THIS SUPPLEMENT CONTAINS THE FOLLOWING ITEMS:

- Original protocol, final protocol, summary of changes
- Original statistical analysis plan, final statistical analysis plan, summary of changes

Original protocol

Trondheim, Norway 20.04.2012

This protocol was developed to cover all aspects of the Generation 100, including planned sub studies.

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Summary
The literature lacks large controlled, randomized studies that look at the effect of exercise training on morbidity and mortality. Generation 100 will be the first randomized, controlled clinical study where the primary objective is to study the effects of long-term exercise training on morbidity and mortality in the elderly. Furthermore, we will investigate whether there is a relationship between the exercise intensity and health benefits, with a particular focus on major health problems in the elderly population. In addition to be a study, this is also an initiative to improve public health in all healthy individuals between 70-75 years of age in the municipality of Trondheim. The participants will either be randomized to supervised exercise or follow current guidelines for physical activity by themselves. Clinical examinations, as well as questionnaires, will be administered to all participants at baseline, after one year, three years, and five years follow-up. Additionally, participants will be followed up by linking to relevant registries for up to 20 years. The study seeks to determine if exercise training gives the seniors a longer active and healthy life.

Background

Aging population

As in many other Western countries, the Norwegian population is aging. Statistics from the Norwegian Department of Health show that between 2010 and 2040, the number of seniors above 67 years of age will double. The aging population will lead to significant societal and economic challenges, since recruitment into nursing and care professions is not increasing in line with the need for senior care. Calculations from the municipality of Trondheim show that recruitment into care professions must more than triple from the current 7% to approx. 25% in the course of the next 20 years in order to maintain current standards of care. Future demand for healthcare services depends on how ill and disabled the elderly will be. Aging is characterized by functional and physiological changes, including decline in maximal oxygen uptake (VO_{2max}) (1), reduced muscle mass (2) and impaired functional capacity (3). In addition, the risk of type 2 diabetes (4), cancer (5), pulmonary diseases (6) and psychological conditions such as depression and dementia all increase with age (7).

Current relevance

Due to the increased proportion of seniors, the entire public health care service will require restructuring. To meet the challenge of an aging population, the Norwegian Research Council has developed a new initiative titled, "More active and health years." The initiative is the largest allotment in the Research Council's 2013 budget proposal. In a 2005 report, the Norwegian Ministry of Health and Care Services suggests multiple solutions to reduce the anticipated financial burden of an aging population. It highlights prevention – with a focus on improved health and increased self-reliance – as an important strategy. This is supported by a major research venture in the EU's 7th Framework, to be announced in July of 2013.

Physical activity

According to WHO, physical inactivity is the fourth major cause of premature death worldwide. Physical inactivity is an independent risk factor for death from cardiovascular disease, which is responsible for approx. 36% of all deaths in Norway. Physical activity is associated with a lower risk of developing diabetes (8), hypertension (9), depression (10), dementia (11), breast cancer (12) and colon cancer (13). There is also evidence that physical training lowers the incidence of falls in seniors with a high risk of falls (14). Nevertheless, there are few population-based studies on the effect of exercise training on risk of falling. Multiple epidemiological studies have shown that physical activity is associated with a reduced risk of premature death (15-17), and that individuals with high physical fitness live longer than individuals with low physical fitness (18, 19). Moreover, the data suggests that the greatest difference in risk of premature death is found in individuals who are inactive compared to those who report even a low level of physical activity (17). From a perspective of public health spending, it is important to note that individuals with a high fitness level experience more years of good health and self-reliance. Randomized, controlled studies have shown that regular exercise training increases fitness (20, 21), and improves several known risk factors for cardiovascular disease (22). Although we currently have evidence that physical activity improves cardiovascular risk profile and is important in maintaining physical capacity, the literature still lacks large randomized studies that document the effects of regular physical activity on morbidity and mortality.

Objectives

The primary objective of this controlled, randomized clinical trial is to determine the effects of regular physical activity on morbidity and mortality in the elderly.

Additionally, we wish to see if there is a difference in change in risk score for cardiovascular death between those who exercise with high and low intensities. See Table 1 for primary and secondary objectives.

Table 1. Primary and secondary objectives

Primary objectives	**Secondary objectives**
Overall mortality	Physical activity level
Death from cardiovascular disease	Hospitalization
Death from cancer	Change in physical functional capacity
Change in risk score for cardiovascular death	Change in medication
Development of cardiovascular disease	Change in quality of life
Development of cancer	Use of health care services
	Development of dementia and depression

In addition to be a controlled, randomized study, we would also like the project to be a public health initiative in the municipality of Trondheim. It is important for us to see if the measures work and can serve as an example of how to implement large health initiatives.

Participants

All men and women between the ages of 70-75 years old (born from 1938 to the end of 1942, n=4548) with a permanent address in the municipality of Trondheim will be invited to participate in the study. The invitation will consist of an informational brochure about the study, a questionnaire, and a response sheet with a consent form. Participants will be asked to return the consent form within 14 days. The criteria for eligibility will be stated clearly in the information brochure (see Table 2 for inclusion and exclusion criteria). We will twice attempt to contact (by mail or telephone) those who do not respond within 1 month, following HUNT3 procedures that have previously been approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (REK number 4.2006.250). If the participation level is too low and fewer than 1500 participants enroll in the study, we wish to have the opportunity to expand the age group to additionally include those who are 76 years old (born in 1937).

National Population Register

The National Population Register will serve as the basis for study recruitment. Based on data from the National Population Register, a research database will be established with access to personal identification number, name, address and marital status. The database will be established in collaboration with the HUNT research center, and with the same procedures as previously used in the Nord-Trøndelag Health Study (HUNT 3), which has prior REK approval (REK number 4.2006.250).

