Moderate-to-vigorous intensity physical activity from young adulthood to middle age and metabolic disease: a 30-year population-based cohort study

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ABSTRACT

Objectives To determine the association between moderate-to-vigorous intensity physical activity (MVPA) trajectories (course over age and time) through the adult life course and onset of metabolic disease (diabetes and dyslipidaemia).

Methods We analysed prospective community-based cohort data of 5115 participants in the Coronary Artery Risk Development in Young Adults study, who were black and white men and women aged 18–30 years at baseline (1985–1986) at four urban sites, collected through 30 years of follow-up. Individualised MVPA trajectories were developed for each participant using linear mixed models.

Results Lower estimated MVPA score at age 18 was associated with a 12% (95% CI 6% to 18%) higher odds of incident diabetes, a 4% (95% CI 1% to 7%) higher odds of incident low high-density lipoprotein (HDL) and a 6% (95% CI 2% to 11%) higher odds of incident high triglycerides. Each additional annual 1-unit reduction in the MVPA score was associated with a 6% (95% CI 4% to 9%) higher annual odds of diabetes incidence and a 4% (95% CI 2% to 6%) higher annual odds of high triglyceride incidence. Analysing various MVPA trajectory groups, participants who were in the most active group at age 18 (over 300 min/week), but with sharp declines in midlife, had higher odds of high low-density lipoprotein and low HDL incidence, compared with those in the most active group at age 18 with subsequent gains.

Conclusion Given recent trends in declining MVPA across the life course and associated metabolic disease risk, young adulthood is an important time period for interventions to increase and begin the maintenance of MVPA.

INTRODUCTION

Metabolic disease, including type 2 diabetes and dyslipidaemia (low high-density lipoprotein cholesterol (HDL-C), high low-density lipoprotein cholesterol (LDL-C) and high triglycerides (TG)) are established risk factors for cardiovascular disease (CVD),[1–3] the leading cause of mortality in the USA.[4] Despite our understanding of the general benefits of moderate-to-vigorous intensity physical activity (MVPA) on preventing type 2 diabetes[5] and dyslipidaemia,[6–8] there is a paucity of longitudinal data regarding the specific trajectories (the course over age and time) of MVPA during young adulthood and the association of MVPA trajectory groups with adult-onset CVD. In particular, there is a need to understand how MVPA in young adulthood affects the incidence of metabolic disease.

Young adulthood may set the baseline for later life physical activity trajectories and, thus, be an important time window for intervention.[9 10] The 2018 US Department of Health and Human Services (HHS) Physical Activity Guidelines recommend a minimum of 150 min of moderate-intensity physical activity per week for adults 18–65 years.[11 12] The Physical Activity Guidelines Scientific Report noted that young adults have unique growth and developmental needs similar to adolescents, who are recommended to have 60 min/day (420 min/week) of MVPA.[11] However, there was insufficient literature on physical activity and health outcomes in young adulthood to confirm current guidance or to support a change to the current approach.[11] Thus, the optimal dose and trajectory patterns of MVPA, particularly in young adulthood, to prevent metabolic disease remains unknown.[13 14]

The objective of this study was to determine the independent associations between the young adult level of MVPA and subsequent changes in MVPA through the transition to midlife and incidence of metabolic disease (diabetes, high LDL-C, low HDL-C, high TG, dyslipidaemia). Second, we examined if specific MVPA trajectory patterns were associated with metabolic disease onset.

METHODS

Study population

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective cohort study that recruited black and white young adults at baseline from 1985 to 1986. Participants (N=5115) were recruited from four urban locations (Birmingham, AL; Chicago, IL; Minneapolis, MN and Oakland, CA) and have been followed up for more than 30 years (years 2, 5, 7, 10, 15, 20, 25, 30 with 90%, 86%, 81%, 77%, 74%, 72%, 72% and 71% retention, respectively). The cohort of participants was designed to be diverse in approximately equal parts by sex, race (black and white), age (18–24 years and 25–30 years at baseline) and educational level (high school or less or higher than high school) within each centre. After conducting the baseline examination, one participant requested to be excluded from all further

analyses. Further details about the study design have been previously published.[15]

Measures

Physical activity

Self-reported MVPA was assessed by the interviewer-administered CARDIA Physical Activity History Questionnaire at each of the nine examinations.[16 17] Participants were asked about the frequency of participation in 13 different activity categories (8 of vigorous and 5 of moderate intensity) within the leisure time and occupational physical activity domains over the prior 12 months. Each activity's intensity was expressed as metabolic equivalents of task (METs), where one MET is defined as the energy used at rest (approximately an oxygen consumption of 3.5 mL/1 kg of body weight/min). Vigorous intensity activities (≥6 METs) included running, racquet sports, bicycling faster than 10 miles/hour, swimming, vigorous exercise classes, sports (eg, basketball, football), heavy lifting, carrying or digging on the job and home activities, such as snow shovelling and lifting heavy objects. Moderate intensity activities (3–5 METs) included non-strenuous sports (eg, softball), walking, bowling/golf, home maintenance (eg, gardening, raking) and callisthenics.[18] Each activity was assigned a frequency based on whether it was performed for ≥1 hour or during any 1 month in the past year, the number of months it was performed at that level and the number of months it was performed on a frequent basis. Intensity scores (3–8 METs) and duration thresholds (2–5 hours/week) were assigned to each activity; activities above these levels of participation were considered frequent.[17] An MVPA score was computed by multiplying the frequency (number of months) of participation by the intensity (METs) of the activity with a weighting factor for the months of more frequent participation.[19] The MVPA score was the sum of all activities expressed in exercise units (EUs). For reference, an MVPA score of 300 EU estimates the HHS recommendations of approximately 150 min of moderate-intensity activity per week.[12 20] Given recent evidence that occupational physical activity does not improve health and may be detrimental, constituting an occupational paradox,[21] we excluded the occupational physical activity question (lifting, carrying or digging on the job) from the MVPA score. Convergent validity of the CARDIA Physical Activity History Questionnaire has been established using report-based measures, including physical activity diaries and detailed quantitative recall questionnaires[16 19 22] and accelerometers.[22–24] It has also been indirectly validated by showing expected relations with physical fitness and measures of body fat,[18 19 25] and has demonstrated adequate test–retest reliability.[19]

Diabetes

Blood was drawn and processed at the central laboratory according to standard procedures at each of the nine CARDIA examinations. Glucose was assayed using the hexokinase method. Diabetes was defined as a fasting glucose ≥126 mg/dL or on diabetic medications but not pregnant for examinations before May 2011. [15 17] Diabetes was defined as fasting glucose ≥126 mg/dL, 2-hour glucose tolerance test ≥200 mg/dL, haemoglobin A1c ≥6.5%, or being on diabetic medications but not pregnant for examinations after May 2011.

Cholesterol

Fasting lipid measures were measured at each of the nine examinations. Total cholesterol was measured enzymatically and defined as high if levels were ≥240 mg/dL.[15] TG were measured enzymatically and defined as high if levels were ≥200 mg/dL.[15] HDL-C was determined after precipitation with dextran sulfate-magnesium chloride and defined as low if levels were <35 mg/dL for males or <45 mg/dL for females.[26] LDL-C was calculated using the Friedewald equation and defined as high if levels were ≥160 mg/dL.[27] Dyslipidaemia was defined as TG ≥150 mg/dL or HDL <35 mg/dL for males, or TG ≥150 mg/dL or HDL <45 mg/dL for females.

Covariates

Age (years), race (black or white), sex (male or female), smoking status (never, former or current smoker), alcohol use (mL of alcohol consumed/day), educational attainment (the highest grade of school completed), family history of diabetes or CVD (yes or no), medical history and medications were reported through a questionnaire. The use of diabetes or dyslipidaemia medications was assessed by self-report at each examination. Body mass index (BMI) was calculated based on measured height and weight at each examination.

Statistical analysis

Summarising physical activity

MVPA trajectories were modelled among all CARDIA participants. We developed a linear mixed model (LMM) for repeated measures of MVPA in order to generate succinct summaries of exercise patterns over time. The MVPA slopes use all observations of the MVPA scores prior to metabolic disease onset in order to use as much of the data for each participant as possible and to stabilise the best linear unbiased predictions. The LMM included fixed effects for a four-level categorisation of sex and race, with age as continuous, and their interactions, as well as random effects for participant and age, with unstructured covariance. Our inclusion of these covariates, along with observed outcomes, makes the LMM assumption of missingness at random more plausible, though this assumption is not ultimately verifiable. From the fixed and random effects estimates provided by this model, we calculated the expected MVPA level at age 18 and annual change for each participant. For ease of interpretation, we changed the sign of both summaries, so as to capture the associations of lower level and faster decline in MVPA with increased metabolic risk.

