

The Long-term Effect of Different Exercise Intensities on High-Density Lipoprotein Cholesterol in Older Men and Women Using the Per Protocol Approach: The Generation 100 Study

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Abstract

Objective: To examine whether 5 years of high-intensity interval training (HIIT) increases high-density lipoprotein cholesterol (HDL-C) concentration more than moderate-intensity continuous training (MICT) and control (CON) in older men and women.

Methods: A total of 1567 older adults (790 [50.4%] women) were randomized (2:1:1) to either CON (n=780; asked to follow the national recommendations for physical activity) or 2 weekly sessions of HIIT (10-minute warm-up followed by 4×4-minute intervals at ~90% of peak heart rate) or MICT (50 minutes of continuous work at ~70% of peak heart rate). Serum HDL-C concentration was measured by standard procedures at baseline and at 1 year, 3 years, and 5 years. The study took place between August 21, 2012, and June 31, 2018. Linear mixed models were used to determine between-group differences during 5 years using the per protocol approach.

Results: Men in HIIT had a smaller reduction in HDL-C (−1.2%) than men in CON (−6.9%) and MICT (−7.8%) after 5 years ($P=.01$ and $P=.03$ for CON vs HIIT and MICT vs HIIT, respectively). No effect of exercise intensity on HDL-C was seen in women. Changes in peak oxygen uptake were associated with changes in HDL-C in both men and women, whereas changes in body weight and fat mass were not.

Conclusion: In men, HIIT seems to be the best strategy to prevent a decline in HDL-C during a 5-year period. No effect of exercise intensity was seen for older women.

Trial registration: ClinicalTrials.gov identifier: NCT01666340.

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Ageing is characterized by functional and physiologic changes^{1,2} that increase the risk for development of chronic diseases, such as cardiovascular disease (CVD).³ Cardiovascular disease is the leading cause of death in older adults, and has globally been the world's biggest killer the last 15 years.⁴ Dyslipidemia, defined as abnormalities in the standard lipid profile, is one of the major risk factors for CVD,⁵ and lipid-modifying agents (LMAs), such as statins, are

the most commonly prescribed medication in older adults, acting as both primary and secondary prevention.⁶ The pharmacologic treatments effectively decrease low-density lipoprotein cholesterol (LDL-C) concentration; however, the effect on high-density lipoprotein cholesterol (HDL-C) concentration is controversial.⁷

Low levels of HDL-C are associated with cardiovascular events and mortality⁸ even when LDL-C levels are low,⁵ and

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improvements in HDL-C and triglyceride levels, in the absence of changes in LDL-C, reduce cardiovascular events.⁹ HDL-C is important in removal of cholesterol from peripheral cells to the liver (reverse cholesterol transport), is anti-inflammatory, and inhibits lipid oxidation.¹ Increasing age slows or reverses several of these processes, leading to disordered lipid metabolism and systemic inflammation that further increases the risk of CVD.¹ One potential approach for increasing HDL-C concentration is aerobic exercise,¹⁰ and high-intensity interval training (HIIT) has been found to be more effective at improving HDL-C concentration than moderate-intensity continuous training (MICT) in younger adults.¹¹ However, the effect of exercise on HDL-C in older adults is unclear.¹² It has been suggested that older adults need a longer time to adapt positively to exercise with respect to HDL-C.¹³ In addition, few studies have examined the effect of identical exercise programs in men and women on HDL-C, and more knowledge is needed to determine whether the optimal training program for older men and women differs with respect to HDL-C adaptation.^{12,14}

The primary aim of this study was to test the hypothesis that 5 years of HIIT increases HDL-C concentration more than MICT and control (CON). We also examined a secondary hypothesis that changes in HDL-C are associated with changes in peak oxygen uptake (VO_2peak), body weight, and fat mass after 5 years of exercise. Only participants who adhered to the prescribed exercise intervention were included in this study (ie, per protocol approach).

METHODS

Study Population and Design

In 2012, all men and women between the ages of 70 and 77 years with a permanent address in the municipality of Trondheim were invited to participate in a randomized controlled trial, the Generation 100 study.¹⁵ Participants were excluded if they had illnesses or disabilities, including cancers and dementia, that prevented exercise or hindered completion of the study. Furthermore, participants with chronic communicable infectious diseases and symptomatic valvular heart disease, hypertrophic

cardiomyopathy, unstable angina, primary pulmonary or uncontrolled hypertension, heart failure, or severe arrhythmias were excluded.¹⁵ Recruitment, intervention program, and laboratory procedures of the Generation 100 study have been described in detail elsewhere.¹⁵ In short, a total of 777 men and 790 women were included in the study and were examined by questionnaires, clinical examinations, blood sampling, and physical tests at baseline and after 1 year and 3 years. Participants were randomized (2:1:1), stratified by sex and cohabiting status, after the health examination at baseline to CON (n=780), MICT (n=387), or HIIT (n=400) for 5 years. The randomization process was performed by the unit for Applied Clinical Research at the Norwegian University of Science and Technology. Personnel were blinded to intervention group during testing. For this particular study, we used a per protocol approach, and participants were included if they had 50% or more adherence to the prescribed exercise intervention during 5 years. After 5 years, 673 participants (350 [52%] women) adhered to the prescribed exercise program or to the national recommendations for physical activity and were included in the study. This included 412 participants (218 women) in CON, 142 participants (80 women) in MICT, and 119 (52 women) in HIIT. The study was approved by the regional ethics committee before study start (REK2012/381 B), and the study was registered in [ClinicalTrials.gov](https://www.clinicaltrials.gov) in August 2012. The participants signed an informed consent form that covers the aim and objectives of the study (REK2018/2138-1). A flowchart of the study is presented in [Figure 1](#).