Table 2. Inclusion and exclusion criteria

Inclusion criteria	
	- Must be able to walk at least 1 km (consecutive) - Born during 1938, 1939, 1940, 1941 or 1942 - Sufficiently good health to be able to participate in the study, as determined by the researchers
Exclusion criteria	
	- Illness or disabilities that preclude exercise or hinder completion of the study - Uncontrolled hypertension - Symptomatic valve disease, hypertrophic cardiomyopathy or unstable angina - Dementia - Active cancer - Test results indicating that study participation is unsafe - Inclusion in other studies conflicting with participation in this one

Individuals who are unable/unwilling to participate
Individuals who are unable or unwilling to participate will also be asked to return the questionnaire to us (by mail or electronically). Individuals who fill out the questionnaire must consent to the use of questionnaire data, as well as linking data to various registries (more information below).

Individuals who are able/willing to participate
Individuals who are able and willing to participate will be asked to return their consent form and questionnaire to us. They will then be contacted within one month to schedule examination 1. If someone wishes to participate but is unable to complete examination 1, we will ask for their consent to use data from the questionnaire and link it to various registries.

Examinations
Questionnaire
Questionnaires will be labeled with barcodes to link them to individuals. The key that links barcode to personal identification number will only be stored in the database. The procedures for assigning project numbers, printing barcodes, and linking to personal identification number will be the same as previously used in HUNT3 (approved by REK and the Norwegian Data Inspectorate). In addition to being uploaded to the database by optical scanning, questionnaires will be stored at the research unit. Participants will receive a questionnaire one year and three years after examination 1. The majority of questionnaire questions were used in HUNT3 (approved by HUNT research center).

Clinical examinations
Participants will be asked to attend medical examinations at baseline, after one year, three years, and five years follow up. The following clinical tests will be performed:

- Medical screening with interview and checks of Consent signed
- Assessment of general health status
- Blood sample
- Blood pressure
- Resting heart rate
- Weight, height and waistline measurements

- Body composition
- Questionnaire
- Walking test
- Grip strength test
- Leg strength test
- Maximal oxygen uptake, maximal heart rate, heart rate 1 minute after testing
- Physical activity level
- Pulmonary function
- Cognitive screening (MMS)

All data from examinations will be recorded both manually and electronically. A Case Report Form (CRF) will be completed for each participant, and forms will have a code linking the data to the participant. Forms will be entered into the project database by optical scanning. After scanning, forms will be locked and stored securely at the K.G. Jebsen Center for Exercise in Medicine, where only data supervisors will have access.

Links to registries
Since several of the primary objectives of the study involve investigating the risk of cardiovascular disease, cancer, hospitalization, and premature death, it is crucial to be able to link participant data to various health registries. To reduce the number of questionnaire questions – and thereby participant workload – we have excluded questions that can be answered by the use of registry data. Participants consent to give the medical supervisor of Generation 100 access to medical records in the event of hospitalization. We wish to connect to the following registries: Cause of Death Registry, Statistics Norway, Norwegian Patient Register (NPR), National Injury Registry, Cancer Registry of Norway, Norwegian Myocardial Infarction Registry, National Population Register, GERICA (use of municipal care services), and the Norwegian Prescription Database. We wish to continue linking our data to the various registries until 2035.

Other projects
Participant consent includes agreement to potentially receive requests to participate in sub studies during the project. Sub study participation is voluntary, and non-participation in sub studies will not have any consequence for participation in the main study. Projects not already described in this protocol must receive REK approval prior to contacting potential participants.

Follow-up
The participant may be contacted 10 years after inclusion of the study with a request to repeat basic examinations. Participation in follow-up examinations is voluntary.

Randomization
Participants are randomized (stratified by sex and cohabiting status) into one of two groups: an exercise training group or a control group. The exercise training group will again be randomized to either high-intensity training or moderate-intensity training. Spouses/partners will be randomized into the same group. The randomization will be performed after the completion of all basic examinations at examination 1. The Unit for Applied Clinical Research at NTNU is developing a web-based randomization procedure to ensure impartial assignments. After randomization, participants will receive verbal and written information about how to exercise and record their training.

Sample size and statistical power
The primary endpoint of the study is overall mortality. In addition, we want to examine the onset of new cardiovascular disease and cancer and examine if there is a difference in change in risk score for cardiovascular diseases. According to Statistics Norway, approx. 2% in this age group die every year. Data from observational studies report that active people have up to 50% reduction in mortality rate compared to inactive people. With a 50% reduction in mortality rate in the exercise group, and a power of 90% ($p<0.05$), 1200 participants are needed (600 in each group).

Intervention
Choice of intervention
Clinical studies have shown that high-intensity exercise training gives a greater increase in VO_{2max} and better cardiovascular adaptations than low- or moderate-intensity training (20, 22, 23). However, little research has been done in an elderly population, and it is unknown which intensity gives the greatest effect on morbidity, mortality and functional capacity in this group. Therefore, we believe that it is important to compare individuals who exercise at moderate and high intensities. Additionally, we think it is important to have a control group that receives current recommendations for physical activity.

High-intensity training group
This group will be asked to complete high-intensity exercise training two times per week. Different models will be described, but interval training will be the primary focus. Participants in this group will be asked to complete approx. 30-minute-long workouts. During this half hour, participants should reach at least 16 on the Borg scale for perceived exertion four times. In the course of 30 minutes, they should be very short of breath four times, each for a duration of approx. 4 minutes. We have previously used the 4x4 model with success and will present it to participants. Sessions start with a light 10-minute warm-up, followed by four 4-minute working periods interspersed by 3-minute active breaks. The intensity during the working periods should be 85-95% of maximal heart rate, corresponding to approx. 16 on the Borg scale. Breaks will consist of relaxed walking, down to 12 on the Borg scale. Within one month of the first examination, participants will attend a group meeting where the principles of training and reporting physical activity will be reviewed thoroughly (see paragraph on reporting exercise training). At the information meeting, participants will also receive information about the various group training sessions available to them. Group sessions with both indoor and outdoor activities will be arranged at various locations near Trondheim City Center three times per week. Participants may choose between a variety of activities (these will vary from week to week), such as: walking/running, spinning, dance, and aerobics. An exercise supervisor will be present at all sessions arranged by the study. Attendance is voluntary, and participants may choose to perform their exercise training individually if they prefer.

