Replacement of Sedentary Time with Physical Activity: Effect on Lipoproteins

CATHERINE M. PHILLIPS[1,2], CHRISTINA B. DILLON[1], and IVAN J. PERRY[1]

[1]*HRB Centre for Diet and Health Research, School of Public Health, University College Cork, Cork, IRELAND; and* [2]*HRB Centre for Diet and Health Research, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Dublin, IRELAND*

ABSTRACT

PHILLIPS, C. M., C. B. DILLON, and I. J. PERRY. Replacement of Sedentary Time with Physical Activity: Effect on Lipoproteins. *Med. Sci. Sports Exerc.*, Vol. 50, No. 5, pp. 967–976, 2018. **Purpose**: Limited data on the relationship between physical activity and lipoprotein particle profiles exist. Our objective was to investigate associations between objectively measured physical activity and lipoprotein particle size and number, and specifically whether substituting daily sedentary behavior with light activity or moderate-to-vigorous physical activity (MVPA) is associated with beneficial alterations to the lipoprotein profile among adults and those at increased cardiometabolic risk (obese and insulin-resistant subjects). **Methods**: Sedentary behavior and physical activity intensity and duration were measured for 7 consecutive days using the GENEActiv accelerometer in a cross-sectional adult cohort (n = 396; mean age, 59.6 ± 5.5 yr). Lipoprotein particle size and subclass concentrations were determined using nuclear magnetic resonance spectroscopy. Isotemporal substitution regression modeling quantified the associations between replacing 30 min·d^{-1} of sedentary behavior with equal amounts of light activity and MVPA on lipoprotein profiles. **Results**: Daily duration of MVPA was inversely associated with large VLDL particles and lipoprotein insulin resistance scores ($P < 0.05$, after adjustment for sedentary time and other confounding factors). Reallocating 30 min of sedentary time with MVPA, but not light activity, was associated with less large VLDL particles resulting in more favorable average VLDL particle size and improved lipoprotein insulin resistance score ($P < 0.05$). Analysis of high-cardiometabolic-risk groups revealed similar beneficial alterations to VLDL profiles ($P < 0.05$) with substitution of sedentary time for MVPA among the insulin-resistant (homeostasis model assessment for insulin resistance ≥75th percentile) but not the obese (body mass index ≥30 kg·m^{-2}) individuals. **Conclusions**: Daily MVPA duration and theoretical replacement of sedentary time with MVPA, but not light activity, were associated with less atherogenic VLDL profiles, particularly among the insulin-resistant individuals. These findings, which require further investigation, highlight the need to develop physical activity interventions aimed at improving atherogenic dyslipidemia and lowering cardiometabolic risk. **Key Words:** MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY, SEDENTARY Behavior, LIPOPROTEIN PROFILE, OBESITY, INSULIN RESISTANCE

Physical activity exerts beneficial health effects including decreased risk of obesity, type 2 diabetes (T2DM), cardiovascular disease (CVD), and cancer and reduced all-cause mortality (1–3). Conversely, sedentary behavior increases risk of these conditions and shortens life expectancy (4–6). Multifactorial mechanisms, including improvements to the atherogenic lipid profile and insulin sensitivity, may underlie the positive associations between physical activity and cardiometabolic outcomes (7,8). Standard lipid tests quantify the cholesterol or triglyceride (TG) content of lipoproteins. In contrast, nuclear magnetic resonance (NMR) spectroscopy simultaneously quantifies the number and size of VLDL, LDL, and HDL particles (9). Several studies have demonstrated associations between lipoprotein subfractions and CVD risk (10–12), particularly LDL (13,14), and HDL subfractions (15). The cholesterol content of lipoprotein particles varies between individuals because of heterogeneity in particle size and in the relative content of cholesterol ester and TG contained in the particle core (16). Evidence suggests that in patients with discordance between cholesterol and particle measures of LDL and HDL, CVD risk tracks with the particle

Address for correspondence: Catherine M. Phillips, Ph.D., HRB Centre for Diet and Health Research, School of Public Health, University College Cork, Cork, Ireland, and School of Public Health, Physiotherapy and Sports Science, University College Dublin, Dublin, Ireland; E-mail: c.phillips@ucc.ie, catherine.phillips@ucd.ie.

Submitted for publication June 2017.
Accepted for publication November 2017.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.acsm-msse.org).

0195-9131/18/5005-0967/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000001511

measures (17). Lipoprotein particle size, in particular large VLDL and small, dense LDL and HDL particles, is associated with increased risk for atherosclerosis and premature CVD (18–21).

Obesity and insulin resistance are linked with proatherogenic alterations in the lipoprotein particle profile (19,22). Limited data on the relationship between physical activity and NMR-derived lipoprotein particle profiles in adults, and especially those with elevated cardiometabolic risk, are available. Although the effects of replacing sedentary time with physical activity on cardiovascular risk biomarkers are now emerging (23), no data in relation to lipoprotein profiles exists. More refined determination of lipoprotein subfractions together with objectively measured sedentary behavior and physical activity will improve our understanding of their contribution to cardiometabolic disease risk and may inform more appropriate lipid targets and physical activity interventions for patients. Therefore, the aims of this study were to (i) determine the relationship between objectively measured sedentary behavior and physical activity duration and intensity with lipoprotein particle profiles in a cross-sectional sample of adults, and (ii) to investigate whether replacing sedentary time with light activity or moderate-to-vigorous physical activity (MVPA) is associated with beneficial alterations to lipoprotein particle size and number among all subjects and those at increased cardiometabolic risk (i.e., obese and insulin-resistant individuals).

MATERIALS AND METHODS

Study design. The Cork and Kerry Diabetes and Heart Disease Study (phase II) was a single-center, cross-sectional study conducted between 2010 and 2011. A population representative random sample (Mitchelstown cohort) was recruited from a large primary care center in Mitchelstown, County Cork, Ireland. Full details have been published elsewhere (24). Cohort participants were randomly selected from all registered attending patients in the 50- to 69-yr age group. Of these 2047 (49.2% male) completed the questionnaire and physical examination components of the baseline assessment (response rate, 67%). Of the 745 cohort participants invited to wear the accelerometer, 475 subjects agreed to participate (response rate, 64%). Ethics committee approval conforming to the Declaration of Helsinki was obtained from the Clinical Research Ethics Committee of University College Cork. All participants provided written informed consent.

Clinical data. Participants attended the clinic in the morning after an overnight fast (minimum 8 h). Fasting blood samples were taken on arrival. Data on age, gender, lifestyle factors, and medication use were gathered through a self-completed general health questionnaire and a food frequency questionnaire. Smoking status was defined as never, former, and current smokers. Alcohol consumption was defined as moderate (women and men consuming <14 and 21 units, respectively, in a typical week) and nonmoderate (women and men consuming ≥14 and 21 units, respectively, in a typical week). Dietary fat (percent energy intake) was calculated from food frequency questionnaire responses. Anthropometric measurements (body weight, height, and waist circumference) were recorded as previously described using calibrated instruments according to a standardized protocol (25). Body mass index (BMI) was calculated and used to classify obesity (BMI ≥30 $kg \cdot m^{-2}$).