Modelling the association of lower MVPA with incident metabolic disease

Unadjusted cumulative incidence of metabolic diseases (diabetes, high LDL-C, low HDL-C, high TG, or dyslipidaemia) by sex and race/ethnicity were estimated using Kaplan-Meier methods. The data for each participant were then expanded to include a record for each age between study entry and either metabolic disease onset, which was assumed to occur at the first visit at which it was detected, or at censoring by the end of the study of loss to follow-up. Pooled logistic models were used to estimate the independent associations of the expected MVPA at age 18 and subsequent annual change with onset of metabolic disease, adjusting for potential confounders, including sex, race, family history of diabetes or CVD, years of education, smoking status, alcohol use and BMI (smoking status, alcohol use and BMI were time varying, with the last observation carried forward), which have been adjusted for in prior analyses of physical activity and CVD risk (directed acyclic graphs are shown in online supplemental appendix 1).[17 28] We scaled the estimated MVPA score at age 18 from high to low per 100 EUs, corresponding to 0.45 SDs, for ease of interpretation. We kept annual reduction in total

Table 1 Baseline demographic and health characteristics of participants in the Coronary Artery Risk Development in Young Adults study

	Total	White women	Black women	White men	Black men	
N	5114	1307	1480	1170	1157	
Baseline demographic characteristics	Median (IQR)/n (%)	Median (IQR)/n (%)	Median (IQR)/n (%)	Median (IQR)/n (%)	Median (IQR)/n (%)	P value
Age (years)	25.0 (22.0–28.0)	26.0 (23.0–28.0)	24.0 (21.0–28.0)	26.0 (23.0–28.0)	24.0 (21.0–28.0)	<0.001
Highest grade of school completed	13.0 (12.0–16.0)	15.0 (12.0–16.0)	13.0 (12.0–14.0)	15.0 (12.0–16.0)	12.0 (12.0–14.0)	<0.001
Family history of diabetes	800 (15.6%)	166 (12.7%)	319 (21.6%)	131 (11.2%)	184 (15.9%)	<0.001
Family history of cardiovascular disease	1022 (20.0%)	250 (19.1%)	310 (20.9%)	227 (19.4%)	235 (20.3%)	0.62
Body mass index (BMI)	23.4 (21.2–26.4)	22.0 (20.3–24.6)	24.2 (21.2–28.9)	23.7 (21.9–26.0)	23.7 (21.7–26.4)	<0.001
<18.5 kg/m^2	237 (4.6%)	91 (7.0%)	95 (6.4%)	20 (1.7%)	31 (2.7%)	
18.5 –<25 kg/m^2	3091 (60.6%)	921 (70.7%)	728 (49.4%)	741 (63.5%)	701 (60.8%)	
25–30 kg/m^2	1170 (23.0%)	195 (15.0%)	337 (22.8%)	334 (28.6%)	304 (26.4%)	
>30 kg/m^2	599 (11.8%)	95 (7.3%)	315 (21.4%)	72 (6.2%)	117 (10.1%)	
Smoking status						<0.001
Never	2856 (56.2%)	685 (52.7%)	885 (60.1%)	670 (57.8%)	616 (53.8%)	
Former	676 (13.3%)	261 (20.1%)	127 (8.6%)	182 (15.7%)	106 (9.3%)	
Current	1546 (30.4%)	355 (27.3%)	461 (31.3%)	307 (26.5%)	423 (36.9%)	
Alcohol (mL of alcohol consumed per day)	5.4 (0.9–15.5)	4.8 (0.9–12.1)	1.8 (0.0–6.9)	11.1 (3.7–23.2)	10.2 (2.0–25.2)	<0.001
MVPA score at enrolment (EU)	312.0 (168.0–528.0)	306.0 (183.0–502.0)	207.0 (90.0–348.0)	396.0 (228.0–612.0)	408.0 (235.0–656.0)	<0.001
Estimated MVPA score at age 18 (EU)	313.4 (208.1–477.5)	297.7 (204.5–431.6)	209.9 (138.6–303.9)	395.8 (271.6–545.4)	445.2 (305.8–611.9)	<0.001
Estimated MVPA score at age 18 (EU), mean (SD)	361.8 (209.5)	330.6 (168.9)	240.8 (144.6)	428.8 (205.9)	484.2 (229.8)	<0.001
Annual reduction in MVPA score (EU)	2.3 (0.3–4.8)	1.2 (–0.7–3.1)	1.6 (0.3–3.3)	2.2 (0.1–4.5)	5.5 (3.4–8.0)	<0.001
Annual reduction in MVPA score (EU), mean (SD)	2.6 (4.0)	1.2 (3.3)	1.8 (3.2)	2.3 (4.0)	5.8 (4.1)	<0.001
Diabetes	32 (0.6%)	7 (0.5%)	14 (1.0%)	6 (0.5%)	5 (0.4%)	0.29
High LDL cholesterol	1096 (21.7%)	260 (20.0%)	298 (20.4%)	298 (25.9%)	240 (21.0%)	0.001
LDL cholesterol	106.0 (87.0–127.0)	102.0 (85.0–123.0)	107.0 (88.0–129.0)	109.0 (89.0–129.0)	106.0 (85.0–127.0)	<0.001
Low HDL cholesterol	1853 (36.6%)	539 (41.5%)	672 (46.1%)	403 (34.7%)	239 (20.9%)	<0.001
HDL cholesterol	52.0 (44.0–61.0)	55.0 (47.0–64.0)	54.0 (46.0–64.0)	45.0 (40.0–53.0)	52.0 (44.0–61.0)	<0.001
High triglycerides	925 (18.3%)	203 (15.6%)	130 (8.9%)	378 (32.6%)	214 (18.7%)	<0.001
Triglycerides	62.0 (45.0–84.0)	62.0 (45.0–81.5)	56.0 (42.0–75.0)	72.0 (52.0–103.0)	60.0 (45.0–82.0)	<0.001
Dyslipidaemia*	2633 (52.0%)	690 (53.2%)	775 (53.1%)	689 (59.3%)	479 (41.8%)	<0.001

A total MVPA score of 300 EU approximates the Health and Human Services recommendations of 150 min of moderate-intensity activity per week.
*Dyslipidaemia is defined as triglycerides ≥150 mg/dL or HDL <35 mg/dL for males or HDL <45 mg/dL for females.
EU, exercise units; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MVPA, moderate-to-vigorous intensity physical activity.

MVPA per 1 EU, corresponding to 0.23 SDs. We tested if BMI category or sex and race modified the effect of MVPA (level and change) on incident metabolic disease. Pooled logistic models estimated the associations of meeting various MVPA thresholds at age 18 (<150, 150–300, 300–600, >600 EU) in combination with annual change categories (gain, loss of <2.5 EU/year, of loss >2.5 EU/year) and onset of metabolic disease, adjusting for confounders (sample sizes shown in online supplemental appendix A). We used Stata V.16.0 (StataCorp) for all analyses.

RESULTS

Table 1 shows the baseline demographic and health characteristics of 5114 participants included in the sample. The sample was 51.6% black and 45.5% male. Demographic and health characteristics of the sample at baseline are shown in table 1. Average MVPA declines from young adulthood in all race and sex groups, particularly in black men (figure 1). Incidence of diabetes and cholesterol outcomes by race and sex are presented in online supplemental figures A–E.

Table 2 shows pooled logistic regression model estimates for the associations of the two MVPA summaries (estimated MVPA level at age 18 and subsequent declines in MVPA) with metabolic disease onset. Model 2.1 adjusted for age only, whereas model 2.2 adjusted for age, race, sex, education, family history, smoking status, alcohol and BMI. In the fully adjusted model (model 2.2), lower estimated MVPA score (per 100 units) at age 18 was associated with a 12% (95% CI 6% to 18%) higher odds of incident diabetes, a 4% (95% CI 1% to 7%) higher odds of incident low HDL, a 6% (95% CI 2% to 11%) higher odds of incident high TG and a 3% (95% CI 0% to 6%) higher odds of incident dyslipidaemia. Each additional annual 1-unit reduction in the MVPA score was associated with a 6% (95% CI 4% to 9%) higher annual odds of diabetes incidence, a 4% (95% CI 2% to 6%) higher annual odds of high triglyceride incidence and a 2% (95% CI 0% to 3%) higher annual odds of dyslipidaemia incidence. Pooled logistic regression model estimates stratified by BMI category (online supplemental appendix B) and race and sex (online supplemental appendix C) are shown in online supplemental appendix 1.