Moderate-intensity training group
This group will be asked to complete 50 minutes of continuous moderate-intensity exercise corresponding to 70% of maximal heart rate – approximately an isocaloric workout compared to the sessions performed by the high-intensity training group. For most, this will be perceived as "talking pace." The workout should be perceived as approx. 13 on the Borg scale. Within one month of the first examination, participants will attend a group meeting where the principles of training and reporting physical activity will be reviewed thoroughly. At the information meeting, participants will also receive information about the various training sessions available to them. Group sessions with both indoor and outdoor activities will be arranged at various locations near Trondheim City Center three times per week.

Participants may choose between a variety of activities (these will vary from week to week), such as: walking/running, spinning, dance, and aerobics. An exercise supervisor will be present at all sessions arranged by the study. Attendance is voluntary, and participants may choose to perform their exercise training individually if they prefer.

Spinning sessions
Every sixth week the two training groups met separately for obligatory supervised spinning sessions (ergometer cycling) with an exercise physiologist, where they exercised with heart rate monitors to ensure recommended exercise intensities.

Control group
The group will be asked to follow current recommendations for physical activity (Norwegian Directorate of Health, 2011), but will not receive further supervision.

Reporting exercise training
Participants in the training group will receive a training log. In addition to general information about the exercise, the log will consist of scannable forms to be completed after each exercise session. Each month, participants will send their exercise logs to the research center either by prepaid envelopes, Internet-based forms, or email. Reporting will be done by use of a system with well-established web-based forms and prior approval (Visma or Questback). For closer monitoring of exercise training intensity, heart rate monitors will be used at the supervised exercise sessions.

Safety
If anyone experiences discomfort during training, they should report this to one of the research supervisors, who will immediately contact the medical supervisor. The research supervisor and medical supervisor will together determine if the event should be reported to the safety committee (more information below) and if the participant should be referred to further medical care.

Stopping criteria for training
Any participant who falls under an exclusion criterion during the study should cease exercise training. For CVD patients the following conditions will count as stopping criteria for exercise training: progressive signs of heart failure (increasing breathlessness during low-intensity exertion, nighttime breathlessness, or edemas), new angina or rapid worsening of angina at low intensities, signs of sudden-onset angina at rest.

Information to participants
Individual
All participants will receive an informational brochure in the mail. This will consist of two parts: A) a brief, tangible, and simple information sheet describing the examinations that will be performed and what the data will be used for, and B) a more detailed description of examinations, what participation entails and how data will be treated. The informational brochure will contain contact information so participants can get their questions answered. The data that is collected in the study may in the future be used for a variety of research projects that cannot currently be predicted; hence it is impossible to inform participants about all projects that will use data from the study. We will emphasize transparency about our primary objectives.

Verbal and written information
All participants will receive verbal and written information about the study, and training guidelines for their assigned intervention. Participants will also receive directions for how to fill in training logs and report back to the researchers. Where possible, participants may elect to receive copies of their test results (e.g. measured fitness, waistline, lipid levels, blood pressure and resting heart rate). Participants will be notified if examinations and/or test results indicate the need for further medical care. The medical supervisor will evaluate if the need for follow-up is immediate – resulting in additional care within a few days – or if referral to primary care is adequate.

Informational meeting
Within one month of examination 1, all participants will be invited to attend informational meetings. These will be held according to group, so participants randomized to the same intervention will attend the same informational meeting.

Internet
There will be extensive updated information about the project on the research group's website: www.ntnu.no/cerg/generasjon100.

Data management
Voluntary participation and consent
All participants recruited to join the study do so voluntary. All who would like to, and who meet the inclusion criteria, will be invited to attend examination 1. At examination 1 (prior to testing) all participants must give written consent that they wish to join the study. It is very important to us that the information about the study provided to participants is sufficiently clear that they can give an informed consent where they understand what participation entails. Participants may at any time withdraw their consent without providing an explanation. Individuals who are excluded during the course of examination 1 or change their mind about participating afterwards may themselves decide if the data already collected about them may be used in the study. We will inquire about why participants no longer wish to be a part of the study, but it is up to the individuals to decide if they want to give a reason or not. All data will be treated confidentially in order to maintain privacy during data processing. All project employees are bound by confidentiality and must sign a non-disclosure agreement. The project will be completed according to the principles of the Declaration of Helsinki. It must be approved by the Regional Committee for Medical and Health Research Ethics prior to start.

Databank
We will create a project databank at the HUNT Research Center. Data from the databank will be available to a variety of research fields for many years to come. Although it is currently challenging to predict all future uses of the material, the purpose of the project is to determine if exercise training has an effect on major health issues for the elderly population in Norway. Any other projects must apply for permission to access and use the data, and a collaboration agreement must be signed by both parties.

Biobank
We will create a separate project biobank. It will be located at St. Olav's Hospital, Emergency, Heart- and Lung Center. Professor Ulrik Wisløff will be responsible for the biobank. Participants who sign the consent also agree to the inclusion of biological materials and analysis results in the project biobank. Data in the biobank will be anonymized, and only selected authorized personnel (4 people) will have access to the identification key linking serial number to participant identity. We wish to store the data for 10 years after completion

of the study, i.e. until 2025. Afterwards we will seek REK approval to move remaining samples to the HUNT Biobank in Levanger, Norway.