Clinical and Biochemical Testing

Participants were asked to be fasting and to avoid tobacco, alcohol, and caffeine for 12 hours and exercise for 24 hours before examination. Blood sampling was standardized and obtained in a sitting position from the left arm vein. Serum HDL-C concentrations were measured immediately by standard procedures at St. Olavs Hospital, Trondheim, Norway. The laboratory at St. Olavs Hospital is under a laboratory quality management system program, and quality assurances were thereby performed frequently. Weight and fat percentage were measured by bioelectrical impedance (Inbody 720, BIOSPACE). Participants with a

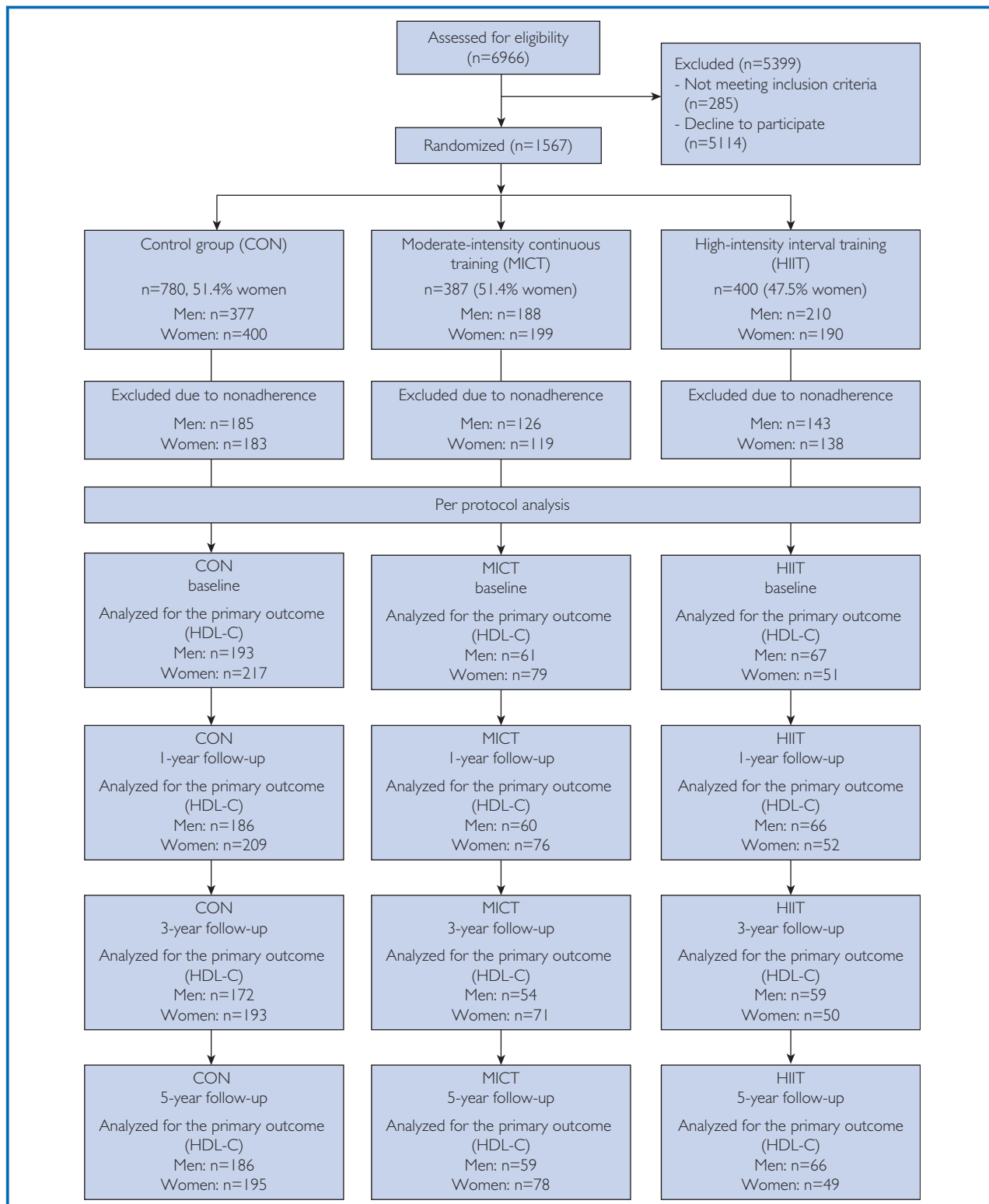


FIGURE 1. Flowchart. Adherence to control (CON), moderate-intensity continuous training (MICT), and high-intensity interval training (HIIT) represents the proportion of men and women who adhered to the prescribed exercise program during 5 years and the proportion of men and women who were analyzed for the primary outcome at each follow-up time. HDL-C, high-density lipoprotein cholesterol.

pacemaker had weight measured on a regular scale. Fat mass was calculated by multiplying fat percentage and body weight divided by 100.

Testing of VO_2peak was performed on a treadmill ($n=656$) or a stationary bike ($n=13$) at the NeXt Move Core Facilities, St. Olavs Hospital, Norway. Stationary bikes were used only for participants who were unable to walk on the treadmill (eg, unstable or acute injury). We mainly used Cortex Meta-Max II ($n=641$) and used Oxycon Pro (Erich Jaeger; $n=28$) as a backup for days with technical difficulties. The same system was used for each participant at all follow-ups. The testing and calibration procedures have been described previously.¹⁵ In short, a facemask (Hans Rudolph) connected to the gas analyzer was attached to the participants before initiation of the test. After 10-minute warm-up at moderate intensity, an individualized protocol was used whereby the load was increased each 1.5 minutes by 1 km/h or 2% inclination. The test was terminated voluntarily or with a plateau in oxygen uptake (VO_2) with increased load (ie, no more than $2 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ between two 30-second segments). Peak oxygen uptake was the average of the 3 highest values during the test. Participants with previous heart diseases were tested under electrocardiographic monitoring, and the American College of Cardiology/American Heart Association guidelines for exercise testing of patients with known CVD were observed.¹⁶ Peak heart rate (HR_{peak}) was determined as the highest measured heart rate during the VO_2peak test. Peak heart rates measured during a VO_2peak test have had good agreement with the maximum heart rate measured in a test designed to measure maximum heart rate in younger adults.¹⁷