Associations between various MVPA thresholds at age 18 combined with categories of subsequent annual change in MVPA and onset of metabolic disease are shown in table 3. In fully

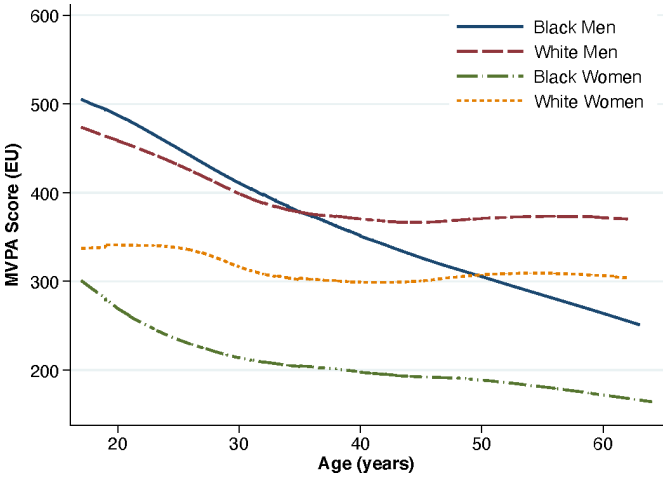

Figure 1 Average moderate-to-vigorous intensity physical activity (MVPA) trajectories, by race and sex. A total MVPA score of 300 exercise units (EU) approximates the Health and Human Services recommendations of 150 min of moderate-intensity activity.

adjusted models treating MVPA as additive (model 3.1), reductions in MVPA in midlife (compared with gains in MVPA) were associated with onset of all metabolic disease outcomes for any given MVPA threshold level at age 18. In fully adjusted models allowing MVPA categories to interact (model 3.2), certain MVPA combinations are notable. For instance, among participants with over twice the minimum recommended MVPA level (>600 EU) at age 18, those with steep subsequent losses (>2.5 EU/year) had 4.74 higher odds (95% CI 1.55 to 14.50) of low HDL incidence and 3.22 higher odds (95% CI 1.23 to 8.47) of high LDL than those with gains in MVPA. In addition, participants with 300–600 EU at age 18 and subsequent gains in MVPA did not have higher odds of most metabolic disease onset compared with participants with >600 EU at age 18 and subsequent gains in MVPA.

DISCUSSION

In this prospective cohort study with 30 years of follow-up, we found that a high level of MVPA in young adulthood is a critical starting point for maintaining lifetime metabolic health. Young adult MVPA is associated with lower incidence of diabetes, low HDL-C and high TG, independent of MVPA levels across later adulthood. Maintaining high levels of MVPA in the adult life course is also important; for any given young adult MVPA set point, decline in MVPA through the adult life course is also associated with incident diabetes and high TG.

These findings add to prior literature on physical activity and metabolic disease[5–8] by leveraging a large longitudinal cohort with 30 years of follow-up data to develop MVPA trajectories throughout the life course. Using these individualised trajectories, we find independent associations with the young adult level of MVPA and subsequent declines in the later adult level of MVPA with diabetes and high TG. It is notable that both estimated MVPA level and slope were independently associated with diabetes and triglyceride onset, even after adjusting for a number of potential confounders.

Our findings indicate that young adult MVPA levels provide protection from subsequent metabolic disease, independent of MVPA levels up through midlife. Thus, young adulthood is an important period for intervention to ensure adequate MVPA levels. Furthermore, our findings indicate that protective levels of activity are higher than the currently recommended minimum. This is an important finding since the HHS Physical Activity Guidelines Scientific Committee Report noted there was insufficient literature on physical activity to inform guidelines in young adults.[11] Physical activity typically declines in the transition from

Table 2 Associations between moderate-to-vigorous intensity physical activity (MVPA) trajectories and onset of metabolic disease in the Coronary Artery Risk Development in Young Adults study

	Model 2.1 (adjusted for age)*			Model 2.2 (fully adjusted)†		
	OR	95% CI	P value	OR	95% CI	P value
Diabetes						
Lower MVPA score (per 100 EUs) at age 18	1.26	1.19 to 1.33	<0.001	1.12	1.06 to 1.18	<0.001
Annual reduction in MVPA score (per 1 EU)	1.14	1.12 to 1.17	<0.001	1.06	1.04 to 1.09	<0.001
High LDL cholesterol						
Lower MVPA score (per 100 EUs) at age 18	0.99	0.96 to 1.02	0.65	0.99	0.95 to 1.02	0.49
Annual reduction in MVPA score (per 1 EU)	1.01	1.00 to 1.02	0.09	1.00	0.99 to 1.02	0.58
Low HDL cholesterol						
Lower MVPA score (per 100 EUs) at age 18	1.16	1.13 to 1.19	<0.001	1.04	1.01 to 1.07	0.019
Annual reduction in MVPA score (per 1 EU)	1.00	0.99 to 1.02	0.43	1.01	1.00 to 1.03	0.09
High triglycerides						
Lower MVPA score (per 100 EUs) at age 18	1.02	0.98 to 1.05	0.40	1.06	1.02 to 1.11	0.008
Annual reduction in MVPA score (per 1 EU)	1.05	1.03 to 1.06	<0.001	1.04	1.02 to 1.06	<0.001
Dyslipidaemia‡						
Lower MVPA score (per 100 EUs) at age 18	1.08	1.06 to 1.11	<0.001	1.03	1.00 to 1.06	0.034
Annual reduction in MVPA score (per 1 EU)	1.02	1.01 to 1.03	<0.001	1.02	1.00 to 1.03	0.026

We scaled estimated MVPA score at age 18 from high to low per 100 EUs, corresponding to 0.45 SDs, for ease of interpretation. We kept annual reduction in MVPA per 1 EU, corresponding to 0.23 SDs.
*Model 2.1 includes: estimated MVPA level at age 18, additional annual reduction in MVPA and age. Separate models are presented for each outcome (diabetes, high LDL, low HDL, high triglycerides, dyslipidaemia).
†Model 2.2 includes: estimated MVPA level at age 18, additional annual reduction in MVPA, age, race, sex, education, family history of diabetes or cardiovascular disease, smoking status, alcohol and body mass index. Separate models are presented for each outcome (diabetes, high LDL, low HDL, high triglycerides, dyslipidaemia).
‡Dyslipidaemia is defined as triglycerides ≥150 mg/dL or HDL <35 mg/dL for males or HDL <45 mg/dL for females.
EU, exercise unit; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3 Associations between moderate-to-vigorous intensity physical activity (MVPA) thresholds at age 18, expected annual reduction of MVPA categories, and onset of metabolic disease in the Coronary Artery Risk Development in Young Adults study

	Diabetes			High LDL			Low HDL			High TG			Dyslipidaemia		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Model 3.1 treating MVPA as additive, fully adjusted*															
Expected MVPA at age 18[a]															
>600 EU	Reference			Reference			Reference			Reference			Reference		
300–600 EU	1.12	0.86 to 1.48	0.40	1.11	0.90 to 1.36	0.32	1.35	1.10 to 1.65	0.003	0.97	0.79 to 1.21	0.81	1.23	1.06 to 1.32	0.005
150–300 EU	1.24	0.93 to 1.65	0.15	0.95	0.76 to 1.19	0.64	1.11	0.90 to 1.38	0.33	1.01	0.80 to 1.28	0.93	1.06	0.90 to 1.24	0.49
0–150 EU	1.50	1.03 to 2.17	0.034	0.78	0.57 to 1.05	0.09	0.80	0.61 to 1.06	0.12	1.02	0.72 to 1.44	0.90	0.83	0.65 to 1.05	0.12
Expected annual reduction in MVPA score															
Gain	Reference			Reference			Reference			Reference			Reference		
Reduction 0–2.5 EU/year	1.80	1.38 to 2.35	<0.001	3.49	2.80 to 4.35	<0.001	4.27	3.54 to 5.15	<0.001	1.98	1.58 to 2.47	<0.001	3.30	2.83 to 3.85	<0.001
Reduction >2.5 EU/year	1.74	1.35 to 2.25	<0.001	2.11	1.70 to 2.62	<0.001	1.97	1.63 to 2.38	<0.001	1.50	1.20 to 1.87	<0.001	1.90	1.63 to 2.22	<0.001
Model 3.2 allowing MVPA categories to interact, fully adjusted*															
>600, gain	Reference			Reference			Reference			Reference			Reference		
>600, loss <2.5 EU/year	1.14	0.18 to 7.08	0.89	1.59	0.49 to 5.19	0.44	1.85	0.47 to 7.34	0.38	3.03	0.85 to 10.78	0.09	2.31	0.77 to 6.94	0.13
>600, loss >2.5 EU/year	2.12	0.52 to 8.71	0.30	3.22	1.23 to 8.47	0.018	4.74	1.55 to 14.50	0.006	3.14	0.98 to 10.04	0.054	4.95	1.86 to 13.18	0.001
300–600, gain	0.81	0.18 to 3.56	0.78	0.78	0.28 to 2.20	0.64	0.61	0.18 to 2.08	0.43	1.17	0.35 to 3.92	0.80	1.18	0.42 to 3.26	0.76
300–600, loss <2.5 EU/year	1.83	0.44 to 7.63	0.41	5.11	1.95 to 13.34	<0.001	10.84	3.57 to 32.87	<0.001	3.72	1.16 to 11.93	0.027	8.69	3.27 to 23.12	<0.001
300–600, loss >2.5 EU/year	2.53	0.63 to 10.26	0.19	3.38	1.30 to 8.80	0.012	6.01	1.99 to 18.19	0.001	3.16	0.99 to 10.04	0.051	6.16	2.33 to 16.34	<0.001
150–300, gain	1.48	0.35 to 6.17	0.59	1.46	0.54 to 3.91	0.45	2.69	0.87 to 8.28	0.09	2.26	0.70 to 7.32	0.18	2.81	1.04 to 7.57	0.041
150–300, loss <2.5 EU/year	3.11	0.76 to 12.68	0.11	5.04	1.93 to 13.15	<0.001	10.66	3.52 to 32.25	<0.001	4.48	1.40 to 14.35	0.011	9.6	3.62 to 25.50	<0.001
150–300, loss >2.5 EU/year	2.16	0.53 to 8.84	0.28	1.95	0.74 to 5.17	0.18	2.35	0.76 to 7.23	0.14	2.34	0.72 to 7.57	0.16	2.71	1.01 to 7.29	0.047
<150, gain	2.40	0.56 to 10.25	0.24	2.02	0.73 to 5.62	0.18	3.88	1.23 to 12.21	0.02	3.48	1.03 to 11.74	0.044	4.22	1.55 to 11.53	0.005
<150, loss <2.5 EU/year	3.03	0.74 to 12.49	0.12	3.25	1.22 to 8.67	0.018	5.76	1.87 to 17.71	0.002	3.34	1.01 to 11.04	0.048	5.23	1.94 to 14.14	0.001
<150, loss >2.5 EU/year	1.35	0.22 to 8.22	0.75	0.43	0.05 to 3.76	0.45	1.15	0.1 to 7.20	0.88	1.21	0.19 to 7.71	0.84	1.44	0.29 to 7.05	0.66