Privacy
All data from the study is theoretically identifiable, i.e. tied to an 11-digit personal identification number. Personal identification number will only be used if necessary, and only a few individuals (4 data supervisors) will have access to the original file. There will be an IT safety binder (from HUNT3) that all data supervisors will read and be familiar with. The data will be anonymized during analysis and when files are provided to others. This means that all personal identifiers such as name, birthday, address, etc. will be removed and replaced by a project-specific code. New integrated IT-systems were developed for use in the third Nord-Trøndelag Health Study (HUNT3), with an emphasis on addressing privacy concerns. The Generation 100 project will use the data systems developed for HUNT3 to collect, manage, and store data. The procedures have been developed in close collaboration with the Norwegian Data Inspectorate and REK and are approved by both.

Data security
The data collected at the examinations will be entered into the database both manually and electronically. Anonymized data files will be treated with the same level of security as identifiable data files with respect to storage and access.

Insurance
All participants are insured by Norwegian Patient Injury Compensation (Norsk Pasientskadeerstatning).

Ethical aspects
Information
Generation 100 is an extensive study, and it is challenging to provide sufficient information to individual participants. Providing sufficient clear information is a high priority, so that participants feel that they know what consenting entails. Moreover, participants will have the opportunity to ask questions at all examinations and informational meetings.

Advantages
There is strong evidence suggesting that regular exercise training gives better health than inactivity. Additionally, participants will learn about exercise, physical activity and health. Participants will receive a wide variety of clinical examinations and follow-up care that they would not have had otherwise (including the control group).

Disadvantages
The risk of exercise is considered very small; however, the risk of complications/death is higher during and immediately following training/testing. Nevertheless, the health benefits from exercise training are sufficiently high that it is considered less harmful than inactivity. All methods have been tested thoroughly by both healthy individuals and various risk groups and are not considered risky or thought to have negative side effects. There will be at least two medical doctors working in the project, who are available if unforeseen problems should arise.

Information security
A lot of sensitive data will be collected and must be handled properly. It is an advantage that the information systems we will use have been developed by HUNT in collaboration with the Norwegian Data Inspectorate and already have been approved by REK. Whenever possible

we will use barcodes instead of personal identification numbers during data collection. Only 4 data supervisors will have access to data files with identifiable information.

Different training groups
The control group will not have access to supervised exercise training. However, they will be advised to follow current guidelines for physical activity. This group will receive "worse" follow-up care than the two other groups. Nevertheless, this reflects the current state of affairs, and we deem it necessary to have a control group receiving the "treatment" currently offered to the public.

Steering committee
The steering committee is the study's executive body. They have developed the study protocol and are responsible for data collection, management and publication. All major scientific and ethical questions will be resolved by majority vote. The group is responsible for finding solutions to unforeseen questions/problems that arise in the course of the study. The steering committee consists of the following people: Professor Ulrik Wisløff, PhD Dorthe Stensvold, PhD, MD Professor Asbjørn Støylen, PhD Øyvind Rognmo, Professor Lars J. Vatten, Professor Jorunn Helbostad, PhD and Professor Sigmund Alfred Anderssen, PhD.

Safety committee
All serious events that occur during the study should be reported to the research unit, which in return will report the event to a safety committee within one week. A research supervisor will fill out a safety report describing the event. Serious events are defined as: medical treatment resulting from the onset of new cardiovascular disease/events, or injuries/fractures. The committee will determine if the groups differ, and if it is ethically justifiable to let the study continue. Participants are encouraged to contact researchers if something unforeseen should occur; additionally, the safety committee will access the various registries once per year to obtain relevant data. The safety committee consists of the following people: Jostein Grimsmo, PhD, MD at Feiringklinikken Hosptial, Norway and Erney Mattsson, Professor at the Department of Circulation and Medical (ISB), NTNU.

Funding
The project will primarily be funded by the K.G. Jebsen Center for Exercise in Medicine. Other major contributors include: Central Norway Regional Health Authority, the Norwegian Research Council, the Norwegian Association for Public Health, and NTNU.

Scientific significance and dissemination
The study will be unique in several ways. It will give the largest cross-sectional data on the elderly in Norway, especially with respect to fitness level, cardiovascular health and functional capacity. It will also be the largest and longest randomized study investigating the effects of exercise on morbidity and mortality. The data collected will be sufficient for a multitude of future research studies. This type of study generally garners widespread interest and media attention and should be of a sufficiently high standard to be published in renowned international scientific journals. We anticipate that the project will determine if exercise – potentially of different intensities – has an impact on morbidity and mortality. In light of the aging population, our data will hopefully contribute to an improved understanding and examples of possible eldercare solutions. Research to improve prevention and treatment will benefit a large proportion of the population and may give a significant economic benefit to society. The goal of the study is to determine if exercise training has an impact on several major health issues that affect the elderly population in Norway.

Final protocol

Protocol for the main study: The effect of 5-years of exercise training on all-cause mortality in older adults – The Generation 100 study

Protocol developed by:
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Summary
The literature lacks large controlled, randomized studies that look at the effect of exercise training on mortality and morbidity. The main aim of The Generation 100 study was to, in a general population of older adults, test the primary hypothesis that 5-years of exercise training lowers all-cause mortality more than controls asked to follow physical activity guidelines given by national health authorities, and an exploratory hypothesis that high intensity training lower mortality more than moderate intensity training. Participants will either be randomized to supervised exercise or follow current guidelines for physical activity by themselves. Clinical examinations, as well as questionnaires, will be administered to all participants at baseline, after one year, three years, and five years. Additionally, participants will be followed up by linking to relevant registries for up to 20 years.

Background

Aging population

As in many other Western countries, the Norwegian population is aging. Statistics from the Norwegian Department of Health show that between 2010 and 2040, the number of seniors above 67 years of age will double. The aging population will lead to significant societal and economic challenges, since recruitment into nursing and care professions is not increasing in line with the need for senior care. Calculations from the municipality of Trondheim show that recruitment into care professions must more than triple from the current 7% to approx. 25% in the course of the next 20 years in order to maintain current standards of care. Future demand for healthcare services depends on how ill and disabled the elderly will be. Aging is characterized by functional and physiological changes, including decline in maximal oxygen uptake (VO_{2max}) (1), reduced muscle mass (2) and impaired functional capacity (3). In addition, the risk of type 2 diabetes (4), cancer (5), pulmonary diseases (6) and psychological conditions such as depression and dementia all increase with age (7).

