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Human Kinetics
COMMENTARY

Metabolism and Exercise During Youth

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Citation 1

Sarzynski MA, Davidsen PK, Sung YJ, et al. Genomic and transcriptomic predictors of triglyceride response to regular exercise. *Br J Sports Med.* 2015; 49:1524–1531. PubMed doi:10.1136/bjsports-2015-095179

Aim: We performed genome-wide and transcriptome-wide profiling to identify genes and single nucleotide polymorphisms (SNPs) associated with the response of triglycerides (TG) to exercise training. ***Methods:*** Plasma TG levels were measured before and after a 20-week endurance training program in 478 white participants from the HERITAGE Family Study. Illumina HumanCNV370-Quad v3.0 BeadChips were genotyped using the Illumina BeadStation 500GX platform. Affymetrix HG-U133+2 arrays were used to quantitate gene expression levels from baseline muscle biopsies of a subset of participants ($N = 52$). Genome-wide association study (GWAS) analysis was performed using MERLIN, while transcriptomic predictor models were developed using the R-package GALGO. ***Results:*** The GWAS results showed that eight SNPs were associated with TG training-response (ΔTG) at $p < 9.9 \times 10^{-6}$, while another 31 SNPs showed p values $< 1 \times 10^{-4}$. In multivariate regression models, the top 10 SNPs explained 32.0% of the variance in ΔTG, while conditional heritability analysis showed that four SNPs statistically accounted for all of the heritability of ΔTG. A molecular signature based on the baseline expression of 11 genes predicted 27% of ΔTG in HERITAGE, which was validated in an independent study. A composite SNP score based on the top four SNPs, each from the genomic and transcriptomic analyses, was the strongest predictor of ΔTG ($R^2 = .14$, $p = 3.0 \times 10^{-68}$). ***Conclusions:*** Our results indicate that skeletal muscle transcript abundance at 11 genes and SNPs at a number of loci contribute to TG response to exercise training. Combining data from genomics and transcriptomics analyses identified a SNP-based gene signature that should be further tested in independent samples.

Commentary

While this research was conducted with adults, it is relevant to those working with children and adolescents (young people) because ethical constraints often mean we must draw upon research with adults to extend our understanding of potential mechanisms. Although the sample size for this study was relatively small, the data are based on biopsies of skeletal muscle, which would not be available from young people completing an exercise intervention to control potentially deleterious triacylglycerol concentrations ([TAG]). An evolving understanding of environmental influences on gene expression, allied to the development of noninvasive methods to examine genomics and transcriptomics, will soon probably lead to an increase in similar studies in young people. Elevated postprandial [TAG] are predisposed to the development and progression of atherosclerosis (11), and independently predict future cardiovascular disease risk in adults (7). Although the clinical manifestations of atherosclerotic disease emerge in adulthood typically, the pediatric origins of atherosclerosis are well established (5). Furthermore, childhood fasting [TAG] predicts young adult cardiovascular disease risk (6). Most people spend the majority of waking hours in a postprandial state, resulting in extended periods of elevated postprandial [TAG]. Considering cardiovascular disease remains the leading cause of mortality worldwide (4), prevention by targeting modifiable risk factors is a high priority on the public health agenda. Therefore, lifestyle modifications that reduce postprandial [TAG] from a young age may delay precursors of atherosclerotic disease leading to important long-term metabolic health benefits (5). There is a relatively long history of research examining the effects of manipulations in exercise and diet on postprandial [TAG] metabolism dating back to 1994, when Hardman's group published their first paper with healthy adults (1). Since then, Thomas, Gill, Stensel, Barrett and Tolfrey, among others, have each extended this work by examining some of the underlying mechanisms

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and exploring acute metabolic responses in children and adolescents. Gill and Tolfrey have, independently, identified considerable interindividual variability in the postprandial [TAG] response to exercise in adults and adolescents, respectively; Gill et al. (3) suggested that the wide ranging [TAG] response to exercise (–32% to +28%) might be underpinned by variation in hepatic fatty acid oxidation following exercise in middle-aged men with type 2 diabetes. Tolfrey and colleagues found that individual variability in high intensity, short-duration exercise intensity explained 42% of the variance in exercise-induced changes in postprandial [TAG] in adolescent boys, which ranged from –34% to +16% (9); however, it has not been possible to identify other determinants of this variability in several other studies where exercise intensity has been more tightly controlled (10).

