Physical Activity is Associated with Lower Insulin and C-peptide during Glucose Challenge in Children and Adolescents with Family Background of Diabetes

Running Title: Physical Activity in Children and Adolescents with Family Background of Diabetes

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Novelty Statement:

What is already known?

Children and adolescents with a family history of diabetes are at increased risk of overweight, obesity, and type 2 diabetes during their lifetimes. However, there is only limited knowledge about the potentially beneficial effects of physical activity in these children.

What does this study add?

Our findings indicate that moderate to vigorous physical activity is associated with lower insulin and C-peptide levels during challenge with oral glucose tolerance tests in children and adolescents with a family background of diabetes mellitus.

What are the clinical implications of the study?

The promotion of physical activity may lower the metabolic risk in these children.

Abstract

Background: Children and adolescents with a family history of diabetes are at increased risk of overweight, but little is known about the potentially beneficial effects of physical activity on these children.

Study Objective: To investigate the association between moderate to vigorous physical activity (MVPA) and metabolic and inflammatory risks in children and adolescents with a family background of type 1 diabetes or gestational diabetes.

Methods: Valid MVPA measurements, made with accelerometers, were available from 234 participants (median age, 10.2 years) who had a first-degree relative with either type 1 or gestational diabetes. Anthropometric and metabolic measurements were made and cytokines measured and were correlated with MVPA measurements, with stepwise adjustment for confounding factors, in a cross-sectional analysis.

Results: MVPA was negatively associated with insulin and C-peptide during challenge with an oral glucose tolerance test. MVPA was also significantly positively associated with the insulin sensitivity index, whereas no consistently significant associations were found between MVPA and body mass index, blood pressure, or cytokine levels.

Discussion: Our findings indicate that physical activity may have beneficial effects on insulin and C-peptide metabolism in children and adolescents with a family background of diabetes, but show no evidence of a protective association with other health-related outcomes.

Key words: child, adolescent, gestational diabetes, exercise, physical activity, obesity, insulin sensitivity, type 1 diabetes

List of abbreviations

BP	Blood pressure
CI	Confidence interval
GDM	Gestational diabetes mellitus
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
IFN	Interferon
IGI	Insulinogenic index
IL	Interleukin
IQR	Interquartile range
ISI	Insulin sensitivity index
LDL	Low-density lipoprotein
MVPA	Moderate to vigorous physical activity
OGTT	Oral glucose tolerance test
POGO	Postpartum Outcomes in Women with Gestational Diabetes and their Offspring
TNF	Tumor necrosis factor
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Introduction

The prevalence of overweight and obesity is rising rapidly, not only in the adult global population but also in children and adolescents, and type 2 diabetes mellitus (T2DM) is increasingly observed in children [1-3]. Recent studies have suggested that the offspring of families with diabetes are at increased risk of overweight and the development of T2DM during their lifetimes, potentially in response to *in utero* exposure to hyperglycemia in a mother with gestational diabetes mellitus (GDM) or type 1 diabetes mellitus (T1DM) or to shared genetic factors [4-8].

In such high-risk children, changes in lifestyle behavior that might prevent overweight, T2DM, and comorbidities such as cardiovascular diseases appear highly relevant [1]. In particular, lifelong high levels of physical activity are recommended to prevent and counteract overweight and T2DM, together with other chronic diseases [9, 10]. According to the World Health Organization guidelines on physical activity, 5–17-year-old children should spend at least 60 minutes in moderate to vigorous physical activity (MVPA) every day to ensure their proper physical development, the prevention of noncommunicable diseases, and their mental well-being [11]. Although studies of the effects of MVPA on cardiometabolic, glucometabolic, and inflammatory biomarkers in the healthy general population of children and adolescents are controversial [12, 13], physical activity is generally reported to have beneficial effects on cardiovascular health and glucose metabolism in children and adolescents suffering T1DM or T2DM [1, 14-16]. Several studies have shown that physical activity also affects cytokine secretion and gene expression [17], and proinflammatory responses to physical activity were detected in adolescents who were obese or suffered T1DM or T2DM [18, 19].

Until now, there has been little information on the effects of physical activity on anthropometric measures and biomarkers in children and adolescents with a family history of diabetes. In this study, we investigated the association between accelerometry-measured daily MVPA, anthropometric and metabolic measurements, and inflammatory and anti-inflammatory cytokines in children and adolescents with a family background of T1DM or maternal GDM.

Methods

Setting and Participants

Physical activity was assessed in children and adolescents who were enrolled in either the TEENDIAB or the POGO (Postpartum Outcomes in Women with Gestational Diabetes and their Offspring) study. Both studies have been described in detail elsewhere [20, 21].

In brief, TEENDIAB was a prospective cohort study conducted in the cities of Munich and Hannover, Germany, that examined the development of T1DM during adolescence. Between 2009 and 2015, 610 children and adolescents, aged 6–16 years, with at least one first-degree relative with T1DM and who were free of any diabetes-associated antibodies, were enrolled. Follow-up visits took place every 6 months (on average) until the age of 18 years by 2016. Written informed consent for participation was given by the children's parents. Ethical approval for the study was given by the Ethical Committees of the Technische Universität München (no. 2149/08) and the Hannover Medical School (no. 5644).

Women who were positive when screened for GDM during at least one pregnancy between 1998 and 2009 were eligible to participate in the POGO study, together with their offspring. Between 2011 and 2015, 148 index children of mothers with a confirmed diagnosis of GDM were recruited. All the study participants attended the study center only once. The study was approved by the Ethical Committee of the Technische Universität München (no. 2937).