Intervention

The HIIT group warmed up for 10 minutes at moderate intensity at approximately 70% of HR_{peak}. Immediately after warm-up, the participants continued with four 4-minute bouts performed at approximately 90% of HR_{peak}, interspersed with 3 minutes of active recovery at approximately 70% HR_{peak}. The session ended with a 5-minute cool-down at approximately 70% HR_{peak}. The MICT group performed a continuous workout at an intensity

of approximately 70% of HR_{peak} for 50 minutes. Both exercise groups were offered supervised exercise sessions twice a week for 5 years. Participants were free to choose the preferred exercise mode (ie, walking, running, cycling), but they met for 1 mandatory supervised spinning session every sixth week. Heart rate monitors and the Borg scale (6-20)¹⁸ were used to promote recommended exercise intensity. The control group was encouraged to follow the national recommendations for physical activity in 2012, which included 30 minutes of physical activity on most days of the week.¹⁹ All groups received verbal and written information at inclusion and at each follow-up time point.

Self-Reported Questionnaires

Adherence to the exercise program was determined from questionnaires previously described,¹⁵ including exercise frequency—How often do you exercise? never or less than once per week [0], once a week [1], 2 or 3 times a week [2.5], nearly every day [5]; duration—For how long do you exercise each time? less than 15 minutes [7.5], 15 to 30 minutes [22.5], 30 to 60 minutes [45], more than 60 minutes [60]; and intensity using the Borg scale—On a scale of 6 to 20, how hard do you exercise?²⁰

Minutes per week were calculated by multiplying frequency and duration (averages denoted in brackets).

As previously described,²¹ the minimum requirements for adherence to HIIT were at least 30 minutes of weekly exercise at 15 or higher on the Borg scale, and the requirements for adherence to MICT were at least 30 minutes of weekly exercise at 11 to 14 on the Borg scale. Adherence of the CON group was determined as 30 minutes or more of weekly physical activity at any intensity. This included the criteria for inclusion in the study and had to be followed for all 5 years.

Information on smoking status and alcohol consumption was determined from questionnaires previously described.¹⁵ Smoking status (Do you smoke? No, I have never smoked; No, I quit smoking; Yes, cigarettes occasionally [parties/vacation, not daily]; Yes, cigars/cigarillos/pipe occasionally; Yes, cigarettes daily; Yes, cigars/cigarillos/pipe daily) was dichotomized to former smoker and current smoker.

Alcohol consumption (How many glasses of beer, wine, or spirits do you usually drink in the course of 2 weeks? and How often do you drink 5 glasses or more of beer, wine, or spirits in one sitting? never; monthly; weekly; daily) was described as average units of alcohol per week and dichotomized (yes/no) to binge drinker, defined as 5 units or more of alcohol weekly. Use of fish oils, omega-3 supplements, and vitamin supplements (How often do you usually take fish oil/omega-3/vitamin supplements? never/rarely; 1 to 3 times/month; 1 to 3 times/week; 4 to 6 times/week; 1 daily; 2 times daily; 3 times daily; 4 or more times per day) at baseline was categorized to yes/no.

Cardiovascular Disease and Lipid-Modifying Agents

Information on use of prescribed medications was obtained from the participants' medical prescription registry. Medication affecting lipid metabolism was defined as LMAs (Anatomical Therapeutic Chemical classification code C10). In addition, history of CVD at inclusion into the study was obtained from the participants' archive at St. Olavs Hospital.

Statistics

Descriptive continuous data are presented as mean and standard deviation and categorical variables as proportion and number of participants. We used linear mixed models with the outcome HDL-C and secondary outcomes (body weight and VO_2peak), 1 at a time, as dependent variables. The individual was included as a random effect. We included time, intervention group (CON vs MICT vs HIIT and MICT vs HIIT), and sex and their 2-way (time \times group, time \times sex, and group \times sex) and 3-way (time \times group \times sex) interactions as categorical covariates. All analyses were adjusted for age and cohabiting status. Because of non-normally distributed residuals, we used bootstrapping with the bias corrected and accelerated method, using 2000 bootstrap samples. The analyses were carried out by the per protocol approach and included participants in MICT and HIIT with 50% adherence to the prescribed exercise program and participants in CON who adhered to the national recommendations for physical activity for the entire duration of the study. We

performed subanalyses whereby participants with CVD or using LMAs at inclusion were excluded. Forward linear regression was used to examine the association between changes in VO_2peak ($\Delta\text{VO}_2\text{peak}$), fat mass (ΔFM), and body weight (Δweight) and changes in HDL-C ($\Delta\text{HDL-C}$) in older men and women. Delta (Δ) values were calculated by subtracting baseline values from the year 5 values. The dependent variable was $\Delta\text{HDL-C}$, and $\Delta\text{VO}_2\text{peak}$, ΔFM , and Δweight were used as independent variables, and we adjusted for smoking status (yes/no).²² A separate model was run for men and women. As some participants changed between treadmill and ergometer bike when performing the VO_2peak test, these were excluded from the analysis ($n=3$) to ensure that changes in VO_2peak were not due to changed modality. A 2-sided P value of less than .05 was considered statistically significant. Because of multiple comparisons, P values between 1% and 5% must be interpreted with caution. All statistical analyses were performed using SPSS version 25 (IBM). Sample size for the main study was calculated on the basis of mortality.¹⁵

RESULTS

Baseline Characteristics

Baseline characteristics of the participants are presented in Table 1. The average age (mean [standard deviation]) was 72.5 (1.9) years for men and 72.6 (2.1) years for women. Women had on average higher HDL-C levels than men (1.94 [0.51] vs 1.58 [0.42] mmol/L, respectively) and lower VO_2peak than men (27.41 [4.98] vs 33.13 [6.45] $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, respectively) at inclusion.

