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The Effect of Long-term Aerobic Exercise and Training Intensity on Blood Pressure in the Elderly

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Abstract

Background: Hypertension, a vascular condition characterized by chronically high blood pressure is especially common among the elderly. Aerobic exercise is one of the best proven nonpharmacological interventions for prevention and treatment of hypertension. However, there is little reliable and available documentation regarding the effect of aerobic exercise and training intensity on blood pressure *in the elderly*. Consequently, there is no prevailing consensus on how aerobic exercise can be recommended and implemented as a nonpharmacological strategy to prevent, treat, and control hypertension.

Objective: Investigate the effect of three years of aerobic exercise with high- or moderate training intensity, versus a control group, on average blood pressure and evaluate the potential of aerobic exercise and training intensity as a nonpharmacological antihypertensive strategy.

Method: A total of 987 elders (489 women), 72.4 ± 0.07 years of age, were randomized to either 3 years of 5 years of two weekly sessions of high-intensity interval training (HIIT: 10 min warm-up followed by 4×4 min intervals at ~85-95% of peak heart rate) or, moderate-intensity continuous training (MICT: 50 min of continuous exercise at ~70% of peak heart rate), or to a control group that were recommended to follow the current national recommendations regarding physical activity. An extensive physical examination, including assessment of average systolic (SBP) and diastolic (DBP) blood pressure, were performed at baseline and after 3 years.

Results: Following 3 years of aerobic exercise, the observed change in average blood pressure (SBP / DBP) was -6.4 ± 1.0 / -3.2 ± 0.5 mm Hg and -3.7 ± 1.0 / -1.2 ± 0.5 mm Hg within the two exercise intervention groups, HIIT and MICT, respectively. The observed change SBP / DBP in the control group was -3.8 ± 0.7 / -1.6 ± 0.4 mm Hg. Three years of aerobic exercise with HIIT reduced average blood pressure (SBP / DBP), in comparison to the control -2.8 ± 1.1 / -1.6 ± 0.6 mm Hg, and compared to aerobic exercise with MICT, -2.7 ± 1.3 / -1.9 ± 0.7 mm Hg.

Conclusion: Long-term aerobic exercise with different training intensities, significantly reduce average blood pressure in elders. The effect of long-term aerobic exercise in the elderly population appears to be intensity dependent and aerobic exercise with HIIT appears to be the superior nonpharmacologic strategy to treat and control hypertension in elders.

Acknowledgements

Table of contents

List of figures

List of tables

Abbreviations

Acronyms commonly used in the present report are listed here.

ACC   American College of Cardiology

AHA   American Heart Association

BMI   Body mass index

CPET   Cardiopulmonary exercise testing

CVD   Cardiovascular disease

DBP   Diastolic blood pressure

ESH   European Society of Hypertension

ESC   European Society of Cardiology

HDL   High-density lipoprotein

HR   Heart rate

HR_{rest} Resting heart rate

HR_{peak} Peak heart rate

HUNT   Helseundersøkelsen in Nord-Trøndelag/ Nord-Trøndelag Health Study

LDL   Low-density lipoprotein

PP   Pulse pressure

PVR   Peripheral vascular resistance

RCT   Randomized controlled trial

RER   Respiratory-exchange-ratio

SBP   Systolic blood pressure

SE   Standard error

TGs   Triglycerides

VO_2 Oxygen uptake

VO_{2max} Maximal oxygen uptake

VO_{2peak} Peak oxygen uptake

WHO   World Health Organization

For simplicity, the definitions of certain age groups, commonly referred to in the present report, are presented here. The definitions described below are used throughout the report if not indicated otherwise.

Oldest old: $\geq$ 80 years of age

Elderly/elders: 70-80 years of age

Older adults: $\geq$ 65 years of age

Middle-aged adults: 50-65 years of age

Young adults: 18-50 years of age.

Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVDs) accounts for approximately 17 million deaths a year, corresponding to 31% of all global deaths, making CVDs the leading cause of death on a worldwide basis.[1,2] The prevalence is especially high among older adults.[3,4] High blood pressure is the main risk factor for development of CVDs and the underlying reason of more than half of the deaths caused by CVDs.[1,5] High blood pressure alone is of the leading causes of death on the global scale, responsible of 13% of all deaths,[6] and the worldwide leading cause of disability-adjusted life years.[7,8] The relationship between blood pressure and risk of CVD is continuous, consistent and independent of other risk factors, it is as simple as the higher blood pressure the greater the risk.[5,9-11] High blood pressure chronically strains the cardiovascular system and, if left untreated, eventually damages arterial vessels and often leads to the development of CVDs such as arteriosclerosis, angina pectoris, congestive heart failure, coronary heart disease and myocardial infarction, as well as stroke and renal disease.[10-15]

Abnormally high blood pressure, termed *hypertension*, have the last two decades been defined as average systolic blood pressure (SBP) $\geq$ 140 mm Hg and/or average diastolic blood pressure (DBP) $\geq$ 90 mm Hg for adults ages 18 years and older.[16] However, the most recent guidelines on prevention, detection, evaluation, and management of high blood pressure in adults, by the American College of Cardiology (ACC) and American Heart Association (AHA), implemented a lower threshold for the clinical definition of hypertension, SBP $\geq$ 130 mm Hg or DBP $\geq$ 80.[17] Although a continuous association exists between higher blood pressure and increased cardiovascular risk, the 2017 ACC/AHA guidelines recommend that blood pressure should be categorized to facilitate decision making, both in the clinical setting and in the public strategies aiming to improve health in the overall population. Thus, blood pressure is categorized into four separate levels based on average SBP and DBP measured in the health care setting: *normal blood pressure* (SBP < 120 mm Hg and DBP < 80 mm Hg), *elevated blood pressure* (120-129 mm Hg and DBP < 80 mm Hg), *hypertension stage 1* (SBP 130-139 mm Hg or DBP 80-89 mm Hg) and *hypertension stage 2* (SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg).[17] The clinical categorization of blood pressure level and diagnosis of hypertension, in the healthcare setting, requires that the average blood pressure of at least two consecutive readings is above the threshold on at least two separate occasions, as described in previous and present guidelines.[16-19]

In 2000, the estimated worldwide prevalence of hypertension was 972 million people, corresponding to 26% of the adult population and the worldwide prevalence of hypertension is expected to increase. The 25 year prognosis estimates that in 2025, approximately 1.56 billons people, 29% of the world population, will be diagnosed with hypertension.[20] The worldwide prevalence of elevated blood pressure and hypertension has indeed increased over the last 40 years, mainly in low- and middle-income countries,[6] whereas the prevalence in high-income countries demonstrate a down-ward trend.[21,22] The implementation of the new clinical definition is expected to increase the previous estimates of present prevalence of hypertension with approximately 14%.[23,24] Thus, hypertension is now more common than ever.

The ongoing increase in prevalence of hypertension is related to a globalization of an unhealthy lifestyle, including physical inactivity, improper dieting, stress, overweight and obesity as well as the rapid growth and demographic ageing of the world's populations.[1,6,25] The prevalence of hypertension increases with age,[1] to the degree that the individual lifetime risk of developing hypertension exceeds 80%.[26] The present estimation is that more than three quarters of the world population above 70 years old are hypertensive.[27] The high lifetime risk of developing hypertension and the high prevalence of hypertension, especially in elders, empathize the need of a public health strategy for the elderly that prevents the development of hypertension in the normotensive and complement the antihypertensive medical treatment in the hypertensive.[16,17]

Blood pressure

Arterial blood pressure, or simply blood pressure, refers to the pressure in the large arteries of the systemic circulation. Arterial blood pressure reflects the driving pressure of the vital blood flow generated by the pumping action of the heart,[28] and can be described as a function of arterial blood flow, *i.e.* cardiac output and peripheral vascular resistance (PVR).[29]

The cardiac cycle, the events that occur from one heart beat to the next, can be divided into two distinct phases; systole and diastole. During systole, ventricular contraction generates energy and as the semilunar valves open, the energy is transformed to kinetic energy and blood is ejected into the aorta. However, blood flow within the systemic circulation is limited by PVR, and the blood does not run of indefinitely throughout cardiovascular tree. Consequently, a portion of the stroke volume and kinetic energy remains in the aorta. A part of the kinetic energy is transferred to the elastic aortic walls, which expand to accommodate the increasing blood volume. The remaining kinetic energy is stored as pressure energy in the aorta, the alleged systolic blood pressure (SBP). In the succeeding events of the cardiac cycle, the aortic pressure

energy is retransformed into kinetic energy as blood continuously flow towards its pressure gradient throughout the systemic circulation. Thus, in diastole as the ventricle relaxes and semilunar valves close, the aortic blood pressure reaches its minimum, the alleged diastolic blood pressure (DBP). However, the blood pressure in the aorta remains relatively high in comparison to the ventricular pressure, as the elastic aortic walls recoil and prevent the pressure from decreasing further. The inherent elastic ability of the aorta to capture and store energy, is a property shared by all large arteries termed arterial elastance. Arterial elastance is an essential component of the cardiovascular system, that maintain the vital driving pressure and continuous blood flow between subsequent heart beats.[29-31] To summarize, SBP and DBP represent physiological factors, including arterial compliance, *i.e.* the inverse of arterial elastance, and PVR, which together define ventricular and vascular load. Thus, the clinical relevance of measuring blood pressure is to assess cardiovascular load and the associated cardiovascular risk.[32]

Blood pressure assessed at the brachial artery in the upper arm is considered to be a strong and independent predictor of morbidity and mortality, and is therefore recognized as the current standard for clinical assessment of cardiovascular risk.[16,17,33,34]

Cardiovascular risk

A meta-analysis of 61 prospective observational studies, evaluating the association of SBP/DBP and accompanying cardiovascular risk in adults 30-80 years of age, demonstrated a log-linear increase in cardiovascular risk with increasing SBP and DBP, respectively. For instance, the hypertensive (SBP $\geq$ 130 mm Hg or DBP $\geq$ 80 mm Hg) have twice the risk of death from stroke, ischemic heart disease or other vascular disease than their counterparts with normal blood pressure (SBP < 120 mm Hg and DBP < 80 mm Hg).[10]

Elevated levels of SBP and DBP are associated with a smaller *relative* risk of a cardiovascular event in older adults than in their younger counterparts. Nonetheless, the corresponding association between higher blood pressure and the *absolute* risk of a cardiovascular event increases with age,[10] as both blood pressure and the absolute risk of incident CVD increase with age.[1,10]

The age-associated rise in blood pressure is highly correlated with increased stiffness of the arterial and arteriolar vessels.[35] From the age of 30 years, SBP and DBP progressively and linearly increase,[9,22] a probable consequence of increasing PVR.[9] Until the age of 50 years,

DBP increases and thereafter stabilizes or begin to decrease. From 60 years of age and on, DBP declines, while SBP continues to increase until the age of ~ 90 years old.[9,22] The decline in DBP and continued increase in SBP indicates a predominance of large artery stiffness in the elderly.[9] Large artery stiffness is considered to be a consequence of arteriosclerotic structural alterations in the arterial and arteriolar blood vessels, and several physiological mechanisms have been suggested to contribute to its increasing prevalence with age. The major structural alterations that occur with increasing age are arterial wall thickening and arterial dilation.[36] This in turn, are consequences of increased wear and tear of the elastic components of the in the central circuit, elastin degeneration, collagen accumulation and arterial calcification, due to increased sodium sensitivity, endothelial dysfunction, altered hormonal relationships, decreased baroreceptor sensitivity and increased responsiveness of the sympathetic nervous system.[36-38] In general, it is difficult to distinguish the physiological alterations in the cardiovascular system that occur with ageing from the pathological changes associated with the development of hypertension and cardiovascular disease. Nevertheless, large artery stiffness occurs with aging in the absence of atherosclerosis and is therefore suggested to be an adaptive mechanism to maintain the vital blood flow and wall tension. Large artery stiffness, reduce arterial compliance, and subsequently leads to an increase in SBP, decrease in DBP and widening of pulse pressure (PP),[36] *i.e.* the difference between peak SBP and end DBP.[32] Whereas in the pathophysiology of hypertension, SBP and DBP increase to a similar degree as a consequence of increasing PVR.[36]

Increased levels of SBP and DBP have, when considered separately, been associated with augmented cardiovascular risk.[10,11] Higher SBP have consistently been associated with an increased risk independently of DBP,[36-38] whereas elevations in DBP, have not always been associated with an increased cardiovascular risk when adjusted for SBP. [39,40] Considering the physiological alterations that occur in the cardiovascular system with increasing age, it is probable that the predictability of the cardiovascular risk factors, SBP and DBP, and their derived components, are affected by age. Indeed, studies have demonstrated that in the middle-aged and older adults, SBP is a much more potent cardiovascular risk factor than DBP,[37,41,42] which for this age-group underestimates both PVR and the subsequent cardiovascular risk. SBP accurately represents PVR, nevertheless, when adjusted for age, gender and other cardiovascular risk factors, SBP underestimates the presence of large artery stiffness and the accompanying cardiovascular risk.[9] Individual studies argue that SBP becomes a less potent cardiovascular risk factor with further aging and decreasing DBP.[42]

Therefore, in the older adults, > 60 years of age, where DBP is negatively associated with cardiovascular risk and SBP underestimates the risk, PP has been suggested as the superior indicator of large artery stiffness and predictor of cardiovascular risk.[9,42] PP have been associated with increased cardiovascular risk independent of SBP and DBP in some studies,[37,43] and combining PP with mean arterial pressure increase the predictability of a cardiovascular event even further,[44] nonetheless there are potential pitfalls of relying on PP assessed in the clinical setting.[45] Therefore, SBP and DBP are prioritized in the present study, as a vast collection of observational studies and clinical trials demonstrate robust evidence for using these measure to assess cardiovascular risk.[10,11,37,40,46] Present and previous clinical guidelines on prevention, detection, evaluation, and management of high blood pressure have also focused on SBP and DBP, especially SBP in the most recent guidelines.[16-19] Combining SBP with DBP, is superior to use a single blood pressure component for predicting the risk of incident CVD.[44]