Assessment of physical activity

Physical activity was assessed between 2011 and 2014 in the TEENDIAB study and in 2011 or 2012 in the POGO study. Of the 391 children and adolescents who were asked to participate in accelerometry across both studies, 234 finally provided valid data (Figure 1). The reasons for refusal were mainly issues of time or comfort, whereas participation was invalid mainly when the device was worn for an insufficient time. Two different accelerometers, actibelt® (The Human Motion Institute, Munich, Germany) and ActiGraph GT1M (ActiGraph LLC, Pensacola, USA), were used to determine the time spent daily in MVPA. actibelt® was used in the TEENDIAB study from 2011 to 2013. ActiGraph GT1M was used in TEENDIAB in 2013 and 2014 and by all POGO participants. Instructions on how to use the accelerometer devices were given during a personal visit to the study center and in written form. The accelerometers were worn on the waist for at least 6 hours daily on at least

4 consecutive weekdays and one weekend day. The participants were instructed to wear the device all day long, except during water-based activities and sleeping. The actibelt® data were processed by the actibelt® provider and analyzed in Microsoft Excel. The ActiGraph GT1M data were processed and analyzed with the ActiLife 6 software. The epoch length was set to 60 seconds. Because the actibelt® device measures activity as low, moderate, or vigorous physical activity and the ActiGraph GT1M device measures it as sedentary, light, moderate, vigorous, and very vigorous, the average daily MVPA was defined as the 'average minutes of moderate or vigorous physical activity' for actibelt®, and the 'average minutes spent in moderate, vigorous, or very vigorous physical activity' for ActiGraph GT1M.

Anthropometric measurements

At each visit in both studies, weight and height were assessed with the same standardized protocols. Height was measured without shoes using a stadiometer with a precision of ± 1 mm, and weight was measured digitally or with a beam scale with a precision of ± 100 g, in light clothing. Height and weight were used to calculate the body mass index (BMI, kg/m^2), which was then transformed into age- and sex-adjusted z-scores and classified into percentiles according to German reference data [22]. Children at or above the 90th and 97th percentiles were defined to be overweight and obese, respectively. Diastolic and systolic blood pressures were measured as the average of two measurements using an auscultatory or oscillometric method in the upper arm while sitting, and were transformed into age-, sex-, and height-adjusted z-scores according to German reference data [23]. In TEENDIAB, Tanner's staging was assessed by the study doctor or local pediatrician using validated questionnaires [24].

Blood markers

The oral glucose tolerance test (OGTT) was performed at the study center after overnight fasting. The study participants ingested a glucose solution containing 1.75 g of glucose per kg bodyweight, or 75 g at maximum. Blood samples were collected at 0, 30, 60, 90, and 120 minutes after ingestion to determine the blood glucose, insulin, and C-peptide levels. The area under the curve (AUC) was calculated for each parameter [25]. Insulin resistance/sensitivity was estimated as the homeostasis model assessment of insulin resistance (HOMA-IR) [26] and the insulin sensitivity index (ISI) [27], and insulin secretion was measured as the insulinogenic index (IGI) [28]. Blood lipids (total, high-density lipoprotein [HDL]– and low-density lipoprotein [LDL]–cholesterol, and triglycerides) and hemoglobin A1c (HbA1c) were determined in the initial blood sample. Cytokines were measured once during the first study

center visit, including interleukin 6 (IL-6 (proinflammatory) and IL-10 (anti-inflammatory) in both studies, and IL-1β, IL-2, IL-8, IL-12p70, interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α) (all inflammatory) in the TEENDIAB study only. Plasma glucose was measured by the hospital laboratories at the two study sites. All other laboratory measurements were made centrally at the Institute of Diabetes Research or the Clinical Chemistry Laboratory, Klinikum rechts der Isar, Technische Universität München. Insulin and C-peptide were determined with an automated immunoassay analyzer (AIA 360; Tosoh, San Francisco, CA). Lipids were measured with an enzymatic colorimetric test on a cobas® 8000 modular analyzer with a c 502 module (Roche Diagnostics, Basel, Switzerland).

Statistical analysis

Because actibelt® measures acceleration on all three orthogonal axes [29] and ActiGraph GT1M measures only vertical acceleration [30], the MVPA measurements from both devices were not directly comparable. Therefore, the MVPA measurements made with each device were transformed into standardized z-scores, which were used for all analyses to avoid any bias caused by the dissimilarity of the devices. The associations between the MVPA z-scores and potential confounders, such as age and sex, were investigated with Spearman's correlation coefficient (r) or a *t* test (as appropriate).

For interleukin readings below the detection limit, half the observed minimum value was imputed. All cytokine measurements were log transformed. Linear regression models with stepwise adjustment for age, sex, BMI, season of the accelerometry measurements, and storage time (for cytokines) were used to estimate the association between the MVPA z-scores and each outcome measure. Analyses were performed separately for the TEENDIAB and POGO subjects and then pooled (with adjustment for study affiliation). The age- and sex-adjusted residuals of the MVPA z-scores [31] were taken from the respective regression models and used to plot the mean patterns for glucose, insulin, and C-peptide during OGTT challenge.

In a sensitivity analysis, all linear regression models were recalculated for the ActiGraph GT1M measurements only. In another sensitivity analysis, linear regression models in TEENDIAB were also adjusted for Tanner's stage.

Data management and analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, North Carolina) and R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Figures

were created with GraphPad Prism version 6.01. The significance level was set at 5% for all analyses without adjustment for multiple testing.

Results

The baseline characteristics of the study population (n = 234) are described in Table 1. Overall, 143 (61.1%) study participants were exposed to hyperglycemia during pregnancy (i.e., to GDM in POGO and to T1DM in TEENDIAB), and the remaining 91 (38.9%) had a father or sibling with T1DM. In total, 104 (44.4%) children used actibelt® and 104 (44.4%) were female. The median age (interquartile range [IQR]) when MVPA was measured was 10.2 years (8.2, 12.8), although the TEENDIAB children were considerably older at that time than the POGO children. Nineteen (8.1%) study participants were overweight and nine (3.8%) were obese. Lipids, blood pressure, HbA1c, and HOMA-IR were in the normal physiological ranges in both study populations.

As mentioned above, the calculation of MVPA differs substantially between the actibelt® and ActiGraph GT1M devices. The median (IQR) daily MVPA measured with actibelt® was 280 minutes per day (218, 324), but was 140 minutes per day (104, 189) when measured with ActiGraph GT1M. The device-specific MVPA z-scores decreased significantly with age ($r = -0.49$, $p < 0.0001$), and boys spent significantly more time in MVPA than girls ($p = 0.001$). The MVPA z-scores were not significantly associated with the seasonality of the measurement ($p = 0.51$), a family history of diabetes ($p = 0.48$), or the BMI z-score ($r = -0.03$, $p = 0.62$).

