

Review

Physical activity, sedentary behavior, and long-term cardiovascular risk in young people: A review and discussion of methodology in prospective studies

Jakob Tarp ^{a,*}, Jan Christian Brønd ^a, Lars Bo Andersen ^{a,b}, Niels Christian Møller ^a,
Karsten Froberg ^a, Anders Grøntved ^a

^a *Research Unit for Exercise Epidemiology, Centre of Research in Childhood Health, Department of Sport Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, Odense 5230, Denmark*

^b *Department of Sports Medicine, Norwegian School of Sport Sciences, Sognsveien 220, Oslo 0806, Norway*

Received 21 February 2016; revised 1 March 2016; accepted 3 March 2016

Available online 1 April 2016

Abstract

The long-term effects of physical activity (PA) or sedentary behavior on cardiovascular health in young people are not well understood. In this study, we use a narrative format to review the evidence for a prospective association with adiposity and other well-established biological cardiovascular risk factors in healthy young people, considering only studies with at least 2 years of follow-up. PA appears to elicit a long-term beneficial effect on adiposity and particularly markers of cardiovascular health. With adiposity, however, a few studies also reported that higher levels of PA were associated with higher levels of adiposity. Time spent sedentary does not appear to be related to adiposity or markers of cardiovascular health independent of PA. We then discuss the uncertainties in the underlying causal chain and consider a number of alternative modeling strategies, which could improve our understanding of the relationship in future studies. Finally, we consider the current methodology for assessing PA and sedentary time.

© 2016 Production and hosting by Elsevier B.V. on behalf of Shanghai University of Sport. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Adiposity; Adolescents; Cardiovascular health; Children; Long-term; Metabolic syndrome score

1. Introduction

Cardiovascular disease (CVD) continues to be the number one cause of death and disability in the world.^{1,2} While CVDs such as coronary heart disease and stroke manifest clinically in middle age or older adulthood, their origins begin much earlier.³ Exposures acting during growth and maturation may exert long-term effects on cardiovascular physiology and have a major impact on the development of CVD. For example, evidence shows that alterations in fetal environment such as exposure to maternal smoking and nutritional status, childhood socioeconomic position and overweight independently predispose to development of CVD in adulthood.^{4–6} Similarly, lack of physical activity (PA) during childhood and youth may

lead to cardiovascular disturbances and progression of atherosclerosis that could contribute to development of CVD in adulthood. Indeed, organizations and governments have identified a population-wide promotion of healthy lifestyle including PA in young people as a key priority for primordial prevention of CVD.⁷ A major advance in population-based studies of the influence of childhood or youth PA on long-term cardiovascular health outcomes has been the application of objective methods to assess PA that prevents bias related to recall and social desirability.⁸ This has also facilitated the possibility to obtain detailed information on frequency, duration, and intensity of PA.

Two earlier reviews, published in 2010 and 2011, respectively, systematically addressed studies on the observational associations between objectively assessed PA and adiposity outcomes.^{9,10} These reviews highlighted the importance of distinguishing between cross-sectional and prospective studies as Jimenez-Pavon and colleagues⁹ found a negative association

Peer review under responsibility of Shanghai University of Sport.

* Corresponding author.

E-mail address: jtarp@health.sdu.dk (J. Tarp).

in 32 of 41 cross-sectional studies (78%), while Wilks and colleagues,¹⁰ who only considered prospective studies, found a negative association in 4 of 10 studies (40%). Because cross-sectional studies have a number of limitations, including inability to infer causality, this inconsistency is important to address by considering recently published experimental and prospective studies. In 2014, Tanaka and colleagues¹¹ published a review on the prospective association between changes in objectively measured sedentary behavior (SED) and measures of adiposity. However, by imposing this restriction the authors were only able to include 3 studies. The review found evidence for a positive association in 1 of the 3 studies. In summary, the previous evidence synthesis did not clearly support a prospective association between PA/SED and adiposity outcomes. In contrast to these reviews on adiposity outcomes, we are aware of no published reviews on the prospective association between PA and biological risk factors in young people.