Current relevance

Due to the increased proportion of seniors, the entire public health care service will require restructuring. To meet the challenge of an aging population, the Norwegian Research Council has developed a new initiative titled, "More active and health years." The initiative is the largest allotment in the Research Council's 2013 budget proposal. In a 2005 report, the Norwegian Ministry of Health and Care Services suggests multiple solutions to reduce the anticipated financial burden of an aging population. It highlights prevention – with a focus on improved health and increased self-reliance – as an important strategy. This is supported by a major research venture in the EU's 7th Framework, to be announced in July of 2013.

Physical activity

According to WHO, physical inactivity is the fourth major cause of premature death worldwide. Physical inactivity is an independent risk factor for death from cardiovascular disease, which is responsible for approx. 36% of all deaths in Norway. Physical activity is associated with a lower risk of developing diabetes (8), hypertension (9), depression (10), dementia (11), breast cancer (12) and colon cancer (13). There is also evidence that physical training lowers the incidence of falls in seniors with a high risk of falls (14). Nevertheless, there are few population-based studies on the effect of exercise training on risk of falling. Multiple epidemiological studies have shown that physical activity is associated with a reduced risk of premature death (15-17), and that individuals with high physical fitness live longer than individuals with low physical fitness (18, 19). Moreover, the data suggests that the greatest difference in risk of premature death is found in individuals who are inactive compared to those who report even a low level of physical activity (17). From a perspective of public health spending, it is important to note that individuals with a high fitness level experience more years of good health and self-reliance. Randomized, controlled studies have shown that regular exercise training increases fitness (20, 21), and improves several known risk factors for cardiovascular disease (22). Although we currently have evidence that physical activity improves cardiovascular risk profile and is important in maintaining physical capacity, the literature still lacks large randomized studies that document the effects of regular physical activity on morbidity and mortality.

Objectives

The main objective of this study was to, in a general population of older adults, test the primary hypothesis that 5-years of exercise training lowers all-cause mortality more than controls asked to follow physical activity guidelines given by national health authorities, and an exploratory hypothesis that high intensity training lower mortality more than moderate intensity training.

Additionally, we wish to see if there is a difference in change in development of cardiovascular disease and cancer between the groups. See Table 1 for primary and secondary objectives.

Table 1. Primary and secondary objectives

Primary objectives	**Secondary objectives**
Overall mortality	Death from cardiovascular disease Death from cancer Development of cardiovascular disease Development of cancer Peak oxygen uptake

Participants

All men and women between the ages of 70-77 years old (born from 1936 to the end of 1942, n=6966) with a permanent address in the municipality of Trondheim will be invited to participate in the study. The invitation will consist of an informational brochure about the study, a questionnaire, and a response sheet with a consent form. Participants will be asked to return the consent form within 14 days. The criteria for eligibility will be stated clearly in the information brochure (see Table 2 for inclusion and exclusion criteria). We will twice attempt to contact (by mail or telephone) those who do not respond within 1 month, following HUNT3 procedures that have previously been approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (REK number 4.2006.250).

National Population Register

The National Population Register will serve as the basis for study recruitment. Based on data from the National Population Register, a research database will be established with access to personal identification number, name, address and marital status. The database will be established in collaboration with the HUNT research center, and with the same procedures as previously used in the Nord-Trøndelag Health Study (HUNT3), which has prior REK approval (REK number 4.2006.250).

Table 2. Inclusion and exclusion criteria

Inclusion criteria	
	- Born during 1936, 1937, 1938, 1939, 1940, 1941 or 1942 - Able to complete the exercise program (determined by the researchers).
Exclusion criteria	
	- Illness or disabilities that preclude exercise or hinder completion of the study - Uncontrolled hypertension - Symptomatic valvular, hypertrophic cardiomyopathy, unstable angina, primary pulmonary hypertension, heart failure and severe arrhythmia - Diagnosed dementia - Cancer that makes participation impossible or exercise contraindicated. Considered individually, in consultation with physician. -Chronic communicable infectious diseases. -Test results indicating that study participation is unsafe - Participation in other studies conflicting with participation in Generation 100

Individuals who are unable/unwilling to participate
Individuals who are unable or unwilling to participate will also be asked to return the questionnaire to us (by mail or electronically). Individuals who fill out the questionnaire must consent to the use of questionnaire data, as well as linking data to various registries (more information below).

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Individuals who are able and willing to participate will be asked to return their consent form and questionnaire to us. They will then be contacted within one month to schedule examination 1. If someone wishes to participate but is unable to complete examination 1, we will ask for their consent to use data from the questionnaire and link it to various registries.

Examinations
Questionnaire
Questionnaires will be labeled with barcodes to link them to individuals. The key that links barcode to personal identification number will only be stored in the database. The procedures for assigning project numbers, printing barcodes, and linking to personal identification number will be the same as previously used in HUNT3 (approved by REK and the Norwegian Data Inspectorate). In addition to being uploaded to the database by optical scanning, questionnaires will be stored at the research unit. Participants will receive a new questionnaire one year, three years, and five years after examination 1. The majority of questionnaire questions were used in HUNT3 (approved by HUNT Research Center).

Clinical examinations
Participants will be asked to attend medical examinations at baseline after one year, three years and five years. The following clinical tests will be performed:

- Medical screening with interview and checks of Consent signed
- Assessment of general health status

- Weight, height and waistline measurements
- Maximal oxygen uptake, maximal heart rate, heart rate 1 minute after testing

All data will be recorded both manually and electronically. A Case Report Form (CRF) will be completed for each participant, and forms will have a code linking the data to the participant. Forms will be entered into the project database by optical scanning. After scanning, forms will be locked and stored securely at the K.G. Jebsen Center for Exercise in Medicine, where only data supervisors will have access.

