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Physical activity is related to insulin sensitivity in children and adolescents, independent of adiposity: a review of the literature

Laura J. Berman^{1,*}, Marc J. Weigensberg², and Donna Spruijt-Metz¹

¹Institute for Health Promotion and Disease Prevention Research, University of Southern California Keck School of Medicine, Los Angeles, CA USA

²Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA USA

Abstract

In adults, there is evidence that physical activity effectively improves insulin sensitivity regardless of adiposity. Whether this is also the case in children and adolescents has been less clear. Whether this is also the case in children and adolescents is less clear. Clarifying this matter may help to identify the best outcomes to target in exercise programs for these age groups, where changes in adiposity may not always be desirable or realistic. A review of the literature was conducted on studies that examined the relationships of physical activity, cardiorespiratory fitness and strength with insulin sensitivity independent of adiposity in children and adolescents. Experimental (intervention) and correlational (longitudinal and cross-sectional) studies on participants ages 18 and younger were identified. A total of 42 studies were included in this review. Sample sizes in the studies ranged from 14 to 4,955 participants, with individual ages ranging from 5 to 19 years. A significant relationship with SI existed in 78% of studies on physical activity, 69% of studies on cardiorespiratory fitness and 66% of studies on strength. In studies that examined both physical activity and cardiorespiratory fitness concurrently, evidence suggests that they are both correlated with insulin sensitivity independent of adiposity, especially when physical activity is at higher intensities. However the strength of this relationship might be influenced by study design, measurement techniques and participant characteristics. This is the first review of its type to take research design into account, and to examine study outcomes according to participant ethnicity, gender, age, pubertal status and weight status.

Introduction

Insulin sensitivity and the role of physical activity in children and adolescents

The decline of physical activity (PA) and insulin sensitivity (SI) during puberty has been well documented [1–3]. Severe, prolonged declines in SI can ultimately lead to type 2 diabetes, which may also increase the risk for hypertension and dyslipidemia [4]. This decline in SI from childhood to adolescence is more severe in ethnic minorities [5] and is exacerbated by adiposity [6]. The past few decades have been marked by an alarming rise in

*Corresponding author: Laura Berman, MPH, USC Keck School of Medicine, 2001 N. Soto Street, MC 9239, Los Angeles, CA 90089, phone 626 665-1620, lberman32@gmail.com.

Conflicts of Interest

None declared.

Ethics

This review includes evidence from previous publications only and does not include any empirical research findings or participant involvement accrued specifically for this review. Therefore, no institutional or national ethical committee has explicitly approved this manuscript. However, all studies involved in this review were approved by their own institutional review boards.

the rates of pediatric overweight, and obesity [7]. In adults, PA has been shown to reduce levels of obesity [8] and improve SI [9, 10] regardless of initial levels of adiposity [11–17]. However, evidence for a relationship that exists independent of adiposity has been less clear in children and adolescents [12, 18–20].

As SI is controlled by both muscle tissue and adipose tissue, PA can also affect and improve SI in adults, children and adolescents through changes in body composition [20, 21]. There are also shorter-term benefits of PA on SI through immediate improvements in substrate utilization [22–24]. However, the specific mechanisms may be different in pediatric versus adult populations [21], as children rely more heavily on fats for energy, whereas adults rely more on carbohydrates [25–27]. If short-term differences in SI response to PA between adults and children exist, longer-term differences in biological responses to PA are also possible.

Relationships and definitions of PA, cardiorespiratory fitness, and strength

Physical activity, cardiorespiratory fitness (CRF) and strength are related concepts that differ physiologically and may each have a unique relationship with SI. It is therefore useful to address them separately. Physical activity is bodily movement that is produced by the contraction of skeletal muscle and results in energy expenditure [28]. One component of overall physical fitness is CRF, which is defined as the ability of the circulatory and respiratory systems to supply fuel during sustained PA and to eliminate fatigue products after supplying fuel [29]. Though significant, the association between PA and CRF in children and adolescents is moderate at best [9, 30, 31] and there is evidence showing that CRF and PA may each be independently associated with SI in these younger ages [9, 32]. This review uses the term PA to refer to all forms of physical activity, including exercise. Exercise is defined as a subset of PA that is planned, structured, and repetitive with an objective to improve or maintain of physical fitness [28], and is considered to be one of many categories of PA. As the term PA is a more inclusive and commonly used and understood in the literature than exercise, the term PA will be used in the remainder of this review. The main independent pathway between PA and SI is likely functioning through muscle, as it is known to be the primary site of insulin-stimulated glucose uptake [33]. Muscle strength has been defined as the amount of external force that a muscle can exert [29]. Strength training, which increases muscle mass and total strength, has also been shown to improve SI in adult populations [34].

Purpose of this review

Uncovering whether PA, CRF and strength can help reduce children's and adolescents' risk for insulin resistance, regardless of adiposity, could have significant implications for setting the most realistic and achievable goals for exercise programs in these age groups and the importance of activity for all different body types. Shaibi et al. examined the relationships of PA and CRF with SI independent of adiposity in their 2008 review, with mixed findings and a brief mention of the potential role of strength training [20]. As more studies have been published on relationships of PA, CRF, strength and SI in pediatric populations since then, a larger knowledge base has formed. This review provides an updated and comprehensive assessment of the literature that takes into account differences in measures, study designs and participant characteristics that may influence the observed relationships of PA, CRF, strength and SI in children and adolescents.

Methods

Measurement Techniques Used by the Literature in this Review

The mixed findings concerning the influence of PA, CRF and strength on SI independent of adiposity in pediatric populations might, in part, be due to the wide range of measurement methods that are used for SI as well as PA, CRF, strength and adiposity. Therefore, the measurement techniques used by the studies in this review are outlined below, and each study's techniques are reflected in the Tables.