Hypertension accounts for more CVD deaths than any other modifiable cardiovascular risk factor. Nevertheless, antihypertensive treatment is one of the leading solutions to prevent cause of death for any reason, second only to cessation of cigarette smoking.[47]

Antihypertensive treatment

Preventing the chronic rise in blood pressure and subsequent development of hypertension, that normally occurs with age, serves as a crucial method to reduce cardiovascular risk, promote healthy ageing and endorse high quality of life in the later stages of life.[1,16] Even though a previously elevated blood pressure can normalize through lifestyle modifications or by the use of antihypertensive medication, the cardiovascular risk remains higher than if hypertension never had been established.[16] Normalization of an elevated blood pressure has also been associated with a reduced progression of dementia and other cognitive impairments, which are more common in the elderly and in individuals with hypertension.[48] Among the elderly, hypertension is not only a leading cause of preventable morbidity and mortality, the extremely high prevalence probably underestimates the contribution of hypertension to premature disability and institutionalization.[49-51] Indeed, the risk of physical disability is higher in older adults with uncontrolled hypertension, than in normotensive and hypertensive with controlled hypertension.[52] The antihypertensive treatment goal in older adults is an average blood pressure, especially SBP, below the hypertensive threshold.[17] The implementation of a lower hypertensive threshold consequently promotes more intensive blood pressure control, which in the elderly have been associated with significantly lower rates of fatal and nonfatal cardiovascular events and reduced all-cause mortality.[53] The present control rate of high blood pressure, *i.e.* the achievement of a suitable blood pressure level during antihypertensive pharmacotherapy, is between 46% and 50% in older adults, 60-80 years of age. However, the control rates decrease considerably with increasing age from the seventh decade of life.[54,55] Taken together, this not only empathize the necessity to prevent the development of hypertension, but also the need of a public health strategy that complements the pharmacological treatment of hypertension.[16,17]

Antihypertensive pharmacotherapy, combining medications that reduce either extracellular fluid volume or peripheral resistance to blood flow,[29] are in addition to nonpharmacological lifestyle modifications the primary treatment of high blood pressure.[17] A vast number of clinical trials have demonstrated that antihypertensive treatment with pharmacological agents not only lower blood pressure but also reduces the risk of cardiovascular and cerebrovascular events and associated mortality.[56-59] A recent systematic review and network meta-analysis of 42 randomized controlled trials (RCTs), which assessed SBP reduction and associated risk with cardiovascular morbidity and mortality, demonstrated a linear association between mean achieved SBP and risk of CVD and all-cause mortality in hypertensive adults treated with

antihypertensive medication.[60] The group with the lowest risk had a mean achieved SBP of 120-124 mm Hg and the had a hazard ratio for major CVD of 0.71, 0.58, 0.46 and 0.36, and all-cause mortality of 0.73, 0.59, 0.51 and 0.47, compared to groups with a mean achieved SBP of 120-124 mm Hg, 130-134 mm Hg, 140-144 mm Hg, 150-154 mm Hg, and ≥ 160 mm Hg, respectively.[60] Another meta-analysis, demonstrated that blood pressure reductions with antihypertensive medication produce similar and proportional reductions in the risk of a cardiovascular event in adults younger and older than 65 years of age.[61] Thus, antihypertensive pharmacological treatment lower blood pressure and associated risk of cardio- and cerebrovascular events as well as reduce all-cause mortality, even in the elderly.[62,63]

The direct and indirect costs of treating the total burden of cardio- and cerebrovascular diseases are enormous, both in the individual and societal perspective, and accounts for a larger proportion of the total health expenditures than any other major diagnostic group.[64] The total burden includes cardio- and cerebrovascular diseases in the presence and absence of hypertension, as well as hypertension in the absence of cardiac disease. Public health strategies that reduce morbidity and mortality, increase quality-adjusted life-years and curtail direct medical costs as well as indirect human costs are in great demand. Suggested strategies with a great potential include an increased control rate of high blood pressure in all adults with CVD or well-established hypertension (SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg), and antihypertensive pharmacological treatment for all hypertensive middle-aged and older adults (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg).[65] A substantial proportion (~60%), of the treatment costs of the total burden the cardio- and cerebrovascular diseases are direct medical costs. Calculated projections by the AHA predict that the annual medical costs of treating the total burden of cardio- and cerebrovascular diseases will increase with 135% within the coming 20 years.[64] The predictions also indicate that a substantial proportion of the expected increase in annual medical costs are due to increased hospitalization. Increased antihypertensive pharmacotherapy is a suggested medical strategy with promising potential to reduce the overall medical costs.[65] Nonetheless, the strategy might be less effective in older adults than in the middle-aged adults, as older adults usually need more than one antihypertensive agent, *i.e.* polypharmacy, to accurately control hypertension. Initiation of antihypertensive polypharmacy in older adults provide cardio- and cerebrovascular benefits, but not completely without other potential risks.[66] The risks include exacerbated orthostatic hypotension, which in turn contribute to an increased risk of falls and/or fractures, as well as medical side effects that negatively affect other cardiovascular risk factors. In addition, as isolated systolic hypertension, *i.e.* a

significant elevation in SBP but not in DBP, is the most prevalent from of hypertension in older adults.[35] There is a risk that the antihypertensive pharmacotherapy, initiated to reduce SBP, induce a redundant antihypertensive effect on DBP. A redundant reduction in DBP is potentially harmful, as it impair organ perfusion, and consequently increase the potential risk of cardio- and cerebrovascular events.[66] Altogether, complementing the public health strategy to treat hypertension with effective antihypertensive nonpharmacological treatments, might be particularly important in the older adults to increase quality-adjusted life-years as well as reduce morbidity and mortality. An increased control rate of hypertension in the older adults may not only provide health and economic benefits at the individual level, but is also probable to noticeably reduce medical costs on the societal level, as the older adults, 65-79 years of age, constitute the age group with the highest treatment costs.[64]

Nonpharmacological interventions that lower blood pressure and associated cardiovascular risk status have a substantial potential to treat and increase the control rate of hypertension in older adult, as well as prevent the chronic rise in blood pressure that usually occurs with age. There are several nonpharmacological lifestyle modifications that demonstrate these properties. The most important and well-documented lifestyle modifications are a diet high in fruits, vegetables, and low-fat dairy products,[67-70] reduced salt intake,[71-74] dietary supplementation of potassium,[75,76] cessation of smoking,[77] reduced alcohol consumption,[78,79] modest weight loss for the obese and overweight,[80-82] and increased physical activity.[83-87]

Physical activity and aerobic exercise

Numerous clinical trials have demonstrated that increased physical activity lowers blood pressure, including several different forms of exercise, such as dynamic resistance training,[83] isometric resistance training,[84,85] and aerobic exercise.[86,87]

Two large meta-analyses, including 93 and 54 RCTs, respectively, examined the effect of aerobic exercise on resting blood pressure in adults. The average reduction in resting SBP/DBP was 3.5/2.1 mm Hg and 3.8/2.6 mm Hg, respectively.[86,87] The observed reduction in average blood pressure (SBP/DBP) differed between blood pressure categories, being greatest in the hypertensive and lowest in the normotensive [*Normal blood pressure*: 0.8/1.1 mm Hg; *Elevated blood pressure or hypertension stage 1*: 2.1/1.7 mm Hg; *Hypertension stage 2*: 8.3/6.7 or 8.3/5.2 mm Hg].[86,87]

One of the meta-analyses examined the effect of aerobic training intensity as well and demonstrated that high and moderate training intensity have similar effects on average

SBP/DBP, -3.6/-3.1 mm Hg and -4.8/-2.3 mm Hg, respectively.[86] Whereas the average effect size of low intensity is significantly smaller, +0.1/+0.3 mm Hg. A separate systematic review concluded that clinical trials, generally report that high and moderate training intensity induce similar reductions in SBP whereas high-intensity training reduce DBP as well[88] In addition, high-intensity training convey greater cardioprotective benfits in comparison with isocaloric moderate-intensity training.[88,89] Nevertheless, there is a considerable variability in the scientific findings regrading the effect of aerobic exercise with high and modrate training intensity on high blood pressure.[89] Individual RCTs have indicated that in the hypertensive, high-intensity training induce a significnatly larger reduction in SBP/DBP than moderate-intensity training.[90] Whereas in the normotensive, neither exercise intervention have demonstrated to reduce SBP/DBP.[91] Which suggests that the blood pressure reducing effect of aerobic exercise, is present and intensity dependent in the hypertensive,[90] but that might not be the case in the normotensive.[91] Indeed, the exercise induced effect on blood pressure is a function of initial blood pressure, in which those with the highest blood pressure prior to intervention experience the greatest reduction in postexercise blood pressure.[92] This in turn might explain some of the differences and controversies between individual trials and national recommendations.

The most resent ACC/AHA guidelines on prevention, detection, evaluation, and management of high blood pressure, recommend regular aerobic exercise. The ACC/AHA guidelines recognize aerobic exercise at a moderate training intensity (65-75% of the heart rate reserve), 90-150 minutes per week, as one of the best proven nonpharmacological interventions for prevention and treatment of hypertension.[17] However, the directives regarding aerobic exercise are general and does not include any specific recommenadtions for the elderly. Systemic reviews of published literature regarding the role of exercise as a treatment of hypertension have suggested that middle-aged adults may obtain greater benefits than older adults.[93,94] Whereas the large meta-analyzes, on which the directives and guidelines derive from,[86,87] demonstrated no statistical differences between subjects older and younger than 50 years in the wide age span indluded.[86] This latter notion was supported in another meta-analysis of 23 RCTs, mainly including older adults, 61 to 83 years old, which demonstrated that aerobic exercise, reduce average SBP/DBP with 5.4/3.6 mm Hg in older adults.[95] However, the same meta-analysis preformed comparison of adults younger and older than 70 years old, and subsequently revealed a significantly greater reduction in DBP among the elderly. A similar trend was observed in SBP, although the difference was not supported statistically.[95] These findings indicate that age may influence the training induced response among older adults,

which in turn might suggest that scientific results on the exercice induced effect on blood pressure in the young and middle-aged cannot be extrapolated to the elderly.

Relatively few RCTs have addressed the effect of aerobic exercise on blood pressure in older adults, and the collection of meta-analyses and systemic reviews of the topic are consequently scare.[95-97] One meta-analytic review of 7 RCTs, including normotensive and hypertensive middle-age and older adults, average age 68-69 years,[96] acknowledged the issue with publication bias. Publication bias is a consequence of the trend of numerous scientific publications only reporting statistically significant differences supporting an alternative hypothesis. [98] The most recent systemic review and meta-analysis, that assessed exercise and other non-pharmacological strategies to reduce blood pressure in older adults, identified 24 relevant RCTs that evaluated the effect of aerobic exercise in older adults. However, the authors acknowledged a high risk of bias in the literature selection, as the literature search was limited to trials and interventions that induced a reduction in blood pressure.[97] Indeed, meta-analytic conclusions based on a narrow selection of available literature might be particularly sensitive to publication bias.[99] On the other hand, the meta-analytic review that acknowledged the issue with publication bias,[96] included 5 RCTs that had assessed the effect of aerobic exercise on blood pressure in older adults.[100-104] Of these, 4 RCTs had assessed but not reported the effect of aerobic exercise on blood pressure, as the exercise intervention did not reduce blood pressure or the effect size was statistically insignificant.[100-103] The authors of the meta-analytic review addressed the issue of potential publication bias by contacting the respective authors in an attempt to retrieve the data. Retrieved data was subsequently reported and included in the systemic review and meta-analysis, which concluded that the aerobic exercise in older adults slightly reduce SBP (~ 2 mm Hg) but not DBP.[96]

Although there are individual RCTs that demonstrate that aerobic exercise does not reduce blood pressure in older adults,[100-103] the general and possibly biased interpretation, is that exercise may elicit a modest reduction in blood pressure (~5/3 mm Hg),[97] as demonstrated in an increasing number of RCTs.[104-113] Nonetheless, there is no prevailing consensus on which training intensity that induce the optimal antihypertensive response in older adults. The few RCTs that have assessed the effect of training intensity in the older adults are inconclusive and the reported results are highly contraindicated between trials.[109-114] Most of the RCTs on the topic have included both middle-aged and older adults, and have compared the effect of aerobic exercise with low and moderate training intensity.[109-111] A RCT that have addressed the effect of high-intensity training on blood pressure in the elderly, demonstrated that moderate and high

training intensity (70% and 80-85% of the heart rate reserve, respectively) reduce SBP to the same extent.[112] Whereas, another RCT, in older adults mainly over 70 years of age, reported that neither exercise intervention, high-intensity interval training and moderate-intensity continuous training, affected average blood pressure.[114] A third RCT, that included middle-aged and older adults, demonstrated that high-intensity interval walking reduced SBP more than moderate-intensity continuous walking.[113] In summary, there is little reliable and available documentation regarding the effect of aerobic exercise and training intensity on blood pressure in the older adults and specifically the elderly. Consequently, there is no prevailing consensus on how aerobic exercise can be recommended and implemented as a nonpharmacological strategy to prevent, treat, and control hypertension.

Numerous organizations and professional committees all over the world, recommend aerobic exercise as an initial nonpharmacological strategy to prevent, treat, and control hypertension. Even though the recommendations of supervised aerobic exercise differ regarding the recommended training intensity, weekly frequency and time per session,[115,116] they all recommend the same type of aerobic exercise to the whole adult population, regardless of age and initial level of blood pressure. In addition, the beneficial effects of lifestyle modifications on general health are expected to accrue over time, and long-term adherence to the recommended lifestyle modification would then maximize both individual and populational benefits.[17] One small clinical trial in young adults, demonstrated that regular aerobic exercise reduced blood pressure and maintained adherence led to further reductions and subsequently concluded that the antihypertensive effect of regular aerobic exercise can be maintained as long as for 3 years.[117] Nevertheless, these findings are not the in alignment with other research findings, which indicate that nonpharmacological interventions targeting new habits of physical activity often results in an impressive rate of behavioral changes, but does not lead to a behavioral maintenance in the long-term.[17] In general, the RCTs that have assessed the effect of aerobic exercise on blood pressure, have been of a relatively short duration,[86,87] and only a few studies have had an intervention period longer than 24 weeks.[86] A large meta-analysis that examined the effect of aerobic exercise and program duration, demonstrated that program duration appeared to influence the average reduction in blood pressure (SBP/DBP), being significantly lower in trials with an intervention period lasting longer than 24 weeks, 0.8/1.7 mm Hg.[86] However, two small RCTs including hypertensive older adults demonstrated that blood pressure decreased during the initial stage of exercise intervention and subsequently stabilized at a significantly lower lever after 9 months of regular exercise.[106,111]

Thus indicating that long-term adherence to supervised aerobic exercise provide individual health benefits in terms of reducing blood pressure in older adults. Whether supervised aerobic exercise can reduce average blood pressure on a populational level of older adults remains to be investigated.

