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

Ida Berglund, MS; Elisabeth Kleivhaug Vesterbekkmo, MD; Kjetil Retterstøl, MD, PhD; Sigmund A. Anderssen, PhD; Maria A. Fiatarone Singh, MD, PhD; Jørn W. Helge, PhD; Stian Lydersen, PhD; Ulrik Wisløff, PhD; and Dorthe Stensvold, PhD

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 4x4-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=0.01 and P=0.03 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.

Aging is characterized by functional and physiologic changes\textsuperscript{1,2} that increase the risk for development of chronic diseases, such as cardiovascular disease (CVD).\textsuperscript{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.\textsuperscript{4} Dyslipidemia, defined as abnormalities in the standard lipid profile, is one of the major risk factors for CVD,\textsuperscript{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.\textsuperscript{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.\textsuperscript{7}

Low levels of HDL-C are associated with cardiovascular events and mortality\textsuperscript{8} even when LDL-C levels are low,\textsuperscript{3} and
improvements in HDL-C and triglyceride levels, in the absence of changes in LDL-C, reduce cardiovascular events. HDL-C is important in removal of cholesterol from peripheral cells to the liver (reverse cholesterol transport), is anti-inflammatory, and inhibits lipid oxidation. Increasing age slows or reverses several of these processes, leading to disordered lipid metabolism and systemic inflammation that further increases the risk of CVD. One potential approach for increasing HDL-C concentration is aerobic exercise, 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. However, the effect of exercise on HDL-C in older adults is unclear. It has been suggested that older adults need a longer time to adapt positively to exercise with respect to HDL-C. 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.

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 (VO₂peak), 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. 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. Recruitment, intervention program, and laboratory procedures of the Generation 100 study have been described in detail elsewhere. 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. 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 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
Assessed for eligibility (n=6966)
- Excluded (n=5399)
  - Not meeting inclusion criteria (n=285)
  - Decline to participate (n=5114)
Randomized (n=1567)
Control group (CON)
  - n=780, 51.4% women
    - Men: n=377
    - Women: n=403
Moderate-intensity continuous training (MICT)
  - n=387 (51.4% women)
    - Men: n=188
    - Women: n=199
High-intensity interval training (HIIT)
  - n=400 (47.5% women)
    - Men: n=210
    - Women: n=190
Excluded due to nonadherence
  - Men: n=185
  - Women: n=183
Excluded due to nonadherence
  - Men: n=126
  - Women: n=119
Excluded due to nonadherence
  - Men: n=143
  - Women: n=138
Per protocol analysis
CON baseline
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=193
    - Women: n=217
MICT baseline
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=61
    - Women: n=79
HIIT baseline
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=67
    - Women: n=51
CON 1-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=186
    - Women: n=209
MICT 1-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=60
    - Women: n=76
HIIT 1-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=66
    - Women: n=52
CON 3-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=172
    - Women: n=193
MICT 3-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=54
    - Women: n=71
HIIT 3-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=59
    - Women: n=50
CON 5-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=184
    - Women: n=195
MICT 5-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=59
    - Women: n=78
HIIT 5-year follow-up
  - Analyzed for the primary outcome (HDL-C)
    - Men: n=66
    - Women: n=49

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 \( \text{VO}_{2}\text{Peak} \) 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 \( \text{VO}_2 \) with increased load (ie, no more than 2 mL·min\(^{-1}·\text{kg}^{-1} \) 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 \( (\text{HRpeak}) \) was determined as the highest measured heart rate during the \( \text{VO}_2\text{peak} \) test. Peak heart rates measured during a \( \text{VO}_2\text{peak} \) test have had good agreement with the maximum heart rate measured in a test designed to measure maximum heart rate in younger adults.\(^{17}\)