Exercise Habits

Detailed exercise habits for men and women in each intervention group are presented in Table 2. After 5 years, there were no differences between the intervention groups in average exercise sessions per week and average duration of each exercise session. Both men and women in CON and MICT had an average intensity of 12 to 13 on the Borg scale of 6 to 20, and men and women in HIIT had an average intensity of 15 on the Borg scale of 6 to 20. Of men in CON, 57% and 37% fulfilled the criteria for MICT and HIIT, respectively.

TABLE 1. Baseline Characteristics of Men and Women in Each Intervention Group^{a,b}

	CON		MICT		HIIT	
	Men (n=194)	Women (n=218)	Men (n=62)	Women (n=80)	Men (n=67)	Women (n=52)
Age (y)	72.5 (1.9)	72.6 (2.1)	72.7 (2.1)	72.6 (2.0)	72.3 (1.9)	72.8 (2.1)
HDL-C (mmol/L)	1.59 (0.43)	1.95 (0.51)	1.53 (0.40)	1.93 (0.49)	1.61 (0.42)	1.90 (0.52)
LDL-C (mmol/L)	3.21 (0.93)	3.68 (0.99)	3.31 (1.05)	3.53 (0.97)	3.19 (0.94)	3.43 (1.03)
TC (mmol/L)	5.33 (1.00)	6.13 (1.02)	5.36 (1.16)	5.95 (1.01)	5.29 (1.00)	5.85 (1.13)
TG (mmol/L)	1.16 (0.57)	1.11 (0.56)	1.16 (0.65)	1.08 (0.55)	1.08 (0.49)	1.15 (0.61)
Weight (kg)	81.5 (9.8)	66.9 (10.2)	81.8 (12.0)	67.5 (9.8)	81.5 (11.5)	66.4 (10.0)
VO ₂ peak (mL·min ⁻¹ ·kg ⁻¹)	32.95 (6.55)	27.45 (4.90)	32.31 (5.57)	26.81 (5.14)	34.42 (6.82)	28.18 (5.03)
CVD	16.5 (32)	10.1 (22)	25.8 (16)	3.8 (3)	19.4 (13)	9.6 (5)
LMA	24.2 (47)	21.6 (47)	27.4 (17)	28.7 (23)	25.4 (17)	36.5 (19)
Smoking status						
Former	47.9 (93)	35.8 (78)	50.0 (31)	33.8 (27)	41.8 (28)	30.8 (16)
Current	5.2 (10)	5.5 (12)	6.4 (4)	8.8 (7)	4.5 (3)	0.0 (0)
Binge drinker ^c	5.7 (11)	3.2 (7)	12.9 (8)	1.3 (1)	10.4 (7)	1.9 (1)
Alcohol (units/wk)	1.9 (1.0)	1.4 (0.9)	2.4 (0.9)	1.1 (0.9)	2.1 (1.3)	1.1 (0.9)
Fish oil ^d	45.4 (88)	31.2 (68)	35.5 (22)	27.5 (22)	37.3 (25)	36.5 (19)
Omega-3 ^d	33.5 (65)	39.4 (86)	37.1 (23)	46.3 (37)	28.4 (19)	46.2 (24)
Vitamins ^d	34.5 (67)	49.5 (108)	32.3 (20)	48.8 (39)	34.3 (23)	40.4 (21)

^aCON, control; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; LDL-C, low-density lipoprotein cholesterol; LMA, lipid-modifying agent; MICT, moderate-intensity continuous training; TC, total cholesterol; TG, triglyceride; VO₂peak, peak oxygen uptake.

^bContinuous data are presented as mean (standard deviation), and categorical data are presented as percentage (number).

^cBinge drinker: more than 5 units of alcohol in 1 sitting, weekly or more often.

^dSupplements: proportion of participants taking supplements monthly or more often.

The corresponding numbers for women were 62% and 23%, respectively.

Changes in HDL-C Over Time in Older Men and Women

The mean between-group differences and changes over time in HDL-C in men and women are presented in Table 3 and Figure 2. After 5 years, HDL-C concentration was significantly reduced in CON and MICT, for both men and women. Men reduced HDL-C concentration by 6.9% ($P<.0001$), 7.8% ($P=.001$), and 1.2% ($P=.31$) for CON, MICT, and HIIT, respectively. The reduction of HDL-C concentration was significantly lower for men in HIIT than for men in CON ($P=.01$) and MICT ($P=.03$) after 5 years. After 5 years, women reduced HDL-C concentration by -7.2% , -6.7% (both $P<.0001$), and -2.6% ($P=.19$) for CON, MICT, and HIIT, respectively; however, the difference between the groups did not reach statistical significance.

We observed no changes in HDL-C in men or women after 1 year. However, men in CON and HIIT significantly improved HDL-C levels by 3.8% and 6.2%, respectively, after 3 years ($P=.002$ and $P=.004$, respectively), whereas no changes were seen in men in MICT at the same time point. Only the change in HIIT reached statistical significance from the change in MICT ($P=.04$) after 3 years. No changes in HDL-C levels were seen in women after 3 years.

The effect of time and intervention remained the same for HDL-C in the sensitivity analysis, in which participants with CVD or taking an LMA at inclusion were excluded (data not shown).

Changes in Body Weight and VO₂peak Over Time in Older Men and Women

The between-group differences and changes in VO₂peak, body weight, and fat mass over time are presented in Table 4.

