Improvements in Glycemic Control After Acute Moderate-Intensity Continuous or High-Intensity Interval Exercise Are Greater in South Asians Than White Europeans With Nondiabetic Hyperglycemia: A Randomized Crossover Study

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OBJECTIVE

To examine whether circulating metabolic responses to low-volume high-intensity interval exercise (LV-HIIE) or continuous moderate-intensity aerobic exercise (CME) differ between white Europeans and South Asians with nondiabetic hyperglycemia (NDH).

RESEARCH DESIGN AND METHODS

Thirteen white Europeans and 10 South Asians (combined median [interquartile range] age 67 [60–68] years, HbA_{1c} 5.9% [5.8–6.1%] [41.0 (39.9–43.2) mmol · mol^{-1}]) completed three 6-h conditions (sedentary control [CON], LV-HIIE, and CME) in a randomized order. Exercise conditions contained a single bout of LV-HIIE and CME, respectively (each ending at 2 h), with meals provided at 0 and 3 h. Circulating glucose (primary outcome), insulin, insulin resistance index (IRI), triglycerides, and nonesterified fatty acids were measured at 0, 0.5, 1, 2, 3, 3.5, 4, 5, and 6 h. Data were analyzed as postexercise time-averaged area under the curve (AUC) adjusted for age, sex, and preexercise AUC.

RESULTS

Glucose was similar in each condition and with ethnicity, with no condition-by-ethnicity interaction ($P \geq 0.28$). However, insulin was lower in LV-HIIE (mean [95% CI] −44.4 [−23.7, −65.1] mU · L^{-1}) and CME (−33.8 [−13.7, −53.9] mU · L^{-1}) compared with CON. Insulin responses were greater in South Asians (interaction $P = 0.03$) such that values were similar in each ethnicity during exercise conditions, despite being 33% higher in South Asians during CON. IRI followed a similar pattern to insulin. Lipids were unaffected by exercise.

CONCLUSIONS

Reductions in insulin and insulin resistance after acute LV-HIIE and CME are greater in South Asians than in white Europeans with NDH. Further trials are required to examine the longer-term impact of LV-HIIE and CME on cardiometabolic health.

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Type 2 diabetes (T2D) is a global health problem affecting >400 million people worldwide (1). Characterized by chronic hyperglycemia and insulin resistance, T2D is associated with increased risk of micro- and macrovascular complications, other metabolic comorbidities, and earlier death (2,3). An additional >300 million individuals are estimated to have elevated circulating glucose concentrations in the fasted state (impaired fasting glucose), in response to a glucose challenge (impaired glucose tolerance), or both but do not yet reach diagnostic criteria for T2D (1). These individuals with nondiabetic hyperglycemia (NDH) are at high risk of developing T2D and subsequent complications (1,4), while dysregulated postprandial metabolism, even at subclinical levels, independently predicts future cardiovascular events (5).

Physical inactivity and low cardiorespiratory fitness (CRF) are independent risk factors for T2D, and strategies to promote physical activity or improve CRF (e.g., structured exercise training) reduce T2D incidence in the general population and in people with NDH (6,7). Regular physical activity and/or exercise provide diverse cardiometabolic benefits, some of which (including improved glucose and lipid metabolism) occur acutely after just a single bout (8–11). Consequently, promotion of physical activity and structured exercise constitute key components of both T2D prevention programs and management consensus reports (1,2,11,12).

The impact of high-intensity interval exercise (HIIE) on cardiometabolic health has received increasing attention over the past 10–15 years (13–15), and HIIE now features within consensus reports for T2D management alongside continuous moderate-intensity aerobic exercise (CME) and resistance exercise training (2,11). Several HIIE protocols exist, varying in intensity and duration of both exercise and recovery intervals. However, an approach comprising 10 × 1-min intervals at near-maximal aerobic capacity, interspersed with 1-min intervals of active recovery (referred to as low-volume [LV]-HIIE hereafter), has been used as a pragmatic model to support high-intensity exercise in clinical populations, eliciting diverse metabolic benefits in individuals with or at risk for T2D (16–20).

South Asian individuals have approximately a two to four times greater age-standardized risk of T2D than white Europeans and higher T2D prevalence for a given BMI (21). They may also transition from NDH to T2D quicker than white Europeans and are typically diagnosed with T2D up to 12 years earlier in life (21,22). While the mechanisms underpinning this increased risk are diverse, complex, and not fully understood, greater insulin resistance across the life course appears to constitute a prominent contributing factor (21).