In the pooled analysis, the MVPA z-scores were significantly associated with insulin sensitivity measured as ISI (β [95% CI] = 0.75 [0.15, 1.35], $p = 0.01$ in the fully adjusted model), but not with insulin resistance (assessed as HOMA-IR or IGI), blood pressure, or lipids (Table 2). Although there was no significant association between daily MVPA and fasting insulin, increasing MVPA z-scores were associated with significantly lower values for insulin during OGTT challenge (e.g., β [95% CI] = −6.42 [−11.13, −1.71], $p = 0.008$, after 120 minutes in the fully adjusted model; Table 3). Similarly, MVPA was not significantly associated with fasting C-peptide, but significantly associated with it at 60–120 minutes during challenge (e.g., β [95% CI] = −1.69 [−3.26, −0.12], $p = 0.04$, after 120 minutes in the fully adjusted model). Higher MVPA tended to be associated with lower blood glucose during challenge, but not significantly. Therefore, the mean patterns of glucose, insulin, and C-peptide levels during OGTT challenge were higher in the study participants with low physical

activity than in those with average or high physical activity (Figure 2). No significant associations between the MVPA z-scores and cytokine levels were observed (Table 4). Most associations were similar in the TEENDIAB and POGO subjects, and were robust to stepwise adjustment.

The effect estimates did not change markedly after the exclusion of the actibelt® measurements or after adjustment for the Tanner stage in TEENDIAB (data not shown). We observed no meaningful interactions between MVPA and sex or age with respect to any outcome variable.

Discussion

This is the first study to examine the association between physical activity and diabetes-related biomarkers in children and adolescents with a family history of T1DM or GDM. We found no significant associations between the daily time spent in MVPA and BMI or blood pressure. However, higher MVPA was associated with lower insulin and C-peptide levels during a 2 hour OGTT in these subjects, whereas there was no clear association with blood glucose during OGTT. Therefore, MVPA was only significantly associated with insulin resistance/sensitivity measured as ISI, which takes into account all insulin measurements during OGTT, but not with HOMA-IR (based on fasting values only) or insulin secretion, measured as IGI (based on fasting and 30 minute values).

The effects of physical activity on cardiometabolic and inflammatory biomarkers in children and adolescents that have been reported in the literature have been controversial [16]. Our findings are consistent with previous results for physical activity in adolescents and adults at high risk of T2DM, which also demonstrated lower insulin and C-peptide levels in the more physically active participants [32]. However, other studies have reported significant associations between increased physical activity and not only lower fasting insulin and C-peptide, but also lower glucose levels, in healthy children and adolescents [33-35]. In contrast to previously published results [18, 19], we found no significant associations between MVPA and cytokine levels.

A particular strength of our data is that physical activity was assessed with accelerometers. Accelerometry is an objective method of measuring physical activity and tends to yield more precise results in children and adolescents than subjective methods of physical activity assessment [36]. Furthermore, MVPA was assessed within a few days of the visit at which the

anthropometric parameters and biomarkers were measured. The internal validity of these measurements is likely to be high because they were performed with standardized protocols that were identical in the two studies. When we considered the external generalizability of our data, it was surprising that the percentage of overweight and obese participants (11.4%) in this seemingly high-risk study population was lower than in the average German population (4–10 years old, 14.9% [37]; 11–17 years old, 18.9% [38]), and that the daily time spent in MVPA seemed relatively high. Our data covered a broad age range of MVPA measurements, and we accommodated potential age- and sex-specific differences in both MVPA and all the outcome variables.

However, several limitations must be noted. For internal reasons, we used two different accelerometers whose outputs are not directly comparable because they do not measure the same type of MVPA. To accommodate for this, device-specific z-scores were calculated and sensitivity analyses were performed. Another limitation of our analysis was the short minimum daily wearing time of the accelerometer (only 6 hours), which may have caused the systematic underestimation of physical activity. Impaired adherence to accelerometry among the study participants also entailed a risk of random errors [39]. However, although no estimates of individual wearing times were available, we assumed that both wearing time and adherence were at least comparable for the two devices, because both devices were similarly comfortable, were worn at the waist, and were fixed by an elastic strap to the belt, and because the instructions given to the participants were identical. Statistical power was another important limitation of these analyses. Compared with other studies, the sample size of our combined TEENDIAB and POGO dataset was reasonable, but may still have been too small to observe associations with some outcome parameters, such as blood glucose, which showed a borderline significant association with MVPA, or cytokine levels, the data for most of which were only available in the TEENDIAB study. Furthermore, we cannot rule out the possibility of some false positive findings because we investigated a large number of outcome variables without formal consideration of multiple testing, and none of the observed associations was strong enough to remain significant after correction for multiple testing with Bonferroni's method (yielding a significance level of $0.05/36 = 0.0014$ based on the number of outcomes investigated; Tables 2–4). Therefore, our study should be seen as mainly exploratory. Furthermore, we were unable to exclude potential confounding by factors such as maternal socioeconomic status because such variables were not available in our data. Apart from that, since all the children studied here had a relative with diabetes, we cannot exclude that the effects observed in our cohorts may differ in children without a family history of diabetes.

Lastly, we cannot infer causality from our observations because we did not have prospective measurements of MVPA, but could only assess cross-sectional associations.

In conclusion, our findings indicate that the promotion of physical activity may benefit children and adolescents with a family history of diabetes by lowering their insulin and C-peptide under OGTT challenge. However, we found no evidence of a similar protective effect of physical activity on other anthropometric or metabolic markers in these subjects.