TABLE 2. Detailed Exercise Description of Participants Who Adhered to the Prescribed Exercise Program for 5 Years^{a,b}

	CON		MICT		HIIT	
	Men	Women	Men	Women	Men	Women
Baseline						
Intensity ^c	13.8 (1.9)	13.1 (1.9)	12.6 (1.8)	12.7 (2.1)	14.4 (2.2)	13.6 (1.9)
Frequency (sessions/week)	2.7 (1.3)	2.9 (1.4)	3.1 (1.4)	2.9 (1.3)	2.7 (1.3)	2.8 (1.2)
Duration (min/session)	47.4 (11.5)	47.6 (10.3)	46.6 (11.1)	47.8 (10.2)	51.0 (8.3)	49.4 (9.0)
Year 1						
Intensity ^c	14.1 (1.8)	13.5 (1.6)	12.7 (1.2)	12.8 (0.9)	15.9 (1.3)	15.4 (1.0)
Frequency (sessions/week)	3.3 (1.3)	3.3 (1.3)	3.1 (1.3)	3.2 (1.2)	3.0 (1.1)	3.1 (1.1)
Duration (min/session)	48.4 (11.4)	47.3 (10.2)	46.5 (11.0)	47.3 (8.5)	51.0 (8.3)	48.0 (9.3)
Year 3						
Intensity ^c	14.1 (1.7)	13.6 (1.5)	12.8 (1.1)	13.0 (0.8)	15.9 (1.3)	15.3 (1.4)
Frequency (sessions/week)	3.3 (1.4)	3.3 (1.4)	3.1 (1.3)	3.1 (1.1)	3.0 (1.2)	3.0 (1.1)
Duration (min/session)	48.0 (11.3)	47.3 (9.9)	46.7 (11.6)	48.1 (9.5)	49.1 (10.1)	49.7 (10.0)
Year 5						
Intensity ^c	13.8 (1.8)	13.3 (1.7)	12.6 (1.2)	12.8 (1.1)	15.4 (1.2)	15.1 (1.8)
Frequency (sessions/week)	3.3 (1.4)	3.2 (1.5)	3.1 (1.3)	3.1 (1.2)	3.0 (1.2)	3.2 (1.3)
Duration (min/session)	47.2 (12.7)	46.2 (10.9)	46.8 (9.8)	48.8 (11.5)	49.9 (8.7)	48.0 (12.4)

^aCON, control; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training.

^bData are presented as mean (standard deviation).

^cExercise intensity is measured by the Borg scale (6–20) and is reported as average intensity per exercise session.

Body weight was significantly reduced for men in CON and HIIT (−1.0% and −1.6%; both $P=.007$) and for women in HIIT (−2.9%; $P=.008$) after 5 years. However, neither men nor women reached statistically significant between-group differences after 5 years. Only men in HIIT (−2.0%) had a larger reduction compared with men in CON (−0.7%) after 1 year ($P=.03$). No between-group differences were seen for women after 1 year.

After 5 years, women in HIIT reduced fat mass significantly more than women in CON and MICT ($P=.05$ and $P=.04$, respectively). Women in HIIT had a significantly larger reduction in fat mass compared with women in CON after 3 years. No between-group differences were observed in women after 1 year. We observed no between-group differences in men at any follow-up times.

After 5 years, $\dot{V}O_{2\text{peak}}$ was significantly reduced for men by −5.0%, −6.1% (both $P<.0001$), and −2.6% ($P=.04$) in CON, MICT, and HIIT, respectively. No between-group differences were observed after 5 years for $\dot{V}O_{2\text{peak}}$ in men. Women in CON and

MICT significantly reduced $\dot{V}O_{2\text{peak}}$ by −3.9% ($P<.0001$) and −2.4% ($P=.008$), and no changes were observed for $\dot{V}O_{2\text{peak}}$ for women in HIIT after 5 years; however, the changes did not reach statistical significance between the groups. After 1 year, men in HIIT improved $\dot{V}O_{2\text{peak}}$ (9.1%; $P<.0001$) more than men in CON (4.1%; $P=.001$) ($P=.007$), and after 3 years, $\dot{V}O_{2\text{peak}}$ was improved more in men in HIIT (4.5%; $P=.03$) compared with men in CON (1.3%) and MICT (−2.4%; $P=.02$ and $P=.011$, respectively). No between-group differences were seen for women in $\dot{V}O_{2\text{peak}}$ during the study.

Predictors of Changes in HDL-C

Regression analysis found that every 1 $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ change in $\dot{V}O_{2\text{peak}}$ increased $\Delta\text{HDL-C}$ by 0.011 mmol/L ($P=.001$) in men. In women, 1 $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ change in $\dot{V}O_{2\text{peak}}$ increased $\Delta\text{HDL-C}$ by 0.016 mmol/L ($P<.001$). Changes in HDL-C were significantly associated with $\Delta\dot{V}O_{2\text{peak}}$ in men ($F_{1,262}=10.835$; $P=.001$; $R^2=0.036$) and women ($F_{1,267}=12.845$; $P<.001$; $R^2=0.042$) after 5 years. Changes in body weight and