SI—There are several ways of measuring SI in children and adolescents, each varying in cost, invasiveness and accuracy. Sometimes referred to as the gold standard of SI measurement, the hyperinsulinemic-euglycemic clamp creates an insulin-stimulated condition in which glucose uptake can be directly measured and is used to calculate the rate of glucose utilization per kilogram of body mass [35]. The frequently sampled intravenous glucose tolerance test (FSIVGTT), often used in concert with the Minimal Model (MinMod) analyses, and the oral glucose tolerance test (OGTT) are also highly regarded techniques that are well correlated with the clamp method [36–38].

Fasting blood values are also commonly used, as these measures are less invasive and have a lower burden on the participant and lower cost to the study than the clamp, FSIVGTT or OGTT methods. Several indirect measures of insulin dynamics have been developed using fasting insulin (FI) and fasting glucose (FG) values such as the FG/FI ratio, the homeostatic model assessment (HOMA), which is a measure of insulin resistance (IR), the quantitative SI check index (QUICKI), and the Insulin Sensitivity Index (ISI) [36, 39]. However fasting measures, especially the FG/FI ratio and QUICKI, are not strongly correlated with clamp [40], particularly not in obese children and adolescents, and especially not in obese girls [41, 42].

PA—The studies in this review measured PA either objectively through accelerometry, pedometry or doubly labeled water, and/or subjectively through self-report questionnaires or interviews. Of the objective methods, accelerometry is considered more accurate than pedometry [42, 43], provides a measurement of the intensity and duration of activity, and is very commonly used in PA and exercise research. Doubly labeled water provides the most accurate objective measurement of energy expenditure [44], but is also the most expensive method. Subjective measures are often the least reliable and may overestimate PA, especially in children and adolescents [2, 43, 45]. In several of the PA interventions, direct, on-site monitoring of participants by study staff was used to ensure adherence to intervention protocols, and the records of this direct monitoring were utilized as a measure of PA [18, 46–52].

CRF—In the studies in this review, CRF was most often assessed through a measure of maximal oxygen uptake, VO_2max , during PA and less commonly peak oxygen uptake, VO_2peak , which is a similar but generally less reliable measure [53]. A few studies used sub-maximal oxygen uptake at a heart rate of 170 beats per minute (VO_2170). VO_2170 is sometimes substituted for VO_2max because reaching a maximal heart rate may be difficult for some participants. One study used peak heart rate (peak HR) during PA to measure CRF, though this measure has been found to moderately correlate with VO_2 measures [54]. Three studies captured CRF through measuring physical working capacity (PWC), a measure of maximal power output (W/kg) at a specified heart rate. PWC has been validated in children [55] and is well correlated with VO_2max [32]. Measuring PWC relative to fat mass (W/kgFM) and fat free mass (W/kgFFM) is sometimes used as an attempt to control for body composition, though retrospectively adjusting for body composition in the analysis phase

has been shown to be more accurate [56]. Two of the 3 studies measured PWC at a heart rate 185 beats per minute and one study measured PWC at a heart rate of 170 beats per minute.

A handful of studies measured CRF by the 20-meter shuttle run, which measures the maximum number of 20 meter laps that can be run at a minimum specified pace [10, 57] and has been shown to be a reliable indicator of CRF in children and adolescents [58]. One study used the Queens College step test, which measures CRF using the maximum heart rates recorded during the second and third minutes of a vigorous stepping exercise.

Strength—There are many ways to measure strength, and technique can vary by muscle [59]. Upper- and lower-body strength are often assessed through maximal strength testing, as was used by the studies in this review. This is generally done by measuring a repetition maximum (RM) in the bench press and leg press, with the squat and double arm curl sometimes being measured as well [60]. One study measured the maximum number of extensions, curl, and lifts at certain weight loads for the chest, triceps, biceps, quadriceps and hamstrings, which is helpful in calculating more muscle-specific strengths [61]. Measurement of isometric elbow and leg flexion are also sometimes used [62].

Adiposity—Studies in this review measured adiposity either directly through dual X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), anthropometric methods such as BMI, BMI percentile, BMI z-score, waist circumference, hip circumference, or skinfold thickness, or a combination of methods. Compared to DEXA, anthropometric methods are generally less invasive, easier and less expensive, but only provide surrogate markers of total fat or body fat percentage and cannot estimate lean mass [63, 64]. One study utilized bioelectrical impedance and skinfolds to measure body composition. Bioelectrical impedance analysis is a generally reliable alternative to DEXA for measuring body fat, especially in participants who fall within a normal fat range [65].

Literature search

The following subsets of words were used in various combinations to conduct a literature search of Pubmed, Ovid Medline, Google Scholar, Cochrane Reviews, and from references cited from gathered articles (1970 to Oct. 5, 2010). The following Mesh terms were searched for: 1) physical activity, exercise, aerobic exercise, (2) fitness (3) strength training, resistance training, (4) insulin, insulin resistance, glucose, and (5) youth, child, adolescents, adolescence, and puberty. To address any possible gaps in the search, the following (non-Mesh) words were also used: cardiorespiratory fitness, strength, insulin sensitivity, teen, and pubertal. Relevant publications cited in the resulting articles were also gathered.