References

1. World Health Organization. Global report on Diabetes. Geneva, 2016. [Cited 2018 May 02]. Available from: http://www.who.int/diabetes/global-report/en/
2. Afshin A, Reitsma MB, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries. *N Engl J Med* 2017; **377**:1496-1497.
3. World Health Organization. Overweight and Obesity: Fact Sheet (No. 311). Geneva, 2017. [Cited 2018 May 02]. Available from: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
4. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. *Diabetologia* 2016; **59**:1396-1399.
5. Kim SY, England JL, Sharma JA, Njoroge T. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: a systematic review. *Exp Diabetes Res* 2011; **2011**:541308.
6. Nehring I, Chmitorz A, Reulen H, von Kries R, Ensenauer R. Gestational diabetes predicts the risk of childhood overweight and abdominal circumference independent of maternal obesity. *Diabet Med* 2013; **30**:1449-1456.
7. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J*, et al.* Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. *J Clin Endocrinol Metab* 2009; **94**:2464-2470.
8. Boerschmann H, Pfluger M, Henneberger L, Ziegler AG, Hummel S. Prevalence and predictors of overweight and insulin resistance in offspring of mothers with gestational diabetes mellitus. *Diabetes Care* 2010; **33**:1845-1849.
9. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2012; **2**:1143-1211.
10. Takemura Y, Kikuchi S, Inaba Y, Yasuda H, Nakagawa K. The protective effect of good physical fitness when young on the risk of impaired glucose tolerance when old. *Prev Med* 1999; **28**:14-19.
11. World Health Organization. Information sheet: Global recommendations on physical activity for health; 5 - 17 years old. Geneva, 2011. [Cited 2018 May 02]. Available from: http://www.who.int/dietphysicalactivity/factsheet_young_people/en/
12. Owens S, Galloway R, Gutin B. The Case for Vigorous Physical Activity in Youth. *American Journal of Lifestyle Medicine* 2016; **11**:96-115.
13. Mead E, Brown T, Rees K, Azevedo LB, Whittaker V, Jones D*, et al.* Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. *Cochrane Database Syst Rev* 2017; **6**:CD012651.
14. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006; **29**:1433-1438.
15. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia* 2012; **55**:542-551.
16. Quirk H, Blake H, Tennyson R, Randell TL, Glazebrook C. Physical activity interventions in children and young people with Type 1 diabetes mellitus: a systematic review with meta-analysis. *Diabet Med* 2014; **31**:1163-1173.
17. Moldoveanu AI, Shephard RJ, Shek PN. The cytokine response to physical activity and training. *Sports Med* 2001; **31**:115-144.
18. Rosa JS, Heydari S, Oliver SR, Flores RL, Pontello AM, Ibardolaza M*, et al.* Inflammatory cytokine profiles during exercise in obese, diabetic, and healthy children. *J Clin Res Pediatr Endocrinol* 2011; **3**:115-121.

19. Nadeau KJ, Zeitler PS, Bauer TA, Brown MS, Dorosz JL, Draznin B*, et al.* Insulin resistance in adolescents with type 2 diabetes is associated with impaired exercise capacity. *J Clin Endocrinol Metab* 2009; **94**:3687-3695.
20. Hummel S, Much D, Rossbauer M, Ziegler AG, Beyerlein A. Postpartum outcomes in women with gestational diabetes and their offspring: POGO study design and first-year results. *Rev Diabet Stud* 2013; **10**:49-57.
21. Ziegler AG, Meier-Stiegen F, Winkler C, Bonifacio E, Group TS. Prospective evaluation of risk factors for the development of islet autoimmunity and type 1 diabetes during puberty--TEENDIAB: study design. *Pediatr Diabetes* 2012; **13**:419-424.
22. Kromeyer-Hauschild K, Wabitsch M, Kkunze D, Geller F, Geiß HC, Hesse V*, et al.* Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. *Monatsschrift Kinderheilkunde* 2001:807-818.
23. Robert-Koch-Institut. Referenzperzentile für anthropometrische Maßzahlen und Blutdruck aus der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS) 2003-2006. *Beiträge zur Gesundheitsberichterstattung des Bundes.* 2nd edn. Berlin, 2011.
24. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *J Youth Adolesc* 1980; **9**:271-280.
25. Tai MM. A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. *Diabetes Care* 1994; **17**:152-154.
26. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**:412-419.
27. Vukovic R, Mitrovic K, Milenkovic T, Todorovic S, Soldatovic I, Sipetic-Grujicic S*, et al.* Insulin-sensitive obese children display a favorable metabolic profile. *Eur J Pediatr* 2013; **172**:201-206.
28. Phillips DI, Clark PM, Hales CN, Osmond C. Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med* 1994; **11**:286-292.
29. Daumer M, Thaler K, Kruis E, Feneberg W, Staude G, Scholz M. Steps towards a miniaturized, robust and autonomous measurement device for the long-term monitoring of patient activity: ActiBelt. *Biomed Tech (Berl)* 2007; **52**:149-155.
30. John D, Tyo B, Bassett DR. Comparison of four ActiGraph accelerometers during walking and running. *Med Sci Sports Exerc* 2010; **42**:368-374.
31. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* 1997; **65**:1220S-1228S; discussion 1229S-1231S.
32. Kriska AM, Pereira MA, Hanson RL, de Courten MP, Zimmet PZ, Alberti KG*, et al.* Association of physical activity and serum insulin concentrations in two populations at high risk for type 2 diabetes but differing by BMI. *Diabetes Care* 2001; **24**:1175-1180.
33. Schmitz KH, Jacobs DR, Jr., Hong CP, Steinberger J, Moran A, Sinaiko AR. Association of physical activity with insulin sensitivity in children. *Int J Obes Relat Metab Disord* 2002; **26**:1310-1316.
34. Ekelund U, Luan J, Sherar LB, Esliger DW, Griew P, Cooper A*, et al.* Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *JAMA* 2012; **307**:704-712.
35. Huus K, Akerman L, Raustorp A, Ludvigsson J. Physical Activity, Blood Glucose and C-Peptide in Healthy School-Children, a Longitudinal Study. *PLoS One* 2016; **11**:e0156401.
36. Corder K, Ekelund U, Steele RM, Wareham NJ, Brage S. Assessment of physical activity in youth. *J Appl Physiol (1985)* 2008; **105**:977-987.
37. Brettschneider AK, Schienkiewitz A, Schmidt S, Ellert U, Kurth BM. Updated prevalence rates of overweight and obesity in 4- to 10-year-old children in Germany. Results from the telephone-based KiGGS Wave 1 after correction for bias in parental reports. *Eur J Pediatr* 2017; **176**:547-551.
38. Brettschneider AK, Schaffrath Rosario A, Kuhnert R, Schmidt S, Wiegand S, Ellert U*, et al.* Updated prevalence rates of overweight and obesity in 11- to 17-year-old adolescents in Germany.