A total MVPA score of 300 exercise units (EU) approximates the Health and Human Services recommendations of 150 min of moderate-intensity activity per week.
*Covariates: age, race, sex, education, family history of cardiovascular disease, smoking status, alcohol and body mass index.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

adolescence to young adulthood due to educational, economic and social transitions.[9 10 29] For instance, young adults may have fewer opportunities for team or organised sports when they transition to the workforce or college, compared with adolescents, who have physical activity requirements and more opportunities for organised team sports in school.[30] The transition to parenthood may also displace leisure time for physical activity.[31]

The MVPA trajectory analysis also identified notable MVPA patterns by race and sex through the life course. For instance, black women have the lowest MVPA levels through the adult life course. Although black men start with high average levels of MVPA in young adulthood, their levels persistently decline throughout the adult life course, similar to findings from the National Health and Nutrition Examination Surveys (NHANES).[32] Physical activity interventions and messaging may particularly focus on black women through adulthood and preventing declines in black men. We also found that black adults have higher diabetes incidence throughout the life course compared with white adults, similar to findings in NHANES.[4 33]

Clinical and public health implications

We find that reductions in MVPA during midlife are associated with an increased incidence of metabolic disease across several outcomes. Public health campaigns and clinicians should focus messaging on maintaining adequate levels of MVPA and preventing declines throughout the adult life course. It is also noteworthy that young adults who were in the most active group at age 18 (over 300 min/week), but had sharp declines in MVPA in midlife, had higher odds of high LDL and low HDL incidence, compared with those in the most active group at age 18 and subsequent gains. Young adults may be more willing to take on immediate risk (eg, not being physically active) if they perceive the outcome is too far into the future, a concept referred to as temporal discounting.[34] Young adults may respond to messaging that promotes optimising health beyond just the need to avoid risk.[35]

Limitations and strengths

Limitations and strengths of this study should be noted. While we adjusted for several potential confounders including age, race, sex, education, family history, smoking status, alcohol and BMI (and behavioural and BMI covariates were time-varying), there is the possibility of unmeasured confounders, such as neighbourhood or genetic factors.[36] In addition, mixed models can produce biased effect estimates in the presence of time-varying confounding affected by prior exposure, which would require causal methods to adjust for this potential bias, such as inverse probability weighting.[37] There may be attenuation bias due to measurement error in MVPA and residual confounding due to measurement error in some confounders such as smoking and alcohol. There was a possibility of selection bias due to censoring, including losses-to-follow-up and competing risks. MVPA was measured simultaneously with other proposed confounders in one visit, which may lead to over-adjustment bias (adjustment for mediators rather than confounders). MVPA was based on self-report and may be subject to information and prevarication bias, and it did not collect information regarding activity intensity. Nonetheless, the same questionnaire was used across the 30-year follow-up period, which is a distinct strength. Because we scaled the estimated MVPA score at age 18 per 100 EUs for ease of interpretation, the ORs for the two MVPA estimates (level at age 18 and annual reduction) are not standardised and should be interpreted in different scales. The sampling design of CARDIA was not representative of all races or ethnicities in the USA, which may limit generalisability; however, the study specifically focused on participants identifying as black or white race.[15] Given the larger proportion of the sample with metabolic disease by age 60, the number of eligible participants in the analysis drops with age.

What are the findings?

⇒ In this prospective longitudinal study with regular 30-year follow-up, we found that low young adult moderate-to-vigorous intensity physical activity (MVPA) was associated with higher odds of diabetes, high triglycerides and low HDL incidence.

⇒ Reductions in MVPA during midlife are associated with an increased incidence of metabolic disease.

How might it impact on clinical practice in the future?

⇒ Given recent trends in declining MVPA across the life course and associated metabolic disease risk, young adulthood and midlife are important time periods for interventions to increase and maintain MVPA.

CONCLUSION

In conclusion, MVPA level in young adulthood and declines in later adulthood are each significantly and independently associated with later life metabolic disease onset. Public health and clinical programmes should emphasise, prioritise and develop interventions to promote MVPA in young adulthood, the time when individuals establish an MVPA set point. Future research could examine the mechanisms and mediators by which MVPA may be related to metabolic disease, such as insulin sensitivity. Regardless of young adult MVPA level, interventions to sustain or increase MVPA across adulthood remain another priority for lifetime metabolic health.

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Contributors JMN conducted the literature search, interpreted findings, and wrote, revised, and edited the manuscript. EV conceptualised the study, analysed data and edited the manuscript. KPG, SS, AKG, KB-D conceptualised the study, interpreted the data and provided critical revisions on the manuscript. AEM, JSR and JPR provided critical revisions on the manuscript. All authors approved the final draft.

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Disclaimer The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health or the US Department of Health and Human Services.

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Patient and public involvement statement Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Patient consent for publication Not required.

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Supplemental Appendix

Moderate-to-vigorous intensity physical activity from young adulthood to middle age and metabolic disease: A 30-year population-based cohort study

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Supplemental Methods

Validity and Reliability of the CARDIA Physical Activity History Questionnaire

The CARDIA Physical Activity History has demonstrated validity comparable to other self-reported physical activity questionnaires, with age-sex adjusted correlation coefficients of 0.31 with accelerometer, 0.54 with four-week physical activity history total score, and 0.63 with $V0_2$ max [1]. There was also acceptable convergent validity with objective accelerometer data collected in 2005-06 in CARDIA with correlation coefficients ranging from 0.32 to 0.36 [2]. Test-retest reliability was good (correlation coefficients of 0.77 to 0.84 after two weeks) [3].

Statistical Analysis: Model Assumption Checks

We used Q-Q plots to assess the normality of the residuals in the first stage LMMs for expected MVPA at age 18 and MVPA loss. Noting that normality is not required for continuous predictors in any regression model, we used categorization of age and BMI to relax the linearity assumption in the second stage pooled logistic regression models for time to various cardiometabolic outcomes. We also ran pooled logistic regression models allowing the MVPA slope to differ by decade of age, using linear splines, with no material effect on conclusions.

Confounder Selection and Directed Acyclic Graphs

A causal directed acyclic graph (DAG) for each outcome (diabetes, LDL cholesterol, HDL cholesterol, and triglycerides) identifies potential confounders (age, race, sex, education, family history of diabetes or CVD, smoking, alcohol, and BMI) based on previous literature and DAGs [4–6]. We also note that insulin is a potential mediator; thus, we did not adjust for insulin in models [7,8]. Since cholesterol may be along the causal pathway for the association between MVPA and diabetes and vice-versa [9,10], we have not adjusted for cholesterol in the models for diabetes. We similarly do not adjust for diabetes in the models with cholesterol outcomes. Further justifications for specific relationships are listed below.