Biological analyses. Fasting serum total cholesterol (Total-C), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), and TG levels were analyzed using enzymatic colorimetric tests (Olympus Life and Material Science Europa Ltd, Lismeehan, Co, Clare, Ireland) on an Olympus 5400 automatic analyzer (Olympus Diagnostica Gmbh, Hamburg, Germany). Fasting plasma glucose (FPG) was determined using a glucose hexokinase assay by Cork University Hospital Biochemistry Laboratory. Serum insulin was determined using a biochip array system (Evidence Investigator; Randox Laboratories, Antrim, United Kingdom). Homeostasis model assessment (HOMA) calculated as [(FPG × fasting serum insulin)/22.5] was used to classify insulin resistance (HOMA-IR ≥75th percentile based on study population). Serum and plasma were aliquoted and stored at −80°C.

Lipoprotein particle profiling. Serum lipoprotein subclass particle concentrations and average particle diameters were measured on frozen serum samples by NMR spectroscopy at LipoScience, Inc (Raleigh, NC) using the LipoProfile-3 algorithm (9). Weighted-average VLDL, LDL, and HDL particle sizes were computed as the sum of the diameter of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its NMR signal. The following subclasses were investigated: large VLDL (including chylomicrons, if present) (>60 nm), medium VLDL (42–60 nm), small VLDL (29–42 nm), large LDL (20.5–23 nm), small LDL (18–20.5 nm), large HDL (9.4–14 nm), medium HDL (8.2–9.4 nm), and small HDL (7.3–8.2 nm). Further summation of the subclass levels provides total lipoprotein particle concentrations. A lipoprotein insulin resistance (LP-IR) score, which is a weighted combination of the lipoprotein parameters most closely associated with insulin resistance (large VLDL, small LDL, and large HDL particles, and VLDL, LDL, and HDL size), was calculated (26).

Accelerometer protocol. Subjects were invited to participate in the objective physical activity assessment as described previously (27). Physical behavior levels were assessed using a GENEActiv accelerometer (ActivInsights Ltd, Kimbolton, Cambridgeshire, United Kingdom). The technical reliability and validity of this accelerometer have been previously reported (28). The triaxial STMicroelectronics accelerometer with a dynamic range of ±6g (g = 9.81 $m \cdot s^{-2}$) was attached to the participants' preferred wrist with a strap (29). Acceleration was sampled at 100 Hz, and the accelerometer was worn for 7 consecutive days. After return of the accelerometer to the coordination center, data were extracted using GENEActiv software and then collapsed using the sum of the vector magnitude ($\sum|\sqrt{x^2 + y^2 + z^2} - g|$) into 60-s epochs (28). Wear and nonwear time was identified by the procedure outlined by van Hees et al. (29). Nonwear time was calculated

for each accelerometer axis on the basis of the SD and the value range. The procedure was carried out on successive blocks of 30 min. A block was categorized as nonwear time if the SD was less than 3.0 mg (1 mg = 0.00981 $m \cdot s^{-2}$) or if the value range was less than 50 mg, for at least two of the three axes. Four hundred and seventy-five subjects wore the accelerometer. Each time interval, from the daytime wear-time (6 AM–12 AM) periods, was categorized on the basis of validated cutoff points for dominant and nondominant wrist wear (27). After exclusion of 16 individuals without data collected due to technical issues, inappropriate location of wear, or nonreturn of the device and 63 participants with invalid wear time (valid wear was defined as >10-h activity on all 7 d of wear), the remaining 396 subjects were included in the current analysis. A flowchart outlining the subject selection for the current analysis of the Mitchelstown cohort is presented in Figure, Supplemental Digital Content 1, Flowchart outlining the subject selection for the current analysis of the Mitchelstown cohort, http://links.lww.com/MSS/B133.

Statistical analysis. Statistical analysis was conducted using PASW Statistics version 18.0 for Windows (SPSS Inc, Chicago, IL) and Stata (version 12; Stata Corp, College Station, TX). Median and 25th and 75th percentiles for average daily minutes spent in sedentary behavior, light activity, and MVPA were calculated. For both physical behavior and lipoprotein profile data, ANOVA, *t*-tests, and nonparametric tests compared mean, percentage, and median values, respectively. Dunn's *post hoc* test using Bonferroni method examined pairwise comparisons across tertiles of activity and lipoprotein parameters. Relationships between lipoprotein parameters and physical behavior were assessed using Spearman correlation coefficients and linear regression after adjustment for covariates (age, gender, smoking status, alcohol consumption, dietary fat intake, lipid-lowering medication, BMI, and daily hours spent in sedentary behavior and physical activity, mutually adjusting for alternative exposures). Isotemporal substitution regression modeling quantified the associations between replacing 30 $min \cdot d^{-1}$ of sedentary behavior with equal amounts of light activity and MVPA on lipoprotein profiles. Isotemporal analyses examined each activity intensity while adjusting for time in other physical behaviors and total time. More specifically, the coefficient from an isotemperol model represents the estimated effects of substituting a specific activity intensity for the category dropped while holding total (wear) time and other activity constant (30). Thus, if we examine the effect of replacing sedentary behavior with light activity, we include light activity, MVPA, and total wear time in the model, whereas a model examining the effects of replacing MVPA with sedentary behavior would include sedentary behavior, light activity, and total time. The coefficients in this analysis represent the replacement of sedentary behavior with light activity or MVPA. The isotemporal model is a linear regression model. Although its primary function here is to determine whether substitution of sedentary behavior with different physical activity behaviors is beneficial to health, it also examines whether this substitution relationship is linear. Thus, the coefficients represent the effects for every 30-min increase substitution on each lipid profile marker. These models are described in greater detail elsewhere (31,32). Before entry into the models, all intensity categories were divided by a constant of 30 such that a unit increase in the activity variable represented a 30-min increase in the given activity intensity. Lipoprotein markers were log transformed for analysis and exponentiated, and β coefficients are presented. Two models were run for each lipoprotein parameter. The first model included age, gender, smoking status, alcohol, and dietary fat intake. Model 2 additionally adjusted for BMI and lipid-lowering medication use. Analysis was performed in the entire data set and in the obese/nonobese and insulin-resistant/nonresistant subgroups. An alpha level of 0.05 was set to evaluate significance.

RESULTS

Clinical and lifestyle characteristics and lipoprotein profiles of study sample and subgroups. The clinical and lifestyle characteristics and lipoprotein profiles of the cohort and subgroups are presented in Table 1. Differences in physical behavior profiles were observed for average daily minutes spent in all intensities for both subgroups ($P < 0.05$). Several features of atherogenic dyslipidemia were observed among the obese and insulin-resistant subjects including higher TG concentrations ($P < 0.001$) and increased numbers of both large ($P < 0.001$) and medium ($P < 0.001$) VLDL particles. Obese and insulin-resistant subjects also had lower HDL-C concentrations ($P < 0.005$) and less large ($P < 0.001$) and more small LDL and HDL particles ($P < 0.001$). Larger VLDL particle size and smaller LDL and HDL particle sizes were reported among the obese and insulin-resistant subjects ($P < 0.001$). Calculated LP-IR scores were higher in both subgroups ($P < 0.001$). Distribution of subjects by gender, BMI, and HOMA-IR groups across tertiles of each activity level is shown in Table 2. No gender differences were noted. Both the obese and insulin-resistant individuals spent greater time in sedentary behavior and less time in MVPA than did their nonobese and non–insulin-resistant counterparts.