Inclusion criteria

Studies that met the following criteria were eligible for inclusion in the review: studies that measured (1) PA, CRF, or strength, (2) SI or insulin resistance (IR), (3) and adiposity or BMI; studies that assessed the relationship(s) between (1) and (2), independent of (3); studies whose participants average age was 18 years or younger at baseline; studies that were an empirically based study of any design; and studies that were published in peer-reviewed journals in English. Studies on only type 1 diabetic youth were excluded. Any article that used the same participant database as another previously published article was only retained if it added novel findings.

Data presentation

Tables 1, 2 and 3 summarize each study's findings of the associations between PA (Table 1), CRF (Table 2) and strength (Table 3) with SI. Basic study designs, measurement techniques, and participant characteristics are also shown in the Tables. Associations were regarded as

significant when the reported p-value was 0.05. The majority of studies did not provide specific r-values for the associations of interest. Additionally, since studies measured the relevant variables with varying methods and often used different statistical analyses, comparing correlation coefficients between studies would not be fruitful. Therefore, a qualitative review was conducted rather than a meta-analysis.

In order to more accurately distinguish each measure's true and independent relationship with SI, many studies measured both PA and CRF and analyzed both variables at once (indicated with an asterisk next to the study name). In the interventions, changes in CRF were considered the result of increases in PA. Race/ethnicity was divided into "African American," "Caucasian," "Hispanic," or "Other." "Other" included studies with participants of two or more ethnicities that were not separately analyzed, that did not state the participants' ethnicities, or that were in participants of a different ethnic group, such as Asian or Native American. Most studies included participants of more than one ethnicity, gender, age group, weight status, body composition, or baseline SI. Any stated differences in the relationship of interest between such variables are described in the "Notes" sections.

Results

A total of 42 studies are included in this review. Sample sizes in the studies ranged from 14 to 4,955 participants. Participant ages ranged from 5 to 19 years. PA and CRF will first be discussed independently and then compared against each other to better assess their relative influences on SI. Results for strength-based studies then follow.

PA

The majority of studies (78%) found significant relationships between SI and PA. Five of the 8 (63%) of the interventions, 3/4 (75%) of the longitudinal studies and 15/17 (88%) of cross-sectional studies found PA to be significantly related to insulin indices independent of adiposity. The intervention and longitudinal studies that did not find significant associations were in participants of varying ethnicities, genders, ages and weight status, and no common characteristics could be identified [46, 47, 50, 66].

Gender and Age—The majority of studies did not provide analyses by gender. Of those that did, the evidence was unclear as to whether the relationship between PA and SI differed in boys versus girls. Two studies found a significant relationship in boys only [57, 67], while 2 found it to be significant in girls only [68, 69]. Two of 4 (50%) studies in only females found there to be an independent relationship between PA and insulin indices, and there were no studies exclusively in males [48, 50, 51, 70].

Age—No differences in the relationship between PA and SI independent of adiposity by age or gender were discerned.

Weight status—In the studies that analyzed results by weight status, there was stronger evidence of significant relationships between PA and insulin indices in overweight participants as compared to their lean or obese counterparts [51, 52, 71]. In 19/22 (86%) of studies whose participants were normal weight or whose weight was not stated, a significant independent association between PA and SI was found. This was true for the one (100%) study in overweight participants and 3/3 (100%) of the studies with obese participants. Zero out of 2 (0%) of studies that combined overweight and obese participants found a significant relationship.

Ethnicity—There was a significant independent relationship between PA and SI in 6/7 (86%) of the studies in Caucasians, 3/3 (100%) in African Americans and 3/5 (60%) in Hispanics. Results from studies that examined several different ethnicities were mixed. While one cross-sectional study found the relationship to exist in African Americans but not in Caucasians or Hispanics [9], two other studies found no ethnic differences in their results [69, 72].

CRF

A majority of studies (69%) also found significant relationships between CRF and insulin indices independent of adiposity. Of the 3 interventions in this review that evaluated whether improvements in CRF were independently associated with the improvements in SI, only 1 found an independent association between changes in CRF and SI [47] while the 2 others did not [18, 46]. However, the 2 longitudinal studies of CRF and SI both found significant independent relationships [57, 73].

Gender—The association between CRF and SI may be different in girls versus boys. Four studies that divided results by gender found a significant association in boys only [57, 67, 74, 75], while none were found to exist only in girls. [75]. Three studies found the relationship to exist in both genders, but the relationship was stronger in boys [73, 74, 76].

Age—Overall evidence of an independent association between CRF and SI did not seem to differ by age between or within studies. Two studies found that the relationship between CRF and SI existed in a large range of ages [32, 57].

Weight status—17/19 (90%) of studies whose participants were normal weight or whose weight was not stated found a significant independent association between CRF and SI. This was true for 0/2 (0%) of the studies in overweight participants and 3/5 (60%) studies in obese participants. One study found the independent association between CRF and insulin indices to be stronger in its leaner participants [74], while 2 others only found a significant relationship to exist only in their heavier participants [75, 77].

Ethnicity—Of the 7 studies that analyzed the relationship between CRF and insulin indices in Caucasians, 5 (71%) were found to be significant. This was true for 2/3 (67%) of the analyses in African Americans, 1/3 (33%) of the analyses in Hispanics, and 12/16 (75%) of the analyses in any study classified as “Other.”

Pubertal stage—Too few studies measured pubertal status to comment on its role in the independent relationship between CRF and SI.

PA and/or CRF

Of the 8 interventions in Tables 1 and 2, 6 (75%) demonstrated that a youth-based PA program led to significant improvements in insulin action that were independently and positively associated with changes in PA and/or CRF. Significant associations of PA and/or CRF with SI were found in 4 of the 5 (80%) longitudinal studies, and 22 of the 27 (82%) cross-sectional studies found at least one independent relationship between PA and/or CRF and insulin indices.