This narrative review aims to give an overview of the evidence from population-based studies relating objectively assessed PA and SED in childhood or youth with long-term (≥ 2 years) cardiovascular risk factor progression. In addition, we will discuss the current methodological challenges and future direction in the objective assessment of PA in large-scale studies following young people over time.

2. Scope of the review

In our discussion we will consider PA as a behavior separately from SED. This is because a body of literature has identified behaviors such as TV-viewing^{12,13} and total sitting time¹³ to predict all-cause and cardiovascular mortality in adults, independent of other domains of PA. Our discussion will consider observational studies which

- Used an objective measure to quantify whole-day PA (i.e., total activity, light PA (LPA), moderate PA (MPA), moderate-to-vigorous PA (MVPA), or vigorous PA (VPA)) or SED at baseline.
- Included healthy, population-based samples of children and adolescents aged ≤ 18 years at baseline and followed the same individuals for a period of ≥ 2 years.
- Related an exposure to any form of the conventional biological risk factors (recommended for use in CVD risk stratification among asymptomatic adults¹⁴) with the addition of indices of insulin-resistance. We considered all forms of adiposity outcomes.
- Were published after October 29, 2009, as this was the final search date in the review by Wilks and colleagues¹⁰ (applies for PA–adiposity investigations only).

We identified relevant studies from our records by conducting a search on PubMed using combinations of the relevant exposures and outcomes and by going through the reference lists of the identified studies. As there are a greater number of studies on adiposity outcomes than studies on biological risk factors, we will address these in separate paragraphs. Furthermore, we will briefly discuss findings from controlled or randomized controlled intervention studies conducted in a general (young) population.

3. How do PA and SED associate with adiposity and biological risk factors?

3.1. PA and adiposity

We identified a total of 13 published studies which fulfilled our criteria.^{15–27} The duration of follow-up ranged from 2 to 7 years with 9 studies covering ≤ 3 years.^{15–18,22–25,27} The studies included samples aged 4–18 years at baseline. The median (25th–75th quartiles) study size was 554 (315–984). Twelve studies used accelerometry as their exposure variable, while 1 used a combination of accelerometry and heart rate.¹⁶ The outcome variables were more heterogeneous. Nine studies (69%)^{17–20,22–24,26,28} reported a significant association between PA and a measure of adiposity such that a higher level of PA was associated with a lower level of adiposity (negative association). Surprisingly, 3 studies reported significant associations in the opposite direction.^{16,20,23} When examining the relative importance of specific PA intensities, significant negative associations were apparent with LPA in 0 of 3 studies (0%), with MPA in 1 of 4 studies (25%)¹⁷ and with VPA in 2 of 4 studies (50%).^{17,24} Finally, significant negative associations with adiposity were found for MVPA in 7 of 8 studies (87%).^{18–20,23–26} Four studies included SED as a covariate, which generally had a small effect on the estimates and only affected the conclusion in 1 study.²⁵ The choice of outcome measure in adiposity studies appeared of importance as all studies (4 in total) that considered MVPA and used a reference method for assessing adiposity such as DXA or densitometry²⁹ reported a negative association with adiposity.^{18,20,23,26} In contrast, 6 of the MVPA studies used a body mass index (BMI)-based measure with significant negative associations to adiposity found in 3 studies, while 2 studies found significant positive associations. The latter appears to be explained by an increase in muscle or bone tissue as both of these studies also reported significant associations between PA and fat free mass. If PA associates with fat free mass, which is suggested in the literature,^{30,31} future studies should use methods which are accurate enough to separate fat mass from lean mass.