TABLE 3. The Exercise Effect on HDL-C in Men and Women^a

Time ^b	Sex	CON		MICT		HIIT		Group × Time MICT vs CON			Group × Time HIIT vs CON			Group × Time HIIT vs MICT		
		No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	Estimate (95% CI)	P value	Estimate (95% CI)	P value	Estimate (95% CI)	P value	Estimate (95% CI)	P value	
0	Men	193	1.59 (0.43)	61	1.53 (0.45)	67	1.61 (0.42)	-0.06 (-0.11, -0.02)	.01	0.02 (-0.03, 0.07)	.45	0.08 (0.02, 0.14)	.009			
	Women	217	1.95 (0.51)	79	1.93 (0.49)	51	1.90 (0.52)	-0.02 (-0.07, 0.03)	.54	-0.06 (-0.15, 0.03)	.20	-0.04 (-0.14, 0.06)	.39			
1	Men	186	1.62 (0.44)	60	1.52 (0.45)	66	1.66 (0.39)	-0.04 (-0.12, 0.04)	.37	0.002 (-0.07, 0.07)	.96	0.04 (-0.05, 0.12)	.42			
	Women	209	1.96 (0.52)	76	1.99 (0.52)	52	1.96 (0.43)	0.04 (-0.05, 0.12)	.33	0.06 (-0.03, 0.16)	.25	0.02 (-0.10, 0.14)	.79			
3	Men	172	1.65 (0.45)	54	1.53 (0.45)	59	1.71 (0.50)	-0.04 (-0.12, 0.04)	.30	0.06 (-0.01, 0.15)	.13	0.11 (0.01, 0.21)	.04			
	Women	193	1.99 (0.52)	71	1.98 (0.48)	50	2.00 (0.44)	0.04 (-0.03, 0.12)	.27	0.07 (-0.02, 0.18)	.19	0.03 (-0.08, 0.16)	.65			
5	Men	186	1.48 (0.38)	59	1.41 (0.33)	66	1.59 (0.41)	-0.004 (-0.07, 0.07)	.91	0.09 (0.02, 0.16)	.01	0.10 (0.01, 0.18)	.03			
	Women	195	1.81 (0.47)	78	1.80 (0.42)	49	1.85 (0.39)	0.02 (-0.05, 0.09)	.54	0.08 (-0.02, 0.20)	.20	0.06 (-0.06, 0.19)	.39			

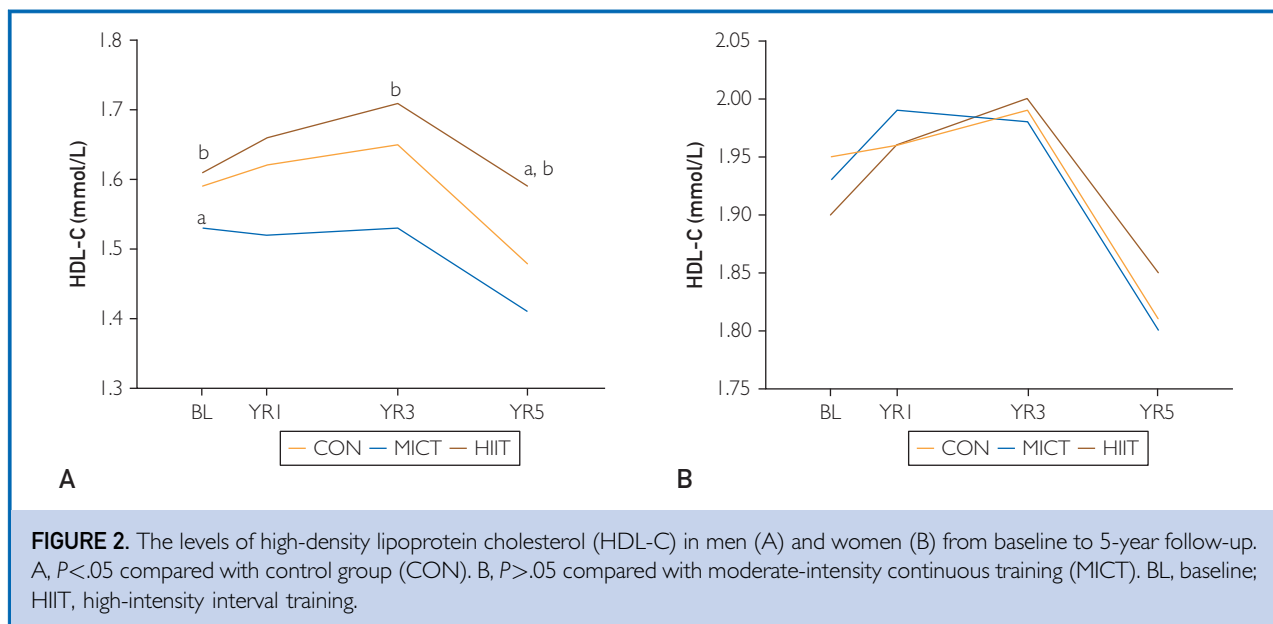
^aCON, control; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training.
^bYears from inclusion.

fat mass were not associated with changes in HDL-C.

DISCUSSION

This study is the first to evaluate the effect of 5 years of different exercise intensities on HDL-C in a large population of older men and women using the per protocol approach. After 5 years, men had a smaller reduction in HDL-C in HIIT compared with CON and MICT. There were no differences in women. Changes in Vo₂peak but not in body weight or fat mass were associated with changes in HDL-C in both men and women.

The effect of exercise on HDL-C in older adults is debated,^{12,13,23} and the variable results are often explained by the heterogeneity of exercise interventions.^{12,24} Studies including younger adults have reported that regular aerobic exercise improves HDL-C levels²⁵ and that higher intensity is superior to moderate intensity for improving HDL-C concentration.¹¹ In our study, we observed a smaller reduction in HDL-C concentration after 5 years in men in HIIT compared with men in MICT and CON. Exercise frequency and duration were similar between groups, and exercise intensity was the only exercise factor differentiating the 3 groups. It has been suggested that initial levels of HDL-C influence the training adaptation as more favorable levels at inclusion lead to smaller changes.²⁶ Men in HIIT had initially higher HDL-C levels compared with the 2 other groups but did also have the largest improvements after 3 years and the only intervention that maintained HDL-C levels after 5 years. Thus, higher initial HDL-C levels did not affect the changes in older men. A longer intervention time has been proposed for older adults for exercise adaptation in lipids and lipoproteins.^{13,27} Interestingly, we observed an increase in HDL-C in men in HIIT and CON after 3 years, indicating that exercise has an effect on HDL-C in older men. However, only men in HIIT improved HDL-C concentration more than men in MICT. Surprisingly, the CON group had a relatively high level of physical activity throughout the study, and a relatively large percentage exercised with high intensity. The lack of significant differences between the HIIT and CON groups after 3 years could be due to the crossover between



the interventions, whereby a relatively high proportion of the CON group exercised with high intensity. However, our data indicate that long-term exercise can improve HDL-C levels in older men. Our data are in line with those of King et al,¹³ who found no changes in HDL-C in middle-aged adults after 1 year but a small, significant increase after 2 years. Our result indicates that HIIT is more efficient than MICT in improving HDL-C levels after 3 years and more efficient than MICT and CON in maintaining HDL-C levels over time in older men. The same trend was seen in women; however, no changes were observed between the intervention groups as all groups were able to maintain their HDL-C levels.