PA versus CRF

Of the 14 studies (intervention, longitudinal or cross-sectional combined) that only examined the relationship of PA with insulin indices, 12 (86%) found a significant positive association that existed independent of adiposity. The same was true for 10 out of 13 (77%)

of the studies that only examined CRF. Surprisingly, one of these studies found CRF to be negatively associated with SI [72].

Of the 13 studies that analyzed the associations of both PA and CRF with insulin indices in the same model, both PA and CRF were found to be independently related to insulin indices in 6 of them. Three found only PA, 2 found only CRF and 2 found neither to be independently related to insulin indices [46, 56].

PA by duration and intensity

There are 10 studies in this review that analyzed the association of PA by intensity level with SI [2, 9, 10, 32, 67, 72, 78–81]. All 10 (100%) found vigorous PA to be independently associated with insulin indices. Moderate to vigorous PA was independently associated with insulin indices in 5/6 (83%) studies, moderate PA in 2/4 (50%) studies, light PA in 1/3 (33%) studies and total PA in 6/9 (67%) studies.

Strength

Table 3 includes 3 interventions that evaluated whether increases in strength were associated with improved insulin action independent of adiposity [50, 61, 82]. All of the studies were in overweight or obese Hispanic adolescents. Two of the 3 (66%) found that improved strength led to improved insulin action independent of changes in adiposity [61, 82].

Discussion

An important implication of this review is that PA may improve or maintain healthy SI in children and adolescents independent of adiposity status or changes in adiposity. This may prove especially helpful since a focus on changes in adiposity through weight loss may not be an age-appropriate or feasible strategy for improving SI in all children and adolescents.

In this review of 42 studies, the majority of the studies that examined the association of PA, CRF or strength with SI found significant relationships independent of adiposity. Studies that provided correlation coefficients found significant positive correlations between PA or CRF and insulin indices to be small to moderate [32, 67, 69, 74, 77, 81, 83]. Some important baseline characteristics, such as insulin resistance, were not commonly measured or analyzed in the studies, though they might have confounding effects on the relationships between PA, CRF, strength and SI. These factors are discussed in the “Other possible moderators” section of the discussion.

PA

Overall, the relationship between PA and SI independent of adiposity existed in participants of all different ages and ethnicities, with evidence being too limited to fairly comment on differences by gender. When looking at studies that analyzed their results by weight status, findings were strongest in the overweight participants. One possibility is that confounding of baseline SI and PA levels by weight status may be impacting results and making them less consistent [2]. Overweight children and adolescents generally have SI profiles that are worse than those of normal weight, but better than those who are obese, who may have had SI profiles that were more severe and no longer able to react as properly to PA. Lean participants are already the most insulin sensitive group and may have simply had the smallest range for further increases in sensitivity [84]. In accordance with our findings on PA by intensity, another explanation may be that obese children and adolescents, who have the lowest rates of vigorous PA [85], are not reaching activity levels high enough to achieve PA’s independent association with SI. It should also be noted that all studies controlled for BMI or adiposity to assess the independent association between PA and SI. As weight status

is highly correlated with these measures, there may be difficulty in disentangling relationships by weight status.

CRF

Study results for CRF were not as consistent across different baseline characteristics as those for PA. An independent relationship between CRF and SI seemed to exist at a similar frequency in all ages and results by weight status were inconclusive, possibly due to limited evidence.

Overall evidence suggests that the relationship between CRF and SI independent of adiposity is more likely to be present in boys than in girls. In addition to having lower SI [86, 87] and being less active [67, 88, 89], girls also tend to have lower CRF [67] and a higher percentage body fat [90]. Several of these differences may be playing a role, and more evidence is needed to examine the mechanisms behind these discrepancies or elucidate the true relationship between CRF and SI independent of these factors.

Results from this review showed an independent relationship between CRF and SI in the majority of studies on Caucasians and African Americans, but not Hispanics. Ethnicity is a significant predictor of both CRF and SI in children and adolescents [67, 72], with Caucasians having both the highest SI and CRF values [84]. Despite the fact that African American children and adolescents have highest levels of PA of the three groups, they have the lowest CRF [9, 72, 91]. They are also less insulin sensitive than Caucasians, even after controlling for differences in body composition [1]. Despite these differences, an independent relationship between CRF and SI was still discernable in African Americans. However, it was not generally discernable in Hispanics, though their CRF is generally better than, and SI is comparable to, African Americans [84]. These disparities in results suggest that genetic differences may exist in how CRF and SI interact across ethnicities.

PA versus CRF

The reviewed literature suggests a somewhat more consistent relationship between PA and SI than between CRF and SI (78% and 69% respectively). Unlike adults, the correlation between PA and CRF has been shown to be relatively weak in children and adolescents [32, 92]. However, when analyzed by PA intensity level, the correlation between CRF and PA is stronger with more vigorous PA intensities [9]. Furthermore, CRF is more likely improved if PA is of a certain intensity, duration and frequency [47, 92]. It may be that regular, high-intensity PA is needed for both CRF and PA to show associations with SI, independent of adiposity. It is also possible that examining both PA and CRF in the same model may introduce collinearity and reduce each variable's individual association with SI, regardless of PA level and amount.

Strength

As muscle is a primary location of insulin-mediated glucose uptake, strength training may improve SI in ways different from aerobic exercise. Of the three published interventions that measured the independent contribution of strength to changes in SI, one found that strength training alone improved both strength and SI without significant changes in fat mass, lean mass, or CRF [82]. Similarly, the second study found that improvements in SI were independent of the increases in muscle mass [61]. These results may indicate that improvements in strength and/or SI may also occur independent of changes in muscle mass in addition to fat mass.