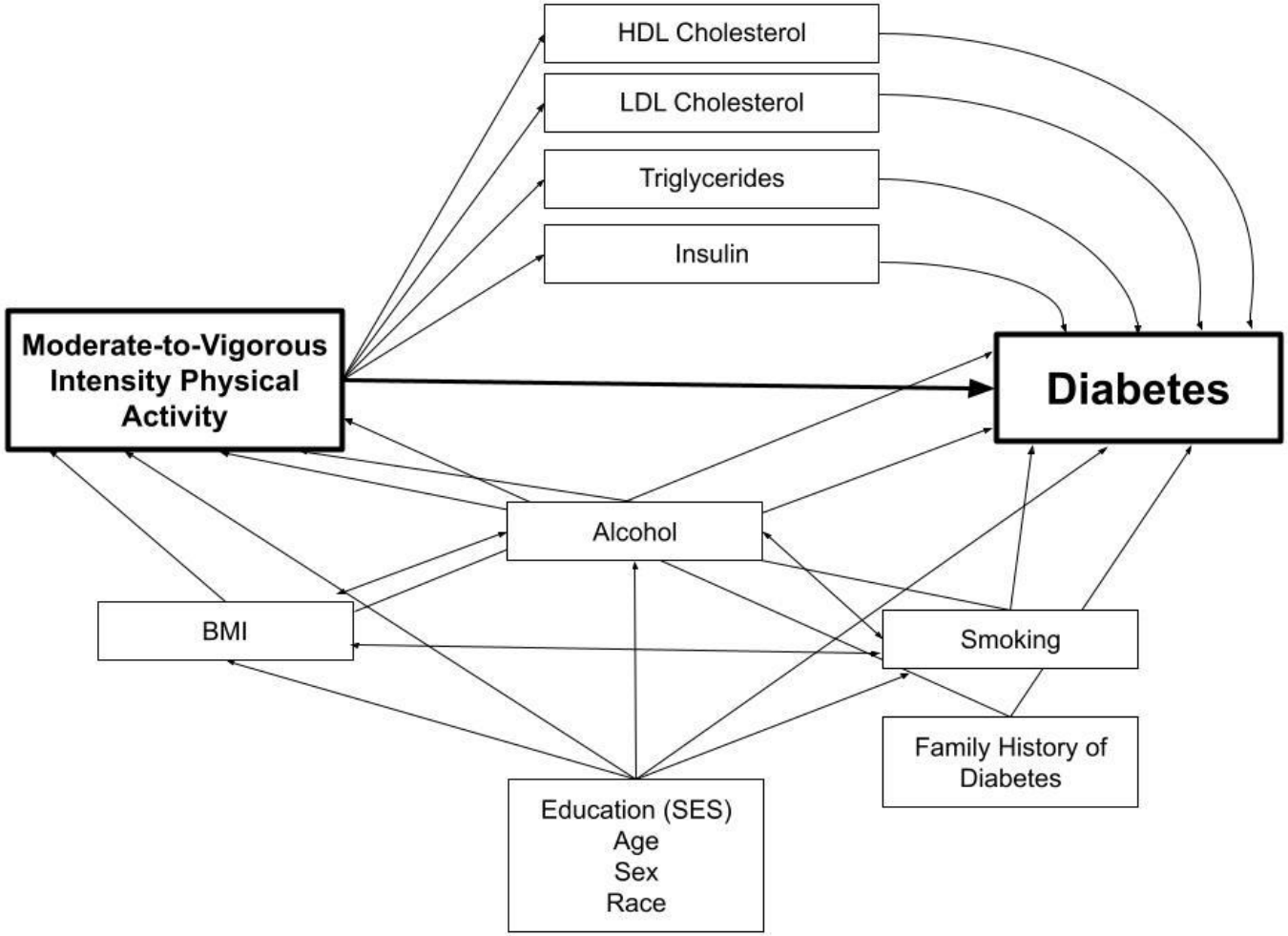
Family history: Having a family history of CVD or diabetes could affect MVPA in different ways. On the one hand, family history of CVD or diabetes could be a proxy for underlying genetics or a genetic condition which could also reflect poor athleticism or an inability to do physical activity [11]. On the other hand, an individual's awareness of their family history of CVD or diabetes may affect their perceived risk for metabolic disease and, in some cases, affect their health-related behaviors such as physical activity [12,13].

Insulin: Physical activity can affect insulin sensitivity and insulin resistance [7]. Insulin sensitivity and insulin resistance play key roles in the development of diabetes. Insulin regulates glucose utilization in the body, and an inability to synthesize insulin or insulin resistance can lead to diabetes [8]. Insulin resistance may explain an impaired secretion and clearance of triglycerides [14]. Although debated, hyperinsulinemia compensatory for insulin resistance may lead to the overproduction of VLDL [10]. Insulin resistance can affect cholesterol-depleted small dense LDL and cholesterol-rich HDL2, which have been referred to as "metabolic LDL and HDL."

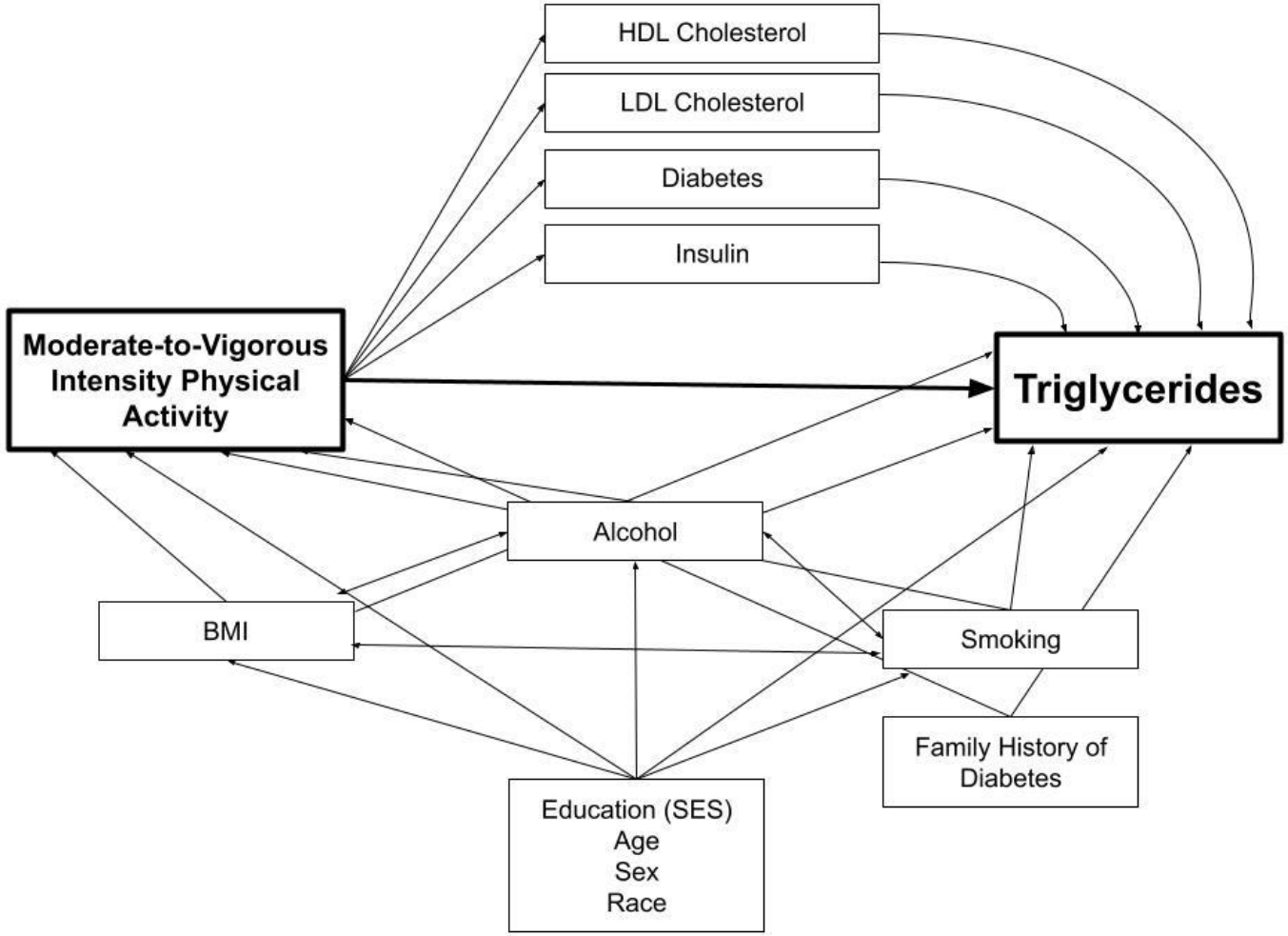
Diabetes and cholesterol: Diabetes and cholesterol may have complex bidirectional relationships and may be interregulated [9,10,14,15]. For instance, diabetes may lead to

dyslipidemia (diabetic dyslipidemia), with high triglycerides, high LDL-cholesterol, and low HDL-cholesterol [9,10]. HDL cholesterol may be inversely associated with diabetes risk. Lowering LDL-cholesterol with statins may paradoxically increase the risk of diabetes [14]. We did not consider diabetes and cholesterol as confounders for each other given that cholesterol may be on the causal pathway for the association between MVPA and diabetes and vice-versa, and that MVPA was upstream of these factors.