The primary aim of this study is to investigate the effect of three years of aerobic exercise with high- or moderate training intensity, versus a control group, on average blood pressure in elders. The secondary aim is to evaluate the potential of aerobic exercise with different training intensities as a nonpharmacological strategy to prevent, treat and control hypertension. In other words, investigate the effect of long-term aerobic exercise and training intensity on blood pressure in three subgroups of the elderly population. Videlicet the normotensive elders, with an average blood pressure below the hypertensive threshold (SBP/DBP) of 130/80 mm Hg, the hypertensive elders with an average blood pressure above the hypertensive threshold *without* prescribed antihypertensive medication and the hypertensive elders *with* prescribed blood pressure medication and hypertension.

Methods

Participants

The present study is a substudy of the Generation 100 study, an exercise intervention study and randomized controlled trial (RCT). The primary aim of the Generation 100 study is to determine the effects of long-term, five years, regular exercise training on morbidity and mortality in an elderly population, 70-77 years of age.[118]

In 2012, the Generation 100 study invited all men ($n = 3245$) and women ($n = 3721$) born from 1 January 1936 to 31 December 1942 with a permanent residential address in the municipality of Trondheim ($n = 6966$), Norway, to participate in the Generation 100 study.[118] Potential participants were identified through the National Population Register. Trondheim was at the time the third largest city in Norway, with a reported population of 176 348 at the beginning of the year.[119]. In Norway, healthcare is financed through general taxes with no or nominal charge and predominately provided by a public system.[120]

Potential participant received an invitation letter containing an informational brochure, a health-related questionnaire and a response sheet with a consent form. Potential participants were asked to return the questionnaire and response sheet with the consent form, regardless of willingness to participate in the baseline examination. The returned questionnaires were used to compare the participating sample with the overall population.[118]

Upon invitation, 3213 elderly men and women responded, corresponding to 46% of the entire population invited. Of the respondents, 1790 reported their interest, while 1422 declined to participate. Interested potential participants were invited to a physical examination, executed from August 2012 to June 2013. After the physical examination 174 participants actively withdrew or did not show up for testing and another 49 participants were excluded due to the exclusion criteria (Figure 1). Health-related exclusion criteria included diagnosed dementia, uncontrolled hypertension, symptomatic valvular hypertrophic cardiomyopathy, unstable angina, primary pulmonary hypertension, heart failure or severe arrhythmia and chronic communicable infectious diseases. Physical exclusion criteria were illness or disabilities that impeded with exercise or made completion of the study unlikely and test results indicating that study participation would be unsafe, the latter was determined by the researchers. Cancer was a potential exclusion criterion, if presence of the disease made participation impossible or exercise contraindicated, consequently cancer was considered individually in consultation with

a physician. Lastly, participants were excluded if they participate in other studies that conflict with the objectives of the Generation 100 study.[118]

After invitation, accepts and declines to participate, exclusions and withdrawals, 1567 participants, 777 men (72.4± 0.08 years) and 790 women (72.5 ± 0.07 years), completed the baseline examination and were included in the Generation 100 study. Gender and date of birth were obtained from the National Population Registry. Age was subsequently calculated from month/year of birth and month/year of inclusion. Participants that were willing and physically able to complete the exercise program, as determined by the researchers at the first physical examination, fulfilled the inclusion criteria. Included participants were then stratified by sex and marital status and randomized 1:1 into an exercise training group ($n = 787$) or to a control group ($n = 780$). The exercise group was further randomized 1:1 into high-intensity interval training (HIIT, $n = 400$) or moderate-intensity continuous training (MICT, $n = 387$) training (Figure 1). Spouses were randomized into the same intervention group to increase motivation. The Unit for Applied Clinical Research at the Norwegian University of Science and Technology developed and executed the randomization procedure to ensure impartial assignments. The participants received both written and verbal information about their assigned intervention. The participants gave informed, written consent to the main study.[118]

The participants were physically examined and filled out health-related questionnaires at baseline, before randomization, and at a 1-year and 3-year follow-up, respectively. A 5-year follow-up has been conducted in the fall of 2017 and spring of 2018. The Generation 100 study was registered in a clinical trials registry in August 2012 (ClinicalTrials.gov, Identifier: NCT01666340). Ethical approval for the Generation 100 study was granted by the Norwegian Ethical Review Board for Medical and Health Research (REK 2012/381).[118]

Characteristics of the Generation 100 study participants are described and compared to the elderly men and women who declined to participate in the study in the Generation 100 study protocol written by Stensvold *et al*.[118] Moreover, the study protocol contains information on how the original sample size was determined and ethical concerns of the main study.

The Generation 100 Study

Invited
(*n* = 6966)

No response (*n* = 3721)

Decline to participate (*n* = 1422)
· Not interested (*n* = 378)
· Exclusion criteria (*n* = 236)
· No reason given (*n* = 808)

Baseline:

Interested (*n* = 1790)

Lost from analysis (*n* = 223)
· Exclusion criteria (*n* = 49)
· Withdrawal (*n* = 174)

Randomized
(*n* = 1567)

Intervention:

Exercise
(*n* = 787)

**Control
(*n* = 780)**

**HIIT
(*n* = 400)**

**MICT
(*n* = 387)**

3-year follow-up:

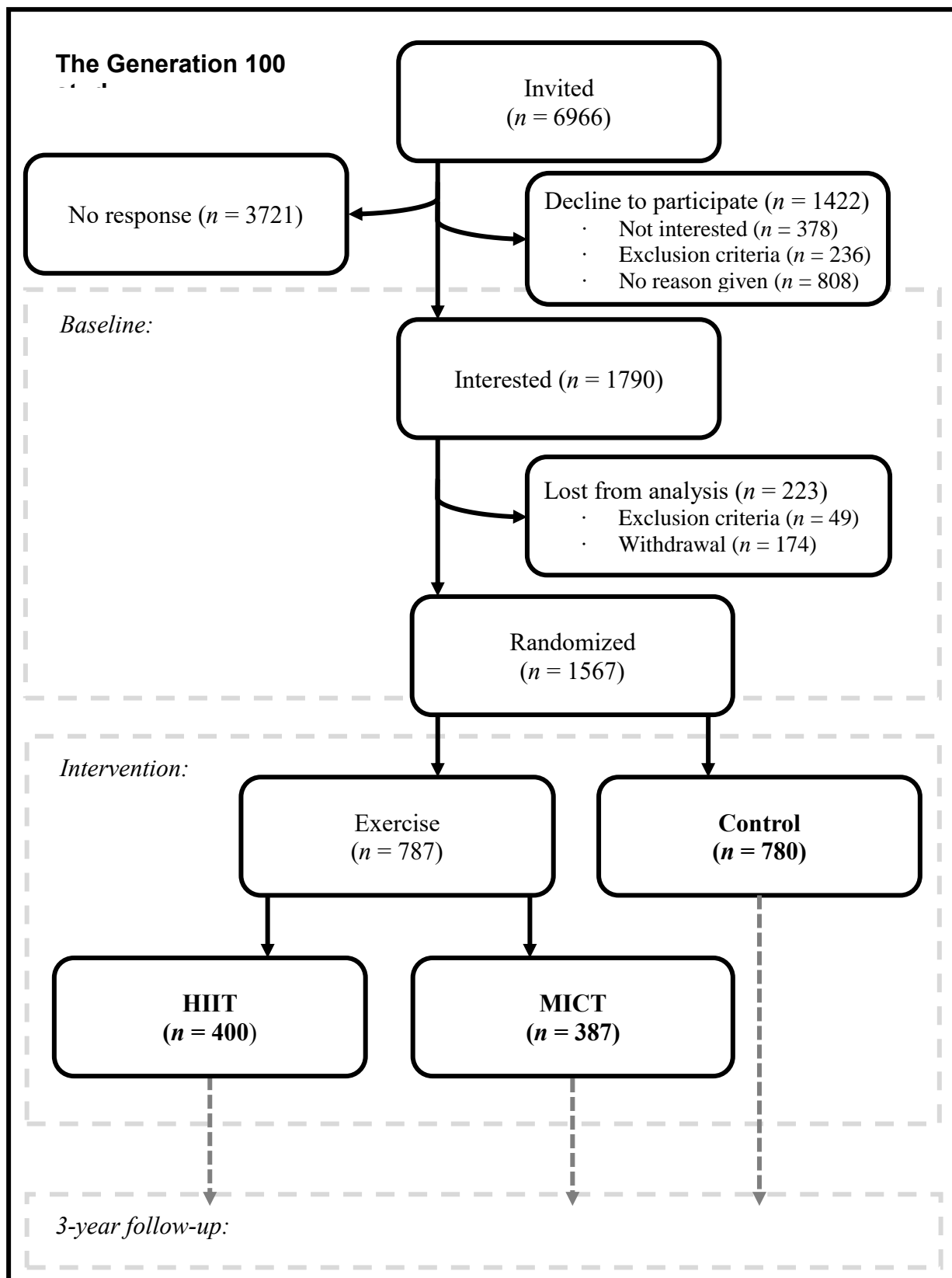**Figure 1:** Flow chart illustrating participant invitation and response, accepts and declines to participate, exclusions and withdrawals, and subsequent randomization in the Generation 100 Study. After the initial physical examination at baseline, participants were randomized into one out of two exercise interventions, high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT), or a control group.

The present study is performed with a subsample from the Generation 100 study. The primary outcome variables of the present study are average systolic (SBP) and diastolic (DBP) blood pressure, as the combination of the two is slightly more informative than either alone for predicting cardiovascular risk from a single blood pressure measurement.[10] Consequently, the subsample consists of Generation 100 study participants that had the main outcome variables, assessed at baseline and at the 3-year follow-up. At total of 1075 participants fulfilled this inclusion criteria.

However, as the primary outcome of the Generation 100 study is to assess the effect of aerobic exercise and training intensity on morbidity and mortality and not blood pressure alone, the main study sample include elders with prescribed pharmacological antihypertensive treatment. Excluding participants with prescribed antihypertensive medication from the present study, would exclude a substantial portion of the target population. In 2012, approximately 50 % of the Norwegian population older than 67 years of age used antihypertensive medication regularly, according to the national statistical institute of Norway and contemporary records from the Norwegian Prescription Database[121,122]

In order to assess and control for a potential confounding effect of pharmacological antihypertensive treatment during the intervention period, a secondary observational analysis is performed to investigate the effect of aerobic exercise and training intensity in participants with an altered and unaltered antihypertensive medical status. Participants with an *altered medical status* include participants that either initiated or withdrew their pharmacological antihypertensive treatment during the intervention period. Whereas participants with an *unaltered antihypertensive medical status*, include participants with or without prescribed antihypertensive medication during the whole the intervention period. A requirement for such an analysis is a complete record antihypertensive medical status of the participants during the intervention period. Subsequently, 88 participants were excluded due to missing or incomplete data on self-reported usage antihypertensive medication (Figure 2).

Overall, 987 participants, 72.4 ± 0.07 years of age, fulfilled the inclusion criteria for the present study. The subsample and main study sample show a similar distribution between the exercise intervention groups [HIIT, $n = 237$, 131 men (55.4%); MIT, $n = 236$, 119 men (50.4%)] and the control group [$n = 514$, 257 men (50.0%)] (Figure 2).
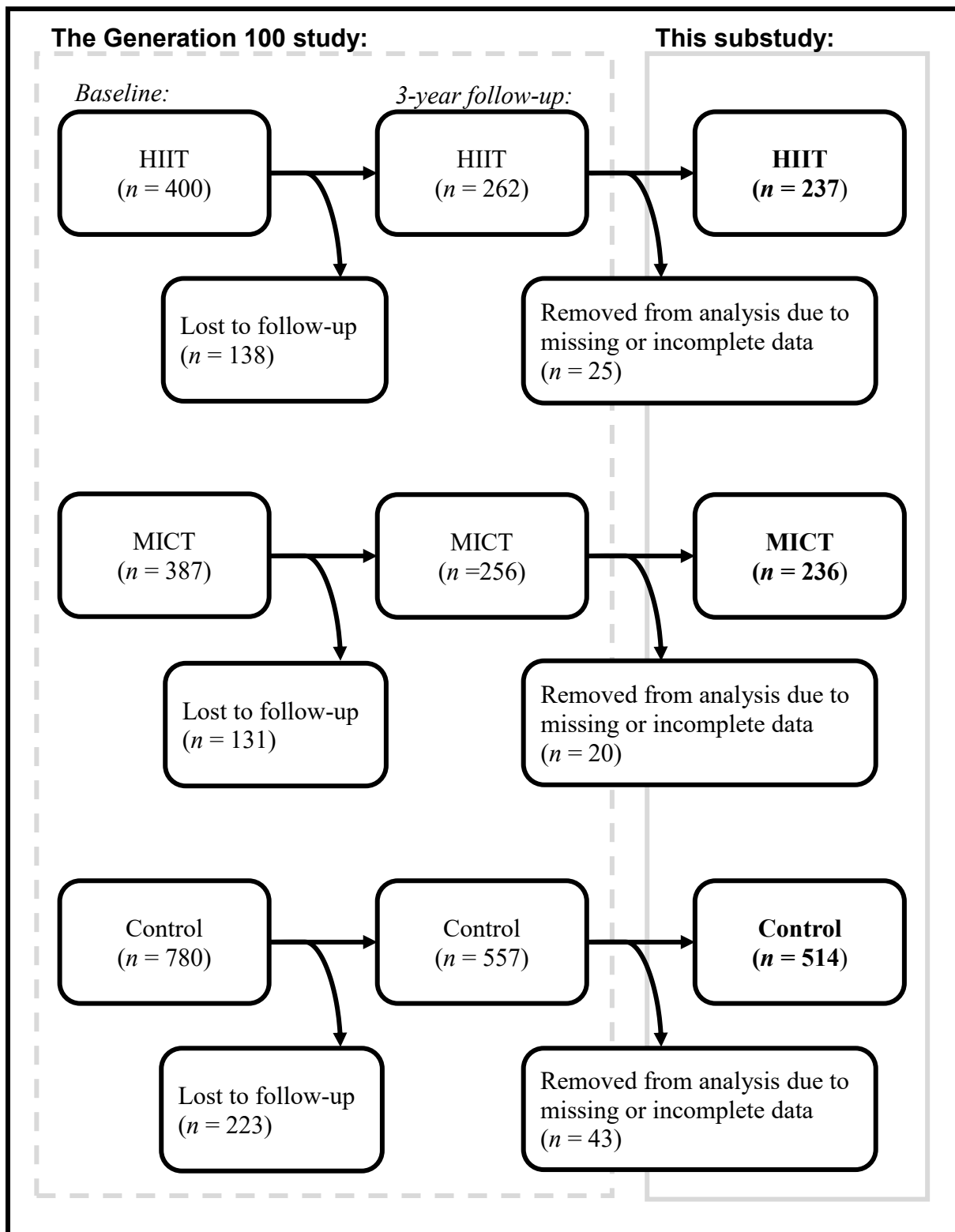
Figure 2: Flow chart illustrating the derivation of the present subsample from the Generation 100 study sample, consisting of two exercise intervention groups, high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT), and a control group. Participants, for which blood pressure was not assessed at the 3-year follow-up, are labeled as *Lost to follow-up*. Participants labeled as *Removed from analysis* include participants that were subsequently excluded due to missing or incomplete data on self-reported usage of antihypertensive medication.