Since all 3 strength training studies were in overweight or obese Hispanic adolescents, these results may not be generalizable to normal weight pediatric populations.

Controlling for lean mass as well as fat

It is worth noting that a total of 10 studies adjusted for both fat mass and lean mass in their analyses [9, 18, 48, 56, 61, 72, 82, 93–95], with 8 out of the 10 studies still finding at least one independent association of SI with PA, CRF or strength, suggesting that additional pathways may exist independent of the amount of lean mass as well as fat mass.

Limitations

One limitation of this review that is inherent to the literature is the lack of consensus on studies' measurement techniques of these important constructs (PA, CRF, strength, adiposity, and SI). Therefore, any review of this literature is currently restricted to being qualitative in nature, as the data does not lend itself to a more quantitative analysis.

Variations in participant characteristics, the number and quality of the study designs, measurement techniques and statistical analyses, and additional variables included in multivariate models all might have contributed to discrepancies in the studies' outcomes. There were also too few studies available to reliably assess the role of pubertal status or other less commonly measured baseline characteristics, such as fat distribution. Since the majority of the studies did not measure strength, implications from this review are often limited to only PA and CRF.

Conclusions

With insulin resistance now occurring as early as childhood, early PA interventions can be of great importance in the prevention and even reversal of this and other metabolic conditions. Many of the metabolic benefits of PA and strength training have been shown to be short-lived [60, 96–98], however, and therefore changes should be made to ensure individuals maintain long-term and consistent PA. Fitness and PA in children have shown to track into adulthood [60, 99] and pubertal declines in PA and CRF are linked to obesity and insulin resistance in adulthood [100]. Establishing healthy activity patterns in childhood can also help develop healthy lifelong PA habits [101]. Focusing on PA as a means of improving SI may be especially helpful since a focus on weight loss may not be an age-appropriate or feasible strategy in all children and adolescents.

The evidence in this review is convincing that successful PA interventions, especially those reaching higher intensities, can impart substantial benefits on SI in children and adolescents without necessarily decreasing adiposity. The benefit may be greatest for those who are at a higher risk for obesity-related health problems. The biggest improvements in SI may be achieved by comprehensively targeting increases in PA, CRF, strength, as they all seem to have a partially unique relationship with SI. This was a qualitative analysis of the literature and has the advantage of including a broad range of studies to provide an overview of current research. However, a future meta-analysis with more stringent inclusion criteria that includes studies with similar methodologies is recommended. Future studies on this subject should measure pubertal stage and examine ways to assess it statistically alongside age. These suggestions would provide additional evidence and understanding beyond those provided by this review.

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Table 1

Evidence of the association between PA and SI, independent of adiposity

Reference	Participant Characteristics				Measurement Methods		Independent association between PA and SI	Notes
	n	Age (mean $\pm$ SD)	Gender	Ethnicity	BMI Percentile	SI/IR	PA (minutes per session, sessions per week, number of weeks/total intervention minutes)	Adiposity
Design: Intervention								
Bell et al. (2007) [18] *	14	12.7 $\pm$ 2.3	F + M	Other	95	M _{LBM}	Aerobic PA (60, 3, 8/1440)	BMI, DEXA, HC, WC
Carrel et al. (2009) [49]	35	12 $\pm$ 0.5	F + M	Cauc	<95	FI, FG, HOMA	Aerobic PA (45, 2.5, 32/4050)	BMI, DEXA
Davis et al. (2009) [102]	41	15.2 $\pm$ 1.1	F	Hisp	85	FI, FG, 2-h I, 2-h G, MinMod	Aerobic + strength training (60, 2, 16/1920)	BMI, DEXA
Kelly et al. (2004) [46] *	25	10.9 $\pm$ 0.4	F + M	Other	85	FI, FG, 2-h G	Aerobic PA (30–50, 4, 8/960–1600)	DEXA
Macias-Cervantes et al. (2008) [51]	32	Control: 7.5 (6.9–8.4) Experimental: 8 (6.1–9.1)	F	Hisp	All	FI, FG, HOMA	Aerobic PA (60, 3, 12/2160), Pedometer	BMI, Skinfolds, WC
McMurray et al. (2000) [47] *	349	12.2 $\pm$ 1.0	F + M	Other	All	FI, FG	Aerobic PA (20, 3, 8/480), Questionnaire	Skinfolds, BMI
Nassis et al. (2005) [48]	19	13.1 $\pm$ 1.8	F	Other	85	HOMA	Aerobic PA (40, 3, 12/1440)	BMI, DEXA, Skinfolds, HC, WC
van der Heijden et al. (2009) [52]	29	14.9	F + M	Hisp	All	MinMod, ISI	Aerobic PA (30, 4, 12/1440)	BMI, DEXA
Design: Longitudinal								
								Sig. in BMI <85th% and >95th%