Results from the telephone-based KiGGS Wave 1 after correction for bias in self-reports. *BMC Public Health* 2015; **15**:1101.
39. Pedisic Z, Bauman A. Accelerometer-based measures in physical activity surveillance: current practices and issues. *Br J Sports Med* 2015; **49**:219-223.

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Authors' contributions

KU reviewed data, undertook the statistical analysis, interpreted the results, and wrote the first and final draft of the manuscript together with AB. MJ and AP contributed to the data management and statistical analysis and reviewed the manuscript. MH, LL, FH, CW, SH, and OK acquired the data and reviewed the manuscript. A-GZ is the principal investigator of the POGO and TEENDIAB studies, designed the studies and concept, interpreted the results, and critically reviewed the manuscript for intellectual content.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Table 1. Characteristics of the study population by cohort affiliation.

Variable		TEENDIAB (N = 171)	POGO (N = 63)
		N (%)	N (%)
Family history of	Mother with GDM	0	63 (100)
Diabetes	Mother with T1DM	80 (46.78)	0
	Other first-degree relative with T1DM	91 (53.22)	0
Accelerometer	Actigraph GT1M	67 (39.18)	63 (100)
Sex	Female	84 (49.12)	20 (31.75)
Season of	Spring (Mar-May)	29 (16.96)	18 (28.57)
Accelerometry	Summer (Jun-Aug)	62 (36.26)	23 (36.51)
Measurement	Autumn (Sept-Nov)	54 (31.58)	15 (23.81)
	Winter (Dec-Feb)	26 (15.20)	7 (11.11)
		Median [IQR]	**Median [IQR]**
Age (years)		11.1 [9.5, 14.0]	6.2 [4.7, 8.8]
BMI z-score		0.0 [-0.7, 0.7]	0.0 [-0.6, 0.8]
Glucose (mmol/l)	Fasting	4.9 [4.6, 6.6]	4.9 [4.6, 5.1]
	30 Minutes	7.3 [6.4, 8.3]	8.1 [7.2, 8.8]
	60 Minutes	5.8 [4.7, 7.1]	6.6 [5.8, 7.1]
	90 Minutes	5.3 [4.8, 6.1]	5.6 [5.1, 6.7]
	120 Minutes	5.3 [4.6, 6.1]	5.8 [5.0, 6.9]
Insulin (µU/ml)	Fasting	7.8 [5.0, 10.3]	3.2 [2.0, 6.2]
	30 Minutes	62.7 [33.0, 88.8]	40.7 [26.6, 56.8]
	60 Minutes	44.5 [26.0, 74.0]	33.3 [22.8, 53.8]
	90 Minutes	34.9 [23.1, 50.0]	25.0 [14.8, 38.5]
	120 Minutes	31.9 [17.5, 48.8]	26.5 [19.5, 33.6]
C-Peptide (ng/ml)	Fasting	1.4 [1.1, 1.9]	0.8 [0.7, 1.2]
	30 Minutes	5.9 [4.2, 7.8]	4.9 [3.4, 6.5]
	60 Minutes	6.1 [4.7, 8.5]	5.5 [4.0, 7.1]
	90 Minutes	5.3 [4.0, 7.0]	4.0 [3.3, 5.3]
	120 Minutes	5.0 [3.7, 6.5]	4.5 [3.7, 5.5]
Cholesterol (mmol/l)		4.1 [3.7, 4.7]	4.4 [4.0, 4.9]

LDL (mmol/l)	2.4 [1.9, 4.0]	2.8 [2.4, 3.3]
HDL (mmol/l)	1.4 [1.0, 1.7]	1.4 [1.2, 1.7]
Triglycerides (mmol/l)	0.9 [0.6, 1.1]	0.7 [0.6, 0.9]
Systolic BP z-score	-0.4 [-1.3, 0.5]	-0.7 [-1.5, 0.3]
Diastolic BP z-score	0.4 [-0.6, 1.1]	0.7 [-0.1, 1.4]
HbA1c (mmol/mol) (%)	34 [33, 37] (5.3 [5.2, 5.5])	36 [33, 38] (5.4 [5.2, 5.6])
HOMA-IR	1.6 [1.1, 2.4]	0.7 [0.4, 1.3]
ISI	6.5 [4.4, 9.7]	11.2 [6.4, 14.6]
IGI	1.1 [0.6, 2.0]	0.7 [0.4, 1.0]
IL-2 (pg/ml)	0.02 [0.003, 0.09]	-
IL-6 (pg/ml)	0.3 [0.2, 0.5]	0.5 [0.3, 1.2]
IL-8 (pg/ml)	9.1 [7.7, 12.0]	-
IL-10 (pg/ml)	0.3 [0.3, 0.5]	0.5 [0.4, 0.9]
IL-1β (pg/ml)	0.03 [0.004, 0.06]	-
IL-12p70 (pg/ml)	0.05 [0.004, 0.1]	-
IFN-γ (pg/ml)	3.8 [3.0, 6.8]	-
TNF-α (pg/ml)	2.8 [2.4, 3.2]	-

BP: blood pressure; BMI: body mass index; GDM: gestational diabetes mellitus; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; IFN: interferon; IGI: insulinogenic index; IL: interleukin; IQR: interquartile range; ISI: insulin sensitivity index; LDL: low-density lipoprotein; TNF: tumor necrosis factor; T1DM: type 1 diabetes mellitus

Table 2. Regression coefficients from linear regression models of MVPA z-scores (predictor variables) and sex-, age- and height-specific blood pressure z-score and metabolic markers (outcome variables) with stepwise adjustment for age, sex (model 1), age- and sex-specific BMI z-score (model 2) and season of accelerometry measurement (model 3), separated by study (POGO/TEENDIAB) and pooled. Pooled models were additionally adjusted for study affiliation. Bold font indicates significant associations ($p<0.05$).