South Asians also have lower CRF and perform less physical activity (particularly moderate- to vigorous-intensity physical activity [MVPA]) than white Europeans (21,23,24), with one study demonstrating that CRF accounted for >66% of the difference in insulin resistance between these ethnicities (23). Cross-sectional analyses suggest that South Asians may require greater habitual physical activity than white Europeans to confer similar cardiometabolic risk, but the benefits observed for a given increase in physical activity may be greater (25). Accordingly, recent experimental evidence demonstrated that the acute postprandial benefits of light-intensity walking in older adults were greater in South Asians than in white Europeans, with a separate trial in young adults showing similar ethnic differences in postprandial lipid metabolism on the day after a strenuous bout of exercise (26,27). Whether similar ethnic differences exist in response to acute moderate- or high-intensity exercise in individuals with NDH has not been explored.

This study examined whether the effects of acute LV-HIIE or CME on circulating glucose and lipid metabolism differ between white European and South Asian men and women with NDH. We hypothesized that glucose and lipid metabolism would be improved after each exercise bout, with greater effects observed in South Asians compared with white Europeans.

RESEARCH DESIGN AND METHODS

Ethical Approval and Study Registration

Ethical approval was provided by an NHS research ethics committee (15-EM-0259) and participants gave informed, written consent to participate. Clinical trials registration was completed before participant recruitment.

Overview of Study Design

This study used a single-site, randomized, crossover design in which South Asian and white European men and women completed three experimental conditions (sedentary control [CON], LV-HIIE, and CME) in a randomized order, stratified by sex and ethnicity. Each condition lasted 6 h and was separated by an ~1-week washout. Participants remained seated and rested throughout each condition, except when completing a single bout of LV-HIIE (total 25 min) or CME (35 min) within the 2nd hour of respective conditions. The primary outcome was postexercise time-averaged total area under the curve (AUC) for plasma glucose.

Participant Eligibility and Recruitment

White European and South Asian men and postmenopausal women were recruited. South Asian ethnicity was defined as anyone identifying themselves as Asian or Asian British (Indian, Pakistani, Bangladeshi), and white Europeans were those identifying as White/Caucasian and descending from any European country. Participants were aged 50–74 years with weight-stable BMI ≥27.5 or ≥25.0 $kg \cdot m^{-2}$ if white European or South Asian, respectively (all <5 kg self-reported weight change within the preceding 6 months). Participants had NDH, defined as HbA_{1c} between 5.7 and 6.4% (39–47 $mmol \cdot mol^{-1}$) or a 2-h plasma glucose concentration between 7.8 and 11.0 $mmol \cdot L^{-1}$ in response to a standard 75-g oral glucose tolerance test (OGTT) performed at our center within the preceding 12 months (1). Participants with controlled hypertension/dyslipidemia were eligible provided that they met all other inclusion criteria, but participants were otherwise free from diagnosed chronic metabolic disease. Individuals who self-reported three or more sessions of vigorous-intensity exercise per week (≥20 min per session) were excluded, as were those with self-reported contraindications to exercise or other study procedures.

Participants were recruited through primary care services, community events, poster advertisement, and existing research databases. Interested individuals underwent telephone prescreening, and those deemed eligible were invited to attend the laboratory for full screening and enrollment procedures.

Experimental Procedures

Preliminary Visit

Self-reported physical activity was determined using a frequency recall questionnaire for various transport-related, sport, and leisure-time physical activities. Body mass, height, and waist circumference were measured to the nearest 0.1 kg, 0.1 cm, and 0.5 cm, respectively. A venous blood sample was collected for the measurement of HbA_{1c}, total cholesterol, and HDL. Seated, rested blood pressure was measured manually by a qualified health care professional and reviewed by a specialist cardiac nurse alongside medical history and resting electrocardiography (Cardiofax GEM; Nihon Kohden, Tokyo, Japan). Individuals with resting cardiac arrhythmias or other potential contraindications to exercise were reviewed by a study clinician and either cleared to proceed or withdrawn from the study as appropriate.

Participants then completed a progressive maximal exercise test on a motorized treadmill (Woodway PPS 70 Plus; Woodway USA, Waukesha, WI), with electrocardiography and blood pressure monitoring throughout. After a 3-min warm-up, participants walked at a self-selected brisk walking speed at a gradient increasing from 0% by 1% per minute. Heart rate (HR) was recorded throughout, as were expired gases for the measurement of $\dot{V}O_2$ and respiratory exchange ratio (METALYZER 3B; Cortex Biophysik GmbH, Leipzig, Germany). Participants were instructed to continue for as long as they could, investing maximum effort, and the test continued until volitional exhaustion or participants reached 100% of their age-predicted maximum HR (85% if taking β-blockers) and respiratory exchange ratio ≥1.15. Tests aborted by the cardiac nurse because of adverse symptoms were classified as incomplete, and these participants were withdrawn. After sufficient recovery (≥15 min), participants were familiarized with LV-HIIE, performing a condensed protocol of three intervals.