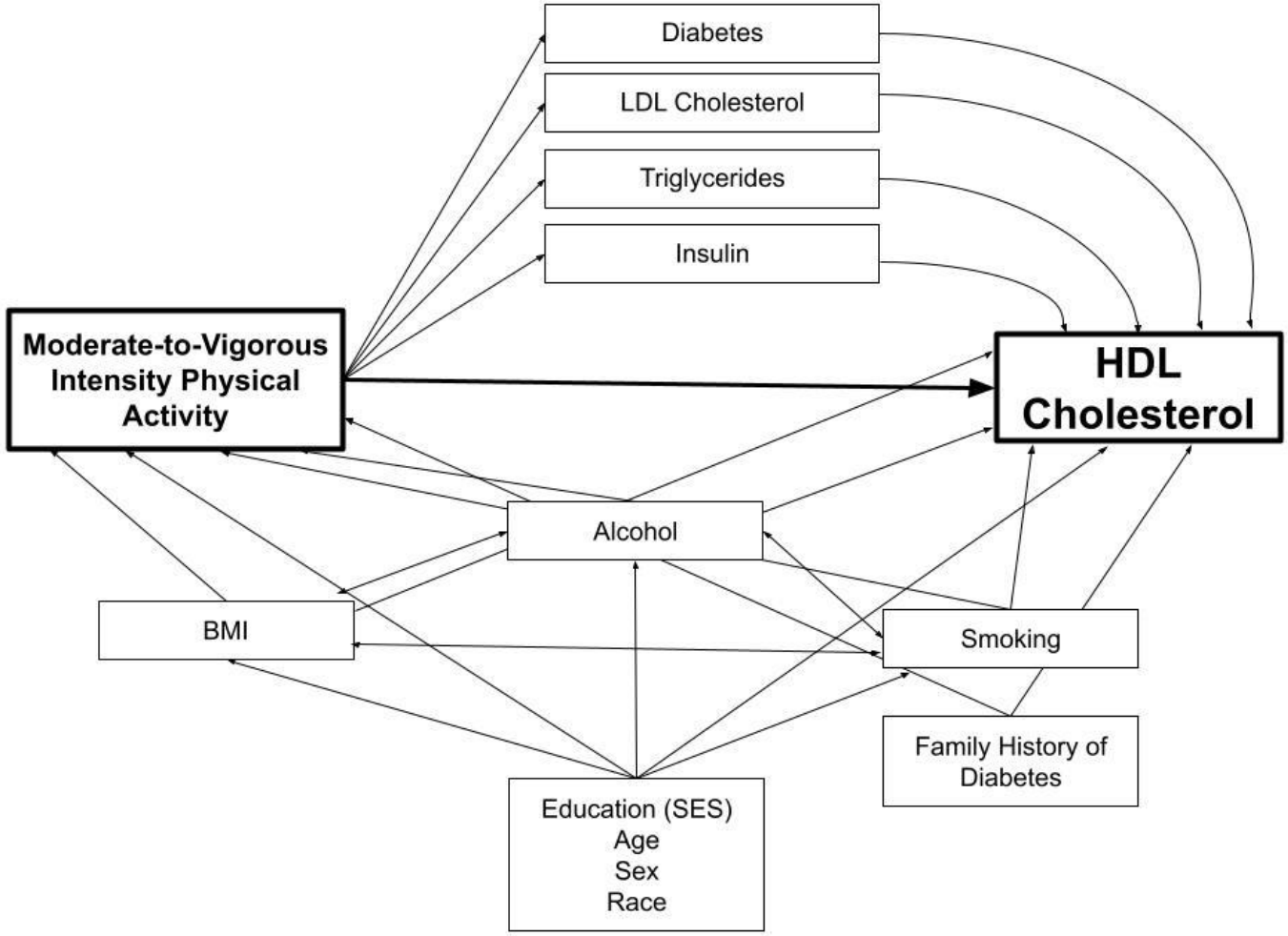
Moderate-to-Vigorous Intensity Physical Activity and Diabetes DAG



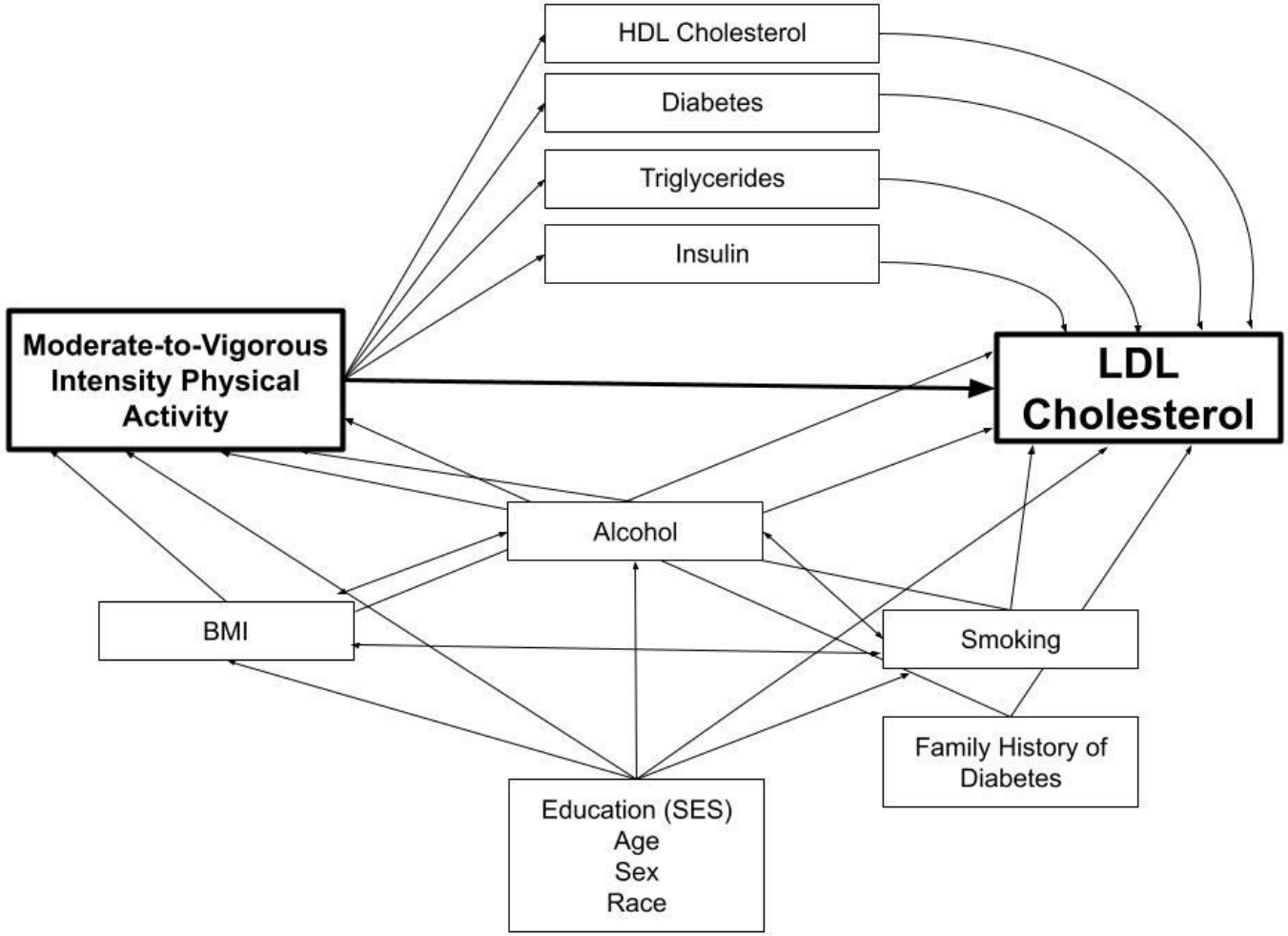
Moderate-to-Vigorous Intensity Physical Activity and Triglycerides DAG



Moderate-to-Vigorous Intensity Physical Activity and HDL Cholesterol DAG



Moderate-to-Vigorous Intensity Physical Activity and LDL Cholesterol DAG



Follow Up

Mean follow-up time was 27.3±6.4 years. Median (interquartile range) was 30 (29, 30) years.

Censoring: Losses to Follow-up and Death

Overall, 9.2% of the sample died by the end of the follow-up period. Of the sample, 34.3% was lost to follow-up by year 30.

		Died		
		No	Yes	Total
Last visit before year 30	No	3,316	42	3,358
	Yes	1,329	426	1,755
	Total	4,645	468	5,113

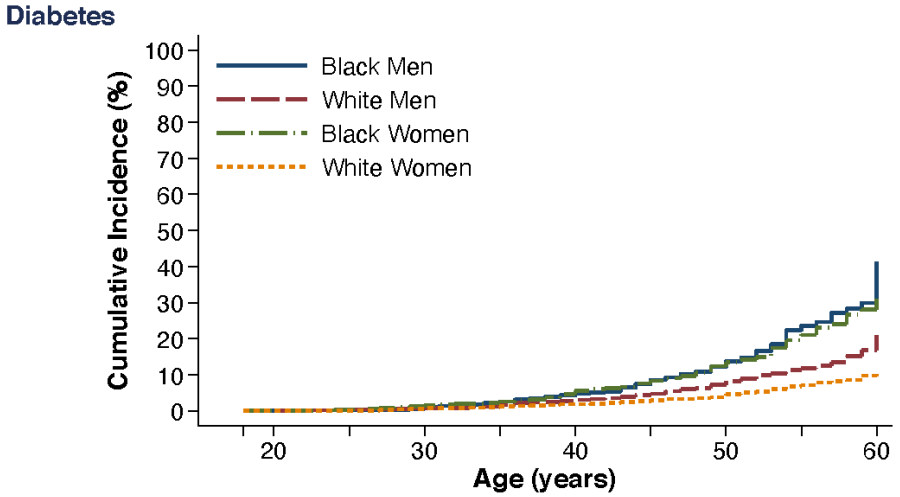
Missing Data

Missing data rates averaged over years

	Available data	
N=36,190	N	%
Exam age	36,190	100.0
Sex	36,190	100.0
Race	36,190	100.0
Highest grade of school completed	36,190	100.0
Family history of diabetes	36,190	100.0
Family history of cardiovascular disease	36,190	100.0
Body mass index (BMI)	35,881	99.1
Smoking status	35,941	99.3
Alcohol	36,188	100.0
MVPA	35,803	98.9
Diabetes	35,487	98.1
LDL cholesterol	35,571	98.3
HDL cholesterol	35,322	97.6
Triglycerides	35,583	98.3
Dyslipidemia[a]	35,572	98.3