3.2. SED and adiposity

We identified a total of 9 published studies which fulfilled our criteria.^{15,20,21,24–27,32,33} The duration of follow-up ranged from 2 to 7 years with 5 studies having ≤ 2.5 years of follow-up.^{15,24,25,27,32} The studies included youth 4–18 years at baseline. The median (25th–75th quartiles) study size was 554 (403–984). Eight studies used accelerometry, while 1 used a combination of accelerometry and heart rate.³² The measures used for outcomes were more heterogeneous. Two studies (22%)^{25,33} reported a significant association between SED and adiposity; more time spent on SED was associated with a higher level of adiposity. One study found an association in the opposite direction, i.e., higher SED associated with lower adiposity.²⁰ Of the 2 studies reporting a positive association, 1 used a relatively high cut-point to define SED (< 1100 counts/min (CPM)),²⁵ which is very likely also to include time spent on LPA.³⁴ This finding is surprising as none of the 3 studies examining LPA separately from SED found an association and 1 of these even found a negative association.^{16,17,27} Six studies used a

cut-point of <100 CPM to define SED,^{15,21,24,26,27,33} which is comparable to the cut-point of 1.5 METs³⁴ used in the combination study. In order to determine the independent association between SED and adiposity, it is important to adjust for other dimensions of PA. This was performed in 7 studies by adjusting for MVPA. The isolated effect of this adjustment was, however, not possible to infer, as either the studies did not report the estimates that were not adjusted for MVPA or the studies adjusted for other covariates when including the adjustment for activity.

3.3. PA, SED, and biological risk factors

We identified a total of 8 published studies which fulfilled our criteria for PA,^{17,20,35–40} while 1 study used SED.²⁰ The study using SED found no significant associations with any of the biological risk factors before or after adjustment for MVPA.²⁰ The duration of follow-up in the PA studies ranged from 3 to 12 years with 4 studies having ≤ 3 years of follow-up. Included participants were 5–16 years at baseline. The median (25th–75th quartiles) study size was 293 (209–466). Seven studies used accelerometry and 1 used pedometers.⁴⁰ Five studies used a composite risk score^{20,35,37–39} and 6 studies provided results for individual risk factors. Four of 5 studies (80%)^{20,37–39} reported a significant negative association between PA and the composite score, meaning that a higher level of PA was associated with a more favorable cardiovascular profile. Results for the individual risk factors were generally coherent with 4 of 5 studies reporting a significant negative association with insulin resistance,^{20,36,38,40} 0 of 3 with glucose, 2 of 3 with triglyceride^{37,38} and 3 of 4 with blood-pressure.^{17,37,38} Two of 3 studies reported significant positive associations with high-density lipoprotein cholesterol (HDL-C).^{20,38} In contrast to studies on adiposity outcomes, studies on biological risk factors included little reporting of specific PA intensities. Only 3 studies gave results for different intensities.^{17,36,39} Two of these studies demonstrated that VPA, but not lower intensities, was significantly associated with the risk factors^{17,39} while 1 study showed similar associations for total activity and MVPA.³⁶ MVPA was used in 5 studies with 4 reporting significant associations.^{20,36–38}

3.4. Intervention studies

Dobbins et al.⁴¹ published a Cochrane-review in 2013 which included a total of 44 randomized-controlled trials with interventions ranging from 12 weeks to 6 years. They found little evidence for an effect on blood-pressure or mean cholesterol. However, another review found that studies in general showed a significant, but small, effect of PA on HDL-C and triglycerides, but no effect on total cholesterol or low-density lipoprotein cholesterol (LDL-C).⁴² A review synthesizing effects on PA, fitness, and motor skills⁴³ concluded that strong interventions carried out by educated physical education (PE) teachers and including around 5 PE lessons per week are needed to improve these parameters. In the Sogndal school-intervention study, the implementation of the intervention was

carefully controlled and included 60 min PA on all school days, and part of the activity was of high intensity.⁴⁴ They found an improvement in cardiovascular fitness of 15% in the least fit quartile compared with the similar quartile in controls. This suggests that the intervention was intensive and in that study, nearly all the biological risk factors also improved.⁴⁴ The intervention in Sogndal was designed based on findings from the Copenhagen School Child Intervention Study wherein an increase in PE lessons from 2 to 4 lessons a week revealed minimal or no changes in risk factors.⁴⁵ Later, the Childhood Health, Activity, and Motor Performance School Study Denmark (the CHAMPS-study DK) tested a PE dose of 6 h per week and found improvements in a composite cardiovascular risk score.⁴⁶ In Iceland, Hrafnkelsson et al.⁴⁷ conducted an intervention wherein PA was gradually increased from 30 to 60 min per school day over 2 years. They did not find improvements in any risk factors, but the study was quite small with only 3 intervention schools included in the cluster randomization. Moreover, accelerometer measurements showed only 4 min more MVPA in the intervention group in the first year and no difference in the second year when compared to the control group.