To assess habitual physical activity, participants were asked to wear a triaxial accelerometer (GENEActiv; Activinsights, Kimbolton, U.K.) on their nondominant wrist for 6 days after the preliminary visit. They were instructed to continue their usual daily activities and encouraged, if possible, to wear the device at all times. A wear log was provided to record whether/when the device was removed along with the time the participants got into and out of bed and an estimate of sleep and wake times. Data were recorded at 100 Hz, downloaded using the manufacturer's software (GENEActiv PC version 2.9), and processed using R package GGIR version 1.10.1 (https://cran.r-project.org) (28). The average magnitude of dynamic acceleration corrected for gravity (Euclidean Norm Minus One) was calculated, averaged over 5-s epochs, and expressed in milligravitational units (m*g*). Data were considered valid when the device was worn for ≥16 h on ≥4 days (including ≥1 weekend day). Time spent sleeping (automated sleep detection), sedentary (<40 m*g*), and in light-intensity physical activity (40–100 m*g*) or MVPA (>100 m*g*) were averaged across valid days. MVPA in bouts of ≥10 min was assessed to reflect periods of structured MVPA and avoid incidental activity.

Experimental Visits

A schematic of experimental conditions is provided in Supplementary Fig. 1. Participants arrived at the laboratory at ~0800 h after an overnight fast of ≥10 h. After ensuring compliance with standardization instructions and confirming willingness to continue, an intravenous cannula (Braun; Pennine Healthcare, Derby, U.K.) was inserted into an antecubital vein. Following a period of habituation (30–60 min), conditions were initiated with the collection of a venous blood sample (0 h), with further samples collected at 0.5, 1, 2, 3, 3.5, 4, 5, and 6 h, for measurement of circulating glucose, insulin, triglycerides (TGs), and nonesterified fatty acids (NEFAs). Identical mixed meals were provided at 0 and 3 h and consumed within 15 min. Meal composition was standardized approximately between participants, prescribed according to baseline body weight (mean ± SD 7.9 ± 0.8 kcal · kg^{-1}, 62 ± 2% carbohydrates, 21 ± 2% fat, 17 ± 1% protein), and each participant consumed the same meals during each of their respective conditions. Meals typically consisted of a white bagel and full-fat margarine with either *1*) full-fat cheddar cheese, fruit jelly, and orange juice or *2*) a meal-replacement shake made with whole milk, with small variations between participants according to food preferences or dietary requirements.

LV-HIIE contained 10 × 1-min intervals on a motorized treadmill at the same brisk walking speed self-selected during the preliminary visit and a gradient predicted to elicit 90% of $\dot{V}O_2$ peak. Intervals were interspersed with 1-min active recovery, walking at 3.5 km · h^{-1} and 0% gradient. CME comprised 30-min continuous walking at the same brisk walking speed and a gradient predicted to elicit 65% of $\dot{V}O_2$ peak. Both exercise bouts were preceded by a 3-min warm-up and followed by a 2-min cool-down (each 3.5 km · h^{-1}, 0% gradient) such that the total duration of LV-HIIE and CME was 25 and 35 min, respectively. LV-HIIE and CME each concluded at 2 h within the respective conditions. Therefore, to account for differences in duration, CME commenced 10 min earlier than LV-HIIE. HR and rating of perceived exertion (29) were recorded at regular intervals throughout each of the bouts. These protocols have been suggested to be closely matched for external work (30).

Standardization Procedures

Before all visits, participants refrained from alcohol and strenuous physical activity for 48 and 72 h, respectively, and attended the laboratory using motorized transport. Participants also recorded all food and energy-containing beverages for 48 h before their first condition and replicated this before subsequent conditions. Physical activity and standing beyond that prescribed in the exercise bouts were restricted throughout conditions, with an activPAL thigh-worn accelerometer (PAL Technologies, Glasgow, U.K.) worn throughout to confirm compliance with these instructions. Data were processed using proprietary software (activPAL Professional Research Edition; PAL Technologies), and time spent sitting and stepping during conditions was calculated.

Biochemical Analyses

HbA_{1c}, plasma glucose, and serum total cholesterol, HDL, and TGs were analyzed using standardized quality-controlled enzymatic assays by the clinical pathology laboratories of University Hospitals of Leicester NHS Trust. Plasma NEFAs were analyzed in a similar manner by Nottingham University Hospitals NHS Trust. Plasma insulin was measured using electrochemiluminescence assay (Meso Scale Diagnostics), with analysis of a given sample repeated if the coefficient of variation between two duplicates was >20%; the mean intraplate coefficient of variation of all analyses was <7.8%.

Sample Size

Assuming a standardized difference of 1 (30,31), a within-person correlation of 0.7 (unpublished data from previous studies in our laboratory [32]), and $P < 0.05$, we required 22 participants to complete all experimental procedures to detect *1*) a condition-by-ethnicity interaction with 80% power (assuming a change in glucose AUC that is twice as large in one group than the other) and *2*) a main effect of condition within each ethnicity with >90% power (≥8 required per group). To allow 10% noncompliance and full counterbalancing, our target sample size was 12 per group.