Lipoprotein particle concentration and size according to tertiles of sedentary behavior and physical activity intensity. Among all subjects, increasing amounts of sedentary time were associated with a range of unfavorable features including increased numbers of large ($P < 0.01$) and medium VLDL particles ($P < 0.05$), greater average VLDL particle size ($P < 0.01$), and higher TG and lower HDL-C concentrations ($P < 0.05$; Table 3). Conversely, more time spent in either light activity or MVPA was associated with less large VLDL particles ($P < 0.05$) and smaller average VLDL particle size ($P < 0.05$). Light activity was additionally positively associated with HDL-C concentrations ($P < 0.05$). *Post hoc* analysis revealed differences between the lowest (T1) and highest (T3) tertiles for all activity intensities for total triglyceride rich lipoproteins (TRL) and large VLDL particles, VLDL particle size, LP-IR, and all of the traditional lipid parameters including TG (17.4% reduction T3 vs T1 light

TABLE 1. Clinical and lifestyle characteristics and lipoprotein profiles of the study sample and subgroups.

	Entire Sample	Normal Weight	Overweight	Obese	*P*	Not Insulin Resistant	Insulin Resistant	*P*
n	396	79	189	128		293	97	
Age, yr	59.58 ± 5.46	58.51 ± 5.43	59.73 ± 5.45	59.58 ± 5.43	0.13	59.49 ± 5.48	59.83 ± 5.44	0.61
Male, %	46	64.6	54.5	46.9	**0.046**	41.7	56.7	**0.01**
BMI, $kg \cdot m^{-2}$	28.86 ± 4.55	23.25 ± 1.54	27.77 ± 1.35	33.95 ± 3.61	<**0.001**	27.54 ± 3.61	32.85 ± 4.86	<**0.001**
Waist, cm	96.27 ± 13.39	82.80 ± 8.24	93.51 ± 10.00	108.70 ± 10.85	<**0.001**	92.56 ± 12.04	107.29 ± 11.29	<**0.001**
FPG, $mmol \cdot L^{-1}$	5.21 ± 1.06	4.86 ± 0.49	5.09 ± 0.80	5.61 ± 1.41	<**0.001**	4.94 ± 0.51	6.01 ± 1.62	<**0.001**
HOMA-IR	2.96 ± 3.25	1.49 ± 0.95	2.14 ± 1.50	5.11 ± 4.72	<**0.001**	1.68 ± 0.80	6.87 ± 4.56	<**0.001**
TG, $mmol \cdot L^{-1}$	1.16 (0.85, 1.63)	0.94 (0.75, 1.31)	1.13 (0.84, 1.55)	1.40 (1.00, 1.93)	<**0.001**	1.05 (0.79, 1.48)	1.58 (1.16, 2.20)	<**0.001**
Total-C, $mmol \cdot L^{-1}$	5.30 (4.60, 6.00)	5.70 (5.00, 6.40)	5.30 (4.72, 5.90)	5.00 (4.30, 5.67)	**0.001**	5.30 (4.72, 6.10)	5.20 (4.32, 5.65)	0.055
HDL-C, $mmol \cdot L^{-1}$	1.43 (1.19, 1.68)	1.72 (1.37, 1.96)	1.46 (1.26, 1.66)	1.26 (1.07, 1.53)	<**0.001**	1.51 (1.28, 1.75)	1.20 (1.03, 1.50)	<**0.001**
LDL-C, $mmol \cdot L^{-1}$	3.10 (2.60, 3.80)	3.40 (2.92, 4.00)	3.22 (2.64, 3.80)	2.90 (2.53, 3.60)	**0.005**	3.20 (2.70, 3.90)	2.90 (2.32, 3.40)	**0.002**
Energy intake, kcal	1976 ± 39	2046 ± 89	1984 ± 61	1920 ± 63	0.522	1958 ± 46	2060 ± 79	0.261
Current smokers, %	14.8	33.0	22.6	16.9	**0.001**	29.2	19.6	0.18
Moderate drinkers, %	68.5	73.2	66.9	67.8	0.69	68.9	67.2	0.79
Sedentary, min	909 (853, 971)	894 (844, 970)	905 (843, 951)	945 (879, 991)	**0.003**	898 (840, 957)	952 (891, 994)	<**0.0001**
Light activity, min	103 (69, 135)	107 (68, 134)	108 (78, 138)	91 (58, 127)	**0.04**	109 (75, 141)	85 (55, 119)	**0.0001**
MVPA, min	62 (32, 103)	70 (42, 110)	67 (38, 104)	45 (23, 80)	**0.0008**	69 (38, 107)	45 (22, 68)	**0.0001**
Lipoprotein particle concentration								
Total TRL, $nmol \cdot L^{-1}$	53.9 (34.2, 84.8)	41.9 (27.1, 68.7)	51.4 (34.2, 82.5)	60.5 (42.4, 99.5)	<**0.001**	48.0 (29.8, 77.4)	69.1 (49.4, 107.8)	<**0.001**
Large VLDL, $nmol \cdot L^{-1}$	1.0 (0.5, 3.05)	0.6 (0.30, 1.0)	0.9 (0.5, 2.4)	2.2 (0.7, 4.8)	<**0.001**	0.8 (0.4, 2.1)	2.9 (1.2, 7.0)	<**0.001**
Medium VLDL, $nmol \cdot L^{-1}$	20.5 (10.7, 34.7)	14.5 (7.4, 21.9)	20.5 (10.2, 34.3)	28.7 (16.3, 47.9)	<**0.001**	17.6 (9.7, 31.6)	29.9 (19.6, 54.5)	<**0.001**
Small VLDL, $nmol \cdot L^{-1}$	28.6 (17.65, 45.7)	24.5 (14.4, 46.2)	29.2 (17.6, 45.3)	29.7 (19.4, 45.9)	0.48	27.3 (16.1, 43.6)	33.0 (20.2, 50.0)	0.11
Total LDL, $nmol \cdot L^{-1}$	1225 (985, 1477)	1205 (972, 1488)	1221 (990, 1517)	1249 (983, 1461)	0.68	1215 (982 1482)	1265 (1029, 1476)	0.29
IDL, $nmol \cdot L^{-1}$	88.0 (49.0, 153.0)	89.0 (39.0, 149.0)	90.0 (53.0, 157.0)	84.5 (41.8, 162.0)	0.81	90.0 (51.5, 151.0)	85.0 (39.5, 159.5)	0.73
Large LDL, $nmol \cdot L^{-1}$	606 (394, 807)	722.5 (557, 931)	614 (405, 807)	468 (300, 678)	<**0.001**	633 (449, 863)	428 (212, 654)	<**0.001**
Small LDL, $nmol \cdot L^{-1}$	523 (97, 826)	126 (81, 633)	509 (94, 819)	607 (355, 937)	**0.001**	477 (90, 743)	708 (458, 1000)	<**0.001**
Total HDL, $\mu mol \cdot L^{-1}$	37.3 (3.85, 9.40)	39.3 (35.7, 44.2)	38.0 (34.5, 42.4)	36.2 (32.6, 39.8)	**0.01**	37.9 (34.5, 42.4)	35.5 (32.4, 40.5)	**0.003**
Large HDL, $\mu mol \cdot L^{-1}$	6.20 (3.85, 9.40)	8.9 (5.7, 13.3)	6.0 (4.1, 9.1)	4.90 (3.3, 7.0)	<**0.001**	6.9 (4.5, 10.4)	4.3 (3.1, 6.5)	<**0.001**
Medium HDL, $\mu mol \cdot L^{-1}$	12.7 (9.00, 16.95)	12.7 (9.7, 18.6)	13.5 (9.1, 17.0)	12.2 (8.7, 16.5)	0.52	12.8 (9.3, 16.9)	11.7 (8.6, 17.1)	0.73
Small HDL, $\mu mol \cdot L^{-1}$	17.3 (13.60, 21.30)	16.3 (12.3, 19.2)	18.0 (14.6, 21.9)	17.8 (14.3, 21.5)	0.14	17.1 (13.5, 20.9)	18.9 (14.9, 21.8)	0.07
Lipoprotein particle size								
VLDL, nm	43.95 (41.02, 47.3)	41.8 (39.8, 46.0)	43.3 (40.8, 46.2)	45.7 (42.8, 49.8)	<**0.001**	43.2 (40.6, 46.2)	46.2 (43.1, 51.9)	<**0.001**
LDL, nm	21.00 (20.50, 21.40)	21.2 (20.9, 21.5)	21.0 (20.6, 21.3)	20.8 (20.3, 21.1)	<**0.001**	21.1 (20.6, 21.4)	20.6 (20.2, 21.0)	<**0.001**
HDL, nm	9.30 (8.90, 9.70)	9.6 (9.2, 10.0)	9.3 (8.9, 9.7)	9.2 (8.8, 9.5)	<**0.001**	9.4 (9.0, 9.8)	9.0 (8.7, 9.3)	<**0.001**
LP-IR score	32.0 (13.0, 52.0)	14.0 (4.0, 38.0)	30.0 (12.0, 48.0)	47.5 (26.8, 59.0)	<**0.001**	25.0 (10.0, 46.5)	51.0 (32.0, 65.0)	<**0.001**