	POGO			TEENDIAB			POOLED		
Outcome Variable	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)
Systolic BP z-score	0.16 [-0.22, 0.53]	0.24 [-0.12, 0.61]	0.22 [-0.14, 0.58]	-0.09 [-0.33, 0.14]	-0.11 [-0.34, 0.12]	-0.12 [-0.35, 0.12]	-0.80 [-0.20, 0.19]	0.00 [-0.19, 0.19]	-0.01 [-0.20, 0.18]
Diastolic BP z-score	0.03 [-0.36, 0.41]	0.04 [-0.35, 0.43]	0.06 [-0.32, 0.44]	-0.07 [-0.26, 0.12]	-0.09 [-0.27, 0.10]	-0.09 [-0.28, 0.10]	-0.02 [-0.19, 0.15]	-0.02 [-0.18, 0.15]	-0.01 [-0.18, 0.15]
Cholesterol (mmol/l)	0.17 [-0.06, 0.40]	0.23 [0.0003, 0.46]	0.25 [0.03, 0.48]	-0.02 [-0.16, 0.12]	-0.02 [-0.15, 0.12]	-0.02 [-0.16, 0.12]	0.04 [-0.08, 0.16]	0.04 [-0.08, 0.15]	0.04 [-0.07, 0.16]
LDL (mmol/l)	3.60 [-4.43, 11.62]	4.98 [-3.26, 13.21]	5.94 [-1.94, 13.82]	-0.06 [-0.19, 0.07]	-0.06 [-0.19, 0.07]	-0.06 [-0.19, 0.07]	-0.01 [-0.12, 0.09]	-0.01 [-0.12, 0.10]	0.00 [-0.11, 0.10]
HDL (mmol/l)	3.69 [-0.25, 7.62]	4.36 [0.25, 8.46]	4.27 [0.18, 8.36]	0.00 [-0.09, 0.11]	0.01 [-0.09, 0.11]	0.00 [-0.10, 0.10]	0.04 [-0.04, 0.11]	0.03 [-0.04, 011]	0.03 [-0.04, 0.02]
Triglycerides (mmol/l)	0.01 [-0.08, 0.10]	0.02 [-0.07, 0.11]	0.03 [-0.06, 0.12]	0.03 [-0.05, 0.10]	0.03 [-0.05, 0.10]	0.03 [-0.04, 0.10]	0.02 [-0.04, 0.07]	0.02 [-0.04, 0.08]	0.02 [-0.04, 0.08]
HbA1c (mmol/mol) (%)	0.74 [-0.71, 2.19] (0.07 [-0.06, 0.20])	0.80 [-0.12, 1.71] (0.07 [-0.01, 0.16])	0.76 [-0.14, 1.67] (0.07 [-0.01, 0.15])	0.41 [-0.24, 1.06] (0.04 [-0.02, 0.10])	0.41 [-0.24, 1.06] (0.04 [-0.02, 0.10])	0.42 [-0.24, 1.08] (0.04 [-0.02, 0.10])	0.50 [-0.10, 1.11] (0.05 [-0.01, 0.10])	0.51 [-0.10, 1.11] (0.05 [-0.001, 0.10])	0.52 [-0.01, 1.04] (0.05 [-0.001, 0.10]

HOMA-IR	0.07	-0.46	-0.33	0.00	0.00	-0.01	-0.06	-0.04	-0.03
	[-1.38, 0.54]	[-1.47, 0.55]	[-1.33, 0.67]	[-0.27, 0.27]	[-0.25, 0.25]	[-0.26, 0.25]	[-0.36, 0.24]	[-0.34, 0.26]	[-0.33, 0.27]
ISI	1.19	0.74	0.71	0.78	0.79	0.74	0.87	0.80	0.75
	[-0.68, 3.06]	[-1.12, 2.60]	[-1.26, 2.68]	[0.07, 1.48]	[0.12, 1.45]	[0.09, 1.40]	[0.22, 1.52]	[0.19, 1.41]	[0.15, 1.35]
IGI	0.05	0.05	0.03	-0.18	-0.19	-0.14	-0.14	-0.12	-0.09
	[-0.28, 0.38]	[-0.34, 0.35]	[-0.31, 0.37]	[-1.06, 0.70]	[-1.07, 0.69]	[-1.03, 0.75]	[-0.84, 0.56]	[-0.82, 0.58]	[-0.80, 0.62]

BP: blood pressure, CI: confidence interval, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, IGI: insulinogenic index, ISI: insulin sensitivity index, LDL: low-density lipoprotein

Table 3. Regression coefficients from linear regression models of MVPA z-scores (predictor variables) and blood glucose, insulin, and C-peptide levels during OGTT challenge (outcome variables) with stepwise adjustment for age, sex (model 1), age- and sex-specific BMI z-score (model 2), and season of accelerometry measurement (model 3), according to study (POGO or TEENDIAB) and pooled. Pooled models were also adjusted for study affiliation. Bold font indicates significant associations ($p < 0.05$).