Data Inclusion

Participants were included in analyses of a given outcome if >50% of data for that outcome were available for each condition. Missing data within included participants were imputed using a regression method previously reported for acute experimental studies (26), with age, sex, ethnicity, BMI, HbA_{1c}, and condition as predictors. Imputations were performed for 4.3% of primary outcome data (glucose) and 5.2% of secondary outcomes data (insulin, TGs, and NEFAs).

Statistical Analysis

Time-averaged total AUC for glucose, insulin, TGs, and NEFAs during pre- and postexercise periods were calculated using the trapezium rule. AUC for glucose and insulin during each period were multiplied to form an insulin resistance index (IRI), as previously described (26). Descriptive data are presented as median (interquartile range [IQR]) and frequency for continuous and categorical variables, respectively. Outcomes data are presented as mean (95% CI), unless otherwise specified.

Data were analyzed using generalized estimating equations with an exchangeable correlation matrix using commercially available software (SPSS version 26; IBM Corporation). Glucose, insulin, IRI, and TG analyses used a γ-distribution because of positively skewed data. All models contained an interaction term between ethnicity and condition and were adjusted for age, sex, and preexercise AUC. Results for condition, ethnicity, and condition-by-ethnicity are reported. To aid interpretation, values across each condition are reported, stratified by ethnicity and for the combined study population (provided in the Supplementary Material). Comparisons between exercise conditions and CON within each ethnicity were performed as exploratory analyses. $P < 0.05$ was considered statistically significant.

RESULTS

Participant Flow and Characteristics

As detailed in Supplementary Fig. 2, 1,118 individuals were invited to participate in the study. Sixty-eight underwent telephone prescreening, and 36 were enrolled (white European [male/female] vs. South Asian [male/female] 17 [8/9] vs. 19 [11/8]). Nine participants were excluded after full screening, with the remaining 27 randomized to an experimental condition sequence. Four individuals withdrew after randomization, two of whom had completed one experimental condition. The remaining 23 (13 [6/7] vs. 10 [7/3]) completed the study and comprised the full analysis set (Table 1).

The white European group was older and had a greater proportion of female participants than the South Asian group. The South Asian group had higher BMI and obesity prevalence but lower median body weight. HbA_{1c} was similar between groups, but the South Asian individuals were more insulin resistant as indicated by higher HOMA of insulin resistance, which was driven by higher fasting insulin.

Eighteen individuals (9 [male/female 4/5] vs. 9 [7/2]) were compliant with free-living physical activity assessment, each providing 2 valid weekend days and 4 valid weekdays of data. Participants were highly sedentary, with the white European group spending ~80 min more time sedentary per day than the South Asian group. MVPA in bouts of ≥10 min was low in both groups and lower in South Asians than in white Europeans. The South Asian group had shorter sleep duration (Table 1).

Compliance With Experimental Procedures and Exercise Responses

As per study design, participants remained seated for almost the entirety of the CON condition (median [IQR] percentage of condition spent sitting 98.0% [97.4–99.2%]), while stepping time was negligible (total time 0.5 [0.2–1.2] min; percentage of condition 0.1% [0.0–0.3%]). Similarly, as intended, stepping time was 25.3 (25.0–26.0) and 37.3 (36.9–37.7) min during the LV-HIIE and CME conditions, respectively.

HR responses were similar across LV-HIIE and CME bouts (mean [95% CI] 119 [114, 124] vs. 118 [112, 124] beats · min^{-1}), while rating of perceived exertion (recorded at the end of each interval) was marginally higher during LV-HIIE (13 [12, 13] vs. 12 [11, 13] arbitrary units [AU]).

Circulating Glucose and Insulin Responses

Circulating glucose and insulin concentrations throughout each condition in white European and South Asian groups are presented in Fig. 1. Glucose and insulin concentrations fluctuated over each condition in both groups, increasing transiently after each meal.

Postexercise glucose AUC did not differ between conditions or ethnicities, and there was no condition-by-ethnicity interaction ($P \geq 0.28$) (Table 2 [stratified values]and Supplementary Table 1 [combined population]). However, in the combined study population, insulin AUC was reduced in both exercise conditions compared with CON by 44.4 (95% CI 23.7, 65.1) mU · L^{-1} (mean 32%) and 33.8 (13.7, 53.9) mU · L^{-1} (24%) in the LV-HIIE and CME conditions, respectively (main effect of condition $P < 0.001$) (Table 2 and Supplementary Table 1). Furthermore, this effect was modulated by ethnicity (interaction $P = 0.03$). The reduction after exercise was substantially greater in the South Asian group to the extent that despite postexercise insulin AUC being 33% higher during the CON condition in the South Asian group, values were similar in both ethnicities during respective exercise conditions (Table 2). In white Europeans, compared with the CON condition, insulin responses were reduced by 23.2 (9.1, 37.2) mU · L^{-1} (19%) during LV-HIIE and by 15.6 (0.4, 30.8) mU · L^{-1} (13%) during CME. In South Asians, the equivalent reductions with exercise were 65.6 (27.9, 103.4) mU · L^{-1} (41%) and 52.1 (11.0, 93.2) mU · L^{-1} (33%) during LV-HIIE and CME, respectively.