Links to registries
Participants consent to give the medical supervisor of Generation 100 access to medical records. In addition, we plan to connect our data to the Cause of Death Registry and Statistics Norway. Patient archive system of the community hospitals will be used to identify clinical outcomes (CVD and Cancer).

Follow-up
The participant may be contacted 10 years after inclusion of the study with a request to repeat basic examinations. Participation in follow-up examinations is voluntary.

Randomization
Participants are randomized (stratified by sex and cohabiting status) into one of two groups: an exercise training group or a control group. The exercise training group will again be randomized to either high-intensity training or moderate-intensity training. Spouses/partners will be randomized into the same group. The randomization will be performed after the completion of all basic examinations at examination 1. The Unit for Applied Clinical Research at NTNU is developing a web-based randomization procedure to ensure impartial assignments. After randomization, participants will receive verbal and written information about how to exercise and record their training.

Sample size and statistical power
The primary endpoint of the study is overall mortality. According to Statistics Norway, approx. 2% in this age group die every year. Currently, there is no data that indicates the magnitude of the effect of exercise on the reduction in mortality, but from observational studies a 50% reduction has been reported. With a 50 % reduction in mortality rate, and a power of 90% ($p<0.05$), 1200 participants are needed (600 in each group). We will try to include 1500 participants to allow for drop-out (approximately 20%).

Intervention
Choice of intervention
Clinical studies have shown that high-intensity exercise training gives a greater increase in VO_{2max} and better cardiovascular adaptations than low- or moderate-intensity training (20, 22, 23). However, little research has been done on an elderly population, and it is unknown which intensity gives the greatest effect on morbidity, mortality and functional capacity in this group. Therefore, we believe that it is important to compare individuals who exercise at moderate and high intensities. Additionally, we think it is important to have a control group that receives current recommendations for physical activity.

High-intensity training group
This group will be asked to complete high-intensity exercise training two times per week. Different models will be described, but interval training will be the primary focus. Participants in this group will be asked to complete approx. 30-minute-long workouts. During

this half hour, participants should reach at least 16 on the Borg scale for perceived exertion four times. In the course of 30 minutes, they should be very short of breath four times, each for a duration of approx. 4 minutes. We have previously used the 4x4 model with success and will present it to participants. Sessions start with a light 10-minute warm-up, followed by four 4-minute working periods interspersed by 3-minute active breaks. The intensity during the working periods should be 85-95% of maximal heart rate, corresponding to approx. 16 on the Borg scale. Breaks will consist of relaxed walking, down to 12 on the Borg scale. Within one month of the first examination, participants will attend a group meeting where the principles of training and reporting physical activity will be reviewed thoroughly (see paragraph on reporting exercise training). At the information meeting, participants will also receive information about the various group training sessions available to them. Group sessions with both indoor and outdoor activities will be arranged at various locations near Trondheim City Center three times per week. Participants may choose between a variety of activities (these will vary from week to week), such as: walking/running, spinning, dance, and aerobics. An exercise supervisor will be present at all sessions arranged by the study. Attendance is voluntary, and participants may choose to perform their exercise training individually if they prefer.

Moderate-intensity training group
This group will be asked to complete 50 minutes of continuous moderate-intensity exercise corresponding to 70% of maximal heart rate – approximately an isocaloric workout compared to the sessions performed by the high-intensity training group. For most, this will be perceived as "talking pace." The workout should be perceived as approx. 13 on the Borg scale. Within one month of the first examination, participants will attend a group meeting where the principles of training and reporting physical activity will be reviewed thoroughly. At the information meeting, participants will also receive information about the various training sessions available to them. Group sessions with both indoor and outdoor activities will be arranged at various locations near Trondheim City Center three times per week. Participants may choose between a variety of activities (these will vary from week to week), such as: walking/running, spinning, dance, and aerobics. An exercise supervisor will be present at all sessions arranged by the study. Attendance is voluntary, and participants may choose to perform their exercise training individually if they prefer.

Spinning sessions
Every sixth week the two training groups met separately for obligatory supervised spinning sessions (ergometer cycling) with an exercise physiologist, where they exercised with heart rate monitors to ensure recommended exercise intensities.

Control group
The group will be asked to follow current recommendations for physical activity (Norwegian Directorate of Health, 2011), but will not receive further supervision.

Reporting exercise training
Participants in the training group will receive a training log. In addition to general information about the exercise, the log will consist of scannable forms to be completed after each exercise session. Each month, participants will send their exercise logs to the research center either by prepaid envelopes, internet-based forms, or email. Reporting will be done by use of a system with well-established web-based forms and prior approval (Visma or Questback). For closer monitoring of exercise training and activity levels, some participants may at times be

supervised by activity monitors, lactate measurements and heart rate monitors. This will be done to see if self-reported training corresponds to actual physical activity and intensity.

Follow-up and reminders about training logs
Participants who do not submit their training logs will be contacted within 14 days – once by telephone/Internet and once by mail to request the logs.

Safety
If anyone experiences discomfort during training, they should report this to one of the research supervisors, who will immediately contact the medical supervisor. The research supervisor and medical supervisor will together determine if the event should be reported to the safety committee (more information below) and if the participant should be referred to further medical care.

Stopping criteria for training
Any participant who falls under an exclusion criterion during the study should cease exercise training. For CVD patients the following conditions will count as stopping criteria for exercise training: progressive signs of heart failure (increasing breathlessness during low-intensity exertion, nighttime breathlessness, or edemas), new angina or rapid worsening of angina at low intensities, signs of sudden-onset angina at rest.