4. Perspectives

An important question when addressing the relationship between PA and biological risk factors is whether the associations are independent or mediated by adiposity.^{48,49} This issue is important for understanding the etiology of cardiometabolic risk and is crucial for public health efforts as an independent effect would mean that an increase in PA would reduce CVD risk, even though no change in adiposity was achieved. Cross-sectional literature suggests that adjusting for adiposity attenuates the association slightly, indicating that the effect of PA on biological risk factors is not entirely explained by adiposity.^{50–53} Our review included 3 studies which adjusted their models for changes in adiposity,^{36,54} with the effect of this adjustment only reported in 1.³⁷ Metcalf and colleagues³⁷ reported that adjusting for change in BMI or waist-circumference had virtually no influence on their estimates. Further, 3 studies included an adiposity measure in their composite score,^{35,38,39} which highlights the complexity of this issue. By doing so, adiposity is treated equal to the biological risk factors, but if adiposity is actually the cause of these,⁵⁵ this could drive the associations. A promising methodological advancement is the emergence of mediation analysis and structured equation models.⁵⁶ These use 2-stage regression to decompose associations into, e.g., total, direct, and indirect effects.⁵⁷ With these more formal quantifications of mediation, it may be possible to assess the relative importance of a putative indirect effect in relation to the direct effect. If the indirect effect is small, from a public health perspective, it is of little importance whether adiposity is a mediator or a confounder. However, more work is needed to improve the methods and address issues such as varying degrees of measurement error in exposure/mediator variables and reverse causation, which are not resolved by using these methods.⁵⁸ Hence, these limitations should be considered when interpreting the models.

The reviewed studies considered numerous different models to investigate the prospective associations. A frequently used model was the “determinant”-model. Here, a follow-up outcome or a change in outcome (the two are equivalent when adjusted for baseline outcome) was regressed on a baseline exposure. However, not all studies adjusted for baseline outcome, which is important as the size and direction of change from baseline to follow-up are expected to be associated with the baseline level of the outcome because of regression to the mean and flooring/ceiling effects. The potential impact of not adjusting for baseline outcome is demonstrated in 1 study where the direction of the association was inverted following this adjustment.²⁰ Another frequent model was the “change”-model in which the absolute change in outcome over time was modeled on the absolute change in exposure. In this model, bias may arise by not adjusting for baseline values of both exposure and outcome. In the reviewed studies, only one considered both in their models of absolute change.⁴⁰ As some studies adjusted for baseline exposure, some adjusted for baseline outcome and some adjusted for neither, this may be the cause of some of the heterogeneity in the study results. The change-model, however, has been criticized for being a “masked” cross-sectional study as it could be the outcome which changed first,¹⁰ again making inference of the causal pathway difficult. To better establish the temporal relationship between PA and cardiovascular risk factors, future studies could attempt to collect (and analyze) repeated measurements of exposures and outcome during follow-up, which enables the possibility to specify a time lag between PA and the change in risk factor. Further, with repeated measurements, a structural equation modeling approach could be used to assess the importance of early life exposure versus change in that exposure over time, while taking into account the correlations between time-points. Interpretation of results was further challenged in several studies as an isotemporal substitution model (ISM)⁵⁹ was used, but only one mentioned this interpretation in their reporting.³² An ISM may arise when multiple intensity domains and total wear time is included in the same model. The interpretation of an ISM would be the effect of changing a unit of time of, e.g., LPA with the same unit of time of MVPA. This is not the same as that of the more frequently used partition model.⁵⁹ We will not favor one model over the other but will recommend that future studies clearly state their models and their interpretation of these. Finally, even though 4 of our reviewed studies considered some form of adjustment for dietary factors, finer control of measures of diet quality and quantity would also help improve future observational studies.