Reference	Participant Characteristics				Measurement Methods			Independent association between PA and SI	Notes
	n	Age (mean $\pm$ SD)	Gender	Ethnicity	BMI Percentile	SI/IR	PA (minutes per session, sessions per week, number of weeks/total intervention minutes)		
Bunt et al. (2003) [44]	90	5, 10	F + M	Other	All	FI, FG, ISI	DLW, Questionnaire	Yes/No	Cross-sectionally not sig. Longitudinally sig. by questionnaire-based PA only
Jago et al. (2008) [10]	384	9.65 $\pm$ 0.43, 15.72 $\pm$ 0.35	F + M	Other	All	FI, FG, HOMA	Accelerometer	Yes	
Metcalfe et al. (2009) [66]	213	5, 6, 7, 8	F + M	Cauc	All	HOMA	Accelerometer	No	
Telford et al. (2009) [57] *	498	8.1 $\pm$ 0.4, 10.1 $\pm$ 0.4	F + M	Cauc	All	FI, FG, HOMA	Pedometer	Yes	Cross-sectionally not sig. at baseline. Longitudinally sig. in males only
Design: Cross-sectional									
Ball et al. (2004) [56] *	95	11.1 $\pm$ 1.7 (F), 11 $\pm$ 1.8 (F)	F + M	Hisp	All	FI, FG MinMod	Interview	No	
Brage et al. (2004) [68]	306	9.7 $\pm$ 0.44	F + M	Cauc	All	FI, FG	Accelerometer	Yes	Sig. in females only
Casazza et al. (2009) [9] *	215	AA: 9.7 $\pm$ 1.4 Hisp: 9.3 $\pm$ 0.21 Cauc: 9.7 $\pm$ 1.7	F + M	AA, Cauc, Hisp	All	FI, MinMod	Accelerometer	Yes	PA sig. in AA only
Ekelund et al. (2007) [32] *	1709	Age 10: 9.7 $\pm$ 0.4 (M), 9.6 $\pm$ 0.4 (F), Age 15: 15.5 $\pm$ 0.5 (M), 15.5 $\pm$ 0.5 (F)	F + M	Other	All	FI, FG	Accelerometer	Yes	
Imperatore et al. (2006) [67] *	1783	15.4 $\pm$ 0.1	F + M	Other	All	FI, FG, QUICKI	Questionnaire	Yes	Sig. in males only
Kasa-Vubu et	53	18.7 $\pm$ 1.3	F	Other	>10 and <95	FI, FG, HOMA	Questionnaire	No	

Reference	Participant Characteristics					Measurement Methods			Independent association between PA and SI	Notes
	n	Age (mean $\pm$ SD)	Gender	Ethnicity	BMI Percentile	SI/IR	PA (minutes per session, sessions per week, number of weeks/total intervention minutes)	Adiposity		
al. (2005) [70] *									Yes/No	
Krekoukia et al. (2007) [103] *	54	10.3 $\pm$ 0.8 (lean M), 10.9 $\pm$ 0.8 (lean F), 9.8 $\pm$ 0.7 (obese M), 10 $\pm$ 0.6 (obese F)	F + M	Cauc	95	FI, HOMA	Accelerometer	BMI, Skinfolds, HC, WC	Yes	
Ku et al. (2000) [72] *	68	AA: 8.9 $\pm$ 1.2 (M), 8.7 $\pm$ 1.9 (F) White: 9.2 $\pm$ 1.6 (M), 9.2 $\pm$ 1.2 (F)	F + M	AA + Cauc	All	FI, MinMod	Questionnaire	BMI, DEXA	Yes	Sig. in both AA and Cauc
Mitchell et al. (2010) [81] *	39	11.8 $\pm$ 2.2	F + M	Other	All	HOMA	Aerobic PA, Accelerometer	BMI, HC, WC	Yes	Sig. for MVPA, but not for avg. PA
Owen et al. (2010) [69]	1,812	9.9 $\pm$ 0.4	F + M	Other	All	FI, FG, HOMA	Accelerometer, Questionnaire	Leg-to-arm bioelectrical impedance, Skinfolds	Yes	No sig. diffs. b/t whites and ethnic minorities
Rizzo et al. (2008) [2]	613	15.5 $\pm$ 0.5	F + M	Other	All	FI, FG, HOMA	Accelerometer	BMI, Skinfolds, WC	Yes	
Rubin et al. (2008) [78] *	437	Normal weight: 12.1 $\pm$ 0.8 (M), 11.8 $\pm$ 0.7 (F); Overweight: 12.1 $\pm$ 0.7 (M), 11.9 $\pm$ 0.8 (F)	F + M	Other	All	FI, FG	Questionnaire	BMI, Skinfolds	Yes	
Sardinha et al. (2008) [79]	308	9.8 $\pm$ 0.3	F + M	Other	All	FI, FG, HOMA	Accelerometer	BMI, DEXA, Skinfolds, WC	Yes	
Schmitz et al. (2002) [71]	357	By PA quartile: 12.79 $\pm$ 1.3,	F + M	Other	All	FI, M _{LBM}	Questionnaire	BMI, Skinfolds, WC	Yes	Sig. in above median %BF and FI only

Reference	Participant Characteristics				Measurement Methods		Independent association between PA and SI	Notes
	n	Age (mean $\pm$ SD)	Gender	Ethnicity	BMI Percentile	SI/IR	PA (minutes per session, sessions per week, number of weeks/total intervention minutes)	Adiposity
		12.78 $\pm$ 1.2, 13.11 $\pm$ 1.2, 13.13 $\pm$ 1.2						
Snitker et al. (2007) [80]	56	13.3 $\pm$ 1.3	F + M	AA	All	FI, FG, 2-h I, 2-h G, ISI	Accelerometer	DEXA
								Yes
								N/A

Abbreviations: PA, physical activity; MVPA, moderate to vigorous PA; SI, insulin sensitivity; AA, African American; Cau, Caucasian; Hisp, Hispanic; M, male; F, female; SI, insulin sensitivity; IR, insulin resistance; MetS, Metabolic Syndrome; DLW, doubly labeled water; FI, fasting insulin; FG, fasting glucose; 2-h I, 2 hour insulin; 2-h G, 2 hour glucose; ISI, insulin sensitivity index; MLBM, glucose utilization per kilogram of lean body mass per minute; MinMod, minimal model; HOMA, homeostatic model assessment; QUICKI, quantitative SI check index; ISI, insulin sensitivity index; BMI, body mass index; BF, body fat; DEXA, dual X-ray absorptiometry; HC, hip circumference; WC, waist circumference.