Information to participants
Individual
All participants will receive an informational brochure in the mail. This will consist of two parts: A) a brief, tangible, and simple information sheet describing the examinations that will be performed and what the data will be used for, and B) a more detailed description of examinations, what participation entails and how data will be treated. The informational brochure will contain contact information so participants can get their questions answered. The data that is collected in the study may in the future be used for a variety of research projects that cannot currently be predicted; hence it is impossible to inform participants about all projects that will use data from the study. We will emphasize transparency about our primary objectives.

Verbal and written information
All participants will receive verbal and written information about the study, and training guidelines for their assigned intervention. Participants will also receive directions for how to fill in training logs and report back to the researchers. Where possible, participants may elect to receive copies of their test results (e.g. measured fitness, waistline, lipid levels, blood pressure and resting heart rate). Participants will be notified if examinations and/or test results indicate the need for further medical care. The medical supervisor will evaluate if the need for follow-up is immediate – resulting in additional care within a few days – or if referral to primary care is adequate.

Informational meeting
Within one month of examination 1, all participants will be invited to attend informational meetings. These will be held according to group allocation, so participants randomized to the same intervention will attend the same informational meeting.

Internet
There will be extensive updated information about the project on the research group's website: www.ntnu.no/cerg/generasjon100.

Data management
Voluntary participation and consent
All participants recruited to join the study do so voluntary. All who would like to, and who meet the inclusion criteria, will be invited to attend examination 1. At examination 1 (prior to testing) all participants must give written consent that they wish to join the study. It is very important to us that the information about the study provided to participants is sufficiently clear that they can give an informed consent where they understand what participation entails. Participants may at any time withdraw their consent without providing an explanation. Individuals who are excluded during the course of examination 1 or change their mind about participating afterwards may themselves decide if the data already collected about them may be used in the study. We will inquire about why participants no longer wish to be a part of the study, but it is up to the individuals to decide if they want to give a reason or not. All data will be treated confidentially in order to maintain privacy during data processing. All project employees are bound by confidentiality and must sign a non-disclosure agreement. The project will be completed according to the principles of the Declaration of Helsinki. It must be approved by the Regional Committee for Medical and Health Research Ethics prior to start.

Databank
We will create a project databank at the HUNT Research Center. Data from the databank will be available to a variety of research fields for many years to come. Although it is currently challenging to predict all future uses of the material, the purpose of the project is to determine if exercise training has an effect on major health issues for the elderly population in Norway. Any other projects must apply for permission to access and use the data, and a collaboration agreement must be signed by both parties.

Biobank
We will create a separate project biobank. It will be located at St. Olav's Hospital, Emergency, Heart and Lung Center. Professor Ulrik Wisløff will be responsible for the biobank. Participants who sign the consent also agree to the inclusion of biological materials and analysis results in the project biobank. Data in the biobank will be anonymized, and only select authorized personnel (4 people) will have access to the identification key linking serial number to participant identity. We wish to store the data for 10 years after completion of the study, i.e. until 2025. Afterwards we will seek REK approval to move remaining samples to the HUNT biobank in Levanger, Norway.

Privacy
All data from the study is theoretically identifiable, i.e. tied to an 11-digit personal identification number. Personal identification number will only be used if necessary, and only a few individuals (4 data supervisors) will have access to the original file. There will be an IT safety binder (from HUNT3) that all data supervisors will read and be familiar with. The data will be anonymized during analysis and when files are provided to others. This means that all personal identifiers such as name, birthday, address, etc. will be removed and replaced by a project-specific code. New integrated IT-systems were developed for use in the third Nord-Trøndelag Health Study (HUNT3), with an emphasis on addressing privacy concerns. The Generation 100 will use the data systems developed for HUNT3 to collect, manage, and store

data. The procedures have been developed in close collaboration with the Norwegian Data Inspectorate and REK and are approved by both.

Data security
The data collected at the examinations will be entered into the database both manually and electronically. Anonymized data files will be treated with the same level of security as identifiable data files with respect to storage and access.

Insurance
All participants are insured by Norwegian Patient Injury Compensation (Norsk Pasientskadeerstatning).

Ethical aspects
Information
Generation 100 is an extensive study, and it is challenging to provide sufficient information to individual participants. Providing sufficient clear information is a high priority, so that participants feel that they know what consenting entails. Moreover, participants will have the opportunity to ask questions at all examinations and informational meetings.

Advantages
There is strong evidence suggesting that regular exercise training gives better health than inactivity. Additionally, participants will learn about exercise, physical activity and health. Participants will receive a wide variety of clinical examinations and follow-up care that they would not have had otherwise (including the control group).

Disadvantages
The risk of exercise is considered very small; however, the risk of complications/death is higher during and immediately following training/testing. Nevertheless, the health benefits from exercise training are sufficiently high that it is considered less harmful than inactivity. All methods have been tested thoroughly by both healthy individuals and various risk groups and are not considered risky or thought to have negative side effects. There will be at least two doctors working in the project, who are available if unforeseen problems should arise.

Information security
A lot of sensitive data will be collected and must be handled properly. It is an advantage that the information systems we will use have been developed by HUNT in collaboration with the Norwegian Data Inspectorate and already have been approved by REK. Whenever possible we will use barcodes instead of personal identification numbers during data collection. Only 4 data supervisors will have access to data files with identifiable information.

Different training groups
The control group will not have access to supervised exercise training. However, they will be advised to follow current guidelines for physical activity. This group will receive "worse" follow-up care than the two other groups. Nevertheless, this reflects the current state of affairs, and we deem it necessary to have a control group receiving the "treatment" currently offered to the public.

Steering committee
The steering committee is the study's executive body. They have developed the study protocol and are responsible for data collection, management and publication. All major

scientific and ethical questions will be resolved by majority vote. The group is responsible for finding solutions to unforeseen questions/problems that arise in the course of the study. The steering committee consists of the following people: Professor Ulrik Wisløff, PhD Dorthe Stensvold, PhD, MD Professor Asbjørn Støylen, PhD Øyvind Rognmo, Professor Lars J. Vatten, Professor Jorunn Helbostad, PhD and Professor Sigmund Alfred Anderssen, PhD.