The use of accelerometry in the assessment of PA and SED in prospective studies is encouraged by its feasibility and higher validity than self-report.⁸ Nevertheless several shortcomings with accelerometers have been identified and include both technical and reactivity issues and controversies regarding how best to define non-wear and various intensity cutoff-points.⁶⁰ The technical shortcoming of the accelerometer is the misrepresentation of important health-related activities like cycling,⁶¹ strength training, static exercise, aquatic activities and the intensity leveling-off with increased running speed.^{62,63}

Misrepresentation of beneficial PAs with moderate and vigorous intensity could explain some of the diversity of the prospective PA and adiposity associations reported. The assessment of SED using the <100 CPM cutoff point has been shown to have an acceptable sensitivity (71.7%) and specificity (67.8%) to estimate sitting time, with no optimal cutoff points for sitting plus standing.⁶⁴ Thus, the SED estimation in the study by Basterfield and colleagues²⁵ included activities with higher intensity than standing and suggests a measure that is far from the concept of SED defined by the posture allocation of sitting. Most studies investigating the association of SED with adiposity did not show any significant association, and this could partly be explained by the sensitivity and specificity of the cutoff point. The definition of the non-wear is also problematic. The definition used across the selected studies is quite different, and it has been shown that various non-wear definitions generate substantially different results with a significant impact on the assessment of SED.⁶⁵ The comparison across different studies seems to require a consensus and harmonization on what definitions of cutoff points should be used and non-wear handled. Additionally, more research is needed to investigate the shortcomings of the accelerometer and how new solutions can be feasibly applied in large-scale studies.

In summary, a beneficial effect of PA on long-term change in adiposity in young people was generally observed, but some studies found the opposite effect. This may be explained by the marker of adiposity used. In observational as well as intervention studies among children or adolescents, PA had a protective association with established biological risk factors. These findings suggest that providing the right opportunities for children and adolescents to engage in PA is important for primordial prevention of CVD. Sedentary behavior did not appear to increase long-term adiposity independent of other activity domains and almost no evidence was available with biological risk factors for this exposure. Future studies should attempt to better decompose the causal chain between PA and CVD risk factors, and there is a need for improved reporting and interpretation of statistical analyses, harmonization of data-reduction and development of methods to distinguish between different SED behaviors.

Authors' contributions

JT identified relevant studies, extracted the information, and drafted the manuscript; JCB, LBA, NCM, KF, and AG identified relevant studies and drafted the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

Competing interests

None of the authors declare competing financial interests.