Physical examinations

All examinations were performed at St. Olavs Hospital in Trondheim. Physical tests and examinations were performed at baseline and at the 3-year follow-up, the latter was executed from August 2015 to June 2016. All test personnel were blinded before intervention in the physical examination. Each individual physical examination was divided onto two separate days. On the first day, the participant attends a clinical examination performed at rest. The clinical examination at rest includes blood sample collection and measurements of height, weight, body composition, waist circumference, blood pressure and resting heart rate. On the second day, the participant attends a symptom-limited incremental work test on a treadmill, cardiopulmonary exercise testing (CPET), to assess cardiorespiratory fitness (CRF). Participants were asked to continue their normal medication routines on both days of the physical examination. All participants with prescribed antihypertensive medication, included in the present study, confirmed that they continued their normal medical routines on the day of the clinical examination at rest.

Clinical examination at rest

The clinical examinations at rest were performed at Clinical Research Facility at St. Olavs Hospital. All participants were asked to fast and restrain from exercise training twelve hours prior to the clinical examination. Moreover, the participants were asked to restrain from alcohol twenty-four hours and refrain from caffeine and nicotine on the day of examination.

The mean fasting time was 8.4 ± 0.2 and 13.3 ± 0.1 hours at baseline and the 3-year follow-up, respectively. Minimum fasting time was 1 hour for 6 (0.6%) participants at baseline and 1 hour or less for 11 (1.1%) participants at the 3-year follow-up.

Height
The participant was asked to stand with their feet placed shoulder-width apart against a wall, height (cm) was then measured with a mechanical telescopic measuring stadiometer (Seca 222, Seca, Hamburg, Germany) to the nearest millimeter.

Body composition and weight
Body composition and weight were measured using bioelectrical impedance (Inbody 720, Biospace, Seoul, Korea). The device is a validated and considered as an appropriate alternative to dual-energy x-ray absorptiometry for assessing body composition.[123,124] The device uses four pairs of electrodes, embedded into the handles and floor scale of the analyzer.[125] Furthermore, the device is auto-calibrated every time the machine is turned off, which is once a week for this

study. Participants were encouraged to go to the toilet right before testing. After five minutes in an upright position the participant stands barefoot on the instrument. Before starting the test, height, age and gender were plotted into the display of the scale. Within two minutes, the scale reports weight (kg), body mass index (BMI; kg/m^2) and fat percentage (%). All variables are obtained with 0.1 decimals of accuracy. Participants with a pacemaker [Baseline: 7 (0.7%); 3-year follow-up: 13 (1.3%)] were not examined with bioelectrical impedance. Instead, body weight is measured using a regular flat scale (Seca 877, Seca, Hamburg, Germany) to the closest 0.1 kg, BMI is subsequently calculated as body weight divided by square height (kg/m^2).

Waist circumference

All clothing and accessories were removed from the participant's abdominal region. The participant was asked to relax, breathe normally and to withstand their position with their feet placed shoulder-width apart and their arms crossed over their chest. The measuring tape was placed in a horizontal line from the uppermost border of the iliac crest around the abdomen. After three normal expirations, waist circumference (cm) was measured to the nearest millimeter.

Blood pressure and heart rate

Before the first measurement, the participant was asked to sit down, in a chair with both back and feet supported, and to relax for five minutes. Time was measured with a digital timer. All clothing was removed from the participants upper arms. The participants arms were supported on armrests. A cuff of suitable size was placed on the participants left upper arm. During the rest period and subsequent measurements, the participant was asked to avoid talking and sit with legs uncrossed during the measurements. Furthermore, the participant was sequestered behind curtains to avoid interaction with the test personnel and ease relaxation. Resting heart rate (HR_{rest}; bpm), SBP (mm Hg) and DBP (mm Hg) were measured twice in each arm, first in the left and then in the right, with a one-minute break between measurements. A third measurement was made if the two initial readings differed in SBP or DBP with $\geq$ 10 mm Hg or $\geq$ 6 mm Hg, respectively. Average SBP and DBP was subsequently calculated for each arm, using the last two measurements.

Blood pressure was measured with Philips IntelliVue MP50 (Philips medizing system, Boeblingen, Germany). The device relies on the oscillometric technique,[126] which uses an inflatable arm-cuff connected to a sensor that detects oscillations in pulsatile blood volume during cuff inflation and deflation. Blood pressure is subsequently calculated from the maximum amplitude using population-based data.[17] The devices are frequently validated and

included in the quality control system at St. Olavs Hospital. Furthermore, the method described here follow the clinical practice recommendations for accurate measurements of blood pressure,[34,127,128] neatly summarized in the most recent guidelines on prevention, detection, evaluation, and management of high blood pressure by the American College of Cardiology (ACC) and American Heart Association (AHA) Task Force on Clinical Practice Guidelines,[17] with only two exceptions.

The method of blood pressure assessment used in the Generation 100 study, was adapted from the Nord-Trøndelag Health (HUNT) Study, an independent longitudinal health study, which used an analogous method.[129]

In the present study hypertension is defined as an average blood pressure above the hypertensive threshold, *i.e.* SBP $\geq$ 130 and DBP $\geq$ 80 mm Hg,[17] or usage of antihypertensive medication, which is a definition commonly used in national health surveys.[27,130,131] Consequently, participants without prescribed antihypertensive medication and with an average blood pressure below the hypertensive threshold are classified as *normotensive*, whereas participants with prescribed antihypertensive medication or an average blood pressure above the threshold are classified as *hypertensive*.[132] In order to assess the effect of aerobic exercise on blood pressure in participants with different initial levels of SBP and DBP, participants are categorized according to the blood pressure categories in the most recent ACC/AHA guidelines on prevention, detection, evaluation, and management of high blood pressure, defined previously in this report (Blood pressure categories).[17]

Clinical practice recommendations for accurate measurements of blood pressure state that blood pressure should be measured in both arms at the first clinical assessment, and if an interarm difference is present the arm with the highest blood pressure reading should be used for subsequent readings in order to avoid systematic errors.[17,127] Therefore, average SBP and DBP at baseline, for respective arm, were used to determine which arm to use in the subsequent analysis.

Blood sampling

Blood samples were collected from an arm vein. Serum levels of triglycerides (TGs; mmol/L), high-density lipoprotein (HDL; mmol/L) and total cholesterol (mmol/L) were measured immediately using quality assured standard procedures at St. Olavs Hospital. Upon blood analysis, low-density lipoprotein (LDL; mmol/L) was subsequently calculated from HDL and total cholesterol.

Cardiopulmonary exercise testing

All CPET was performed at the core facility NeXt Move, Norwegian University of Science and Technology (NTNU) located at St. Olavs Hospital. All participants were asked to refrain from alcohol, caffeine and nicotine on the day of examination.

CPET was performed on a motorized treadmill (PPS55 Med, Woodway GmbH, Weil am Rhein, Germany). Participants with leg pain or impaired balance, 19 of 976 (1.9%), were tested on an exercise bicycle (Corvial 906900, Lode B.V. Medical Technology, Groningen, Netherlands). Participants had a familiarization period during an 8-10 minutes warm-up. The warm-up workload at baseline was based on self-reported physical activity level, heart rate (HR; bpm) monitoring, and perceived physical exertion level using the Borg scale.[133] The perceived exertion ought to be *fairly light* and correspond to level 10 or 11 on the Borg scale. The warm-up workload settings, speed (km/h) and inclination (%) on the treadmill or rate of energy transfer (W) on the exercise bike, determined at baseline were also used at the 3-year follow-up.

After the warm-up, an individualized protocol, using portable indirect calorimeter systems, was used to measure maximal oxygen uptake (VO_{2max}; L/min and mL/kg/min). Two gas analyzers, Cortex MetaMax II [$n = 935$ of 976 (95.7%); Cortex, Leipzig, Germany] or Oxycon Pro [$n = 41$ of 976 (4.2%); Erich Jaeger, Hoechberg, Germany], were used in this study. Calibration of the gas analyzers include daily calibration of barometric pressure, volume calibration between every test with a 3-L standardized and motorized mechanical lung (Motorized Syringe with Metabolic Calibration Kit, VacuMed, AkuMed AS, Oslo, Norway) and gas calibration after every fourth test or if the ambient air measurement was rejected. Gas calibrations were performed using ambient air and a reference gas containing 5% carbon dioxide and 15% oxygen (Scott Medical Products, Breda, Netherlands).

During the CPET, participants were breathing into an appropriately sized mask (Hans Rudolph, Inc, Shawnee, Kansas, USA) connected to the gas analyzer. HR was measured using a HR monitor (S610i, Polar Electro Oy, Kempele, Finland). Every 10 seconds, the gas analyzer reports the 30 second average of HR, oxygen uptake (VO_2; L/min and mL/kg/min), carbon dioxide output (VCO_2; L/min) and respiratory-exchange-ratio (RER). HR, VO_2, inclination, speed, RER and perceived exertion, on the Borg scale, [133] were registered at two submaximal levels, and at maximal effort.

The individualized CPET protocol started with a steady state measurement, 3 minutes, with the same workload settings used during the warm-up. The first steady state, was followed by a 2% increase in inclination on the treadmill or a 25 W increase on the exercise bicycle in a second

steady state measurement for 2 minutes. After completion of the two submaximal steady state measurements, workload was gradually increased until voluntary exhaustion or maximal VO_2 (VO_{2max}) was reached. Workload on the treadmill was increased about every minute with either 1 km/h in speed or 2% in inclination, whereas workload on the exercise bicycle was increased with 10 W every 30 seconds. Tests were aborted if the participants reported to have chest pain, nausea or dizziness at any stage. During the treadmill CPET, participants were encouraged not to hold on to the treadmill railing. In the case of loss of balance, the participants were instructed to gently place their hand on the railing, without grab hold of the railing or putting on too much pressure.

The Generation 100 study criteria for reaching VO_{2max} are an observed level off in VO_2 in the last 60 seconds of the test, *i.e.* VO_2 does not increase more than 2 ml/kg/min despite increased workload, and a RER above or equal to 1.05. For participants not fulfilling these criteria, the highest reached oxygen uptake at voluntary exhaustion, peak oxygen uptake (VO_{2peak}; ml/kg/minute) was registered in lieu. Maximal or peak oxygen consumption was calculated as the mean of the three successively highest VO_2 recordings. Peak RER was defined as the highest RER value observed among the three highest VO_2 values. At baseline, 62.6% (605 of 967) of the participants fulfilled the criteria for VO_{2max}, and the portion fulfilling the criteria was decreased to 58.6% (535 of 913) at the 3-year follow-up. For simplicity, the term VO_{2peak} is used to represent both VO_{2max} and $VO_{2peak,}$ throughout the rest of this report. Peak heart rate (HR_{peak}; bpm) was calculated by adding 5 beats to highest observed HR during the test.[134]

Participants with previously known cardiovascular disease (CVD) [n = 119 of 976 (12.2 %)] were tested with the same individual protocol, under supervision of a physician and electrocardiographic monitoring, in accordance to the ACC/AHA guidelines for exercise testing of patients with known CVD.[135]

Questionnaire

Participants filled out a questionnaire in connection to the physical examination at baseline and at the 3-year follow up. The questionnaire contained 21 questions regarding health, daily life, education level, social environment, exercise and physical activity. The questionnaire is attached in the appendix (Questionnaire). Answers to question 7, 10, 14, 16, 17 and 21 are included in the present study.

The questionnaire was used to assess information regarding the participants physical activity, smoking habits, alcohol consumption and self-reported usage of antihypertensive medication. Self-reported physical activity, *i.e.* engagement in physical activity with the intention of exercising, was defined as low, moderate or high corresponding less than once a week, 1-3 times per week and almost every day, respectively. Smoking habit was dichotomized as either current smoker or current non-smoker. Data on alcohol consumption during the last two weeks were used to determine the number of units of alcohol consumed per week and to assess drinking status dichotomized as either heavy drinker or non-heavy drinker. A heavy drinker is defined as > 7 and $10 >$ units of alcohol/week for women and men, respectively.[136] Self-reported usage of antihypertensive medication is dichotomized as with or without prescribed antihypertensive medication. Furthermore, the questionnaire provides information about the participants medical history prior to intervention, as self-reported presence of current and/or previous disease: stroke, diabetes, kidney disfunction, cancer, hypothyroidism, hyperthyroidism and CVDs, including myocardial infarction, angina pectoris, heart failure, atrial fibrillation, and another unspecified CVD.