		POGO			TEENDIAB			POOLED		
Outcome Variable		Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)
Glucose (mmol/l)	Fasting	0.08 [-0.06, 0.22]	**0.64 [0.11, 1.18]**	0.09 [-0.04, 0.21]	0.03 [-0.05, 0.11]	0.03 [-0.05, 0.11]	0.05 [-0.02, 0.11]	0.05 [-0.03, 0.12]	0.05 [-0.02, 0.12]	0.05 [-0.02, 0.11]
	30 Min	0.43 [-0.14, 0.99]	**0.64 [0.11, 1.18]**	**0.73 [0.18, 1.27]**	-0.20 [-0.49, 0.10]	-0.20 [-0.50, 0.10]	-0.16 [-0.44, 0.13]	-0.06 [-0.32, 0.19]	-0.06 [-0.31, 0.20]	-0.04 [-0.29, 0.22]
	60 Min	-0.08 [-0.61, 0.45]	-0.02 [-0.45, 0.40]	-0.01 [-0.45, 0.43]	-0.18 [-0.50, 0.15]	-0.18 [-0.50, 0.15]	-0.15 [-0.47, 0.17]	-0.16 [-0.45, 0.10]	-0.17 [-0.43, 0.10]	-0.16 [-0.43, 0.10]
	90 Min	0.01 [-0.61, 0.64]	0.14 [-0.29, 0.58]	0.23 [-0.19, 0.66]	**-0.28 [-0.53, -0.03]**	**-0.29 [-0.54, -0.04]**	**-0.27 [-0.51, -0.02]**	-0.23 [-0.46, 0.005]	-0.21 [-0.43, 0.01]	-0.21 [-0.43, 0.01]
	120 Min	-0.31 [-0.87, 0.25]	-0.36 [-0.84, 0.13]	-0.24 [-0.71, 0.24]	-0.15 [-0.38, 0.09]	-0.15 [-0.38, 0.08]	-0.13 [-0.35, 0.09]	-0.18 [-0.39, 0.04]	-0.17 [-0.37, 0.04]	-0.16 [-0.36, 0.05]
	AUC	1.42 [-44.0, 46.3]	13.42 [-18.5, 45.3]	21.55 [-9.8, 52.9]	-22.78 [-48.3, 2.7]	-23.22 [-48.6, 2.2]	-19.45 [-43.9, 5.0]	-18.67 [-40.7, 3.4]	-17.51 [-38.8, 3.8]	-16.09 [-37.0, 4.8]
Insulin (µU/ml)	Fasting	2.02 [-4.37, 20.51]	-6.53 [-18.25, 5.19]	-1.59 [-6.37, 3.19]	0.07 [-1.06, 1.19]	0.05 [-1.00, 1.10]	0.07 [-0.99, 1.14]	-0.27 [-1.65, 1.11]	-0.18 [-1.55, 1.19]	-0.10 [-1.48, 1.28]
	30 Min	-9.41 [-21.13, 2.32]	-6.53 [-18.25, 5.19]	-4.89 [-17.18, 7.40]	-5.05 [-16.17, 43.29]	-5.26 [-12.12, 1.60]	-5.17 [-23.38, 42.11]	**-6.13 [-12.19, -0.07**]	-5.56 [-11.35, 0.24]	-5.47 [-11.33, 0.40]
	60 Min	-10.91 [-23.41, 1.59]	-8.77 [-21.43, 3.89]	-6.32 [-19.20, 6.56]	-6.60 [-13.93, 0.72]]	-6.68 [-13.73, 0.36]	-6.31 [-13.43, 0.81]	**-7.89 [-14.10, -1.67]**	**-7.25 [-13.24, -1.26]**	**-6.84 [-12.87, -0.80]**
	90 Min	-6.98 [-16.07, 2.12]	-7.40 [-17.24, 2.44]	-5.58 [-14.84, 3.67]	-4.57 [-9.80, 0.65]	-4.72 [-9.60, 0.16]	-4.53 [-9.47, 0.42]	**-5.21 [-9.70, -0.71]**	**-4.70 [-9.02, -0.38]**	**-4.45 [-8.82, -0.07]**

	120 Min	**-10.11 [-18.18, -2.04]**	**-10.15 [-18.69, -1.61]**	-8.45 [-17.03, 0.14]	**-6.47 [-12.24, -0.70]**	**-6.39 [-11.90, -0.89]**	**-6.09 [-11.59, -0.59]**	**-7.18 [-12.00, -2.36]**	**-6.69 [-11.38, -2.01]**	**-6.42 [-11.13, -1.71]**
	AUC	-490.09 [-1467.4, 487.2]	-249.26 [-1219.2, 720.6]	-231.04 [-1225.7, 763.7]	**-730.74 [-1279.07, -182.4]**	**-730.60 [-1234.76, -226.4]**	**-717.69 [-1226.51, -208.9]**	**-708.41 [-1181.25, -235.6]**	**-632.58 [-1071.01, -194.2]**	**-610.17 [-1051.26, -169.1]**
C-Peptide (ng/ml)	Fasting	-1.80 [-7.20, 3.61]	-6.18 [-13.80, 1.45]	-0.95 [-6.32, 4.43]	0.01 [-0.12, 0.13]	0.01 [-0.11, 0.12]	0.01 [-0.11, 0.13]	-0.17 [-1.27, 0.94]	-0.18 [-1.29, 0.94]	-0.13 [-1.24, 0.98]
	30 Min	-5.57 [-12.72, 1.58]	-6.18 [-13.80, 1.42]	-4.68 [-12.55, 3.19]	-0.31 [-0.74, 0.12]	-0.32 [-0.73, 0.09]	-0.29 [-0.70, 0.12]	-1.42 [-2.93, 0.10]	-1.41 [-2.93, 0.11]	-1.32 [-2.85, 0.22]
	60 Min	-6.02 [-13.12, 1.08]	-6.63 [-14.20, 0.95]	-5.09 [-12.89, 2.71]	-0.40 [-0.86, 0.05]	-0.41 [-0.85, 0.03]	-0.37 [-0.81, 0.08]	**-1.63 [-3.16, -0.10]**	**-1.62 [-3.15, -0.07]**	-1.52 [-3.07, 0.03]
	90 Min	-6.13 [-13.45, 1.18]	-6.89 [-14.68, 0.91]	-5.36 [-13.35, 2.63]	**-0.47 [-0.90, -0.03]**	**-0.45 [-0.86, -0.04]**	**-0.42 [-0.84, -0.001]**	**-1.89 [-3.50, -0.29]**	**-1.88 [-3.50, -0.27]**	**-1.81 [-3.44, -0.19]**
	120 Min	-6.43 [-13.75, 0.89]	-7.13 [-14.93, 0.66]	-5.58 [-13.59, 2.43]	**-0.56 [-1.02, -0.09]**	**-0.55 [-0.99, -0.12]**	**-0.52 [-0.96, -0.09]**	**-1.79 [-3.33, -0.25]**	**-1.77 [-3.32, -0.22]**	**-1.69 [-3.26, -0.12]**
	AUC	-0.18 [-0.45, 0.09]	-0.07 [-0.31, 0.17]	-0.06 [-0.31, 0.20]	**-0.19 [-0.37, -0.005]**	**-0.18 [-0.34, -0.01]**	-0.16 [-0.33, 0.01]	**-0.19 [-0.35, -0.04]**	**-0.16 [-0.30, -0.02]**	**-0.15 [-0.29, -0.01]**

AUC: area under the curve; CI: confidence interval

Table 4. Regression coefficients from linear regression models of MVPA z-scores (predictor variables) and cytokines (outcome variables per pg/ml, log-transformed) with stepwise adjustment for age, sex, and storage time (model 1), age- and sex-specific BMI z-score (model 2), and season of accelerometry measurement (model 3), according to study (POGO or TEENDIAB) and pooled. Pooled models were also adjusted for study affiliation. In POGO, only IL-6 and IL-10 were measured. Bold font indicates significant associations ($p < 0.05$).