References

1. GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries,

- 1990–2013: quantifying the epidemiological transition. *Lancet* 2015; **386**:2145–91.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**:2095–128.
 3. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999; **340**:115–26.
 4. Cohen S, Janicki-Deverts D, Chen E, Matthews KA. Childhood socioeconomic status and adult health. *Ann NY Acad Sci* 2010; **1186**:37–55.
 5. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med* 2007; **357**:2329–37.
 6. Godfrey KM, Barker DJ. Fetal programming and adult health. *Public Health Nutr* 2001; **4**:611–24.
 7. Kraus WE, Bittner V, Appel L, Blair SN, Church T, Despres JP, et al. The National Physical Activity Plan: a call to action from the American Heart Association: a science advisory from the American Heart Association. *Circulation* 2015; **131**:1932–40.
 8. Warren JM, Ekelund U, Besson H, Mezzani A, Geladas N, Vanhees L, et al. Assessment of physical activity—a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010; **17**:127–39.
 9. Jimenez-Pavon D, Kelly J, Reilly JJ. Associations between objectively measured habitual physical activity and adiposity in children and adolescents: systematic review. *Int J Pediatr Obes* 2010; **5**:3–18.
 10. Wilks DC, Besson H, Lindroos AK, Ekelund U. Objectively measured physical activity and obesity prevention in children, adolescents and adults: a systematic review of prospective studies. *Obes Rev* 2011; **12**: e119–29.
 11. Tanaka C, Reilly JJ, Huang WY. Longitudinal changes in objectively measured sedentary behaviour and their relationship with adiposity in children and adolescents: systematic review and evidence appraisal. *Obes Rev* 2014; **15**:791–803.
 12. Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *JAMA* 2011; **305**:2448–55.
 13. Thorp AA, Owen N, Neuhaus M, Dunstan DW. Sedentary behaviors and subsequent health outcomes in adults: a systematic review of longitudinal studies, 1996–2011. *Am J Prev Med* 2011; **41**:207–15.
 14. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010; **122**:e584–636.
 15. 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**:704–12.
 16. Collings PJ, Wijndaele K, Corder K, Westgate K, Ridgway CL, Sharp SJ, et al. Objectively measured physical activity and longitudinal changes in adolescent body fatness: an observational cohort study. *Pediatr Obes* 2016; **11**:107–14.
 17. Carson V, Rinaldi RL, Torrance B, Maximova K, Ball GD, Majumdar SR, et al. Vigorous physical activity and longitudinal associations with cardiometabolic risk factors in youth. *Int J Obes (Lond)* 2014; **38**:16–21.
 18. Metcalf BS, Hosking J, Jeffery AN, Voss LD, Henley W, Wilkin TJ. Fatness leads to inactivity, but inactivity does not lead to fatness: a longitudinal study in children (EarlyBird 45). *Arch Dis Child* 2011; **96**: 942–7.
 19. Mitchell JA, Pate RR, Espana-Romero V, O’Neill JR, Dowda M, Nader PR. Moderate-to-vigorous physical activity is associated with decreases in body mass index from ages 9 to 15 years. *Obesity (Silver Spring)* 2013; **21**:E280–93.
 20. Stamatakis E, Coombs N, Tiling K, Mattocks C, Cooper A, Hardy LL, et al. Sedentary time in late childhood and cardiometabolic risk in adolescence. *Pediatrics* 2015; **135**:e1432–41.
 21. van Sluijs EM, Sharp SJ, Ambrosini GL, Cassidy A, Griffin SJ, Ekelund U. The independent prospective associations of activity intensity and dietary energy density with adiposity in young adolescents. *Br J Nutr* 2016; **115**: 921–9.
 22. White J, Jago R. Prospective associations between physical activity and obesity among adolescent girls: racial differences and implications for prevention. *Arch Pediatr Adolesc Med* 2012; **166**:522–7.