It has been speculated that women have an attenuated response to exercise in regard to HDL-C compared with men.²⁸ In our study, none of the interventions were superior in regard to HDL-C levels in women. Several previous studies have failed to find an exercise effect on HDL-C in older women.²⁹⁻³¹ However, in a meta-analysis of younger, healthy women, HDL-C increased by 3% after exercise.³² The women in our study had initially high levels of HDL-C that previously have been found to influence the training response.²⁶ Intensity is important to limit the reduction seen in HDL-C in men, but our results indicate that higher exercise intensity

is not crucial for women. It could be that a higher exercise dose (ie, exercise frequency or duration) is more important for changes in HDL-C in older women, as seen in younger women.³³

Changes in Fitness and Body Composition

Current guidelines recommend weight loss to improve an abnormal lipid profile.⁵ Our data found that that reduction in body weight or reduction in fat mass is not necessary to improve HDL-C concentration in older men. However, the absolute change in our study was relatively small, and we cannot determine whether a larger reduction in body weight or fat mass could have led to improvements in HDL-C levels. It has previously been confirmed that changes in HDL-C are associated with changes in fat mass but not $VO_{2\text{peak}}$ in younger adults.²² However, in the older adults in this study, we found changes in HDL-C to be associated with changes in $VO_{2\text{peak}}$ and not with changes in body weight or fat mass. The association between Δ HDL-C and Δ $VO_{2\text{peak}}$ has previously been confirmed in older adults,^{32,34} and higher $VO_{2\text{peak}}$ is associated with higher levels of HDL-C in men.³⁵ This could indicate that in older adults, changes in fitness seem to be of more importance than changes in body composition for altering HDL-C levels. No difference was

TABLE 4. The Exercise Effect on Vo_2peak , Body Weight, and Fat Mass in Men and Women^a

Time ^b	Sex	CON		MICT		HIIT		Group × Time MICT vs CON		Group × Time HIIT vs CON		Group × Time HIIT vs MICT	
		No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	Estimate (95% CI)	P value	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Vo_2peak ($\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$)													
0	Men	193	32.95 (6.55)	61	32.31 (5.57)	67	34.42 (6.82)	-0.51 (-1.56, 0.46)	.26	1.67 (0.73, 2.57)	<.001	2.18 (1.11, 3.27)	<.001
	Women	214	27.45 (4.90)	79	26.81 (5.14)	51	28.18 (5.03)	-0.64 (-1.37, 0.09)	.07	0.83 (-0.25, 2.04)	.11	1.47 (0.20, 2.76)	.009
1	Men	185	34.30 (7.35)	59	34.09 (7.12)	67	37.55 (6.35)	0.31 (-1.05, 1.77)	.68	1.80 (0.49, 2.96)	.007	1.49 (-0.10, 3.03)	.08
	Women	209	29.28 (5.59)	77	28.57 (5.15)	51	30.99 (5.89)	-0.19 (-1.26, 0.82)	.68	0.99 (-0.47, 2.41)	.18	1.18 (-0.34, 2.70)	.15
3	Men	172	32.51 (7.78)	50	31.52 (6.52)	62	35.97 (7.41)	-0.45 (-1.81, 0.93)	.52	1.87 (0.46, 3.16)	.02	2.33 (0.65, 3.92)	.01
	Women	191	27.29 (5.43)	68	26.62 (5.61)	50	29.13 (5.43)	-0.05 (-1.07, 0.98)	.93	1.33 (-0.06, 2.63)	.06	1.38 (-0.17, 2.86)	.09
5	Men	175	31.31 (7.05)	52	30.34 (6.55)	62	33.52 (7.03)	-0.69 (-2.08, 0.71)	.35	0.85 (-0.55, 2.13)	.23	1.54 (-0.10, 3.03)	.08
	Women	183	26.39 (5.28)	70	26.17 (5.07)	49	28.20 (5.27)	0.37 (-0.55, 1.26)	.43	1.41 (0.09, 2.62)	.06	1.04 (-0.44, 2.41)	.18
Body weight (kg)													
0	Men	194	81.5 (9.8)	62	81.8 (12.0)	66	81.5 (11.5)	0.45 (-0.64, 1.39)	.24	-0.19 (-1.04, 0.51)	.61	-0.64 (-1.52, 0.09)	.18
	Women	218	66.9 (10.2)	80	67.5 (9.8)	52	66.4 (9.9)	0.45 (-0.24, 1.06)	.09	-0.46 (-1.37, 0.31)	.34	-0.91 (-1.92, -0.01)	.09
1	Men	192	80.9 (10.1)	62	80.5 (11.9)	67	79.9 (11.4)	-0.71 (-1.58, 0.18)	.12	-0.94 (-1.71, -0.09)	.03	-0.23 (-1.28, 0.91)	.66
	Women	216	66.3 (10.2)	79	66.1 (9.3)	51	64.5 (8.1)	-0.29 (-1.08, 0.49)	.46	-0.55 (-1.63, 0.53)	.28	-0.26 (-1.36, 0.87)	.67
3	Men	182	81.2 (10.0)	55	82.0 (12.5)	63	79.7 (9.8)	-0.02 (-1.09, 1.01)	.96	-0.93 (-1.83, -0.00)	.05	-0.91 (-2.03, 0.26)	.12
	Women	203	66.7 (10.3)	73	67.3 (9.9)	52	65.5 (8.5)	-0.32 (-1.11, 0.51)	.41	-0.91 (-2.15, 0.32)	.11	-0.59 (-1.88, 0.59)	.35
5	Men	187	80.7 (10.0)	59	81.4 (12.2)	66	80.2 (11.8)	0.03 (-1.03, 1.02)	.97	-0.55 (-1.57, 0.55)	.27	-0.58 (-1.76, 0.72)	.37
	Women	200	66.5 (10.4)	78	67.1 (10.3)	51	64.5 (7.9)	0.12 (-0.82, 1.17)	.80	-1.19 (-2.57, 0.18)	.07	-1.31 (-2.78, 0.13)	.07
Fat mass (kg)													
0	Men	192	20.1 (6.5)	62	20.6 (8.5)	66	20.5 (6.7)	0.55 (-0.16, 1.32)	.11	0.34 (-0.26, 0.93)	.25	-0.21 (-0.97, 0.45)	.60
	Women	217	23.4 (7.8)	80	23.4 (7.4)	52	23.3 (7.0)	-0.03 (-0.60, 0.47)	.93	-0.17 (-0.91, 0.52)	.67	-0.14 (-1.04, 0.75)	.77
1	Men	189	20.1 (6.8)	62	20.0 (8.5)	65	19.7 (6.8)	-0.62 (-1.52, 0.27)	.17	-0.61 (-1.40, 0.15)	.12	0.01 (-0.97, 1.01)	.99
	Women	215	23.0 (7.6)	79	22.6 (6.9)	50	21.7 (5.9)	0.03 (-0.74, 0.83)	.93	-0.71 (-1.74, 0.31)	.12	-0.73 (-1.80, 0.36)	.16
3	Men	181	21.0 (6.9)	54	21.2 (8.7)	62	21.1 (6.9)	-0.49 (-1.41, 0.40)	.29	-0.20 (-1.02, 0.61)	.62	0.29 (-0.71, 1.33)	.59
	Women	200	23.7 (7.6)	73	23.8 (7.6)	52	22.7 (6.1)	-0.06 (-0.81, 0.69)	.87	-1.00 (-2.05, 0.05)	.05	-0.95 (-2.05, 0.20)	.01
5	Men	184	21.0 (6.7)	59	21.8 (9.0)	65	21.9 (7.5)	0.06 (-0.91, 1.07)	.90	0.24 (-0.66, 1.23)	.59	0.18 (-0.89, 1.36)	.74
	Women	198	23.6 (7.9)	78	24.0 (7.8)	51	22.2 (5.8)	0.21 (-0.65, 1.04)	.63	-1.20 (-2.43, 0.09)	.05	-1.40 (-2.78, -0.06)	.04