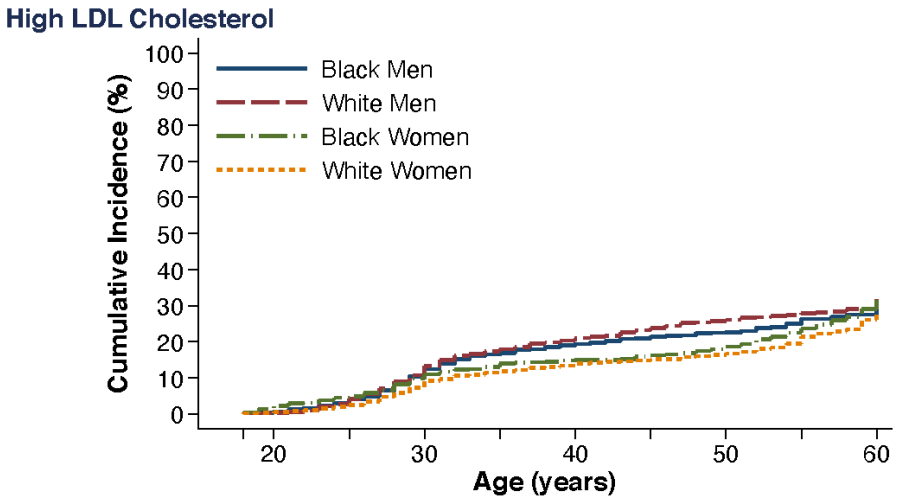
[a] Dyslipidemia defined as triglycerides≥150 mg/DL or HDL<35 mg/DL for males or HDL<45 mg/DL for females

Supplemental Figure A. Diabetes incidence, by race and sex



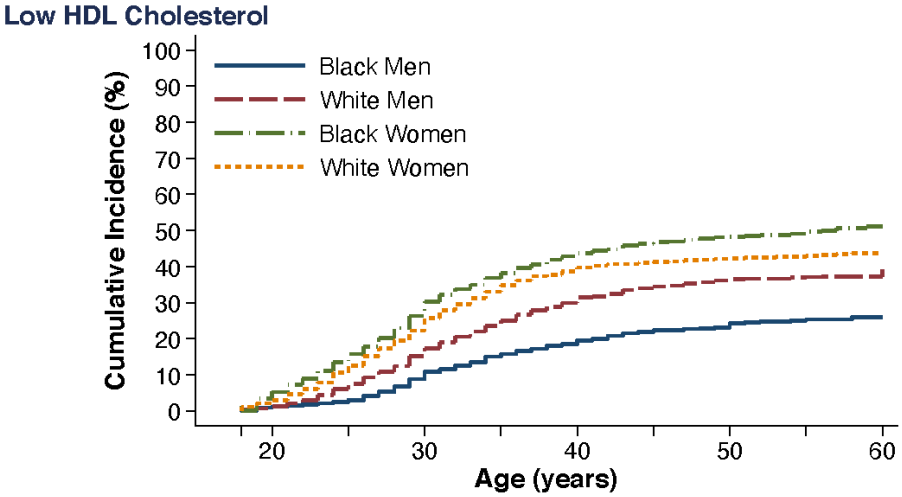
No. at Risk									
Black Men	1147	1089	1003	916	824	725	564	271	43
White Men	1166	1145	1092	1033	969	899	778	498	98
Black Women	1472	1415	1330	1236	1149	1043	822	436	77
White Women	1306	1283	1231	1183	1118	1068	956	621	122

Supplemental Figure B. High LDL cholesterol incidence, by race and sex



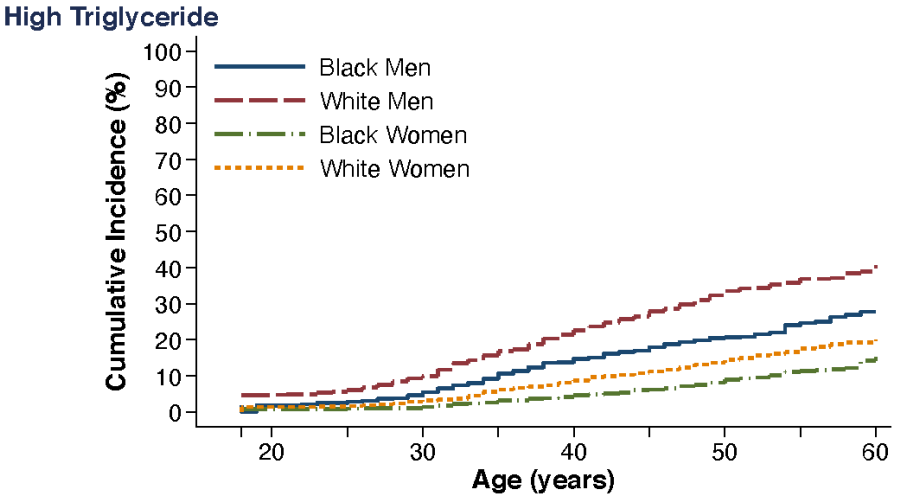
No. at Risk									
Black Men	1144	1060	900	780	690	602	472	217	32
White Men	1165	1119	980	863	797	729	616	401	77
Black Women	1452	1355	1218	1102	1026	946	763	403	76
White Women	1302	1259	1148	1061	993	943	838	535	103

Supplemental Figure C. Low HDL cholesterol incidence, by race and sex



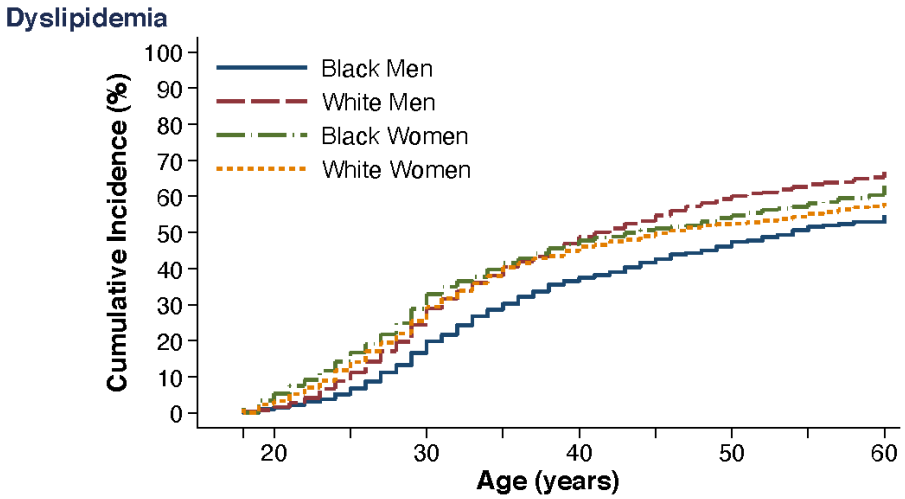
No. at Risk									
Black Men	1138	1067	930	804	709	612	484	239	33
White Men	1159	1083	941	810	714	640	552	371	70
Black Women	1424	1239	1010	809	699	621	497	282	52
White Women	1279	1152	971	815	718	666	602	414	81

Supplemental Figure D. High triglyceride incidence, by race and sex



No. at Risk									
Black Men	1127	1064	963	848	745	650	503	255	37
White Men	1112	1085	994	879	781	699	569	377	76
Black Women	1463	1409	1335	1231	1149	1052	850	458	84
White Women	1289	1265	1201	1127	1053	981	865	570	112

Supplemental Figure E. Dyslipidemia incidence, by race and sex



No. at Risk									
Black Men	1137	1039	852	677	558	463	341	160	25
White Men	1158	1051	840	662	550	471	363	242	49
Black Women	1423	1229	977	773	652	576	448	244	44
White Women	1276	1137	933	758	650	583	508	349	63