Sarzynski et al. (8) used a combination of genomic and transcriptomic profiling techniques to identify genes and single nucleotide polymorphisms (SNPs), also known as sequence variants or allelic variants, associated with exercise training-induced changes in fasting plasma [TAG] concentration in a subsample of 49 white adults from the HERITAGE Family Study. A primary driver behind this research was concern that exercise, normally considered to be "safe" for most healthy individuals, led to an adverse metabolic outcome; in this case, an increase in [TAG] of at least 2 technical errors greater than no change (≥ 0.42 mmol/L) in a mixed race/sex sample of 1,687 exercisers (2). Without prior experience of experimental genetic research, the descriptions of genome-wide association study (GWAS) SNP genotyping, affymetrix microarray analysis, baseline ribonucleic acid (RNA) gene signature, and SNP summary score were challenging. Nevertheless, the possibility that this research might transfer to acute exercise postprandial lipaemia measures in young people was an exciting prospect and the main reason why this publication is featured here. Sarzynski et al. (8) found that numerous genes and SNPs contributed to the genetic and transcriptomic variation in the chronic exercise training response of [TAG] (i.e., 20 weeks of training, 3·week^{-1}). Specifically, 4 SNPs explained all of the genetic variance of the white participants' [TAG] response to exercise training in the HERITAGE Family Study. Using an independent study for validation, 27% of the [TAG] exercise response was predicted by a molecular signature based on the baseline expression levels of 11 genes; this procedure was accomplished using a multivariate variable selection based on a genetic algorithm method that seeks to identify the best subset of genes for maximizing the fitness of the regression model. The authors explained that their SNP summary score, derived by combining genomics and transcriptomics, could potentially be used as an a priori predictor of a trait response to regular exercise; from this, more effective preventive or treatment pathways might be identified. However, it is recognized that these initial findings need to be validated in further independent studies before the possibility of individualized exercise training programs could be considered realistically to manage [TAG] concentrations. In their discussion, the authors expand on how the genetic effect of regular exercise may be exerted through 3 different pathways (heparan sulfate glycosaminoglycan and glycosphingolipid biosynthesis and cell-adhesion molecules), but they note that the effect of exercise requires further clarification. Similarly, the pathway analysis showed that oxidative phosphorylation and mitochondrial dysfunction pathways were prominent transcriptomic predictor models for the [TAG] response to exercise training. Importantly, they concluded that the genes most important in modifying changes in fasting [TAG] in response to regular exercise are not the same as the loci controlling variation in population [TAG] concentrations. Sarzynski et al. (8) explain that, regardless of the "biological plausibility of the identified variants, identifying predictors of favourable and unfavourable TAG response to regular exercise could help to optimise therapeutic strategies" (p.1530)—this is certainly a long-term objective of ours when considering the effect of exercise (and dietary) manipulations on postprandial [TAG] in young people. Mindful of the various study limitations provided by the authors at the tail end of their manuscript, I am keen to see whether their findings can transfer to acute exercise models of postprandial lipaemia in young people.

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Citation 2

Bond B, Cockcroft EJ, Williams CA, Harris S, Gates PE, Jackman SR, Armstrong N, Barker AR. Two weeks of high-intensity interval training improves novel but not traditional cardiovascular disease risk factors in adolescents. *Am J Physiol Heart Circ Physiol.* 2015; 309(9):H1039–H1047. doi:10.1152/ajpheart.00360.2015

High-intensity interval training (HIIT) improves traditional cardiovascular disease (CVD) risk factors in adolescents, but no study has identified the influence of HIIT on endothelial and autonomic function in this group. Thirteen 13- to 14-yr-old adolescents (6 girls) completed six HIIT sessions over 2 wk. Each training session consisted of eight to ten 1-min repetitions of cycling at 90% peak power interspersed with 75 s of unloaded cycling. Traditional (triglycerides, cholesterol, glucose, insulin, and blood pressure) and novel [flow-mediated dilation (FMD), heart rate variability (HRV)] CVD risk factors were assessed in a fasted and postprandial state before (PRE), 1 day after (POST-1D), and 3 days after (POST-3D) training. Aerobic fitness was determined PRE and POST-3D. Two weeks of HIIT had no effect on aerobic fitness or traditional CVD risk factors determined in the fasted or postprandial state ($p > .15$). Compared with PRE, fasted FMD was improved POST-1D [$p = .003$, effect size (ES) = 0.70] but not POST-3D ($p = .32$, ES = 0.22). Fasted FMD was greater POST-1D compared with POST-3D ($p = .04$, ES = 0.48). Compared with PRE, postprandial FMD was greater POST-1D ($p < .001$, ES = 1.01) and POST-3D ($p = .01$, ES = 0.60). Fasted HRV was greater POST-1D ($p = .001$, ES = 0.71) and POST-3D ($p = .02$, ES = 0.44). The test meal lowered HRV in all laboratory visits ($p < .001$, ES = 0.59), but there were no differences in postprandial HRV between visits ($p > .32$ for all). Two weeks of HIIT enhanced endothelial function and HRV without improvements in traditional CVD risk factors. However, most of this favorable adaptation was lost POST-3D, suggesting that regularly performing high-intensity exercise is needed to maintain these benefits.