Values are presented as mean ± SD, percent, and median (25th, 75th percentiles). Sedentary time and physical activity are average number of minutes spent in each type of behavior per activity per day. *P* values were generated by comparing medians across groups using nonparametric tests. ANOVA, *t*-tests, and nonparametric tests were used to compare mean, %, and median values, respectively, in subgroups. Boldface indicates $P < 0.05$.

EPIDEMIOLOGY

activity) and total, LDL, and HDL (7.4% increase T3 vs T1 light activity) cholesterol concentrations ($P < 0.05$). The following exceptions are noted: sedentary behavior (LDL-C), light activity (VLDL size and cholesterol), and MVPA (TG (despite a 15.5% reduction), cholesterol, and HDL-C). Correlation analyses presented in Supplementary Table 1 support the aforementioned findings between sedentary behavior, light activity, and MVPA, with large VLDL particle concentration and VLDL particle size among all subjects (see Table, Supplemental Digital Content 2, Spearman correlation coefficients between lipoprotein variables, sedentary behavior, and physical activity intensity among all subjects and subgroups, http://links.lww.com/MSS/B134). Regression analysis presented in Supplementary Table 2 shows that MVPA was statistically significantly inversely associated with both large VLDL particles and LP-IR score after adjustment for sedentary time and other confounding factors, whereas the associations noted between sedentary time and numbers of large VLDL particles and VLDL particle size in model 1 were no longer significant in the fully adjusted model, which additionally takes BMI, lipid-lowering medication, and average daily hours spent in light activity and MVPA into account (see Table, Supplemental Digital Content

TABLE 2. Distribution of subgroups according to tertiles of physical activity intensity.

	Male	Female	*P*	Normal Weight	Overweight	Obese	*P*	Non-IR	IR	*P*
Sedentary										
Tertile 1 (569–872 min)	37.9	29.4	0.191	39.2	38.1	22.7	**0.001**	39.6	16.5	<**0.0001**
Tertile 2 (873–951 min)	30.2	36.0		29.1	37.0	30.5		33.8	32.0	
Tertile 3 (952–1075 min)	31.9	34.6		31.7	24.9	46.9		26.6	51.6	
Light										
Tertile 1 (4–81 min)	35.2	31.8	0.589	31.7	28.0	42.2	0.103	28.7	46.4	**0.004**
Tertile 2 (82–121 min)	30.8	35.5		34.2	34.4	31.2		34.1	29.9	
Tertile 3 (122–332 min)	34.1	32.7		34.2	37.6	26.6		37.2	23.7	
MVPA										
Tertile 1 (0–42 min)	25.3	40.2	**0.002**	25.3	30.2	43.0	**0.02**	29.0	43.3	<**0.0001**
Tertile 2 (43–82 min)	33.5	33.2		36.7	31.7	33.6		31.7	39.2	
Tertile 3 (83–346 min)	41.2	26.6		38.0	38.1	23.4		39.3	17.5	

Values are presented as percent. *P* values were generated using nonparametric tests comparing distribution among gender, BMI, and HOMA-IR groups across tertiles of sedentary behavior and physical activity intensity. Boldface indicates $P < 0.05$.

TABLE 3. Lipoprotein particle size and concentration according to tertiles of sedentary behavior and physical activity intensity among the whole cohort.