	POGO			**TEENDIAB**			**POOLED**		
Outcome Variable	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)	Model 1 β (95 % CI)	Model 2 β (95 % CI)	Model 3 β (95 % CI)
log IL-2				0.02 [-0.14, 0.18]	0.02 [-0.14, 0.18]	0.02 [-0.14, 0.18]			
log IL- 6	-0.07 [-0.19, 0.05]	-0.08 [-0.20, 0.05]	-0.09 [-0.21, 0.02]	0.00 [-0.10, 0.09]	-0.01 [-0.11, 0.09]	0.00 [-0.09, 0.10]	-0.03 [-0.10, 0.05]	-0.02 [-0.10, 0.05]	-0.02 [-0.10, 0.05]
log IL- 8				0.023 [-0.05, 0.09]	0.020 [-0.05, 0.09]	0.028 [-0.04, 0.10]			
log IL-10	**-0.09 [-0.17, -0.004]**	-0.09 [-0.17, 0.0004]	-0.08 [-0.17, 0.01]	**0.07 [0.02, 0.11]**	**0.06 [0.02, 0.11]**	**0.06 [0.02, 0.11]**	0.02 [-0.02, 0.06]	0.02 [-0.02, 0.06]	0.02 [-0.02, 0.06]
log IL-1β				-0.02 [-0.16, 0.11]	-0.03 [-0.16, 0.10]	-0.02 [-0.16, 0.11]			
log IL-12p70				-0.04 [-0.18, 0.09]	-0.05 [-0.18, 0.09]	-0.05 [-0.18, 0.08]			
log IFN-γ				0.01 [-0.06, 0.09]	0.01 [-0.06, 0.09]	0.02 [-0.06, 0.09]			
log TNF-α				0.03 [-0.001, 0.07]	0.03 [-0.003, 0.06]	0.03 [-0.0004, 0.07]			

CI: confidence interval; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor

Figure 1. Flow chart of the study population.

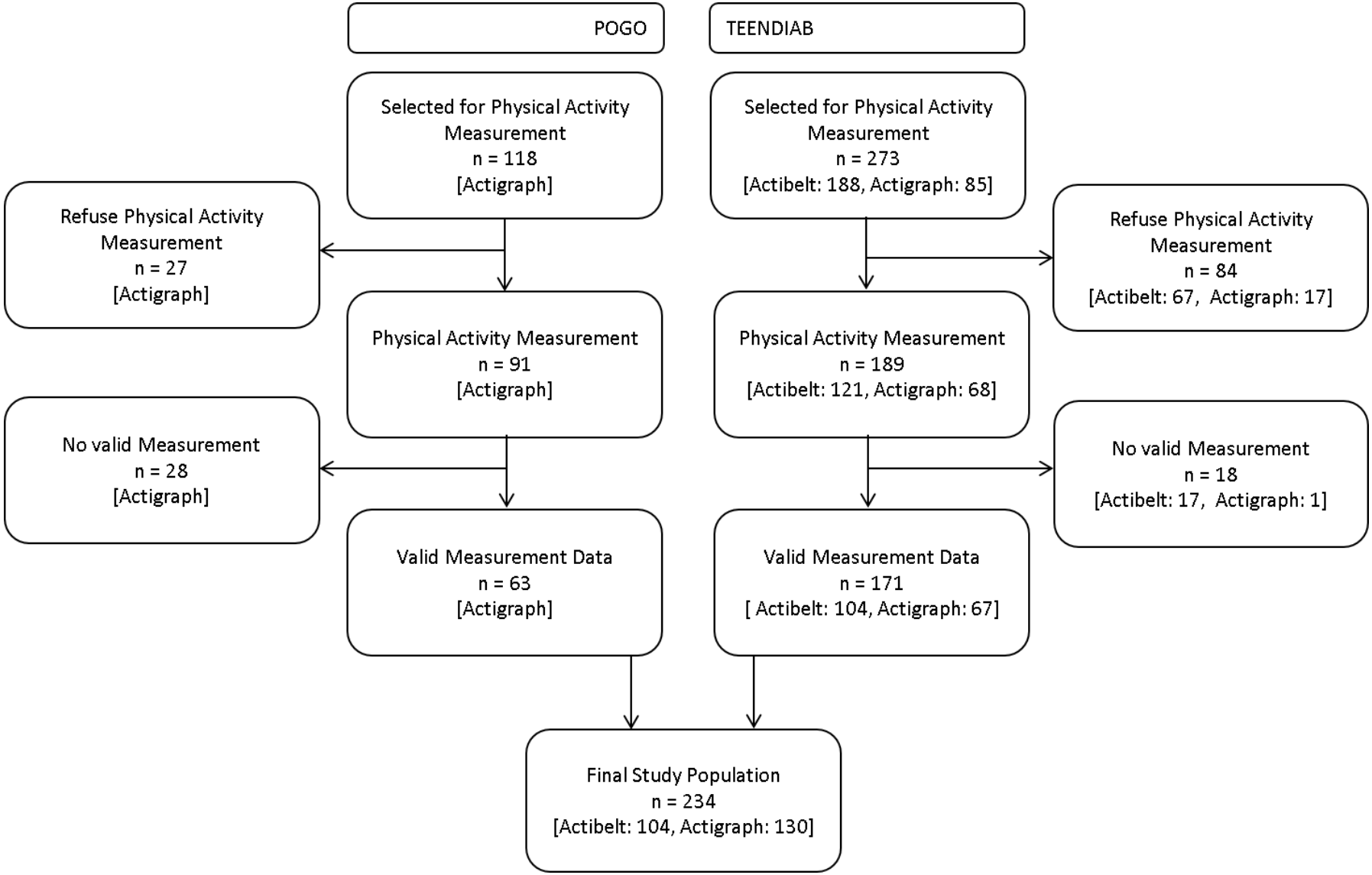

Figure 2. Mean glucose, insulin, and C-peptide levels after 0, 30, 60, 90, and 120 minutes of challenge with the oral glucose tolerance test, according to subgroups defined by the daily time spent in moderate to vigorous physical activity (MVPA). The lower quartile of age- and sex-adjusted residuals of the MVPA activity z-scores was defined as 'less active' and the highest quartile was defined as 'highly active'.