^aCON, control; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; Vo_2peak , peak oxygen uptake.^bYears from inclusion.

observed between the groups after 5 years; however, men in HIIT had a larger improvement in VO_2peak after 3 years compared with men in CON and MICT. As men in HIIT had a smaller reduction in HDL-C concentration after 5 years, this could indicate a delay in lipid metabolism in relation to fitness in older men.

Strengths and Limitations

A main strength of this randomized controlled trial is the long intervention period and that the effect of exercise is examined in men and women separately. The use of both the intention-to-treat and the per protocol approaches has been requested by the literature.¹² The Generation 100 study has previously used the intention-to-treat approach.²¹ In an unpublished study using the intention-to-treat approach, no changes were observed in HDL-C after 5 years of exercise. The per protocol approach allows us to examine the effect of exercising twice weekly for 5 years. However, a higher exercise volume could have altered our results as a higher exercise volume has previously been reported to be more important for altering blood lipids.²³ The exercise programs are considered safe to perform by older adults as no severe events were reported during the 5 years.²¹ We performed sensitivity analysis whereby we excluded participants with CVD or taking an LMA. The results were similar to the main analysis, indicating that the presence of CVD did not affect our results. Men and women in HIIT had lower adherence compared with MICT at all follow-up times. Thus, HIIT might not be suitable for all older adults but seems to be efficient in older men who manage to regularly exercise with higher intensities. The adherence to exercise was based on data from questionnaires. A common weakness of self-reported questionnaires is response bias,³⁶ and objective measures of physical activity have been recommended as a more accurate method.³⁷ However, accelerometers' activity thresholds are developed for younger adults and are inaccurate in measuring activities other than walking and running.³⁸ The questionnaires used in this study have sensitivity in predicting physical activity level³⁹ and thus are considered to be a suitable tool to assess exercise intensity. Diet was not part of the intervention; however, dietary data have found that

participants did not report a change in their diet throughout the intervention period.²¹

CONCLUSION

Our data found that HIIT seems to be the best strategy to prevent a decline in HDL-C during a 5-year period in men. No effect of exercise intensity was seen for older women. Changes in VO_2peak but not in body weight or fat mass correlate with changes in HDL-C in both men and women.

ACKNOWLEDGMENTS

The authors would like to thank the participants for their enthusiastic participation in the project. We recognize the invaluable contribution and excellent assistance of the Clinical Research Facility at St. Olavs Hospital, NeXt Move Core Facilities, and employees and students from our research group throughout the data collection process at Generation 100.

Abbreviations and Acronyms: CON, control; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; HRpeak, peak heart rate; LDL-C, low-density lipoprotein cholesterol; LMA, lipid-modifying agent; MICT, moderate-intensity continuous training; VO_2peak , peak oxygen uptake

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Grant Support: This work was supported by the Research Council of Norway; The K.G. Jebsen Foundation for Medical Research, Norway; Norwegian University of Science and Technology (NTNU); Central Norway Regional Health Authority; St. Olavs hospital, Trondheim, Norway; and the National Association for Public Health, Norway. The funding organisations had no role in the design and conduct of the study; in the collection, analysis, and interpretation of

the data; or in the preparation, review, or approval of the manuscript.

Potential Competing Interests: The authors report no competing interests.

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