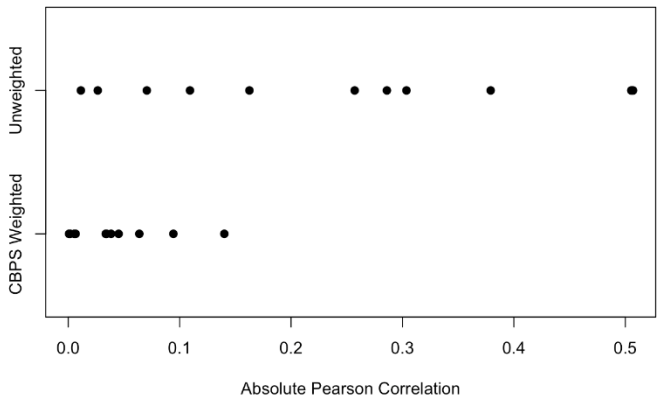


Figure S15. Propensity score for screen time, 1st follow-up

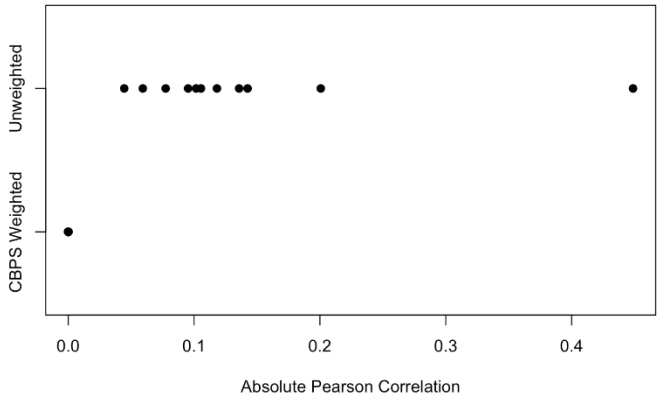


Figure S16. Propensity score for moderate-to-vigorous physical activity, 2nd follow-up

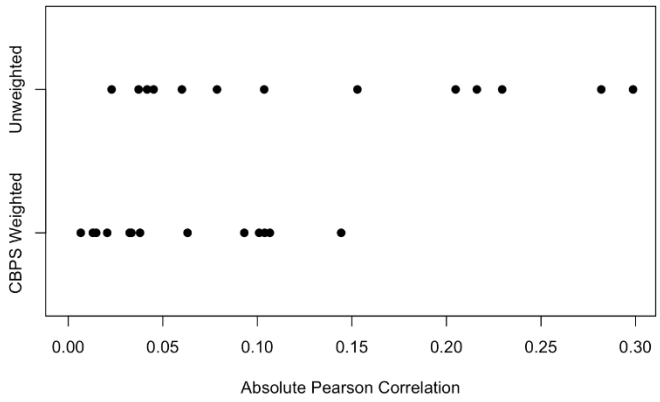


Figure S17. Propensity score for sedentary time, 2nd follow-up

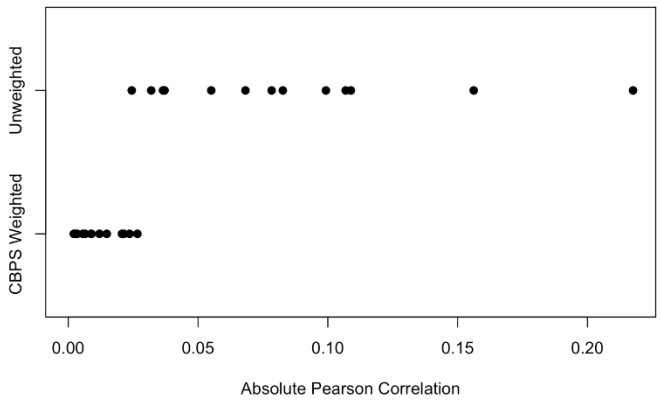
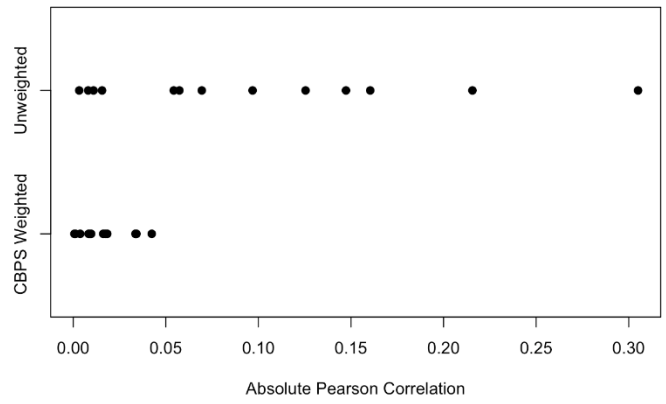
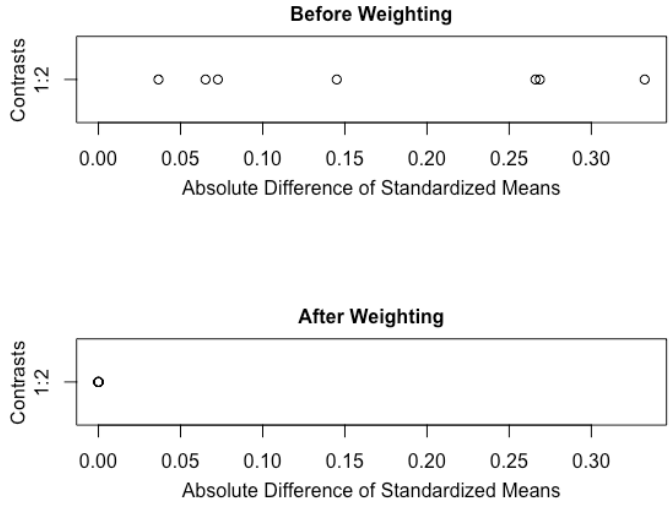


Figure S18. Propensity score for screen time, 2nd follow-up



Figures S19-S20. Examination of covariate balance for the censoring weights with Love plots

Figure S19. Censoring weights model, 1st follow-up



Legend. Each dot represents a covariate. Dots beside "Unweighted" indicate the standardized mean difference between the covariates and the censored and not censored before weighting with the probability of censoring score. Dots beside "CBPS Weighted" represent the standardized mean difference between the covariates and the censored and not censored after probability of censoring score. The lower the difference after weighting, the more the pseudopopulation has balanced characteristics across censored and not censored. A general consensus is that a

standardized mean difference below 0.1 after weighting is ideal. Standardized mean differences before and after weighting can be obtained with the balance() function in the CBPS package in R.

Figure S20. Censoring weights model, 2nd follow-up