Interventions

Exercise

Participants in the exercise intervention groups were instructed estimate their exercise intensity by rating their perceived exertion during exercise in accordance to the Borg 6-20 scale.[133] The Generation 100 study organized and offered group training sessions to the participants of the exercise groups. Attendance to group training sessions was generally voluntary, and participants may have chosen to perform their exercise individually. However, one mandatory session was provided once every sixth week. The type of training activities are expected to vary during the year and may have included both indoor and outdoor activities such as: walking, running, or any combination thereof, as well as cross-country skiing and aerobics.[118]

High-intensity interval training

The HIIT group was assigned to and asked to complete a training regimen consisting of two weekly 40-min workouts. The assigned workouts are designed in accordance to a high-intensity 4×4 min interval model. Participants are supervised to perform a light 10 min warm-up followed by four 4 min high-intensity intervals interspersed with 3 min active breaks. The training intensity during the high-intensity intervals ought to correspond to 85-95 % of peak heart rate, equivalent to approximately 16, between *hard* and *very hard*, on the Borg scale. Whereas the active breaks between the high-intensity intervals ought to consist of at a lower training intensity, approximately 12, between *fairly light* and *somewhat hard*, on the Borg scale. Approximately 12 on the Borg corresponds to 60-70 % of peak heart rate.[133,137] Training is organized and offered to the participants twice a week at different walking locations around Trondheim. Every sixth week the participants are invited to an organized and mandatory spinning session, where the participants exercise with a heart rate monitor to ensure exercise at the requested intensity described above.[118]

Moderate-intensity continuous training

The MICT workout was designed to be isocaloric in relation to the HIIT workout. Therefore, the randomized MICT group was assigned to and asked to complete a training regimen consisting of two weekly workouts, each consisting of a 50-min continuous workout at 70% of peak heart rate. The exercise intensity should be perceived as *somewhat hard*, approximately 13, on the Borg scale.[133,137] MICT has also been defined and described to the participant as exercising at 'talking pace', where the performer can maintain a conversation without gasping for air.[138,139] As for the HIIT group, the MICT group is invited to an organized and mandatory

spinning session every sixth week. During this session, the participants exercise with a heart rate monitor to ensure that they exercise at the requested moderate intensity described above.[118]

Control

The randomized control group was instructed to follow the current, in 2012, national recommendations for physical activity in Norway, which are provided by *Helsedirektoriatet*.[140] Accordingly, the participants were recommended to perform 30 min of moderate-level physical activity almost every day. No further supervision was provided to the participants of the control group.[118]

Adherence

Participants in the exercise intervention groups were asked, in connection to the physical examination at the 3-year follow-up, whether they exercised as prescribed by the Generation 100 study. Whereas the participants of the control group were asked if they followed the general recommendation.

Statistical analyses

Continuous variables, including height, weight, BMI, fat percentage, waist circumference, SBP, DBP, HR_{rest}, TGs, total cholesterol, HDL, LDL, HR_{peak} and the two measures of VO_{2peak}, were examined for normality and homogeneity of variances to ensure that the assumptions for linear models were fulfilled. Continuous variables that fulfilled the assumptions was compared with analysis of variance (ANOVA) to determine differences between the two exercise intervention groups and the control group, heron collectively referred to as the *intervention groups*. One continuous variable did not fulfill the assumptions for a linear model, and TGs was in lieu analyzed with the non-parametric independent samples Kruskal-Wallis test to distinguish differences between intervention groups. Comparisons of categorical variables, including BMI category, blood pressure category, antihypertensive medication, smoker, heavy drinker, physical activity and adherence, between intervention groups were made with Pearson's chi square test. Parameters assessed at baseline, prior to intervention, are referred to as *preintervention*, whereas parameters assessed at the 3-year follow-up, after intervention, are referred to as *postintervention*. All variables were compared between groups pre- and postintervention.

All variables were also compared for parameter differences between genders pre- and postintervention. Continuous variables were analyzed for differences between genders within and between intervention groups with Student's t-test and ANOVA, respectively and TGs was analyzed with the non-parametric independent samples Mann-Whitney test. Whereas Pearson's chi square test was used for the categorical variables. Gender differences were detected within groups, but not between groups.

The intervention effect of the main outcome variables, SBP (ΔSBP) and DBP (ΔDBP), within groups was calculated and analyzed with the paired samples t-test. There were no significant differences between genders in ΔSBP and ΔDBP. Genders were therefore pooled in the analysis to increase statistical power.

The intervention effect of the main outcome variables, ΔSBP and ΔDBP, was calculated as the postintervention parameter minus the preintervention parameter. The intervention effects of the main outcome variables, between groups were compared with analysis of covariance (ANCOVA). The preintervention parameter was set as the covariate. Prior to the ANCOVA, ΔSBP and ΔDBP, were examined for normality, homogeneity of variances, collinearity, homoscedasticity and homogeneity of the regression slope. All assumptions for the ANCOVA were fulfilled for the primary analysis of the effect of long-term aerobic exercise and training

intensity on SBP and DBP, and the secondary analysis investigating the intervention effect in different subgroups, including normotensive participants without prescribed antihypertensive medication and hypertensive participants with or without prescribed antihypertensive medication. On the contrary, the assumption of homogeneity of the regression slope was not fulfilled in the observational analysis, which examines and compare the intervention effect between participants with and without prescribed antihypertensive medication. The covariate was not independent from the factor, since participants with prescribed antihypertensive medication demonstrated a higher SBP and DBP than those without. The comparisons between groups was therefore performed with ANOVA instead of ANCOVA.

The change in the main outcome variables, ΔSBP and ΔDBP, were analyzed for correlation with the change of other physiological and continuous variables with Pearson Product-Moment Correlation. Pearson's correlation coefficient (r) is provided for continuous variables with a statistical correlation to either ΔSBP or ΔDBP.

All statistical analyses are made on the intention-to-treat principle. Thus, comparisons between intervention groups and subsequent data analyses are made according to the participants assigned group affiliations, regardless of possible crossover and/or adherence to the intervention.

Descriptive data are presented as average followed by standard error, *mean ± SE*, for continuous variables and counts followed by percentages, *counts (%)*, for categorical variables if not specified otherwise. All statistical analyses were made with a selected significance level of $\alpha = 0.05$.

A priori assessment of the statistical sensitivity indicated that a total sample size of 987, with a significance level of $\alpha = 0.05$ and a statistical power of $1-\beta = 0.9$ would be sensitive enough to detect a small difference in effect size (*f = 0.113*) on SBP between intervention groups. The effect size corresponds to group difference of average 2 mm Hg, assuming the same variance in ΔSBP as in preintervention SBP. The standard deviation in preintervention SBP was ~17.7 mm Hg.[141]

All statistical analyses were made in IBM SPSS Statistics Version 24.0.0.0, whereas power analyses were made in G*Power Version 3.1.9.2.

Ethical concerns

The Generation 100 study has been conducted according to the SPIRIT Statement: Defining Standard Protocol Items for Clinical Trials.[118,142] All participants signed a written consent form and ethical approval for the Generation 100 study was granted by the Norwegian Ethical Review Board for Medical and Health Research (REK 2012/381).

At a first impression, aerobic exercise with HIIT and MICT may seem to be a substantial physical exertion for the elderly. However, the training intensity is based on individual physiological measures, HR_{peak} in the present study, and the individuals perceived exertion. The participants are not asked to exercise beyond reasonable limits for exertion. For instance a brisk walk can be adequate as vigorous activity.[143] Old age is not a contraindication to exercise, and exercise can usually be initiated safely in older adults. [144] There is a small risk associated with exercise, as heavy physical exertion can cause cardiovascular complications. The risk is highest during and immediately after heavy exertion, and particularly in people who have been habitually sedentary. Nevertheless, increasing habitual physical activity is associated with a progressively lower relative risk of incident cardiovascular complication.[145] Thus, the risk of exercise is considered to be diminutive, and the potential disadvantages are likely to be outweighed by the health benefits of regular exercise, including prevention of incident cardiovascular events, disability and cognitive impairment, even among older adults.[144]

The health risks associated with inactivity is considered to be greater than the risks associated exercise.[144] The control group is not assigned to nor provided with supervised aerobic exercise, but are in lieu advised to follow the national guidelines for physical activity, which can be considered as the 'intervention' offered to the public.

Results

Preintervention

Descriptive characteristics of the participants, including preintervention body composition, blood lipid profile, cardiorespiratory fitness and self-reported lifestyle-related parameters, are summarized in Table 1. Preintervention systolic (SBP) and diastolic (DBP) blood pressure, subsequent blood pressure categorization, heart rate at rest, and self-reported usage of antihypertensive medication are presented on in Table 2. There were no significant differences between the intervention groups, for any variable, prior to intervention (*p > 0.05*).

Table 1: Descriptive characteristics of the participants preintervention.

Preintervention:	HIIT *n = 237*	MICT *n = 236*	Control *n = 514*
Age (years)	72.3 ± 0.1	72.4 ± 0.1	72.2 ± 0.1
Height (cm)	170.8 ± 0.6	170.8 ± 0.6	170.2 ± 0.4
Body composition			
Weight (kg)	75.3 ± 0.9	75.6 ± 0.9	74.3 ± 0.5
Body mass index (BMI; kg/m^2)	25.7 ± 0.2	25.8 ± 0.2	25.6 ± 0.1
BMI category (%)			
Underweight (BMI <18.5 kg/m^2)	1 (0.4)	5 (2.1)	3 (0.6)
Normal weight (BMI 18.5-24.9 kg/m^2)	114 (48.3)	94 (39.8)	223 (43.4)
Overweight (BMI 25.0-29.9 kg/m^2)	97 (41.1)	113 (47.9)	239 (46.5)
Obese (BMI $\geq$ 30.0 kg/m^2)	24 (10.2)	24 (10.2)	49 (9.5)
Body fat (%)	29.0 ± 0.5	29.2 ± 0.5	29.5 ± 0.3
Waist circumference (cm)	93.3 ± 0.7	93.6 ± 0.7	93.3 ± 0.4
Blood lipid profile			
Triglycerides (mmol/L)	1.11 ± 0.04	1.12 ± 0.04	1.10 ± 0.02
Cholesterol (mmol/L)	5.63 ± 0.07	5.58 ± 0.07	5.71 ± 0.05
High-density lipoprotein (mmol/L)	1.72 ± 0.03	1.75 ± 0.03	1.77 ± 0.02
Low-density lipoprotein (mmol/L)	3.40 ± 0.06	3.33 ± 0.07	3.45 ± 0.04
Cardiorespiratory fitness			
Peak oxygen uptake (L/min)	2.29 ± 0.04	2.21 ± 0.04	2.20 ± 0.03
Peak oxygen uptake (L/kg/min)	30.4 ± 0.4	29.4 ± 0.4	29.8 ± 0.3
Peak heart rate (bpm)	158 ± 1.0	157 ± 1.0	158 ± 0.7
Lifestyle			
Smoker (%)	14 (6.0)	19 (8.1)	32 (6.3)
Heavy drinker× (%)	14 (6.0)	16 (6.9)	48 (9.4)
Physical activity (%)			
Low (< 1 day/week)	13 (5.5)	14 (5.9)	43 (8.4)
Moderate (1-3 days/week)	170 (71.7)	167 (70.8)	360 (70.2)
High (> 3 days/week)	54 (22.8)	55 (23.3)	110 (21.4)
Diabetes (%)	13 (5.5)	9 (3.8)	22 (4.3)

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; *n:* sample size.
Continuous variables are presented as *mean ± SE*. Categorical variables are presented as *counts (%)*.
×*Heavy drinker* is defined as > 7 and 10 > units of alcohol/week for women and men, respectively.[136]

Table 2: Descriptive characteristics of the participants blood pressure preintervention.

Preintervention:	HIIT $n = 237$	MICT $n = 236$	Control $n = 514$
SBP (mm Hg)	137 ± 1.1	137 ± 1.2	137 ± 0.8
DBP (mm Hg)	76 ± 0.6	76 ± 0.6	76 ± 0.4
Blood pressure category× (%)			
Normal blood pressure	36 (15.2)	37 (15.7)	80 (15.6)
Elevated blood pressure	33 (13.9)	33 (14.0)	78 (15.2)
Hypertension stage 1	72 (30.4)	66 (28.0)	128 (24.9)
Hypertension stage 2	96 (40.5)	100 (42.4)	228 (44.4)
Heart rate at rest (bpm)	64 ± 0.7	64 ± 0.7	64 ± 0.5
Antihypertensive medication (%)	63 (26.6)	74 (31.4)	169 (32.9)

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; *n:* sample size.
SBP: Systolic blood pressure; DBP: Diastolic blood pressure.
Continuous variables are presented as *mean ± SE*. Categorical variables are presented as *counts (%)*.
×*Normal blood pressure*: SBP < 120 mm Hg and DBP < 80 mm Hg; *Elevated blood pressure*: SBP 120-129 mm Hg and DBP < 80 mm Hg; *Hypertension stage 1*: SBP 130-139 mm Hg or DBP 80-89 mm Hg; *Hypertension Stage 2*: SBP > 140 mm Hg or DBP > 90 mm Hg.[17]

Preintervention average blood pressure (SBP/DBP) in the elderly participants was 136.8 ± 0.9 / 76.1 ± 0.3 mm Hg, and 760 of 987 elders, corresponding to 77% of the whole subsample, were classified as hypertensive prior to intervention. The participants classified as hypertensive included 690 participants with an average blood pressure above the hypertensive threshold,[17] of which 236 (34%) had prescribed antihypertensive medication. Seventy of the hypertensive participants had an average blood pressure below the threshold, but were classified as hypertensive due to self-reported usage of prescribed antihypertensive medication. About half (53%) of the participants with an average blood pressure above the hypertensive threshold, were over the threshold in SBP only, whereas 42 of 690 (6%) had an average blood pressure above the hypertensive threshold in DBP only. At baseline, the highest blood pressure reading was assessed in the left or right arm for 477 (48%) and 468 (47%) participants, respectively. Four (< 1%) participants had blood pressure assessed in the left arm only, and 3 participants (< 1%) only in the right arm. The arm with the highest SBP reading, was used for the 35 participants (4%) that indicated no interarm difference. In total, 503 (51%) of the blood pressure readings are assessed in the left arm, and 484 (49%) are assessed in the right arm.