	Sedentary				Light Activity				MVPA			
	Tertile 1 (*n* = 132)	Tertile 2 (*n* = 132)	Tertile 3 (*n* = 132)	*P*	Tertile 1 (*n* = 132)	Tertile 2 (*n* = 132)	Tertile 3 (*n* = 132)	*P*	Tertile 1 (*n* = 132)	Tertile 2 (*n* = 132)	Tertile 3 (*n* = 132)	*P*
Lipoprotein particle size												
VLDL size	42.8 (40.4–46.1)	44.3 (41.6–47.4)	44.8 (41.9–48.0)	**0.009**	44.7 (42.1–47.9)	42.8 (40.8–46.4)	43.9 (40.4–47.4)	**0.04**	44.4 (41.8–47.2)	44.6 (41.2–49.2)	42.8 (40.5–46.1)	**0.013**
LDL size	21 (20.5–21.4)	20.9 (20.6–21.4)	21.0 (20.5–21.3)	0.94	21.0 (20.5–21.3)	20.9 (20.6–21.4)	21.0 (20.6–21.4)	0.69	21.0 (20.7–21.3)	20.9 (20.4–21.4)	20.9 (20.4–21.3)	0.36
HDL size	9.3 (8.9–9.7)	9.3 (8.9–9.7)	9.3 (8.9–9.7)	0.82	9.3 (8.9–9.7)	9.3 (8.9–9.7)	9.3 (8.9–9.7)	0.75	9.4 (9.0–9.7)	9.2 (8.8–9.8)	9.3 (8.8–9.6)	0.09
Lipoprotein particle numbers												
Total TRL	50.4 (29.4–74.1)	56.9 (34.6–95.8)	56.5 (37.5–84.8)	0.15	56.9 (37.5–94.2)	53.2 (36.8–86.4)	50 (26.5–77.4)	0.06	54.4 (37.4–78.6)	55.3 (33.4–97.9)	53.1 (30.9–82.9)	0.65
Large VLDL	0.8 (0.4–2.0)	1.1 (0.5–3.5)	1.3 (0.6–3.5)	**0.007**	1.45 (0.60—3.7)	0.9 (0.5–2.3)	0.8 (0.4–2.7)	**0.02**	1.2 (0.6–3.4)	1.15 (0.5–3.6)	0.8 (0.4–2.1)	**0.02**
Medium VLDL	17.1 (10.7–30.3)	21.9 (10.8–45.6)	21.8 (10.6–38.7)	**0.02**	23 (10.0–48.0)	20.5 (11.4–34.2)	18.5 (10.6–31.6)	0.09	20.9 (10.5–35.6)	20.3 (10.7–44.4)	19.5 (11.6–31.8)	0.40
Small VLDL	28.3 (15.8–46.0)	29.2 (16.4–48.3)	28.5 (19.8–43.2)	0.96	30.5 (19.6–44.0)	29.2 (18.2–48.1)	25.3 (14.2–45.4)	0.25	27.6 (18.9–43.0)	29.8 (16.4–48.3)	29.8 (17.0–47.0)	0.87
IDL	901 (51–137)	90 (50–172)	82 (46–162)	0.79	80 (51–153)	95 (46–160)	91 (51–144)	0.82	90 (43–168)	83 (46–143)	96 (52–147)	0.554
Total LDL	1266 (1035–1524)	1248 (988–1510)	1193 (918–1364)	0.06	1189 (905–1373)	1277 (1038–1526)	1243 (997–1498)	0.05	1185 (902–1404)	1245 (1011–1493)	1261 (996–1538)	0.09
Large LDL	613 (419–850)	608 (392–797)	565 (363–775)	0.52	595 (327–745)	598 (943–837)	620 (390–813)	0.28	615 (419–804)	610 (346–812)	586 (391–793)	0.659
Small LDL	568 (110–829)	521 (93–907)	492 (96–740)	0.55	497 (94–812)	544 (113–880)	554 (92–828)	0.69	445 (94–691)	596 (94–931)	572 (110–895)	**0.034**
Total HDL	37.5 (35.4–41.9)	37.3 (33.9–41.7)	37.0 (33.2–41.7)	0.28	37.0 (33.7–41.7	37.1 (34.0–42.3)	37.6 (35.3–416)	0.64	37.7 (33.4–42.7)	36.8 (33.7–41.5)	37.3 (34.9–41.7)	0.65
Large HDL	6.35 (4.05–8.95)	6.1 (3.45–9.85)	6.0 (3.9–8.9)	0.88	6.0 (3.7–96)	6.2 (3.8–9.0)	6.3 (4.2–9.8)	0.63	6.2 (4.4–9.9)	5.8 (3.4–9.9)	6.3 (3.7–8.8)	0.34
Medium HDL	12.6 (9.5–16.7)	13.7 (9.35–16.8)	12.5 (8.7–17.1	0.69	12.8 (8.7–17.5)	13.6 (10.1–17.1)	12.1 (8.8–16.1)	0.21	12.5 (8.7–18.0)	12.8 (9.0–16.7)	13.3 (9.7–17.0)	0.87
Small HDL	18.4 (14.9–22.6)	16.7 (13.8–20.4)	16.7 (13.1–20.5)	0.11	16.8 (13.1–20.6)	16.8 (14.3–21.1)	18.5 (14.5–21.6)	0.28	16.6 (12.5–20.5)	17.3 (14.0–20.4)	18.1 (14.9–22.1)	0.141
LP-IR score	25 (13–48)	34 (12–56)	34 (12–56)	0.29	38 (13–55)	33 (13–49)	27 (12–51)	0.30	33 (11–48)	35 (12–58)	27 (16–48)	0.47
Lipid profile												
TG, mmol·L^{-1}	1.09 (0.79–1.48)	1.21 (0.84–1.76)	1.3 (0.91–1.64)	**0.04**	1.32 (0.89–1.71)	1.15 (0.85–1.61)	1.09 (0.80–1.51)	0.10	1.29 (0.91–1.56)	1.18 (0.84–1.82)	1.09 (0.82–1.48)	0.15
Total-C, mmol·L^{-1}	5.3 (4.8–6.1)	5.4 (4.8–6.0)	5.0 (4.3–5.7)	**0.0075**	5.0 (4.3–5.7)	5.5 (4.8–6.1)	5.3 (4.7–6.0)	**0.02**	5.1 (4.3–5.8)	5.4 (4.7–6.0)	5.3 (4.7–6.1)	0.148
HDL-C, mmol·L^{-1}	1.5 (1.3–1.7)	1.42 (1.2–1.68)	1.36 (1.12–1.65)	**0.03**	1.36 (1.1–1.65)	1.49 (1.22–1.71)	1.46 (1.25–1.71)	**0.03**	1.40 (1.2–1.7)	1.41 (1.18–1.74)	1.46 (1.24–1.64)	0.900
LDL-C, mmol·L^{-1}	3.2 (2.8–3.9)	3.3 (2.7–3.8)	2.95 (2.3–3.6)	**0.013**	3.0 (2.4–3.6)	3.3 (2.7–3.9)	3.2 (2.7–3.7)	**0.02**	3.0 (2.4–3.7)	3.2 (2.7–3.7)	3.2 (2.8–3.9)	**0.03**

Values are presented as median (25th–75th percentile). NMR-derived particle sizes are presented in nanometers, and particle concentrations are expressed as nanomoles per liter for LDL and VLDL particles and micromoles per liter for HDL particles. *P* values were generated using Kruskal–Wallis analysis comparing lipoprotein particle size and concentrations across tertiles of sedentary behavior and physical activity intensities. Boldface indicates $P < 0.05$.

3, Association between sedentary behavior and physical activity intensity with selected lipoprotein parameters among all subjects, http://links.lww.com/MSS/B135).

Replacing sedentary behavior with physical activity: effect on lipoprotein particle profile. Reallocating 30 min of sedentary time with MVPA was negatively associated with large VLDL, small LDL particles, and LP-IR scores and positively associated with large HDL particles ($P < 0.05$), resulting in more favorable average VLDL, LDL, and HDL particle diameters ($P < 0.05$). Data on these selected lipid parameters are presented in Table 4. The beneficial alterations to VLDL particle size, large VLDL particle concentration, and LP-IR scores remained in the fully adjusted model ($P < 0.05$). No statistically significant associations were observed when 30 min of sedentary behavior was substituted for light activity ($P > 0.05$). Examination of the high-cardiometabolic-risk groups revealed that when stratified by HOMA-IR, reallocation of 30 min of sedentary time with MVPA was negatively associated with large VLDL particle concentration ($B = -0.32$; 95% confidence interval (CI), −0.63 to −0.015; $P < 0.05$) and VLDL particle size ($B = -0.06$; 95% CI, −0.11 to −0.004; $P < 0.05$) among the insulin-resistant individuals, but not among the non–insulin-resistant individuals ($B = -0.07$ (95% CI, −0.14 to 0.008; $P > 0.05$) for large VLDL particle concentration and $B = -0.01$ (95% CI, −0.03 to 0.0001; $P > 0.05$) for VLDL particle size), in the fully adjusted model. No significant findings were observed when sedentary time was replaced with light activity or MVPA among the obese or nonobese individuals ($P > 0.05$; data not shown).

TABLE 4. Replacing 30 min of sedentary time with physical activity: associations with selected lipoprotein parameters among all subjects.