Similar patterns were observed for IRI, with values being lower during LV-HIIE and CME conditions compared with CON by 344 (95% CI 159, 530) AU (mean 35%) and 272 (89, 455) AU (27%), respectively, and with a greater response observed in the South Asian individuals compared with the white European individuals (Fig. 2, Table 2, and Supplementary Table 1). Compared with the CON condition, IRI

Table 1—Participant characteristics of the whole study population and stratified by ethnicity

	All (n = 23)	White European (n = 13)	South Asian (n = 10)
Sex, *n*			
Male	13	6	7
Female	10	7	3
Anthropometry			
Age (years)	67 (60–68)	68 (66–70)	59 (52–67)
Body weight (kg)	80.5 (71.9–93.8)	84.6 (75.5–91.2)	78.7 (68.9–96.1)
BMI (kg · m^{-2})	30.0 (28.4–32.8)	28.8 (28.4–32.8)	30.6 (26.7–32.3)
Obesity prevalence, *n* (%)*	13 (57)	6 (46)	7 (70)
Waist circumference (cm)†	100.8 (97.6–109.1)	101.6 (98.0–106.9)	99.5 (95.0–109.5)
Glycemic control and insulin sensitivity			
HbA_{1c} (%)	5.9 (5.8–6.1)	5.9 (5.8–6.0)	6.1 (6.0–6.1)
HbA_{1c} (mmol · mol^{-1})	41.0 (39.9–43.2)	41.0 (39.3–42.1)	42.6 (41.8–43.2)
Fasted plasma glucose (mmol · L^{-1})	5.3 (5.0–5.6)	5.3 (5.1–5.7)	5.4 (5.0–5.6)
Fasted plasma insulin (mU · L^{-1})	12.6 (8.8–16.9)	10.7 (8.6–18.7)	15.4 (10.0–17.8)
HOMA of insulin resistance	3.09 (2.11–4.31)	2.97 (1.93–4.20)	3.38 (2.39–4.35)
Fasted plasma NEFAs (mmol · L^{-1})	0.47 (0.35–0.59)	0.56 (0.40–0.65)	0.40 (0.35–0.51)
Adipose tissue IRI	37.5 (24.2–47.5)	37.5 (27.1–49.3)	39.3 (20.1–50.4)
Blood pressure and circulating lipids			
Systolic blood pressure (mmHg)	136 (118–140)	140 (133–141)	124 (112–140)
Diastolic blood pressure (mmHg)	79 (75–86)	80 (76–89)	76 (71–84)
Total cholesterol (mmol · L^{-1})†	5.1 (4.5–5.7)	5.3 (4.4–5.6)	5.1 (4.6–6.0)
HDL (mmol · L^{-1})†	1.40 (1.15–1.60)	1.50 (1.30–1.70)	1.30 (1.08–1.40)
Fasted plasma TGs (mmol · L^{-1})	1.63 (1.25–2.36)	1.37 (1.21–2.26)	1.74 (1.44–2.75)
Physical activity, fitness, sedentary behavior, and sleep			
Absolute $\dot{V}O_2$ peak (L · min^{-1})	2.09 (1.75–2.38)	2.21 (1.83–2.37)	1.96 (1.68–2.41)
Relative $\dot{V}O_2$ peak (mL · kg^{-1} · min^{-1})	25.0 (21.7–27.5)	25.4 (21.9–28.8)	25.0 (21.4–28.3)
Sleep duration (min · day^{-1})†	375 (341–436)	393 (357–472)	343 (293–408)
Sedentary time (min · day^{-1})†	656 (610–724)	691 (617–709)	611 (596–805)
Light-intensity physical activity (min · day^{-1})†	166 (133–233)	162 (130–201)	170 (154–263)
MVPA (min · day^{-1} in bouts ≥10 min)†	5.4 (3.2–17.8)	6.0 (5.1–24.5)	2.5 (0.0–15.4)

Data are median (IQR) unless otherwise indicated. *Ethnicity-specific BMI thresholds were used to categorize obesity prevalence (BMI ≥30.0 and ≥27.5 kg · m^{-2} in white European and South Asian groups, respectively). †Data not available for all participants: waist circumference, n = 22 (1 South Asian female missing); total cholesterol and HDL, n = 21 (1 white European male and 1 white European female missing); all sleep, sedentary behavior, and activity variables: n = 18 (2 white European males, 2 white European females, and 1 South Asian female missing).

was reduced in white Europeans by 158 (71, 244) AU (18%) during LV-HIIE and by 119 (14, 224) AU (14%) during CME. In South Asians, equivalent reductions in IRI were 531 (169, 892) AU (48%) and 425 (46, 805) AU (38%), respectively.