A summary of the participants' medical history and prevalence of previous cardiovascular disease (CVD), stroke, kidney disease is reported in the appendix (Table A1).

The effect of long-term aerobic exercise and training intensity

Blood pressure

Following 3 years of aerobic exercise, the observed change in average blood pressure (SBP / DBP) was -6.4 ± 1.0 / -3.2 ± 0.5 mm Hg ($p < 0.001$) and -3.7 ± 1.0 / -1.2 ± 0.5 mm Hg ($p < 0.001$) within the two exercise intervention groups, high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT), respectively. Whereas the observed change (SBP / DBP) in the control group was -3.8 ± 0.7 / -1.6 ± 0.4 mm Hg ($p < 0.001$). Three years of aerobic exercise with HIIT reduced average blood pressure (SBP / DBP), in comparison to the control -2.8 ± 1.1 / -1.6 ± 0.6 mm Hg ($p < 0.010$), and compared to aerobic exercise with MICT, -2.7 ± 1.3 / -1.9 ± 0.7 mm Hg ($p < 0.035$). There were no significant differences between the change in the MICT group, -0.1 ± 1.1 / +0.3 ± 0.6 mm Hg ($p > 0.637$), compared to the control (Figure 3).
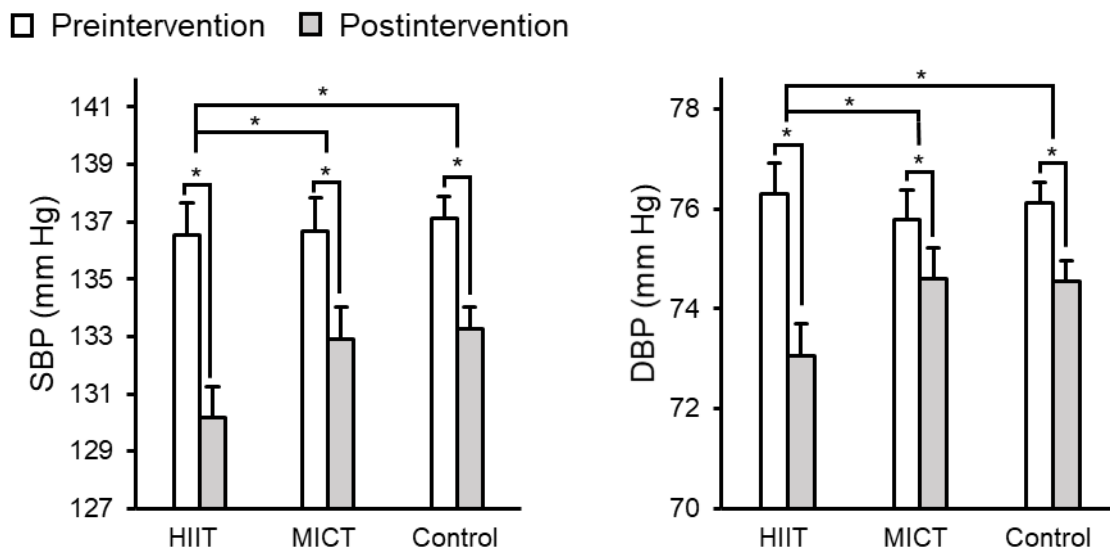
Figure 3: Average systolic (SBP) and diastolic (DBP) blood pressure pre- and postintervention 3 years of aerobic exercise with high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT), respectively, in comparison to a control. *The white and grey bars represent average blood pressure pre- and postintervention, respectively, whereas the error bars represent the standard error of the mean. * Represents a statistically significant effect or difference between groups ($p < 0.05$).*

In addition, 39% of the participants in the HIIT group demonstrated a reduction in SBP ≥ 10 mm Hg, whereas the corresponding proportion in the MICT and control group was 33% and 32%, respectively. An increase in SBP ≥ 10 mm Hg was observed in 10%, 13%, and 17% of the participants in the HIIT, MICT and control group, respectively. However, these differences between the exercise intervention groups and control group were not supported statistically ($p = 0.079$). There were no statistical differences in the proportions of participants that reduced or increased DBP between the exercise intervention groups and the control group

($p = 0.364$). Proportions corresponding to 17%, 11% and 14% of the participants in the HIIT, MICT and control group, demonstrated a reduction in DBP $\geq$ 10 mm Hg, respectively. Whereas 6% of the participants in the HIIT group and 8% of the participants in the MICT and control group demonstrated an increase in DBP $\geq$ 10 mm Hg.

A pooled analysis of the two exercise interventions and subsequent comparison with the control group, demonstrated that the observed change, after 3 years of aerobic exercise, on average blood pressure (SBP / DBP) is negligible, -1.4 $\pm$ 0.9 / -0.7 $\pm$ 0.5 mm Hg, and statistically insignificant ($p > 0.099$), when training intensity is disregarded. The average effect size in the exercise group was -5.1 $\pm$ 0.7 / -2.2 $\pm$ 0.4 mm Hg ($p < 0.001$). Average blood pressure (SBP / DBP) postintervention, was 131.5 $\pm$ 0.8 / 73.8 $\pm$ 0.5 mm Hg in the exercise intervention group and 133.3 $\pm$ 0.8 / 74.5 $\pm$ 0.42 mm Hg in the control group. Average blood pressure postintervention in the whole sample was 132.4 $\pm$ 0.5 / 74.2 $\pm$ 0.3 mm Hg.

Aerobic exercise as a nonpharmacological strategy

To prevent and treat hypertension

The effect of aerobic exercise and training intensity in normotensive elders and hypertensive elders without antihypertensive medication was assessed in 628 participants without prescribed antihypertensive medication during the whole intervention period. Average blood pressure prior to intervention categorized 113 of the normotensive participants within the blood pressure range of *normal blood pressure* and 109 participants within the range of *elevated blood pressure*. Whereas 182 and 224 hypertensive elders were categorized within the blood pressure range of *hypertension* stage *1* and *stage 2*, respectively (Table 3).

Table 3: Average blood pressure within blood pressure categories across intervention groups, prior to exercise intervention in participants without prescribed antihypertensive medication.

Preintervention:		**HIIT**	*n*	**MICT**	*n*	**Control**	*n*
Blood pressure category×							
Normal blood pressure	SBP (mm Hg)	111.6 ± 1.1	28	110.3 ± 1.3	27	111.0 ± 0.9	58
	DBP (mm Hg)	67.1 ± 1.2		67.7 ± 1.3		67.9 ± 0.8	
Elevated blood pressure	SBP (mm Hg)	125.0 ± 0.6	25	125.6 ± 0.5	26	124.7 ± 0.4	58
	DBP (mm Hg)	70.5 ± 1.3		71.3 ± 1.0		71.5 ± 0.6	
Hypertension stage 1	SBP (mm Hg)	131.8 ± 0.7	56	133.3 ± 0.8	42	133.0 ± 0.7	84
	DBP (mm Hg)	77.7 ± 0.9		75.6 ± 1.2		77.3 ± 0.7	
Hypertension stage 2	SBP (mm Hg)	150.6 ± 1.5	51	152.6 ± 1.9	58	151.0 ± 1.0	115
	DBP (mm Hg)	81.0 ± 1.3		79.5 ± 1.1		79.6 ± 0.8	

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; *n:* sample size.
SBP: Systolic blood pressure; DBP: Diastolic blood pressure.
×*Normal blood pressure*: SBP < 120 mm Hg and DBP < 80 mm Hg; *Elevated blood pressure*: SBP 120-129 mm Hg and DBP < 80 mm Hg; *Hypertension stage 1*: SBP 130-139 mm Hg or DBP 80-89 mm Hg; *Hypertension Stage 2*: SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg.[17]

The observed changes in average blood pressure within preintervention blood pressure categories across intervention groups are presented in Figure 4.
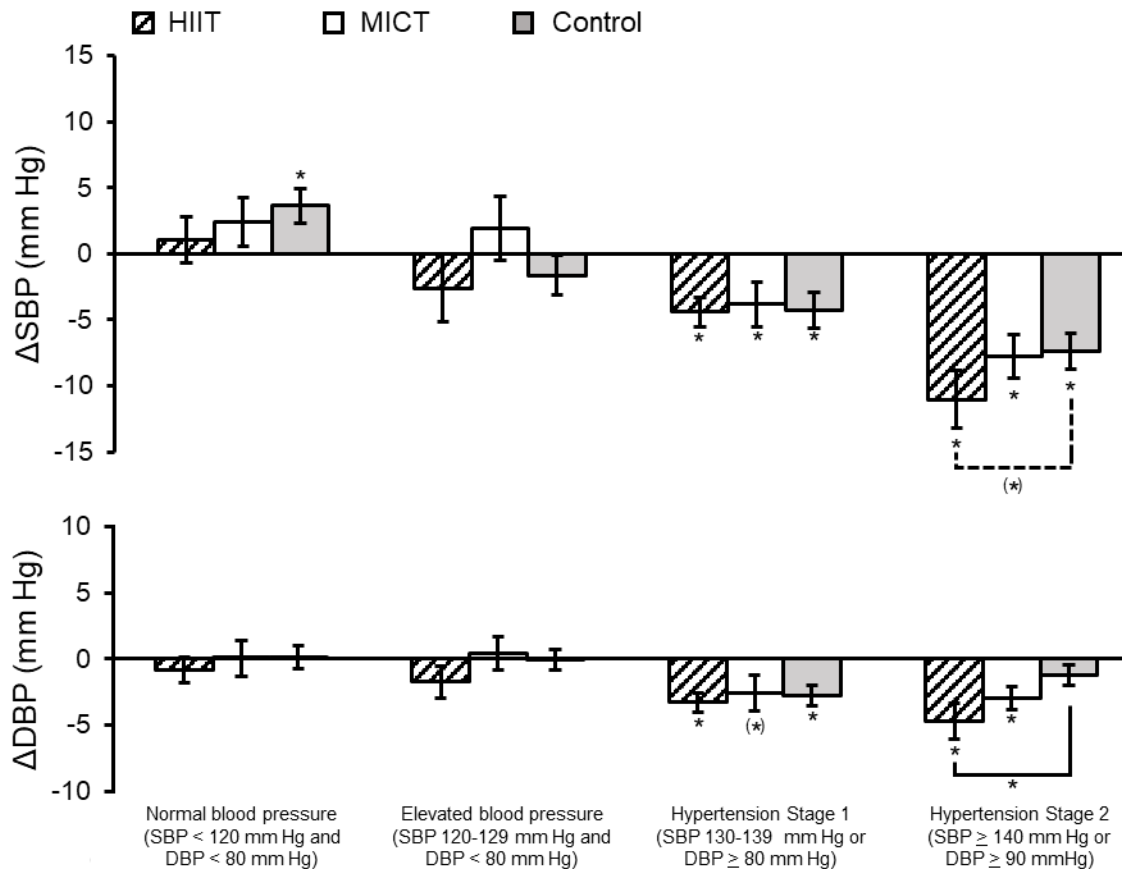
Figure 4: The observed change (Δ) in average systolic (SBP) and diastolic (DBP) blood pressure, within different blood pressure categories,[17] after 3 years of aerobic exercise with high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT), and the observed change in a contemporary control group without supervised aerobic exercise. *The striped, white and grey bars represent the average effect size in the HIIT, MICT and control group, respectively, whereas the error bars represent standard error of the mean. * Represents a statistically significant effect or difference between groups ($p < 0.05$), whereas (*) represent a tendency to a statistical difference between groups ($p < 0.100$).*

Normal blood pressure

Average SBP increased postintervention in participants with an average blood pressure within the range of *normal blood pressure* preintervention (Figure 4). However, the increase was negibale and statistically insignificant in the exercise intervention groups, $+1.0 \pm 1.8$ mm Hg ($p = 0.556$) and $+2.4 \pm 1.9$ mm Hg ($p = 0.209$) in HIIT and MICT, respectively. Whereas the observed increase in the control group was statistically significant, $+3.6 \pm 1.3$ mm Hg ($p = 0.008$). Nonetheless, the observed change in the exercise intervention groups were not statistically distinguishable from the observed change in the control group ($p > 0.276$). No change was observed in average DBP after 3 years of aerobic exercise within the exercise intervention groups ($p > 0.834$), nor in comparison to the control group ($p > 0.438$).

In conformity with the observed change in average blood pressure, a substantial portion (71%) of the 113 participants with *normal blood pressure* preintervention remained within the *normal blood pressure* category postintervention [HIIT: 21 (75%); MICT: 18 (67%); Control: 41 (71%)].

Elevated blood pressure

No change was observed in average blood pressure (SBP/DBP) in any of the exercise intervention groups after 3 years of aerobic exercise, nor in the control group in the participants within the range of *elevated blood pressure* preintervention ([Figure 4](#)). There were no statistical differences between any of the exercise intervention groups nor in comparison with the control ($p \geq 0.123$).

In contrast to the participants with *normal blood pressure* preintervention, a relatively small portion (31%) of the 109 participants with *elevated blood pressure* remained within the same blood pressure range postintervention. Thirty-two (29%) elders with *elevated blood pressure* preintervention were above the hypertensive threshold postintervention [HIIT: 5 (20%); MICT: 9 (34%): Control: 18 (31%)]. Whereas 43 participants, corresponding to 39% of the participants with *elevated blood pressure* preintervention reduced their blood pressure and were subsequently recategorized within the *normal blood pressure* range postintervention [HIIT: 13 (52%); MICT: 8 (30%); Control: 22 (38%)].