Safety committee

All serious events that occur during the study should be reported to the research unit, which in return will report the event to a safety committee within one week. A research supervisor will fill out a safety report describing the event. Serious events are defined as: medical treatment resulting from the onset of new cardiovascular disease/events, or injuries/fractures. The committee will determine if the groups differ, and if it is ethically justifiable to let the study continue. Participants are encouraged to contact researchers if something unforeseen should occur; additionally, the safety committee will access the various registries once per year to obtain relevant data. The safety manager will be Erney Mattsson, Professor at the Department of Circulation and Medical (ISB), NTNU.

Funding

The project will primarily be funded by the K.G. Jebsen Center for Exercise in Medicine. Other major contributors include: Central Norway Regional Health Authority, the Norwegian Research Council, the Norwegian Association for Public Health, and NTNU.

Scientific significance and dissemination

The study will be unique in several ways. It will give the largest cross-sectional data on the elderly in Norway, especially with respect to fitness level, cardiovascular health and functional capacity. It will also be the largest and longest randomized study investigating the effects of exercise on morbidity and mortality. The data collected will be sufficient for a multitude of future research studies. This type of study generally garners widespread interest and media attention and should be of a sufficiently high standard to be published in renowned international scientific journals. We anticipate that the project will determine if exercise – potentially of different intensities – has an impact on morbidity and mortality. In light of the aging population, our data will hopefully contribute to an improved understanding and examples of possible eldercare solutions. Research to improve prevention and treatment will benefit a large proportion of the population and may give a significant economic benefit to society. The goal of the study is to determine if exercise training has an impact on several major health issues that affect the elderly population in Norway.

Summary of changes Protocol

The following amendments to the original protocol have been made.

- Amendment No1; Inclusion and exclusion criteria August 2012,
- Amendment No2, Safety Committee, June 2013
- Amendment No3: Outcome measures July 2013
- Amendment No4; Drop-outs, August 2013
- Amendment No5; Primary and Secondary outcomes, October 2014

Amendment No1.

Due to safety reasons during the clinical testing, we excluded people with chronic communicable infectious diseases. In addition, we realized that the inclusion criterion "must be able to walk at least 1 km", was hard to test, and this criterion was changed to "able to complete the exercise program (determined by the researchers). Also, the criterion "active cancer" was changed to "cancer that makes participation impossible or exercise contraindicated. Considered individually, in consultation with physician". These changes were included in the protocol 08. August 2012, before the inclusion of the first patient.
We realized that the number of participants included was lower than expected. We therefore expanded the age-range and included also people born in 1936 and 1937.

Amendment No2.

Jostein Grimsmo were not able to be a part of the safety committee, thus Erney Mattsson become the safety manager in the study. Changes made in June 2013.

Amendment No3.

By a mistake the outcome was change in July 2013. The reported outcome measures were related to the first PhD project, and instead of registering a new clinical trial, the candidate added the primary aims to the original trial. The mistake was noticed in May 2014, and the primary outcome was then changed back to what has always been the main outcome, mortality.

Amendment No4.

In August 2013 reasons for drop-out was changed to comprise; excluded, withdrew or died. Thus, participants who stops training for more than 6 months due to any reason, but still wanted to be in the study, were not excluded.

Amendment No5.

In October 2014, the principal investigators changed the primary aim to be more specific and clearer, and changed the secondary outcomes of the study to include changes in cardiovascular diseases, cancer, and peak oxygen uptake. Change in risk score, physical activity level, hospitalization, physical function capacity, medication, use of health care services, and development of dementia and depression will be presented in separate studies.

Original Statistical analysis plan

As specified in the protocol paper the primary combined endpoint of the study is overall mortality (24). Further, as described in the protocol paper (24); "All comparisons of change between the groups will be done by the intention-to-treat principle. Thus, data will be analyzed according to the group participants were assigned to, regardless of possible crossover and/or adherence to the intervention. Non-adherence will be defined as having performed less than 50% of the prescribed training sessions over the five years. Survival and morbidity analysis will be done by performing chi-square and log-rank tests. Cox regression analyses will be used to compute hazard ratios of all-cause mortality and onset of new diseases between the groups. The precision of the estimates will be assessed by 95% confidence intervals. All statistical tests will be two-sided."

Final Statistical analysis plan

The original plan was not very specific on how the analysis would be performed; thus, a more detailed plan was formed before (13 February 2019) any analysis was conducted. For the VO_{2peak} and SF 8 we plan to use a linear mixed model with the clinical variables one at a time as dependent variable. Time point (0,1,3,5 years), intervention group, and their interaction as categorical covariates, and participant nested within cohabiting pair as random effects. Participants had been randomized such that a cohabiting pair was randomized to the same group. Hence, it is appropriate to use a three-level mixed model, with participant nested within cohabiting pair. In addition, we adjust for variables used as stratification variables in the randomization (sex, cohabitation status). We will adjust for age at inclusion, which is plausibly important prognostic factor, as recommended by (25) and (26). In the mixed model, we will adjust for baseline as recommended by (27). Normality of residuals will be checked by visual inspection of QQ plots. In these analyses, if a person is dead, we regard that as missing data after the person is dead. In a sensitivity analysis, we will exclude the persons who died during the study from the analysis. The main analysis for survival, will be a Cox proportional hazards regression, adjusting for the covariates listed above.

Summary of changes Statistical analysis plan

The following amendments to the original statistical analysis plan have been made.

- Amendment No1; Exclusion of VO_{2peak} data

Amendment No1:
Participants should have been tested on the same machine (treadmill or bike) at every examination. For those who had test both on treadmill and bike, we deleted the bike measurements. In total 41 persons had data both from treadmill and bike, bike measurements were deleted, and values given as missing.

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