	Large VLDL		Small LDL		Large HDL		VLDL Size		LDL Size		HDL Size		LP-IR
	ß Coefficients (95% CI)												
Model A													
Sedentary, min·d^{-1}		Replaced		Replaced		Replaced		Replaced		Replaced		Replaced	
Light, min·d^{-1}	0.03 (−0.05 to 0.12)		0.09 (−0.18 to 0.21)		−0.03 (−0.084 to 0.02)		0.01 (−0.001 to 0.027)		−0.002 (−0.004 to 0.005)		−0.004 (−0.009 to 0.0004)		0.09 (−0.002 to 0.18)
MVPA, min·d^{-1}	−0.14 (−0.21 to −0.06)**		−1.12 (−0.22 to −0.007)*		0.06 (0.01 to 0.11)*		−0.03 (−0.04 to −0.012)***		0.003 (0.0004 to 0.005)*		0.005 (0.0006 to 0.01)*		−0.13 (−0.21 to −0.05)**
Model B													
Sedentary, min·d^{-1}		Replaced		Replaced		Replaced		Replaced		Replaced		Replaced	
Light, min·d^{-1}	0.03 (−0.05 to 0.11)		0.09 (−0.02 to 0.20)		−0.03 (−0.08 to 0.02)		0.01 (−0.005 to 0.03)		−0.002 (−0.004 to 0.0005)		−0.004 (−0.009 to 0.0005)		0.08 (−0.003 to 0.17)
MVPA, min·d^{-1}	−0.10 (−0.18 to −0.02)*		−0.08 (−0.18 to 0.03)		0.04 (−0.14 to 0.08)		−0.02 (−0.4 to −0.008)**		0.002 (−0.001 to 0.004)		0.003 (−0.001 to 0.008)		−0.08 (−0.16 to 0.001)*

Data are standardized ß coefficients (95% CI). Coefficients are based on average daily sedentary and physical activity duration. Results were expressed as regression coefficients that represented the change in outcome observed when 30 min of sedentary behavior was substituted with 30 min of an alternate activity intensity (light activity or MVPA). Model A was adjusted for age, gender, dietary fat intake, smoking status, alcohol consumption, and alternative physical behavior intensities. Model B was additionally adjusted for BMI and lipid-lowering medication use.

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.0001$.

DISCUSSION

The current findings suggest that independent of potential confounders and time spent in other activities, both daily time spent in MVPA and theoretical replacement of 30 min of sedentary time with MVPA, but not light activity, were associated with a more favorable lipoprotein profile characterized by less large VLDL particles resulting in more favorable average VLDL particle size and improved LP-IR score. We further examined whether replacement of sedentary behavior with physical behavior modulates obesity and insulin resistance–associated dyslipidemia. Similar beneficial associations between substitution of sedentary time for MVPA on VLDL particle size and large VLDL concentration were observed among the insulin-resistant individuals only.

Lipoprotein profiling identified a less favorable lipoprotein profile among the high-cardiometabolic-risk groups including increased numbers of large VLDL and small proatherogenic LDL and HDL particles, higher LP-IR scores, elevated TG, and reduced HDL-C concentrations. VLDL overproduction is a hallmark of dyslipidemia in obesity and insulin resistance (33,34). The predominance of large VLDL may reflect hepatic overproduction of TG packaged into VLDL particles overloaded with TG. We have previously demonstrated increased expression of microsomal TG transfer protein, which is responsible for hepatic and intestinal TRL assembly,

in human T2DM subjects and animal models of insulin resistance, obesity, and diabetes (35–37). Large VLDL particles may be more important in terms of CVD risk than smaller VLDL particles (19) because they are associated with the proatherogenic small, dense LDL phenotype. Relative to LDL particles, these large lipid-enriched VLDL particles are more efficiently hydrolyzed by lipoprotein lipase, have greater capacity to penetrate the endothelial wall, and are preferentially retained in the arterial intima (38). VLDL particles may also be directly taken up by macrophages (without any modifications like LDL) to create foam cells, the hallmark cells of atherosclerotic plaque. Hepatic overproduction of large TG-rich VLDL may initiate diabetic dyslipidemia (39). The pathway from obesity and insulin resistance toward overt T2DM represents a progressive phenotype, with dyslipidemia frequently preceding T2DM by many years. Thus, interventions to improve dyslipidemia characterized by elevated TG and large VLDL particles may help to attenuate atherogenesis and the progression from obesity and insulin resistance toward overt T2DM and related cardiometabolic disease. Although interest in TG in the context of CVD has fluctuated over the last four decades, the recent recommendation by the European Atherosclerosis Society to treat mild to moderately elevated TG to prevent CVD (40) further emphasizes this point.

A recent cross-sectional study reported unfavorable associations between sedentary time and insulin secretion and insulin sensitivity (41). Interestingly, their prospective analysis indicates that less sedentary time may partly negate some of the deleterious effects of increasing BMI on glucose-insulin homeostasis. Examination of the high-cardiometabolic-risk groups in the current work revealed that when stratified by HOMA-IR, reallocation of 30 min of sedentary time with MVPA was negatively associated with large VLDL particle concentration and VLDL particle size among the insulin-resistant individuals but not among the non–insulin-resistant individuals, suggesting that insulin resistance is driving the VLDL-related results. Interestingly, substitution of sedentary time with light activity or MVPA was not associated with any significant changes to the lipoprotein profile among the obese individuals. The LP-IR score developed by LipoScience is an alternative means of assessing a patient's insulin resistance status based on lipoprofile data, which in turn may help predict risk of future T2DM independent of glucose concentration. LP-IR scores were higher among the obese and not surprisingly among the insulin-resistant subjects and were not modulated by physical activity intensity or duration in these subgroups (data not shown). However, correlation analysis of the cohort as a whole revealed a positive association between sedentary behavior and LP-IR scores. Furthermore, regression analysis identified negative associations between MVPA and LP-IR scores. Moreover, isotemporal modeling analysis revealed that substitution of sedentary time with MVPA, but not light activity, was associated with more favorable LP-IR scores, illustrating one of the many health benefits of MVPA.

Objective measurement of physical activity over a 7-d period revealed a trend toward increased sedentary time and less time engaged in light activity and MVPA among the obese and insulin-resistant individuals. Our analysis suggests that reallocating sedentary behavior with MVPA, but not light activity, may be associated with a less atherogenic lipoprotein profile. Limited data on lipoprotein subfractions and sedentary behavior or physical activity, either subjectively or objectively measured, exist. Frazier-Wood et al. (42) reported associations between screen time and numbers of large VLDL, large HDL, and small LDL particles in women, but not men. Aadland et al. (43) identified positive associations between accelerometer-derived sedentary behavior and small VLDL particles, large LDL particles, and TG, whereas MVPA was positively associated with large HDL particles, HDL size, HDL-C, and apolipoprotein A1. Although these findings were based on only 73 subjects, they indicate differential effects of sedentary behavior and MVPA on lipoprotein profiles. In the current work, the primary association between replacing sedentary time and physical activity seems to be on VLDL particles, most likely through altered hepatic TRL production, secretion, and/or uptake. Consistent with this are the results from the isotemporal substitution analysis wherein beneficial alterations to VLDL particle size and concentration were identified when 30 min of sedentary time was displaced with MVPA, but not light activity. Our findings are also in keeping with the idea proposed by Tremblay et al. (44) that sedentary behavior is distinct from lack of MVPA, has independent and different effects on metabolic health, and thus should be treated as a separate entity. Supporting this notion are data from a recent harmonized meta-analysis of more than 1 million men and women which demonstrate that the negative health outcomes associated with sedentary time (in particular, increased mortality risk) may be counteracted by high levels of moderate activity (45). Such findings may be particularly encouraging for those whom prolonged daily periods of sitting cannot be avoided.