Hypertension stage 1

The observed change in average SBP, after 3 years of aerobic exercise, in participants with an average blood pressure within the range of *hypertension stage 1* preintervention, was -4.4 ± 1.1 mm Hg ($p < 0.001$) and -3.8 ± 1.7 mm Hg ($p = 0.033$) within the two exercise intervention groups, HIIT and MICT, respectively ([Figure 4](#)). Whereas the observed change in the control group was -4.4 ± 1.4 mm Hg ($p = 0.004$). Although blood pressure decreased within all intervention groups, the observed change in the exercise intervention groups were not statistically distinguishable from the observed change in the control group ($p > 0.753$). Average DBP decreased postintervention in the participants with *hypertension stage 1*, the average decrease was -3.2 ± 0.7 mm Hg ($p < 0.001$) and -2.6 ± 1.4 mm Hg ($p = 0.064$) in the exercise intervention groups, HIIT and MICT, respectively, and -2.7 ± 0.8 mm Hg ($p = 0.001$) in the control group. Thus, the observed change in DBP in the two exercise intervention groups was indifferent ($p > 0.718$) from the observed change in the control group ([Figure 4](#)).

Average blood pressure categorized 182 participants within the range of *hypertension stage 1 preintervention,* of these 84 (46%) reduced their average blood pressure below the hypertensive threshold postintervention [HIIT: 29 (50%); MIIT: 19 (45%); Control: 37 (44%)]. Whereas, average blood pressure increased significantly in 21% of the participants with *hypertension stage 1* preintervention, and consequently 57 elders were recategorized within the blood pressure category of *hypertension stage 2* [HIIT: 8 (11%); MICT: 18 (27%); 31 (24%)].

Stage 2 hypertension

Average blood pressure (SBP / DBP) decreased in the participants with *stage 2 hypertension* preintervention. The observed reduction was -11.0 ± 2.2 / -4.7 ± 1.4 mm Hg ($p \leq 0.001$) and -7.8 ± 1.7 / -2.9 ± 0.9 mm Hg ($p \leq 0.001$) within the two exercise intervention groups, HIIT and MICT, respectively. Whereas in the control group, the average reduction in SBP and DBP was, -7.3 ± 1.4 mm Hg ($p < 0.001$) and -1.2 ± 0.8 mm Hg ($p = 0.124$), respectively (Figure 4).

A statistical tendency indicates that the observed reduction in average blood pressure (SBP / DBP) in the HIIT group is of greater magnitude than the reduction observed in control, -4.0 ± 2.6 / -3.0 ± 1.3 mm Hg ($p \leq 0.098$). There were no statistical differences ($p \geq 0.129$) between the between the HIIT and MICT group, nor between the MICT and control group (Figure 4).

A considerable proportion (59%) of the 224 participants with *hypertension stage 2* preintervention remained within the same blood pressure category postintervention [HIIT: 21 (41%); MICT: 37 (64%); Control: 74 (64%)], and 58 elders (26%) were recategorized within the range of *hypertension stage 1* [HIIT: 18 (35%); MICT: 14 (24%); Control: 26 (23%)]. The remaining 15% lowered their average blood pressure under the hypertensive threshold [HIIT: 12 (24%); MICT:7 (12%); Control: 15 (13%)].

To control hypertension

The effect of long-term aerobic exercise and training intensity in elders with prescribed antihypertensive medication was assessed in the 287 participants with prescribed antihypertensive medication during the whole intervention period (Medical status). Although the participants with prescribed antihypertensive medication had a higher SBP preintervention than participants without pharmacological antihypertensive treatment (Table A3A-B). There were no differences between the intervention groups of participants with prescribed antihypertensive medication, for which average blood pressure (SBP / DBP) preintervention was 140.5 ± 1.0 / 76.9 ± 0.6 mm Hg ($p > 0.544$).

The observed change, after 3 years of aerobic exercise and training intensity, in average SBP in the participants with prescribed antihypertensive medication was -8.0 ± 2.3 mm Hg ($p = 0.001$) and -4.9 ± 2.1 mm Hg ($p = 0.022$) within the two exercise intervention groups, HIIT and MICT, respectively. A slight and statistically insignificant decrease was observed in the control group, -2.3 ± 1.5 mm Hg ($p = 0.126$). Three years of aerobic exercise with HIIT reduced average SBP in comparison to the control, -4.8 ± 2.3 mm Hg ($p = 0.043$), whereas the observed reduction in average SBP in the MICT groups was statistically insignificant in comparison with the control -2.7 ± 2.1 mm Hg ($p = 0.205$). However, the difference in the observed change in SBP was statistically insignificant ($p = 0.457$) between the two exercise interventions (Figure 5).

The observed change, after 3 years of aerobic exercise with HIIT, on average DBP in the hypertensive participants with prescribed antihypertensive medication was -4.3 ± 1.0 mm Hg ($p < 0.001$) and a small decrease in average DBP was observed in the control group, -1.5 ± 0.7 mm Hg ($p = 0.042$). There was no observed change in average DBP, -0.2 ± 1.0 mm Hg ($p = 0.872$) within the MICT group. Three years of aerobic exercise with HIIT reduced DBP in comparison to aerobic exercise with MICT, -4.5 ± 1.4 mm Hg ($p = 0.001$), as well as in comparison to the control, -2.9 ± 1.2 mm Hg ($p = 0.017$). Whereas, the observed change in average DBP -1.6 ± 1.1 mm Hg ($p = 0.145$) in the MICT group was negibale and statistically insignificant in comparison to the observed change in the control group (Figure 5).
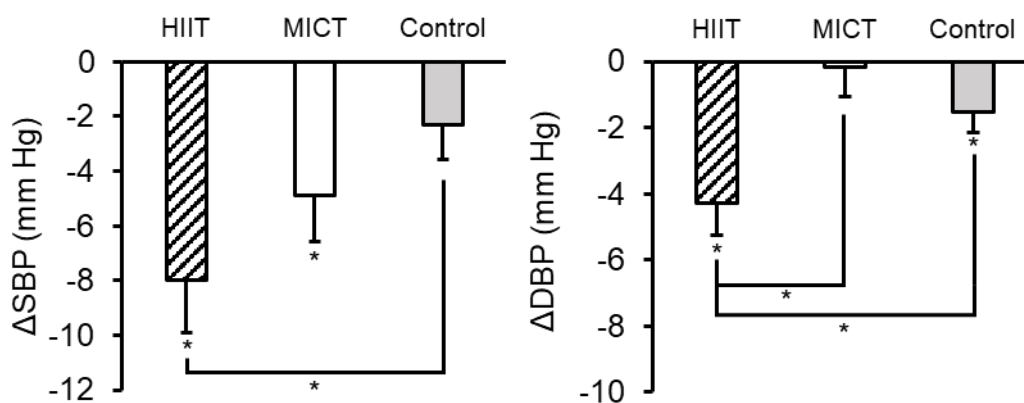
Figure 5: The observed change (Δ) in average systolic (SBP) and diastolic blood pressure (DBP) in hypertensive participants with prescribed antihypertensive medication, after of 3 years of aerobic exercise with high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT). *The bars represent average effect, whereas the error bars represent the standard error of the mean. * Represents a statistically significant effect or difference between groups ($p < 0.05$).*

The observed change after 3 years of aerobic exercise in the participants with prescribed antihypertensive medication was greatest in the participants with an average blood pressure above the hypertensive threshold, *i.e.* SBP $\geq$130 mm Hg or DBP $\geq$ 80 mm Hg, preintervention. The effect of HIIT on average SBP was especially high in participants with *hypertension stage 1* (SBP 130-139 mm Hg or DBP 80-89 mm Hg). The 11 elders in the HIIT group demonstrated a reduction in average SBP corresponding to -10.0 $\pm$ 3.4 mm Hg ($p = 0.020$), which was ~ 30 times greater than the negibale reductions observed in the 20 and 40 participants of the MICT ($p = 0.824$) and control group ($p = 0.794$), respectively. Preintervention SBP in the participants with prescribed antihypertensive medication and an average blood pressure within the blood pressure range of *hypertension stage 1*, was 133.4 $\pm$ 0.5 mm Hg and there were no differences between the intervention groups prior to intervention ($p > 0.197$). Participants with *stage 2 hypertension* (SBP $\geq$ 140 mm Hg or DBP $\geq$ 80 mm Hg) also demonstrated a great reduction in SBP. The greatest reduction in average SBP was observed in the HIIT group ($n = 33$), -13.2 $\pm$ 2.5 mm Hg ($p < 0.001$). Although the relative reduction in SBP was 10.7% and 37.5% greater in the HIIT group than in the MICT ($n = 37$) and control group ($n = 84$), respectively, the differences were not supported statistically ($p > 0.286$). The preintervention level of SBP in the participants with prescribed antihypertensive medication and an average blood pressure within the blood pressure range of *hypertension stage 2*, was 152.4 $\pm$ 1.0 mm Hg and there were no differences between the intervention groups prior to intervention ($p > 0.670$).

Average DBP was unchanged in the participants within the range of *hypertension stage 1*, regardless of group affiliation ($p > 0.509$). Whereas in the participants within the range of *hypertension stage 2*, average DBP decreased, -6.0 $\pm$ 1.2 mm Hg ($p < 0.001$), after 3 years of aerobic exercise with HIIT and a decrease in average DBP was observed in the control group as well, -4.2 $\pm$ 0.9 mm Hg ($p < 0.001$).

The observed change in average DBP, after 3 years of aerobic exercise with MICT, was negibale and statistically insignificant, ($p = 0.509$), and corresponded to 12.4% and 20.1% of the reduction observed in the HIIT and control group, respectively ($p < 0.001$).

Blood pressure category

The proportion of participants with an average blood pressure within the normal range increased in all intervention groups, especially in the HIIT group, in which the prevalence increased with 11.8 % postintervention (Table 4).The postintervention blood pressure categorization differed from the preintervention blood pressure categorization (Table 2), and the postintervention distribution differed between the intervention groups, ($p = 0.038$). The prevalence of hypertension stage decreased with 16.5 % within the HIIT group, and was approximately 12% lower in the HIIT group than in the MICT and control group postintervention (Table 4).

Table 4: Postintervention blood pressure categorization.

	HIIT	MICT	Control
Postintervention:	*n = 237*	*n = 236*	*n = 514*
***Blood pressure category*ˣ** [Counts (%)]			
Normal blood pressure	64 (27.0)	49 (20.8)	105 (25.0)
Elevated blood pressure	45 (19.0)	51 (21.6)	94 (18.3)
Hypertension stage 1	71 (30.0)	50 (21.2)	131 (24.5)
Hypertension stage 2	57 (24.1)	86 (36.4)	184 (35.8)

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; *n:* sample size.
ˣ*Normal blood pressure*: SBP < 120 mm Hg and DBP < 80 mm Hg; *Elevated blood pressure*: SBP 120-129 mm Hg and DBP < 80 mm Hg; *Hypertension stage 1*: SBP 130-139 mm Hg or DBP 80-89 mm Hg; *Hypertension Stage 2*: SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg.[17] SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Antihypertensive medication

In total, 306 (31%) of the elderly participants had prescribed antihypertensive medication prior to intervention (Table 2). Postintervention, the quantity with prescribed antihypertensive medication increased to a total of 340, corresponding to 34% of the whole sample [HIIT: 71 (30%); MICT: 80 (34%); Control: 189 (37%)]. There were no statistically significant differences in self-reported usage of antihypertensive medication between groups postintervention. The participants antihypertensive medical status is addressed in more detail in the appendix of this report (Medical status).

The potential confounding effect of pharmacological antihypertensive treatment a during the intervention period was assessed in an observational analysis, addressed in the appendix of this report (Medication).

Postintervention

Descriptive characteristics of the participants postintervention, including body composition, blood lipid profile, cardiorespiratory fitness and self-reported lifestyle-related parameters, are summarized in Table 5.

Table 5: Descriptive characteristics of the participants postintervention.

Postintervention:	HIIT $n = 237$	MICT $n = 236$	Control $n = 514$
Height (cm)	$170.4 \pm 0.6^*$	$170.5 \pm 0.6^{\,n}$	$169.8 \pm 0.4^*$
Body composition			
Weight (kg)	$74.6 \pm 0.9^*$	75.4 ± 0.9	74.3 ± 0.5
Body mass index (BMI; kg/m^2)	$25.5 \pm 0.2^*$	25.9 ± 0.2	25.7 ± 0.1
__BMI category__ (%)			
Underweight (BMI <18.5 kg/m^2)	0 (0.0)	5 (2.1)	3 (0.6)
Normal weight (BMI 18.5-24.9 kg/m^2)	120 (50.6)	89 (37.7)	215 (41.8)
Overweight (BMI 25.0-29.9 kg/m^2)	98 (41.4)	114 (48.3)	245 (47.7)
Obese (BMI $\geq$ 30.0 kg/m^2)	19 (8.0)	28 (11.9)	53 (9.9)
Body fat (%)	$29.4 \pm 0.5^*$	$30.2 \pm 0.5^*$	$30.4 \pm 0.4^*$
Waist circumference (cm)	93.0 ± 0.7	$94.3 \pm 0.7^*$	93.7 ± 0.5
Blood lipid profile			
Triglycerides (mmol/L)	$0.99 \pm 0.03^*$	$1.2 \pm 0.03^*$	$1.00 \pm 0.02^*$
Cholesterol (mmol/L)	$5.41 \pm 0.07^*$	$5.39 \pm 0.07^*$	$5.55 \pm 0.05^*$
High-density lipoprotein (mmol/L)	$1.76 \pm 0.03^*$	1.77 ± 0.03	$1.80 \pm 0.02^*$
Low-density lipoprotein (mmol/L)	3.35 ± 0.07	3.32 ± 0.06	3.45 ± 0.04
Cardiorespiratory fitness			
*Peak oxygen uptake (L/min)	2.32 ± 0.04	$2.17 \pm 0.04^*$	$2.17 \pm 0.03^*$
*Peak oxygen uptake (ml/kg/min)	31.2 ± 0.5	$29.0 \pm 0.5^*$	$29.3 \pm 0.3^*$
Peak heart rate (bpm)	$155 \pm 1.1^*$	$152 \pm 1.1^*$	$152 \pm 0.8^*$
Heart rate at rest (bpm)	$62 \pm 0.7^*$	62 ± 0.7	64 ± 0.5
Lifestyle			
Smoker (%)	12 (5.1)	16 (6.9)	28 (5.5)
Heavy drinker$^{\times}$ (%)	19 (8.2)	11 (4.8)	42 (8.3)
__Physical activity__ (%)			
Low (< 1 day/week)	4 (1.7)	7 (2.9)	28 (5.5)
Moderate (1-3 days/week)	164 (69.2)	157 (67.1)	312 (61.4)
High (> 3 days/week)	69 (29.1)	70 (29.9)	158 (33.1)

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; *n:* sample size.
Continuous variables are presented as *mean ± SE*. Categorical variables are presented as *counts (%)*.
$^{\times}$*Heavy drinker* is defined as > 7 and 10 > units of alcohol/week for women and men, respectively.[136]
$^{\,n}$ The change *within* the group is statistically *significant* ($p < 0.05$).
* The difference *between* one or more groups is statistically *significant* ($p < 0.05$).