Appendix A. Models with categorized total expected physical activity score

	Total	White women	Black women	White men	Black men
N	5,113	1,307	1,480	1,169	1,157
Baseline demographic characteristics	n (%)	n (%)	n (%)	n (%)	n (%)
>600, gain	54 (1.1)	14 (1.1)	1 (0.1)	27 (2.3)	12 (1.0)
>600, loss <2.5 EU/year	58 (1.1)	17 (1.3)	3 (0.2)	24 (2.1)	14 (1.2)
>600, loss >2.5 EU/year	557 (10.9)	68 (5.2)	39 (2.6)	175 (15.0)	275 (23.8)
300-600, gain	354 (6.9)	139 (10.6)	51 (3.4)	130 (11.1)	34 (2.9)
300-600, loss <2.5 EU/year	440 (8.6)	154 (11.8)	67 (4.5)	174 (14.9)	45 (3.9)
300-600, loss >2.5 EU/year	1257 (24.6)	252 (19.3)	221 (14.9)	286 (24.5)	498 (43.0)
150-300, gain	465 (9.1)	206 (15.8)	131 (8.9)	103 (8.8)	25 (2.2)
150-300, loss <2.5 EU/year	676 (13.2)	225 (17.2)	284 (19.2)	127 (10.9)	40 (3.5)
150-300, loss >2.5 EU/year	615 (12.0)	95 (7.3)	252 (17.0)	74 (6.3)	194 (16.8)
<150, gain	226 (4.4)	74 (5.7)	126 (8.5)	24 (2.1)	2 (0.2)
<150, loss <2.5 EU/year	383 (7.5)	62 (4.7)	289 (19.5)	24 (2.1)	8 (0.7)
<150, loss >2.5 EU/year	27 (0.5)%	1 (0.1)	16 (1.1)	0 (0.0)	10 (0.9)

Appendix B. Associations between moderate-to-vigorous intensity physical activity (MVPA) trajectories and onset of metabolic outcomes in the CARDIA Study, stratified by BMI classification

	Estimated lower MVPA score (per 100 Exercise Units) at age 18			Additional annual reduction in MVPA score (per 1 Exercise Unit)		
	OR [a]	95% CI	p	OR [a]	95% CI	p
Diabetes			0.77[b]			0.90[b]
BMI <18.5 kg/m^2	1.31	0.79, 2.17	0.29	1.02	0.82, 1.26	0.88
BMI 18.5 - 25 kg/m^2	1.05	0.89, 1.23	0.59	1.05	0.99, 1.10	0.08
BMI 25-30 kg/m^2	**1.13**	**1.00, 1.27**	**0.048**	**1.05**	**1.00, 1.11**	**0.04**
BMI >30 kg/m^2	**1.13**	**1.05, 1.20**	**<0.001**	**1.07**	**1.04, 1.10**	**<0.001**
High LDL cholesterol			**<0.001[b]**			**0.002[b]**
BMI <18.5 kg/m^2	1.19	0.89, 1.57	0.24	1.00	0.93, 1.08	0.98
BMI 18.5 - 25 kg/m^2	1.06	1.00, 1.13	0.038	**1.03**	**1.01, 1.05**	**<0.001**
BMI 25-30 kg/m^2	0.98	0.93, 1.03	0.46	1.00	0.98, 1.02	0.78
BMI >30 kg/m^2	**0.89**	**0.82, 0.96**	**0.002**	**0.96**	**0.93, 0.99**	**0.018**
Low HDL cholesterol			**0.01[b]**			0.14[b]
BMI <18.5 kg/m^2	1.10	0.94, 1.28	0.24	1.05	0.97, 1.14	0.21
BMI 18.5 - 25 kg/m^2	**1.08**	**1.03, 1.13**	**<0.001**	**1.03**	**1.01, 1.05**	**0.002**
BMI 25-30 kg/m^2	**1.06**	**1.01, 1.12**	**0.025**	1.01	0.99, 1.04	0.17
BMI >30 kg/m^2	0.96	0.90, 1.02	0.15	0.99	0.96, 1.02	0.43
High triglyceride			**0.001[b]**			**0.022[b]**
BMI <18.5 kg/m^2	1.04	0.69, 1.58	0.84	1.22	0.87, 1.71	0.25
BMI 18.5 - 25 kg/m^2	**1.23**	**1.11, 1.36**	**<0.001**	**1.09**	**1.04, 1.14**	**<0.001**
BMI 25-30 kg/m^2	**1.10**	**1.02, 1.18**	**0.018**	**1.04**	**1.01, 1.07**	**0.009**
BMI >30 kg/m^2	0.98	0.92, 1.04	0.46	1.01	0.98, 1.04	0.58
Dyslipidemia[c]			**<0.001[b]**			**<0.001[b]**
BMI <18.5 kg/m^2	1.13	0.97, 1.32	0.12	1.02	0.95, 1.09	0.59
BMI 18.5 - 25 kg/m^2	**1.10**	**1.05, 1.14**	**<0.001**	**1.04**	**1.02, 1.06**	**<0.001**
BMI 25-30 kg/m^2	**1.05**	**1.00, 1.09**	**0.048**	1.02	1.00, 1.04	0.10
BMI >30 kg/m^2	**0.93**	**0.88, 0.98**	**0.007**	0.98	0.95, 1.01	0.18

Note: Boldface indicates statistical significance ($p<0.05$). We scaled estimated physical activity score at age 18 from high to low per 100 Exercise Units, corresponding to 0.45 SDs, for ease of interpretation. We kept annual reduction in total physical activity per one Exercise Unit, corresponding to 0.23 SDs

[a] Model includes: estimated MVPA level at age 18 (left column), annual reduction in MVPA (right column), age, race, sex, education, family history of diabetes or cardiovascular disease, smoking status, alcohol, and body mass index.

[b] Tests for interactions with BMI and physical activity. P for interaction listed above stratified outcomes.

[c] Dyslipidemia defined as triglycerides≥150 mg/DL or HDL<35 mg/DL for males or HDL<45 mg/DL for females

Appendix C. Associations between moderate-to-vigorous intensity physical activity (MVPA) and onset of metabolic outcomes in the CARDIA Study, stratified by race and sex

	Estimated lower MVPA score (per 100 Exercise Units) at age 18			Additional annual reduction in MVPA score (per 1 Exercise Unit)		
	OR [a]	95% CI	p	OR [a]	95% CI	p
Diabetes			**<0.001[b]**			0.24[b]
White women	**1.50**	**1.35, 1.66**	**<0.001**	**1.09**	**1.02, 1.16**	**0.01**
Black women	**1.15**	**1.06, 1.25**	**0.001**	**1.09**	**1.05, 1.13**	**<0.001**
White men	**1.27**	**1.18, 1.36**	**<0.001**	**1.14**	**1.09, 1.20**	**<0.001**
Black men	**1.13**	**1.06, 1.21**	**<0.001**	**1.08**	**1.03, 1.12**	**<0.001**
High LDL cholesterol			**0.002[b]**			0.17[b]
White women	**1.06**	**1.01, 1.11**	**0.021**	**1.04**	**1.01, 1.07**	**0.007**
Black women	1.05	0.99, 1.12	0.13	1.02	1.00, 1.05	0.10
White men	0.98	0.94, 1.01	0.19	1.01	0.99, 1.03	0.39
Black men	0.99	0.95, 1.03	0.55	1.00	0.97, 1.02	0.89
Low HDL cholesterol			**<0.001[b]**			0.85[b]
White women	**1.11**	**1.07, 1.15**	**<0.001**	**1.03**	**1.01, 1.06**	**0.007**
Black women	1.04	0.99, 1.10	0.09	**1.04**	**1.02, 1.07**	**0.001**
White men	**1.16**	**1.11, 1.20**	**<0.001**	**1.04**	**1.02, 1.06**	**<0.001**
Black men	**1.27**	**1.20, 1.33**	**<0.001**	1.03	1.00, 1.05	0.08
High triglyceride			**<0.001[b]**			0.37[b]
White women	**1.23**	**1.15, 1.31**	**<0.001**	**1.08**	**1.03, 1.12**	**<0.001**
Black women	**1.61**	**1.41, 1.84**	**<0.001**	**1.11**	**1.04, 1.17**	**<0.001**
White men	0.99	0.96, 1.04	0.80	**1.05**	**1.02, 1.08**	**<0.001**
Black men	**1.11**	**1.04, 1.18**	**<0.001**	**1.05**	**1.02, 1.09**	**0.005**
Dyslipidemia[c]			0.07[b]			0.053[b]
White women	**1.11**	**1.08, 1.15**	**<0.001**	**1.05**	**1.03, 1.08**	**<0.001**
Black women	**1.10**	**1.05, 1.16**	**<0.001**	**1.05**	**1.02, 1.07**	**<0.001**
White men	**1.07**	**1.04, 1.10**	**<0.001**	**1.05**	**1.03, 1.07**	**<0.001**
Black men	**1.12**	**1.07, 1.16**	**<0.001**	1.01	0.99, 1.03	0.40

Note: Boldface indicates statistical significance ($p<0.05$). We scaled estimated physical activity score at age 18 from high to low per 100 Exercise Units, corresponding to 0.45 SDs, for ease of interpretation. We kept annual reduction in total physical activity per one Exercise Unit, corresponding to 0.23 SDs

[a] Model includes: estimated MVPA level at age 18 (left column), annual reduction in MVPA (right column), age, race, sex, education, family history of diabetes or cardiovascular disease, smoking status, alcohol, and body mass index.

[b] Tests for interactions with race/ethnicity and sex. P for interaction listed above stratified outcomes.

[c] Dyslipidemia defined as triglycerides≥150 mg/DL or HDL<35 mg/DL for males or HDL<45 mg/DL for females

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