**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 \( \Delta V_O2_{peak} \), fat mass (\( \Delta FM \)), and body weight (\( \Delta weight \)) and changes in HDL-C (\( \Delta HDL-C \)) in older men and women. Delta (\( \Delta \)) values were calculated by subtracting baseline values from the year 5 values. The dependent variable was \( \Delta HDL-C \), and \( \Delta V_O2_{peak} \), \( \Delta FM \), and \( \Delta weight \) were used as independent variables, and we adjusted for smoking status (yes/no).\(^2\) A separate model was run for men and women. As some participants changed between treadmill and ergometer bike when performing the \( V_O2_{peak} \) test, these were excluded from the analysis (n=3) to ensure that changes in \( V_O2_{peak} \) 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.\(^1\)

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 \( V_O2_{peak} \) than men (27.41 [4.98] vs 33.13 [6.45] mL·min\(^{-1} \)·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.
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.
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, VO2peak was significantly reduced for men by −3.9% (P < .0001) and −2.4% (P = .008), and no changes were observed for VO2peak 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 VO2peak (9.1%; P < .0001) more than men in CON (4.1%; P = .007), and after 3 years, VO2peak 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 VO2peak during the study.

### Predictors of Changes in HDL-C

Regression analysis found that every 1 mL·min⁻¹·kg⁻¹ change in VO2peak increased ΔHDL-C by 0.011 mmol/L (P = .001) in men. In women, 1 mL·min⁻¹·kg⁻¹ change in VO2peak increased ΔHDL-C by 0.016 mmol/L (P < .001). Changes in HDL-C were significantly associated with ΔVO2peak in men (F1,262 = 10.835; P = .001; R² = 0.036) and women (F1,267 = 12.845; P < .001; R² = 0.042) after 5 years. Changes in body weight and

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**Table 2. Detailed Exercise Description of Participants Who Adhered to the Prescribed Exercise Program for 5 Years**

| Year | CON | MICT | HIIT |
|------|-----|------|------|
|      | Men | Women | Men | Women | Men | Women |
| **Baseline** |     |       |     |       |     |       |
| Intensity | 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 | 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 | 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 | 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) |

*CON, control; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training.

Data are presented as mean (standard deviation).

Exercise intensity is measured by the Borg scale (6-20) and is reported as average intensity per exercise session.
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, and the variable results are often explained by the heterogeneity of exercise interventions. Studies including younger adults have reported that regular aerobic exercise improves HDL-C levels and that higher intensity is superior to moderate intensity for improving HDL-C concentration. 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. 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. 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

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

| Time | Sex | No. | Mean (SD) | p value | Estimate (95% CI) | p value |
|------|-----|-----|-----------|---------|-------------------|---------|
| 0    | Men | 193 | 1.59 (0.43) | 0.06 | 0.002 (0.02, 0.08) | 0.01 |
| 0    | Women | 217 | 1.61 (0.43) | 0.06 | 0.002 (0.02, 0.08) | 0.01 |
| 0    | Men | 209 | 1.64 (0.44) | 0.06 | 0.002 (0.02, 0.08) | 0.01 |
| 0    | Women | 217 | 1.62 (0.44) | 0.06 | 0.002 (0.02, 0.08) | 0.01 |
| 0    | Men | 175 | 1.48 (0.40) | 0.06 | 0.002 (0.02, 0.08) | 0.01 |
| 0    | Women | 201 | 1.51 (0.43) | 0.06 | 0.002 (0.02, 0.08) | 0.01 |

*CON, control; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training.*

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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.26 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 Vo2peak in younger adults.22 However, in the older adults in this study, we found changes in HDL-C to be associated with changes in Vo2peak and not with changes in body weight or fat mass. The association between ΔHDL-C and ΔVo2peak has previously been confirmed in older adults,22,24 and higher Vo2peak 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

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**FIGURE 2.** The levels of high-density lipoprotein cholesterol (HDL-C) in men (A) and women (B) from baseline to 5-year follow-up. A, P<.05 compared with control group (CON). B, P>.05 compared with moderate-intensity continuous training (MICT). BL, baseline; HIIT, high-intensity interval training.
| Time | Sex | CON | MICT | HIT | Group × Time MICT vs CON | Group × Time HIT vs CON | Group × Time HIIT vs CON |
|------|-----|-----|------|-----|--------------------------|-------------------------|--------------------------|
|      |     | No. | Mean (SD) | No. | Mean (SD) | No. | Mean (SD) | Estimate (95% CI) | P value | Estimate (95% CI) | P value | Estimate (95% CI) | P value |
| 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 |

**TABLE 4.** The Exercise Effect on VO2peak, Body Weight, and Fat Mass in Men and Women

- **Time**: bYears from inclusion.