Circulating Lipids Responses

In both groups and in each condition, circulating TG and NEFA concentrations increased and decreased, respectively, during the course of each condition (Supplementary Fig. 3). Postexercise TG AUC was similar in each condition and each ethnicity, and there was no condition-by-ethnicity interaction ($P \geq 0.09$) (Table 2 and Supplementary Table 1). NEFA AUC was 0.06 (95% CI 0.02, 0.11) mmol · L^{-1} higher in the South Asian group compared with the white Europeans (main effect of ethnicity $P = 0.01$) but no different between conditions, and there was no condition-by-ethnicity interaction ($P \geq 0.16$) (Table 2 and Supplementary Table 1).

CONCLUSIONS

This study demonstrated that a single bout of LV-HIIE or CME had no effect on circulating glucose concentrations in white European or South Asian men and women with NDH. However, LV-HIIE and CME each reduced circulating insulin and IRI compared with prolonged sitting, with greater effects observed in South Asians. Responses were greater in South Asians to the extent that insulin and IRI were similar in both ethnicities during respective exercise conditions, despite each being ~30% higher during prolonged sitting in the South Asian group.

There are several possible reasons that our glucose findings contrast our hypotheses and a separate crossover trial reporting reduced postexercise glucose during an OGTT in individuals with NDH (33). Definitions and principal diagnostic criteria for NDH and T2D are derived from measures of hyperglycemia (1). However, the pathophysiology of these interrelated conditions is highly complex, and the regulation of circulating glucose in humans is tightly controlled (4). Several complex adaptive mechanisms typically occur years before manifest hyperglycemia to maintain normal or minimally elevated glucose concentrations for as long as possible (4). Therefore, in individuals with early glycemic dysregulation, nonglucose measures, including circulating insulin and indices of insulin resistance, may be more sensitive to changes with interventions, particularly acute interventions, than circulating glucose itself, as is the case in the current study. Several studies have demonstrated that in contrast to people with T2D (34,35), circulating glucose concentrations are unaffected by acute exercise in individuals with normoglycemia (27,36–38), with reductions in circulating insulin apparent in those who are overweight or obese and/or with glucose concentrations approaching NDH (37,38). In the current study, while all participants met our criteria for NDH (1), it is noteworthy

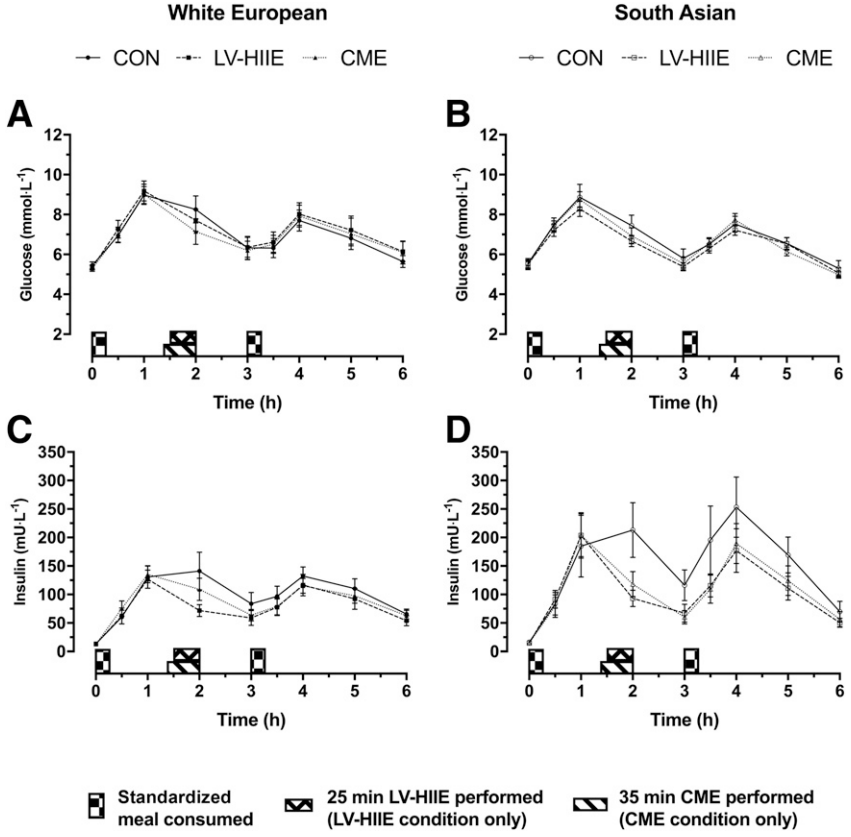

Figure 1—Circulating glucose (*A* and *B*) and insulin (*C* and *D*) responses across experimental conditions for white European and South Asian groups. Data are mean (SEM).