Commentary

This experimental study captures many features that are important when considering cardiometabolic health in adolescents and has numerous novel features worthy of inclusion in this special feature. The main premise for this research is that so-called traditional risk factors appear to account for only ~60% of exercise-induced cardiovascular disease (CVD) risk reduction. Therefore, "novel" risk factors are being targeted increasingly to explain the remaining 40% proportion of variance or "risk factor gap". Bond and colleagues (1) focused on endothelial function and heart rate variability (HRV; autonomic function) as novel markers to compare and contrast with the traditional measures that included systolic blood pressure (SBP), plasma (glucose), insulin, triacylglycerol ([TAG]), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and glutathione peroxidase (GTP), which is an enzyme involved in cellular antioxidation. Whether GTP is a traditional or novel risk factor is probably open to debate. Low volume, high-intensity interval training (HIIT) provided the exercise stimulus in the 6 training sessions spread over 2 weeks, which capitalizes on the current vogue for this type of exercise and is similar to previously published acute studies with adolescents (3,6) spawned from studies with sedentary (4) and type 2 diabetic adults (5). Another novel feature of this research was the inclusion of postprandial measures to overcome the limitation of previous studies that have relied on the less dynamic fasting plasma concentrations of the traditional risk factors listed above. The study was designed so that it was possible to separate the acute response, from the last exercise session, and the chronic 2-week training adaptation by including preexercise, and 1-day postexercise and 3-day postexercise measurements; however, a nonexercise matched control group was not included, but the authors suggested this is consistent with the HIIT literature. Major strengths of this study were the tight control, standardization or quantification of objectively measured free-living physical activity and dietary intake/composition 48 hours before each laboratory visit, and the carefully supervised progressive HIIT program.

All but one of the measures described under the traditional CVD risk factor subheading (including peak

mechanical power [PP] and cardiorespiratory fitness) did not change significantly ($p \geq .18$) over the 2-week intervention period and the 2 effect sizes provided were trivial ($d \leq 0.12$). These results stood regardless of whether the measures were fasted or postprandial. If you are wondering what changed significantly, it was PP ($p = .002$), but the effect was still small ($d = 0.32$). It was not possible to discern whether the study was powered adequately to detect meaningful changes in these variables in asymptomatic, moderately fit, healthy teenage girls and boys; this is particularly pertinent when considering the 3 drop-outs, but most likely the participant baseline characteristics are the greatest barrier to change (a common limitation in my own research over the years). A summary of the effect sizes, to accompany the traditional probability values, would have been welcome for the metabolic measures. In contrast, statistically significant changes ($p \leq .04$) in the novel risk factors (flow-mediated dilation [FMD], baseline arterial diameter, and HRV) over the 6 training sessions were found; effect sizes ranged from small to large ($d = 0.39–0.97$). Closer examination of the results revealed that the 1-day postexercise effects were larger than those found 3 days after the last exercise training session (compared with the preexercise baseline). There were also some subtle but noteworthy differences between fasting and postprandial measures that support the notion that the body's response to digesting a meal provides a more insightful window to metabolism than overnight fasting conditions—it was clear that test meal consumption promoted a reduction in FMD and HRV while increasing plasma [TAG] across all visits compared with fasting. This is perhaps unsurprising given the test breakfast meal had a very high energy content of 7134 kJ (~1704 kcal)—this equates to approximately 96%, 91%, and 82% of the samples' measured mean daily energy intakes in the 48 hours preceding the pre, 1-day post, and 3-day post laboratory visits respectively. The authors highlighted the primary study outcomes as: (i) a HIIT-induced improvement [*sic*] in endothelial function and HRV in boys and girls; (ii) changes in novel and traditional CVD risk factors may occur independently; and (iii) the changes in endothelial function and HRV were transient (%Δ1-day > %Δ3-day), which suggest their findings may reflect an acute response from the last exercise training bout rather than a chronic physiological or metabolic adaptation. Given the "training" was only 6 sessions over 2 weeks, this might be expected in a population where training effects have often been reported to be blunted compared with adults; however, I recognize the research design matches some features of the study that led to the recent resurgence in HIIT from Canada (2). From a public health perspective, if these results can be replicated with a larger sample of representative young people, future exercise or physical activity policies should continue to recommend that this is experienced regularly. Bond et al. (1) do indicate this may need to be repeated every day to realize the health benefits in adolescents, but I suspect the risk of repetitive strain or overuse injuries will need to be considered very carefully for young people who wish to partake only in high intensity exercise. My interpretation of the authors' perspective on HIIT for adolescents is that it is another form of exercise to choose from and may work best if blended with other intensities and durations. This may be important from a motivational standpoint and could influence long-term adherence to habitual exercise during childhood and adolescence. Finally, the authors provided some reflections on possible underlying mechanisms drawn from a variety of literature sources—this speculation can be interesting when ethical barriers to invasive procedures are precluded in young people, though it is possible some future studies may address these gaps in our knowledge.

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