 23. Jauregui A, Villalpando S, Rangel-Baltazar E, Lara-Zamudio YA, Castillo-Garcia MM. Physical activity and fat mass gain in Mexican school-age children: a cohort study. *BMC Pediatr* 2012; **12**:109. doi: 10.1186/1471-2431-12-109
 24. Latt E, Maestu J, Ortega FB, Raask T, Jurimae T, Jurimae J. Vigorous physical activity rather than sedentary behaviour predicts overweight and obesity in pubertal boys: a 2-year follow-up study. *Scand J Public Health* 2015; **43**:276–82.
 25. Basterfield L, Pearce MS, Adamson AJ, Frary JK, Parkinson KN, Wright CM, et al. Physical activity, sedentary behavior, and adiposity in English children. *Am J Prev Med* 2012; **42**:445–51.
 26. Kwon S, Burns TL, Levy SM, Janz KF. Which contributes more to childhood adiposity—high levels of sedentarism or low levels of moderate-through-vigorous physical activity? The Iowa Bone Development Study. *J Pediatr* 2013; **162**:1169–74.
 27. Treuth MS, Baggett CD, Pratt CA, Going SB, Elder JP, Charneco EY, et al. A longitudinal study of sedentary behavior and overweight in adolescent girls. *Obesity (Silver Spring)* 2009; **17**:1003–8.
 28. White IR, Carpenter J, Horton NJ. Including all individuals is not enough: lessons for intention-to-treat analysis. *Clin Trials* 2012; **9**:396–407.
 29. Hu F. *Obesity epidemiology*. New York, NY: Oxford University Press; 2008.
 30. Strong WB, Malina RM, Blimkie CJR, Daniels SR, Dishman RK, Gutin B, et al. Evidence based physical activity for school-age youth. *J Pediatr* 2005; **146**:732–7.
 31. Hughes JM, Novotny SA, Wetzsteon RJ, Petit MA. Lessons learned from school-based skeletal loading intervention trials: putting research into practice. *Med Sport Sci* 2007; **51**:137–58.
 32. Collings PJ, Wijndaele K, Corder K, Westgate K, Ridgway CL, Sharp SJ, et al. Prospective associations between sedentary time, sleep duration and adiposity in adolescents. *Sleep Med* 2015; **16**:717–22.
 33. Mitchell JA, Pate RR, Beets MW, Nader PR. Time spent in sedentary behavior and changes in childhood BMI: a longitudinal study from ages 9 to 15 years. *Int J Obes (Lond)* 2013; **37**:54–60.
 34. Trost SG, Loprinzi PD, Moore R, Pfeiffer KA. Comparison of accelerometer cut points for predicting activity intensity in youth. *Med Sci Sports Exerc* 2011; **43**:1360–8.
 35. Andersen LB, Bugge A, Dencker M, Eiberg S, El-Naaman B. The association between physical activity, physical fitness and development of metabolic disorders. *Int J Pediatr Obes* 2011; **6**(Suppl. 1):S29–34.
 36. Jago R, Wedderkopp N, Kristensen PL, Moller NC, Andersen LB, Cooper AR, et al. Six-year change in youth physical activity and effect on fasting insulin and HOMA-IR. *Am J Prev Med* 2008; **35**:554–60.
 37. Metcalf BS, Voss LD, Hosking J, Jeffery AN, Wilkin TJ. Physical activity at the government-recommended level and obesity-related health outcomes: a longitudinal study (Early Bird 37). *Arch Dis Child* 2008; **93**:772–7.
 38. Ried-Larsen M, Grontved A, Kristensen PL, Froberg K, Andersen LB. Moderate-and-vigorous physical activity from adolescence to adulthood and subclinical atherosclerosis in adulthood: prospective observations from the European Youth Heart Study. *Br J Sports Med* 2015; **49**:107–12.
 39. Ried-Larsen M, Grontved A, Moller NC, Larsen KT, Froberg K, Andersen LB. Associations between objectively measured physical activity intensity in childhood and measures of subclinical cardiovascular disease in adolescence: prospective observations from the European Youth Heart Study. *Br J Sports Med* 2014; **48**:1502–7.
 40. Telford RD, Cunningham RB, Shaw JE, Dunstan DW, Lafferty AR, Reynolds GJ, et al. Contrasting longitudinal and cross-sectional relationships between insulin resistance and percentage of body fat, fitness, and physical activity in children—the LOOK study. *Pediatr Diabetes* 2009; **10**:500–7.