* Study appears in both Tables 1 and 2.

Table 2

Evidence of the association between CRF and SI, independent of adiposity

Reference	Participant Characteristics				Measurement Methods		Independent association between CRF and SI	Notes	
	n	Age (mean ± SD)	Gender	Ethnicity	BMI Percentile	SI/IR	CRF (minutes per session, sessions per week, number of weeks/ total intervention minutes)	Adiposity	Yes/No
Design: Intervention									
Bell et al. (2007) [18]*	14	12.7 ± 2.32	F + M	Other	95	M _{LBM}	VO ₂ 170 (60, 3, 8/1440)	BMI, DEXA, HC, WC	No
Kelly et al. (2004) [46]*	25	10.9 ± 0.4	F + M	Other	85	FI, FG, 2-h G	VO ₂ max (30–50, 4, 8/960–1600)	DEXA	No
McMurray et al. (2000) [47]*	349	12.2 ± 1.0	F + M	Other	All	FI, FG	VO ₂ max (20, 3, 8/480)	BMI, Skinfolds	Yes
Design: Longitudinal									
Allen et al. (2007) [73]	106	12.8 ± 1.4, 14.8 ± 1.4	F + M	Other	95	FI, HOMA	VO ₂ max	BMI, DEXA	Yes
Telford et al. (2009) [57]*	498	8.1 ± 0.4, 10.1 ± 0.4	M	Cauc	All	FI, FG, HOMA	Shuttle run	BMI, DEXA	Yes
Design: Cross-sectional									
Ball et al. (2004) [56]*	95	11.1 ± 1.7 (M), 11 ± 1.8 (F)	F + M	Hisp	All	FI, FG, MinMod	VO ₂ max	DEXA	No
Bouglet et al. (2010) [76]	241	11.9 ± 2.2	F + M	Other	All	FI, FG, HOMA	VO ₂ max	BMI, DEXA	Yes
Females p=0.005, males p<0.0001									

Sig. in males and females at baseline, but in males only at follow-up

Females p=0.005, males p<0.0001

Reference	Participant Characteristics				Measurement Methods			Independent association between CRF and SI	Notes
	n	Age (mean $\pm$ SD)	Gender	Ethnicity	BMI Percentile	SI/IR	CRF (minutes per session, sessions per week, number of weeks/total intervention minutes)		
Brufani et al. (2008) [93]	55	9.68 $\pm$ 1.3	F + M	Cauc	95	FI, FG, 2-h I, 2-h G, HOMA, ISI, QUICKI	VO ₂ max	Adiposity	Yes/No
Casazza et al. (2009) [9] [*]	215	AA: 9.7 $\pm$ 1.4 Hisp: 9.3 $\pm$ 0.21 Cauc: 9.7 $\pm$ 1.7	F + M	AA, Cauc, + Hisp	All	FI, MinMod	VO ₂ 170	BMI, DEXA	Yes CRF sig. in AA, Hisp. and Cauc
Cummings et al. (2010) [75]	1078	15.03 $\pm$ 0.1	F + M	Other	All	HOMA	VO ₂ max	BMI, WC	Yes Sig. in males with BMI > 85th% only
Eisenmann et al. (2007) [104]	375	7.7 $\pm$ 0.7	F + M	Cauc	All	FI, FG, FI/FG, FG/FI, HOMA, QUICKI	PWC-170	BMI, Skinfolds	Yes
Ekelund et al. (2007) [32] [*]	1709	Age 10: 9.7 $\pm$ 0.4 (M), 9.6 $\pm$ 0.4 (F); Age 15: 15.5 $\pm$ 0.5 (M) 15.5 $\pm$ 0.5 (F)	F + M	Other	All	FI, FG	W/kg (FFM)	BMI, Skinfolds, WC	Yes
Gutin et al. (2004) [74]	282	AA: 16.2 $\pm$ 1.2 (M), 16.3 $\pm$ 1.3 (F) Cauc: 16.3 $\pm$ 1.2 (M), 15.8 $\pm$ 1.2 (F)	F + M	AA + Cauc	All	FI, FG, HOMA, QUICKI	VO ₂ 170	BMI, DEXA	Yes Sig. in males only
Imperatore et al. (2006) [67] [*]	1783	15.4 $\pm$ 0.1	F + M	Other	All	QUICKI	VO ₂ max	BMI	Yes Sig. in males only
Jago et al. (2010) [105]	4955	11.3 $\pm$ 0.6	F + M	Other	All	FI, FG	Shuttle run	BMI, WC	Yes 20% AA, 20% Cauc, 60% Hisp
Kasa-Vubu et al.	53	18.7 $\pm$ 1.3	F	Other	10-95	FI, FG, HOMA	VO ₂ max	DEXA	Yes