Although our findings make a novel contribution to the knowledge base, it is important to bear in mind that they are based on theoretical rather than actual replacement of a portion of time spent in sedentary behavior with physical activity and warrant further investigation. Our data are useful in providing proof of concept, but they may also inform the development of well-designed randomized controlled trials assessing the effect of different substitution interventions, ideally with longitudinal analysis of hard outcomes (such as CVD, T2DM, or mortality). Data arising from such investigations will provide greater evidence to guide behavior change, policy, and clinical practice recommendations. Current recommendations to increase activity with moderate-intensity activities are undoubtedly of value, but the promotion of less sedentary behavior particularly among the least active who are at greatest cardiometabolic risk is also warranted. Examination of overweight/obese subjects with T2DM demonstrated favorable consequences of replacing prolonged unbroken sedentary time with either nonprolonged sedentary time or light activity on BMI and waist circumference (46). In a study of overweight sedentary male subjects randomized to 6 months

of one of three exercise regimes (high or low amount of vigorous activity, low amount of moderate activity), only the moderate-intensity exercise resulted in sustained VLDL and TG-lowering medication, and greater reductions in large VLDL concentration and size (47). Although this study did not examine obese or insulin-resistant individuals, their findings support the promotion of reducing sedentary time and increasing moderate activity with a view of improving the lipoprotein profile. More recently, Sarzynski et al. (48) conducted a meta-analysis to examine lipoprotein subclass responses to regular exercise as measured in 10 exercise interventions from six cohorts. Despite differences in study populations and exercise regimens, meta-analysis showed that regular exercise was associated with reduced concentrations of large VLDL particles and a shift toward larger LDL and HDL particles (48).

Examination of exercise programs of differing amounts and intensities demonstrated that the greatest improvements to the lipid profile among sedentary overweight adults are related to the amount of activity rather than the intensity (49). Our data, in particular examination of lipoprotein particle size and concentration according to tertiles of sedentary behavior and physical activity intensity, also highlight the importance of activity duration. One potential explanation for this may be nonexercise activity thermogenesis, that is, the energy expenditure of everyday living excluding purposeful exercise. It has been proposed that nonexercise activity thermogenesis activation through increasing standing or ambulatory time may be useful in reversing obesity (50). Moreover, longer duration of daily nonsedentary activities (defined as behaviors that require muscle power, walking, and standing) has been associated with lower prevalence of insulin resistance, even after adjusting for leisure-time activity level (51). Thus, it is plausible that the metabolic benefits associated with reduced sedentary time and/or increased MVPA among insulin-resistant individuals may extend beyond lipid parameters.

Two main strengths of our study are the use of NMR to determine lipoprotein profiles and the use of a valid and reliable accelerometer capable of assessing time spent in sedentary, light activity, and MVPA categories. However, the cross-sectional study design limits inference regarding causality, and although we controlled for confounding factors, we cannot exclude the possibility that unmeasured confounders, such as genotype, may also influence our observations. Physical activity data were collected over a 1-wk period, which may not reflect longer-term habitual physical activity levels. Generalizability of our findings may also be limited. The Mitchelstown cohort (response rate, 67%) was a random sample of middle-age adults from an area representative of both urban and rural populations in Ireland. Our previous research suggests that approximately 98% of Irish adults are registered with a general practitioner and that, even in the absence of a universal patient registration system, it is possible to perform population-based epidemiological studies that are representative of the general population using these methods (52). Within the subsample examined in the current analysis, women were more likely to agree to wear the accelerometer. However, it should be noted that there were no statistically significant differences in age, gender, HOMA, or BMI between all subjects included (n = 396) and excluded (n = 77) in the final analysis. Furthermore, we reported high levels of MVPA among our cohort using the GENEActiv accelerometer. It is important to note that 55% of this population were engaged in farming and other manual labor, contributing to higher activity levels. Comparison of the GENEActiv accelerometer with other physical activity devices has mainly been conducted in children and adolescent populations (53–57). However, three studies have compared the GENEActiv accelerometer with other devices in adult populations (58–60). Rowlands et al. (59,60) compared the GENEActiv acceleration levels with those measured by the ActiGraph GT3X+. Their data suggest that habitual activity level, in particular MVPA, and activity patterns may compare well between devices. Pavey et al. (58) compared sedentary time estimation with the activPAL. Positive comparisons between devices were observed, indicating that both devices provide similar descriptive estimates of sedentary time in adult population samples.

CONCLUSIONS

In conclusion, our results represent a novel and important contribution to the knowledge base, supporting the hypothesis that replacing a portion of sedentary time with MVPA is associated with beneficial modifications to VLDL particle size and number and LP-IR score among adults, particularly among insulin-resistant individuals. Although these findings require further investigation, they highlight the need to develop physical activity interventions aimed at improving atherogenic dyslipidemia and lowering cardiometabolic risk.

This work was supported by research grants from the Irish Health Research Board (reference HRC/2007/13 to I. J. P.) and the Irish Heart Foundation (Noel Hickey Bursary supported by an educational grant from Pfizer Healthcare Ireland to C. M. P).

None of the authors had any financial or personal conflict of interest to disclose. The results of the present study do not constitute endorsement by the American College of Sports Medicine. We declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

C. M. P., C. B. D., and I. J. P. contributed to the conception and design of the study, or analysis of the data, drafting of the manuscript, or critical revision of the manuscript for important intellectual input. All authors approved the final version.

REFERENCES

1. Haskell WL, Blair SN, Hill JO. Physical activity: health outcomes and importance for public health policy. *Prev Med*. 2009;49(4): 280–2.
2. Kesaniemi YK, Danforth E Jr, Jensen MD, Kopelman PG, Lefèbvre P, Reeder BA. Dose–response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc*. 2001;33(6 Suppl):S351–8.
3. Sattelmair J, Pertman J, Ding EL, Kohl HW 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation*. 2011;124(7):789–95.

4. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med*. 2015;162(2):123–32.
5. Ford ES, Caspersen CJ. Sedentary behaviour and cardiovascular disease: a review of prospective studies. *Int J Epidemiol*. 2012;41(5):1338–53.
6. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380(9838):219–29.
7. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. *Diabetes Care*. 2010;33(12):2692–6.
8. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107(24):3109–16.
9. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clin Lab Med*. 2006;26(4):847–70.
10. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009;119(7):931–9.
11. Parish S, Offer A, Clarke R, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. *Circulation*. 2012;125(20):2469–78.
12. Krauss RM. Lipoprotein subfractions and cardiovascular disease risk. *Curr Opin Lipidol*. 2010;21(4):305–11.
13. Shiffman D, Louie JZ, Caulfield MP, Nilsson PM, Devlin JJ, Melander O. LDL subfractions are associated with incident cardiovascular disease in the Malmö Prevention Project Study. *Atherosclerosis*. 2017;263:287–92.
14. Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med*. 2009;150(7):474–84.
15. El Harchaoui K, Arsenault BJ, Franssen R, et al. High-density lipoprotein particle size and concentration and coronary risk. *Ann Intern Med*. 2009;150(2):84–93.
16. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol*. 2002;90(8A):22i–9.
17. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011;5(2):105–13.
18. Arsenault BJ, Lemieux I, Despres JP, et al. HDL particle size and the risk of coronary heart disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Atherosclerosis*. 2009;206(1):276–81.
19. Garvey WT, Kwon S, Zheng D, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003;52(2):453–62.
20. Mora S, Caulfield MP, Wohlgemuth J, et al. Atherogenic lipoprotein subfractions determined by ion mobility and first cardiovascular events after random allocation to high-intensity statin or placebo: the justification for the use of statins in prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. *Circulation*. 2015;132(23):2220–9.
21. Rizzo M, Pernice V, Frasheri A, Berneis K. Atherogenic lipoprotein phenotype and LDL size and subclasses in patients with peripheral arterial disease. *Atherosclerosis*. 2008;197(1):237–41.
22. Magkos F, Mohammed BS, Mittendorfer B. Effect of obesity on the plasma lipoprotein subclass profile in normoglycemic and normolipidemic men and women. *Int J Obes (Lond)*. 2008;32(11):1655–64.
23. Buman MP, Winkler EA, Kurka JM, et al. Reallocating time to sleep, sedentary behaviors, or active behaviors: associations with cardiovascular disease risk biomarkers, NHANES 2005–2006. *Am J Epidemiol*. 2014;179(3):323–34.
24. Kearney PM, Harrington JM, Mc Carthy VJ, Fitzgerald AP, Perry IJ. Cohort profile: The Cork and Kerry Diabetes and Heart Disease Study. *Int J Epidemiol*. 2013;42(5):1253–62.
25. Phillips CM, Dillon C, Harrington JM, et al. Defining metabolically healthy obesity: role of dietary and lifestyle factors. *PLoS One*. 2013;8(10):e76188.
26. Frazier-Wood AC, Garvey WT, Dall T, Honigberg R, Pourfarzib R. Opportunities for using lipoprotein subclass profile by nuclear magnetic resonance spectroscopy in assessing insulin resistance and diabetes prediction. *Metab Syndr Relat Disord*. 2012;10(4):244–51.
27. Dillon CB, Fitzgerald AP, Kearney PM, et al. Number of days required to estimate habitual activity using wrist-worn GENEActiv accelerometer: a cross-sectional study. *PLoS One*. 2016;11(5):e0109913.
28. Esliger DW, Rowlands AV, Hurst TL, Catt M, Murray P, Eston RG. Validation of the GENEA accelerometer. *Med Sci Sports Exerc*. 2011;43(6):1085–93.
29. van Hees VT, Renstrom F, Wright A, et al. Estimation of daily energy expenditure in pregnant and non-pregnant women using a wrist-worn tri-axial accelerometer. *PLoS One*. 2011;6(7):e22922.
30. Hamer M, Stamatakis E. Prospective study of sedentary behavior, risk of depression, and cognitive impairment. *Med Sci Sports Exerc*. 2014;46(4):718–23.
31. Mekary RA, Lucas M, Pan A, et al. Isotemporal substitution analysis for physical activity, television watching, and risk of depression. *Am J Epidemiol*. 2013;178(3):474–83.
32. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol*. 2009;170(4):519–27.
33. Gill JM, Sattar N. Hepatic VLDL overproduction: is hyperinsulinemia or insulin resistance the culprit? *J Clin Endocrinol Metab*. 2011;96(7):2032–4.
34. Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients*. 2013;5(4):1218–40.
35. Phillips C, Mullan K, Owens D, Tomkin GH. Intestinal microsomal triglyceride transfer protein in type 2 diabetic and non-diabetic subjects: the relationship to triglyceride-rich postprandial lipoprotein composition. *Atherosclerosis*. 2006;187(1):57–64.
36. Phillips C, Bennett A, Anderton K, et al. Intestinal rather than hepatic microsomal triglyceride transfer protein as a cause of postprandial dyslipidemia in diabetes. *Metabolism*. 2002;51(7):847–52.
37. Phillips C, Owens D, Collins P, Tomkin GH. Microsomal triglyceride transfer protein: does insulin resistance play a role in the regulation of chylomicron assembly? *Atherosclerosis*. 2002;160(2):355–60.
38. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*. 2016;118(4):547–63.
39. Taskinen MR. Pathogenesis of dyslipidemia in type 2 diabetes. *Exp Clin Endocrinol Diabetes*. 2001;109(2 Suppl):S180–8.
40. Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;2(8):655–66.
41. Lahjibi E, Heude B, Dekker JM, et al. Impact of objectively measured sedentary behaviour on changes in insulin resistance and secretion over 3 years in the RISC study: interaction with weight gain. *Diabetes Metab*. 2013;39(3):217–25.
42. Frazier-Wood AC, Borecki IB, Feitosa MF, Hopkins PN, Smith CE, Arnett DK. Sex-specific associations between screen time and lipoprotein subfractions. *Int J Sport Nutr Exerc Metab*. 2014;24(1):59–69.

43. Aadland E, Andersen JR, Anderssen SA, Kvalheim OM. Physical activity versus sedentary behavior: associations with lipoprotein particle subclass concentrations in healthy adults. *PLoS One*. 2013;8(12):e85223.
44. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. *Appl Physiol Nutr Metab*. 2010;35(6):725–40.
45. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet*. 2016;388:1302–10.
46. Healy GN, Winkler EA, Brakenridge CL, Reeves MM, Eakin EG. Accelerometer-derived sedentary and physical activity time in overweight/obese adults with type 2 diabetes: cross-sectional associations with cardiometabolic biomarkers. *PLoS One*. 2015; 10(3):e0119140.
47. Slentz CA, Houmard JA, Johnson JL, et al. Inactivity, exercise training and detraining, and plasma lipoproteins. STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol (1985)*. 2007;103(2):432–42.
48. Sarzynski MA, Burton J, Rankinen T, et al. The effects of exercise on the lipoprotein subclass profile: a meta-analysis of 10 interventions. *Atherosclerosis*. 2015;243(2):364–72.
49. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med*. 2002;347(19):1483–92.
50. McCrady-Spitzer SK, Levine JA. Nonexercise activity thermogenesis: a way forward to treat the worldwide obesity epidemic. *Surg Obes Relat Dis*. 2012;8(5):501–6.
51. Uemura H, Katsuura-Kamano S, Yamaguchi M, Nakamoto M, Hiyoshi M, Arisawa K. Abundant daily non-sedentary activity is associated with reduced prevalence of metabolic syndrome and insulin resistance. *J Endocrinol Invest*. 2013;36(11):1069–75.
52. Hinchion R, Sheehan J, Perry I. Primary care research: patient registration. *Ir Med J*. 2002;95(8):249.
53. Fairclough SJ, Noonan R, Rowlands AV, van Hees V, Knowles Z, Boddy LM. Wear compliance and activity in children wearing wrist- and hip-mounted accelerometers. *Med Sci Sports Exerc*. 2016;48(2):245–53.
54. Hildebrand M, van Hees VT, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. *Med Sci Sports Exerc*. 2014;46(9):1816–24.
55. McCann DA KZ, Fairclough SJ, Graves LEF. A protocol to encourage accelerometer wear in children and young people. *Qual Res Sport Exerc Health*. 2016;8(4):319–31.
56. Noonan RJ, Boddy LM, Kim Y, Knowles ZR, Fairclough SJ. Comparison of children's free-living physical activity derived from wrist and hip raw accelerations during the segmented week. *J Sports Sci*. 2017;35(21):2067–72.
57. Rowlands AV, Rennie K, Kozarski R, et al. Children's physical activity assessed with wrist- and hip-worn accelerometers. *Med Sci Sports Exerc*. 2014;46(12):2308–16.
58. Pavey TG, Gomersall SR, Clark BK, Brown WJ. The validity of the GENEActiv wrist-worn accelerometer for measuring adult sedentary time in free living. *J Sci Med Sport*. 2016;19(5):395–9.
59. Rowlands AV, Fraysse F, Catt M, et al. Comparability of measured acceleration from accelerometry-based activity monitors. *Med Sci Sports Exerc*. 2015;47(1):201–10.
60. Rowlands AV, Yates T, Davies M, Khunti K, Edwardson CL. Raw accelerometer data analysis with GGIR R-package: does accelerometer brand matter? *Med Sci Sports Exerc*. 2016;48(10): 1935–41.