41. Dobbins M, Husson H, DeCorby K, LaRocca RL. School-based physical activity programs for promoting physical activity and fitness in children and adolescents aged 6 to 18. *Cochrane Database Syst Rev* 2013;2:CD007651. doi: 10.1002/14651858.CD007651.pub2
42. Andersen LB, Riddoch C, Kriemler S, Hills AP. Physical activity and cardiovascular risk factors in children. *Br J Sports Med* 2011;45:871–6.
43. Kriemler S, Meyer U, Martin E, van Sluijs EM, Andersen LB, Martin BW. Effect of school-based interventions on physical activity and fitness in children and adolescents: a review of reviews and systematic update. *Br J Sports Med* 2011;45:923–30.
44. Resaland GK, Anderssen SA, Holme IM, Mamen A, Andersen LB. Effects of a 2-year school-based daily physical activity intervention on cardiovascular disease risk factors: the Sogndal school-intervention study. *Scand J Med Sci Sports* 2011;21:e122–31.
45. Bugge A, El-Naaman B, Dencker M, Froberg K, Holme IM, McMurray RG, et al. Effects of a three-year intervention: the Copenhagen School Child Intervention Study. *Med Sci Sports Exerc* 2012;44:1310–7.
46. Klakk H, Andersen LB, Heidemann M, Moller NC, Wedderkopp N. Six physical education lessons a week can reduce cardiovascular risk in school children aged 6–13 years: a longitudinal study. *Scand J Public Health* 2014;42:128–36.
47. Hrafnkelsson H, Magnusson KT, Thorsdottir I, Johannsson E, Sigurdsson EL. Result of school-based intervention on cardiovascular risk factors. *Scand J Prim Health Care* 2014;32:149–55.
48. Steele RM, Brage S, Corder K, Wareham NJ, Ekelund U. Physical activity, cardiorespiratory fitness, and the metabolic syndrome in youth. *J Appl Physiol* 2008;105:342–51.
49. Ekelund U, Ward HA, Norat T, Luan J, May AM, Weiderpass E, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC). *Am J Clin Nutr* 2015;101:613–21.
50. Brage S, Wedderkopp N, Ekelund U, Franks PW, Wareham NJ, Andersen LB, et al. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). *Diabetes Care* 2004;27:2141–8.
51. Brage S, Wedderkopp N, Ekelund U, Franks PW, Wareham NJ, Andersen LB, et al. Objectively measured physical activity correlates with indices of insulin resistance in Danish children. The European Youth Heart Study (EYHS). *Int J Obes Relat Metab Disord* 2004;28:1503–8.
52. Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European youth heart study. *Diabetologia* 2007;50:1832–40.
53. Owen CG, Nightingale CM, Rudnicka AR, Sattar N, Cook DG, Ekelund U, et al. Physical activity, obesity and cardiometabolic risk factors in 9- to 10-year-old UK children of white European, South Asian and black African-Caribbean origin: the Child Heart and Health Study in England (CHASE). *Diabetologia* 2010;53:1620–30.
54. Evenson KR, Neelon B, Ball SC, Vaughn A, Ward DS. Validity and reliability of a school travel survey. *J Phys Act Health* 2008;5:S1–15.
55. Goodman E, Dolan LM, Morrison JA, Daniels SR. Factor analysis of clustered cardiovascular risks in adolescence: obesity is the predominant correlate of risk among youth. *Circulation* 2005;111:1970–7.
56. Hayes AF. Beyond Baron and Kenny: statistical mediation analysis in the new millennium. *Commun Monogr* 2009;76:408–20.
57. Hildebrand M, Kolle E, Hansen BH, Collings PJ, Wijndaele K, Kordas K, et al. Association between birth weight and objectively measured sedentary time is mediated by central adiposity: data in 10,793 youth from the International Children's Accelerometry Database. *Am J Clin Nutr* 2015;101:983–90.
58. VanderWeele TJ. *Explanation in causal inference: methods for mediation and interaction*. New York, NY: Oxford University Press; 2015.
59. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol* 2009;170:519–27.
60. Pedisic Z, Bauman A. Accelerometer-based measures in physical activity surveillance: current practices and issues. *Br J Sports Med* 2015;49:219–23.
61. Tarp J, Andersen LB, Ostergaard L. Quantification of underestimation of physical activity during cycling to school when using accelerometry. *J Phys Act Health* 2015;12:701–7.
62. Brage S, Wedderkopp N, Franks PW, Andersen LB, Froberg K. Reexamination of validity and reliability of the CSA monitor in walking and running. *Med Sci Sports Exerc* 2003;35:1447–54.
63. John D, Miller R, Kozey-Keadle S, Caldwell G, Freedson P. Biomechanical examination of the 'plateau phenomenon' in ActiGraph vertical activity counts. *Physiol Meas* 2012;33:219–30.
64. Ridgers ND, Salmon J, Ridley K, O'Connell E, Arundell L, Timperio A. Agreement between activPAL and ActiGraph for assessing children's sedentary time. *Int J Behav Nutr Phys Act* 2012;9:15.
65. Winkler EA, Gardiner PA, Clark BK, Matthews CE, Owen N, Healy GN. Identifying sedentary time using automated estimates of accelerometer wear time. *Br J Sports Med* 2012;46:436–42.