**VO2peak**

- **Group × Time MICT vs CON**
- **Group × Time HIT vs CON**
- **Group × Time HIIT vs CON**

**Body weight (kg)**

- **Men**
  - 0: 193 (81.5 kg), 61 (78.8 kg), 67 (81.5 kg), 0.45 (-0.64, 1.39), 24, -0.19 (-1.04, 0.51), 0.61, -0.64 (-1.52, 0.09), 0.18
  - 1: 214 (76.5 kg), 79 (72.5 kg), 51 (78.1 kg), 0.45 (-0.24, 1.06), 0.09, -0.46 (-1.37, 0.31), 0.34, -0.91 (-1.92, -0.01), 0.09
  - 3: 185 (74.3 kg), 59 (70.2 kg), 67 (79.9 kg), -0.71 (-1.58, 0.18), 0.12, -0.94 (-1.71, -0.09), 0.03, -0.23 (-1.28, 0.91), 0.66
  - 5: 172 (72.0 kg), 50 (68.0 kg), 62 (76.5 kg), 0.24 (-1.08, 0.49), 0.46, -0.55 (-1.63, 0.03), 0.28, -0.26 (-1.36, 0.87), 0.67

**Fat mass (kg)**

- **Men**
  - 0: 192 (20.1 kg), 62 (20.6 kg), 66 (20.5 kg), 0.55 (-0.16, 1.32), 0.11, 0.34 (-0.26, 0.93), 0.25, -0.21 (-0.97, 0.45), 0.60
  - 1: 217 (23.4 kg), 80 (23.4 kg), 52 (23.3 kg), -0.03 (-0.60, 0.47), 0.93, -0.17 (-0.91, 0.52), 0.67, -0.14 (-1.04, 0.75), 0.77
  - 3: 189 (20.1 kg), 62 (20.0 kg), 65 (19.7 kg), -0.62 (-1.52, 0.27), 0.17, -0.61 (-1.40, 0.15), 0.12, 0.01 (-0.97, 1.01), 0.99
  - 5: 175 (23.8 kg), 59 (22.6 kg), 50 (21.7 kg), -0.03 (-0.74, 0.83), 0.93, -0.71 (-1.74, 0.31), 0.12, -0.73 (-1.80, 0.36), 0.16

**Note:**
- CON, control; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; VO2peak, peak oxygen uptake.
- aCON, control; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; VO2peak, peak oxygen uptake.
- bYears from inclusion.
observed between the groups after 5 years; however, men in HIIT had a larger improvement in VO\textsubscript{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.\textsuperscript{12} The Generation 100 study has previously used the intention-to-treat approach.\textsuperscript{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.\textsuperscript{21} The exercise programs are considered safe to perform by older adults as no severe events were reported during the 5 years.\textsuperscript{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,\textsuperscript{30} and objective measures of physical activity have been recommended as a more accurate method.\textsuperscript{37} However, accelerometers’ activity thresholds are developed for younger adults and are inaccurate in measuring activities other than walking and running.\textsuperscript{30} The questionnaires used in this study have sensitivity in predicting physical activity level\textsuperscript{39} 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.\textsuperscript{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\textsubscript{2peak} but not in body weight or fat mass correlate with changes in HDL-C in both men and women.

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Correspondence: Address to Dorthe Stensvold, PhD, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, NTNU, Postbox 8905, 7491 Trondheim, Norway (dorthe.stensvold@ntnu.no).

ORCID
Ilda Berglund: https://orcid.org/0000-0001-9462-548X; Jann W. Helge: https://orcid.org/0000-0001-9724-5423; Ulrik Wisløff: https://orcid.org/0000-0002-7211-3587

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