that 16 (70%) had normal fasting glucose ($<$5.6 mmol · L^{-1}). Furthermore, as exercise intensity increases, proportional utilization of carbohydrate metabolism also increases, with accordant stimulation of hepatic glucose production (39). In individuals with normoglycemia or NDH, circulating glucose concentrations at the end of acute moderate- to vigorous-intensity exercise are often greater than those immediately before, with effects extending into the postprandial period of meals coming shortly after exercise (33,36,37). It is therefore plausible that in our recruited population, any favorable effects of acute exercise promoting a reduction in circulating glucose may have been masked by simultaneous increases in hepatic glucose output during and after exercise. Importantly, however, we sampled mixed venous blood from an antecubital vein, and therefore changes in glucose uptake or output in different tissues cannot be inferred. Thus, this remains a speculative explanation that warrants further investigation.

Previous evidence in a European population suggests that a 20% reduction in insulin AUC during an OGTT may confer an ~10% reduction in coronary mortality risk (40). Therefore, while acknowledging that the effect in South Asians is not known and that the current study was an acute crossover trial, these data suggest that the magnitude of postexercise insulin reduction observed in our study may be clinically meaningful (white European vs. South Asian: LV-HIIE 19 vs. 41%, CME 13 vs. 33%). Our findings that reductions in insulin and IRI were greater in South Asians than in white Europeans also extends evidence from two previous studies exploring the impact of regular light-intensity walking to break prolonged sitting (26,32). In these previous analyses, reductions in insulin and IRI after light-intensity walking were greater in South Asians compared with white Europeans. However, postwalking concentrations in South Asians were still similar to prolonged sitting in white Europeans (26,32). In the current study, the effects of LV-HIIE and CME on circulating insulin and IRI were not only greater in South Asians but also greater to the extent that values were similar in both ethnicities during respective exercise conditions. This experimental finding supports observational evidence that physical inactivity and low CRF may be prominent factors contributing to the excess risk of insulin resistance and cardiovascular disease in South Asians (23,24). This study, therefore, adds to mounting evidence highlighting the public health importance of targeting low levels of physical activity and CRF in South Asian communities to address inequalities in cardiometabolic health. Furthermore, it suggests that both CME and LV-HIIE are effective at acutely improving insulin resistance in South Asians, supporting an evidence base that allows for greater personalization of exercise interventions in South Asian communities.

While fasted NEFA and TG concentrations were higher in South Asians in the current study, as previously reported (26,27), neither were affected by exercise. This is likely due to the duration of observation in the current study, which was limited to 4 h postexercise. Evidence suggests that the impact of acute exercise on postprandial lipid metabolism may only become apparent when examined several hours later (10).

Important strengths of this study include the fully powered randomized crossover design with strict standardization procedures and robust analytical methods in a multiethnic population. While acknowledging that the intended sample size to allow full counterbalancing was not reached ($n = 24$), we emphasize that the number of participants recruited met the minimum required according to our a priori sample size calculation (total $n \geq 22$, $n \geq 8$ per group). Certain limitations and consequences of our study design are also noteworthy. Experimental procedures were performed in a laboratory setting, thus limiting ecological validity. Our results also predominantly reflect changes in postprandial metabolism because participants were fed twice within the 6-h conditions (~90 min before the exercise bouts and 1 h after them). Participants were middle-aged to older adults (range 50–73 years), and thus, results cannot be generalized to younger or older individuals. Similarly, we recruited a migrant South Asian population living in the U.K. Therefore, results may not be generalizable to South Asians living elsewhere, particularly in low- or middle-income countries. Some differences in participant characteristics between groups were apparent

Table 2—Postexercise responses for glucose, insulin, IRI, TGs, and NEFAs during each condition in each ethnicity group