Reference	Participant Characteristics				Measurement Methods			Independent association between CRF and SI	Notes
	n	Age (mean $\pm$ SD)	Gender	Ethnicity	BMI Percentile	SI/IR	CRF (minutes per session, sessions per week, number of weeks/total intervention minutes)		
(2005) * [70]								Yes/No	
Krekoukia et al. (2007) [103] *	54	Lean: 10.3 $\pm$ 0.8 (M), 10.9 $\pm$ 0.8 (F); Obese: 9.8 $\pm$ 0.7 (M), 10 $\pm$ 0.6 (F)	F + M	Cauc	95	FI, HOMA	VO ₂ max (from PWC-170)	BMI, Skinfolds, HC, WC	No
Ku et al. (2000) [72] *	68	8.9 $\pm$ 1.2 (M), 8.7 $\pm$ 1.9 (F)	F + M	AA + Cauc	All	FI, MinMod	VO ₂ max	BMI, DEXA	Yes
Lee et al. (2006) [106]	122	AA: 11.9 $\pm$ 0.3 Cauc: 11.7 $\pm$ 0.3	F + M	AA + Cauc	All	IS (Clamp)	VO ₂ max	BMI, DEXA	No
Mitchell et al. (2010) [81] *	39	11.8 $\pm$ 2.2	F + M	Other	All	HOMA	Shuttle run, VO ₂ max	BMI, HC, WC	No
Morinder et al. (2009) [95]	228	12.9 $\pm$ 2.2	F + M	Other	95	MinMod	VO ₂ max	BMI, DEXA	Yes
Nadeau et al. (2010) [107]	27	Control: 15.6 $\pm$ 1.8 Type 1 diabetics: 14.8 $\pm$ 2.6	F + M	Other	All	M	VO ₂ peak, VO ₂ Kinetics	BMI, DEXA, HC, WC	Yes
Rubin et al. (2008) [78] *	437	Normal weight: 12.1 $\pm$ 0.8 (M), 11.8 $\pm$ 0.7 (F); Overweight: 12.1 $\pm$ 0.7 (M), 11.9 $\pm$ 0.8 (F)	F + M	Other	All	FI, FG	VO ₂ max	BMI, Skinfolds	Yes
Ruiz et al. (2007) [77]	873	9.6 $\pm$ 0.4	F + M	Other	All	FI, FG, HOMA	W/kg	BMI, Skinfolds, WC	Yes

Sig. in highest BF and WC tertiles only

Sig. in both control and type 1 diabetic groups

Reference	Participant Characteristics				Measurement Methods			Independent association between CRF and SI	Notes
	n	Age (mean $\pm$ SD)	Gender	Ethnicity	BMI Percentile	SI/IR	CRF (minutes per session, sessions per week, number of weeks/total intervention minutes)	Adiposity	
Shaibi et al. (2005) [94]	163	11.2 $\pm$ 1.7	F + M	Hisp	85	FG, 2-hr glucose	VO ₂ max	BMI, DEXA, WC	Yes/No
Suriano et al. (2010) [108]	180	10.9 $\pm$ 2.1	F + M	Other	All	FI, FG, HOMA	Peak HR	BMI, WC	No

Abbreviations: AA, African American; Cauc, Caucasian; Hisp, Hispanic; M, male; F, female; SI, insulin sensitivity; IR, insulin resistance; MetS, Metabolic Syndrome; Clamp, hyperinsulinemic-euglycemic clamp; FI, fasting insulin; FG, fasting glucose; FG/FI, fasting glucose to insulin ratio; FI/FG, fasting insulin to glucose ratio; 2-h I, 2 hour insulin; 2-h G, 2 hour glucose; M, glucose utilization per kilogram of body mass per minute; MLBM, glucose utilization per kilogram of lean body mass per minute; IS, insulin-stimulated glucose disposal rate; MinMod, minimal model from FSIVGTT; HOMA, homeostatic model assessment; QUICKI, quantitative SI check index; ISI, insulin sensitivity index; Peak HR, average of minute-2 HR and minute-3 (completion) heart rates during step test; PWC-170, physical working capacity at 170 beats per minute; VO₂max, maximal oxygen uptake attained during test; VO₂peak, maximal oxygen uptake attainable by subject; VO₂170, maximal oxygen uptake at 170 beats per minute; VO₂kinetics, the behavior of VO₂ following the onset of PA; W/kg, watts per kilogram of body mass; W/kg (FFM), watts per kilogram of fat-free mass; BF, body fat; BMI, body mass index; DEXA, dual X-ray absorptiometry; HC, hip circumference; WC, waist circumference.

*Study appears in both Tables 1 and 2

Table 3

Evidence of the association between strength and SI, independent of adiposity

Reference	Participant Characteristics					Measurement Methods			Independent association between strength and SI
	n	Age (mean ± SD)	Gender	Ethnicity	BMI Percentile	SI/IR	Strength intervention (minutes per session, sessions per week, number of weeks/total intervention minutes)	Adiposity	
Design: Intervention									
Davis et al. (2009) [50]	54	15.5 ± 1.0	F + M	Hispanic	85	FI, FG, 2-h I, 2-h G, HOMA	1 RM sets in bench press and leg press (60, 2, 16/1920)	BMI, DEXA	No
van der Heijden et al. (2010) [61]	12	15.5 ± 0.5	F + M	Hispanic	95	FI, ISI	3 RM sets in chest, triceps, biceps, quadriceps and hamstring muscles (60,2,12/1440)	BMI, DEXA, MRI	Yes
Shaibi et al. (2006) [82]	22	15.1 ± 0.5	M	Hispanic	85	FI, FG, MinMod	1 RM sets in bench press and leg press (60, 2,	BMI, DEXA	Yes

Hisp, Hispanic; M, male; F, female; SI, insulin sensitivity; FI, fasting insulin; FG, fasting glucose; 2-h I, 2 hour insulin; 2-h G, 2 hour glucose; MinMod, minimal model from FSIVGTT; HOMA, homeostatic model assessment; ISI, insulin sensitivity index; BMI, body mass index; DEXA, dual X-ray absorptiometry, MRI, magnetic resonance imaging; RM, repetition maximum