	White European			South Asian			*P* value		
	CON	LV-HIIE	CME	CON	LV-HIIE	CME	Trt	Eth	Int
Primary outcome									
Glucose (mmol · L^{-1})	7.29 (6.35, 8.22)	7.27 (6.40, 8.13)	7.15 (6.20, 8.11)	6.68 (5.88, 7.49)	6.37 (5.88, 6.85)	6.42 (5.91, 6.93)	0.51	0.28	0.58
Secondary outcomes									
Insulin (mU · L^{-1})	119.7 (92.8, 146.7)	96.5 (76.3, 116.7)***	104.1 (87.0, 121.2)*	159.7 (112.4, 207.0)	94.1 (74.9, 113.3)†††	107.7 (81.3, 134.0)†	**<0.001**	0.45	**0.03**
IRI (AU)	874 (658, 1,091)	717 (533, 900)***	755 (586, 925)*	1,115 (708, 1,521)	584 (431, 736)††	689 (484, 894)†	**<0.001**	0.93	**0.03**
TGs (mmol · L^{-1})	1.97 (1.83, 2.11)	2.03 (1.83, 2.24)	1.95 (1.71, 2.19)	2.20 (1.91, 2.50)	2.18 (2.00, 2.36)	2.25 (2.00, 2.50)	0.95	0.17	0.09
NEFAs (mmol · L^{-1})	0.08 (0.04, 0.12)	0.12 (0.08, 0.16)	0.16 (0.11, 0.21)*	0.19 (0.15, 0.22)	0.19 (0.15, 0.22)	0.18 (0.14, 0.23)	0.26	**0.01**‡	0.16

Data are mean (95% CI) time-averaged AUCs. Models were adjusted age, sex, and preexercise AUC. *P* values are for analyses performed with all data combined (i.e., the entire study population). *P* values in bold are statistically significant. Eth, effect of ethnicity; Int, treatment-by-ethnicity interaction; Trt, effect of treatment condition. *$P < 0.05$, ***$P < 0.001$ vs. CON condition in white European group only; †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ vs. CON condition in South Asian group only. ‡Pairwise comparison: white European 0.12 (0.09, 0.15) vs. South Asian 0.18 (0.15, 0.22). Data for each condition in the combined population can be found in Supplementary Table 1.

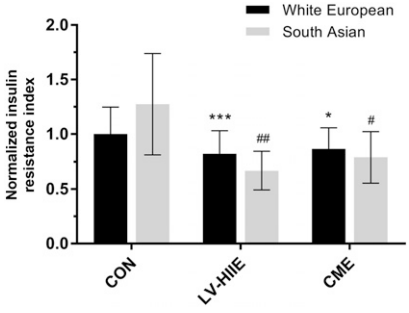

Figure 2—Postexercise response of the IRI during each condition in each ethnicity group. Data are mean (95% CI). For ease of interpretation, data are normalized to the estimated marginal mean of the adjusted postexercise AUC during the CON condition in the white European group. $*P < 0.05$, $***P \leq 0.001$, CON vs. white European; $\#P < 0.05$, $\#\#P < 0.01$, CON vs. South Asian.

(most prominently age, sex distribution, systolic blood pressure, and obesity prevalence). Age and sex were included a priori as covariates within our statistical analysis plan, but nevertheless, the potential for other between-group differences to confound our results cannot be excluded. Most prominently, this study examined the effects of a single bout of LV-HIIE and CME. While each have been shown to elicit cardiometabolic benefits for individuals with NDH or T2D when performed regularly (i.e., exercise training) (6–12,14,15), data in South Asians are lacking, and evidence from other ethnic groups or multiethnic cohorts may not be generalizable. Cultural sensitivity in terms of appeal, uptake, and sustainability of different physical activity/exercise interventions also remains an essential consideration. Therefore, trials examining the long-term impact of different approaches to promoting physical activity and structured exercise in South Asians, including LV-HIIE and CME, are greatly needed.

In conclusion, a single bout of LV-HIIE or CME reduces circulating insulin concentrations and IRI, but not glucose or lipids, for up to 4 h postexercise in white European and South Asian men and women with NDH. Greater effects were observed in South Asians to the extent that values for insulin and IRI were similar in each ethnicity during respective exercise conditions, despite 30% higher responses during prolonged sitting in South Asians. Intervention trials specifically in South Asians are required to assess the efficacy and effectiveness of LV-HIIE and CME over a prolonged period to further examine their potential to improve cardiometabolic health in this high-risk group.

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Duality of Interest. J.A.S. and T.Y. have received a grant in support of an investigator-initiated trial from AstraZeneca, unrelated to the current study. K.K. chaired the Public Health Guidance on Detection and Prevention of Diabetes. M.J.D. has acted as consultant, advisory board member, and speaker for Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; as an advisory board member for Servier and Gilead Sciences; and as a speaker for Napp, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Janssen. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. C.J., K.K., M.J.D., and T.Y. generated the study idea and designed the protocol. J.A.S., C.J., N.A.C., C.L.E., J.H., J.A.K., M.M., A.V.R., and H.L.W. contributed to data collection and/or analysis of study outcomes. J.A.S. and T.Y. performed and interpreted the data analysis and drafted the manuscript. C.J., N.A.C., C.L.E., J.H., J.A.K., K.K., M.M., A.V.R., D.J.S., H.L.W., D.R.W., and M.J.D. reviewed the manuscript, providing substantial academic and/or clinical input. All authors approved the final manuscript. J.A.S. is the guarantor of the work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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