Several physiological variables changed within the intervention groups during the 3-year intervention period ($p < 0.05$), including height, weight, body mass index (BMI), body fat percentage, waist circumference, peak oxygen uptake (VO_{2peak}), blood triglycerides (TGs), cholesterol, and high-density lipoprotein (HDL). Nevertheless, only four variables, BMI

category, the two measures of VO_{2peak} and self-reported physical activity, demonstrated statistical differences ($p < 0.05$) between the intervention groups postintervention. (Table 5).

Postintervention, the prevalence of obesity was slightly higher in the MICT group than in the HIIT and control group, and the proportion of participants within the normal weight range was higher in the HIIT group than in the MICT and control group. The prevalence of overweight increased in the MICT and control group, consequently, the prevalence was slightly lower in the HIIT group than in the MICT and control group postintervention (Table 5).

The two measures of VO_{2peak} increased slightly in in the HIIT group, although the increase was not supported statistically, whereas the slight decrease in VO_{2peak} in the MICT and control group was statistically significant. Consequently, VO_{2peak} was higher in the HIIT group than in the MICT and control group postintervention (Table 5).

Self-reported physical activity postintervention was similar in the two exercise intervention groups. Whereas, the distribution between self-reported low, moderate and high amount of weekly physical activity within the control group was significantly different from the distribution within the two exercise intervention groups (Table 5). Nevertheless, all intervention groups reported a similar change in weekly physical activity, a considerable amount, ~ 71%, reported the same amount preintervention and postintervention, whereas ~ 9% reported a decrease in weekly physical activity, and ~20 % reported an increase in the amount of weekly physical activity ($p = 0.219$).

The other self-reported lifestyle-related variables, the number of smokers and heavy drinkers, were statistically indifferent between intervention groups postintervention, and there were no statistical differences between intervention groups in the proportion of participants that altered their smoking habits and alcohol consumption during the intervention period ($p > 0.05$).

A statistically positive correlation ($p < 0.05$), was found between ΔSBP and the change in weight ($r = 0.110$), BMI ($r = 0.126$) and blood serum HDL ($r = 0.085$). Whereas ΔDBP demonstrated to be positively correlated with age ($r = 0.110$) and the change in weight ($r = 0.090$), BMI ($r = 0.110$), blood serum TGs ($r = 0.109$) and total cholesterol ($r = 0.069$) and negatively correlated with the two measures of VO_{2peak}, not adjusted for body weight ($r = -0.077$) and adjusted for body weight ($r = -0.114$). Although a statistical correlation exists, the correlation coefficient is relatively small, and less than 2% of the variance in ΔSBP and ΔDBP can be explained by any of the covariates.

Adherence

Self-reported adherence to the prescribed exercise interventions was 54.6 % (125 of 229) and 78.6% (180 of 229) for the HIIT and MICT group, respectively. Self-reported adherence to the national recommendation of 30 minutes of daily physical activity, in the control group was 88.8% (435 of 490) at the 3-year follow-up. Prior to exercise intervention, the self-reported adherence to the national recommendations for physical activity was 73.6% (723 of 948) in the whole study sample.

Discussion

The primary finding of the present study is that the effect of long-term aerobic exercise on average blood pressure in elders appears to be intensity dependent. In the present study, elders were assigned to supervised aerobic exercise, either high-intensity interval training (HIIT) or moderate-intensity continuous (MICT), or a control group without supervised aerobic exercise. After 3 years, average blood pressure was significantly lower both within the exercise intervention groups, HIIT and MICT, and the control group. Analyses made on the intend-to-treat principle, demonstrated that 3 years of aerobic exercise with HIIT provide a superior reduction in average blood pressure in comparison to the control and compared to aerobic exercise with MICT. Whereas 3 years of aerobic exercise with MICT did not reduce average blood pressure in comparison to the control. Secondary finding suggests that long-term aerobic exercise, HIIT and MICT, does not reduce average blood pressure in normotensive elders. Nonetheless, aerobic exercise with HIIT and MICT seems to prevent the age-associated rise in blood pressure to similar extents and thus, appears as equal nonpharmacological strategies to prevent hypertension in normotensive elders. On the contrary, long-term aerobic exercise with HIIT and MICT significantly reduce average blood pressure in hypertensive elders, and aerobic exercise with HIIT appears to be the nonpharmacological strategy with superior potential to treat and control hypertension in the elderly.

The effect of long-term aerobic exercise and training intensity

The present study demonstrates that effect of long-term aerobic exercise, on average blood pressure was negligible in comparison to the control, when the effect of training intensity was disregarded. However, the results indicate that aerobic exercise with HIIT provided greater reduction in average blood pressure than aerobic exercise with MICT and the control. Consequently, suggesting that the potential blood pressure reducing effect of long-term aerobic exercise in elders is intensity dependent. Aerobic exercise with HIIT reduced average systolic blood pressure (SBP), with additionally ~3 mm Hg in comparison to aerobic exercise with MICT and the control. The difference between groups is relatively small, at least in comparison to the effect size reported in previous randomized controlled trials (RCTs).[90,113] The relatively small difference in average SBP is a probable consequence of the considerably longer intervention period, as RCTs with a longer intervention periods are characterized by unsupervised exercise sessions and lower adherence. This in turn also explain why RCTs with an intervention period longer than six months generally demonstrate a smaller reduction in average blood pressure than RCTs with a shorter intervention period.[86] Nevertheless, a

systematic review on primary strategies to prevent hypertension, reasoned that even small decrements in the distribution of SBP are likely to result in a substantial reduction in the burden of diseases related to hypertension. A reduction in average SBP corresponding to 3 mm Hg on the populational level have been associated with a reduction in the relative burden of fatal stroke (-8%) and coronary heart disease (-5%), as well as reduced all-cause mortality (-4%).[146]

In the middle-aged and older adults, SBP is considered a much more potent cardiovascular risk factor than diastolic blood pressure (DBP).[37,41,42] Observational studies have demonstrated that DBP is negatively correlated with cardiovascular risk in older adults, > 60 years of age.[9,42] Interestingly, the present study found a negative correlation between the change in DBP and the change in cardiorespiratory fitness (CRF), expressed as the change in peak oxygen uptake (VO_{2peak}). Peak oxygen uptake reflects the body's peak capacity of oxygen uptake and utilization; from the initial air inspiration and oxygen diffusion over the alveolocapillary membrane of the lungs, to the binding of oxygen to hemoglobin in the blood and subsequent transport through the cardiovascular system to the muscles, were oxygen diffuse over the muscle cell membrane and is lastly utilized by enzymes in the mitochondria of the cell in the final steps of oxygen consumption. Peak oxygen uptake is considered to be a strong and independent cardiovascular risk factor, and an improvement in VO_{2peak} is associated with a lower cardiovascular risk and all-cause mortality, regardless of gender, age and other cardiovascular risk factors.[147] A negative correlation between the change in VO_{2peak} and the change DBP indicate that an increase in VO_{2peak} is associated with a simultaneous decrease in DBP and vice versa. Thus, as an increase in VO_{2peak} is associated with lower cardiovascular risk and all-cause mortality, the results might suggest that an exercise induced decrease in DBP is positively associated with a reduced risk of incident cardiovascular event and all-cause mortality. This is merely a speculation and a validation of the association between achieved DBP and actual cardiovascular risk is needed to confirm the suggested relationship.

As SBP and DBP combined are more informative than either alone for predicting cardiovascular risk from a single blood pressure measurement, [10,44] thus SBP and DBP should be evaluated together. Three years of aerobic exercise with HIIT reduced average SBP and DBP to the same relative extent ~ 5%. Whereas aerobic exercise with MICT reduced SBP, ~3%, to somewhat greater extent than DBP, ~2%. The relative reduction in average blood pressure in the MICT group was equivalent to that of the control. Previously, RCTs that have evaluated the effect of aerobic exercise with HIIT and MICT, with the same definition and similar method as the present study, have reported contradictory findings. The other RCTs have been of a

considerable shorter duration, 12 weeks, and with relatively small sample sizes, n = 22-38, which might limit the comparability with the present study. One trial, in older adults, reported no change in DBP with either HIIT or MICT.[114] Whereas another trial, in young and middle-aged adults, reported that aerobic exercise with HIIT significantly reduced DBP with 9% in comparison to the reduction of 7% observed in the MICT group.[148] Both studies reported that neither exercise intervention affected average SBP.[114,148] A third trial, also in young and middle-aged adults, reported that both exercise interventions reduced SBP and DBP with ~10 mm Hg and ~6 mm Hg, respectively. However, the reduction in SBP was statistically significant in both exercise intervention groups, whereas the reduction in DBP was only supported statistically in the HIIT group.[149] A more comprehensive trial, in the same age group, investigated the effect of the same exercise interventions on 24-hour ambulatory blood pressure, and demonstrated that HIIT significantly reduced ambulatory SBP, ~12.0 mm Hg, in comparison to MICT, ~ 4.5 mm Hg. In addition, aerobic exercise with HIIT reduced ambulatory DBP, ~ 8.0 mm Hg, to a greater extent than aerobic exercise with MICT, ~3.5 mm Hg, but the difference was not supported statistically.[90]

Aerobic exercise as a nonpharmacological strategy

To prevent hypertension

The results indicate that 3 years of aerobic exercise might prevent the age-associated rise in SBP in elders with an average blood pressure within the range of *normal blood pressure*. However, supervised aerobic exercise, regardless of training intensity, did not lower the progressive development towards hypertension in comparison to the unsupervised control. Thus, the potential effect of aerobic exercise on blood pressure within the range of *normal blood pressure* seems to be independent of training intensity.

Three years of aerobic exercise prescribed on an intend-to-treat principle did not affect average blood pressure, regardless of training intensity, in elders with an average blood pressure within the range of *elevated blood pressure* prior to intervention. However, a relatively larger proportion of the elders in the HIIT group (52%) were recategorized within the *normal blood pressure* range postintervention, in comparison to the corresponding proportions in the MICT and control group (~34%). In addition, a smaller proportion of the elders in the HIIT group (20%) was above the hypertensive threshold postintervention, in comparison to the corresponding proportions in the MICT and control group (~32%). The preferable distribution of postintervention blood pressure recategorization in the HIIT group, indicates that long-term

aerobic exercise with HIIT might lower blood pressure and subsequently prevent the development of hypertension on the individual level, at least in comparison with aerobic exercise with MICT and the unsupervised control. Thus, aerobic exercise with HIIT may be a superior nonpharmacological strategy to prevent hypertension on the individual level, but the benefits seem to be limited to the individual level as none of the exercise interventions lower blood pressure on the populational level.

Interestingly, several of the previous RCTs that have assessed the effect of aerobic exercise in older adults and demonstrated that aerobic exercise does not reduce average blood pressure, included a substantial portion of normotensive older adults.[100-103,114] There is nothing in the results of the present study suggest that normotensive elders cannot gain other cardioprotective benefits of aerobic exercise, although it has not been addressed in detail.

To treat hypertension

The results of the present study indicate that the benefits of aerobic exercise as nonpharmacological strategy to treat hypertension, might be restricted to the elders with an average blood pressure within the range of *hypertension stage 2*. In the present study, aerobic exercise with HIIT reduced average SBP and DBP, with 4 mm Hg and 3 mm Hg, respectively, in comparison to the control in elders with *hypertension stage 2*. In addition, the proportion of the participants with *hypertension stage 2* that demonstrated a significant decrease in blood pressure, and were recategorized within the range of a lower blood pressure category postintervention, was considerable larger in the HIIT group (59%) than in the MICT and control group (36%). In contrast, long-term aerobic exercise with HIIT did not reduce average blood pressure in comparison to the control, in elders with *hypertension stage 1*. However, the proportion of the participants with *hypertension stage 1* that demonstrated a significant increase in blood pressure and were recategorized within the range *hypertension stage 2*, was considerable smaller in the HIIT group (11%) than in the MICT and control group (~26%). Therefore, aerobic exercise with HIIT may not be a superior nonpharmacological strategy to treat *hypertension stage 1*, but effectively prevent the progression of *hypertension stage 1* to *hypertension stage 2*. At least in comparison to aerobic exercise with MICT and the control.

Long-term aerobic exercise with MICT did not reduce average blood pressure in comparison to the control, in elders with *hypertension stage 1* or *2*. Thus, the long-term effect of aerobic exercise on average blood pressure in hypertensive elders seems to be intensity dependent.

To control hypertension

The results of the present study indicate that long-term aerobic exercise with HIIT reduce average SBP and DBP with approximaterly 5 mm Hg and 3 mm Hg in comparison to the control, respectibely, in hypertensive elders with prescribed antihypertensive medicaiton. Whereas long-term aerobic exercise with MICT does not reduce average blood pressure in comparison with the unsupervised control. Thus, the effect of long-term aerobic blood pressure in hypertensive elders with presciribed antihypertensive medication seems to be intensity-dependent.

Previous RCTs that have assesed the effect of aerobic exercise on blood pressure in older adults, demonstrated three common metodilogical shortcomings regarding antihypertensive medication. Firstly, RCTs have unadequatly reported whether the particpants used antihypertensive medication during the intervention period.[100-103] Seconly, have not included usage of antihypertensive medication as a variable in the randomization process and subsequently ended up with an uneven distirbution between the intervention groups.[104,111] Thirdly, some RCTs have simply limited their inclusion to participants without presciribed blood pressure medication,[108-110,112,113] and consequently excluded a large portion of the target population of hypertensive older adults.[150] Elders with antihypertensive medication have been underrepresented in the research examining the effect of aerobic exercise on blood pressure. Thus, the present study may contribute with novel information regarding aerobic exercise as a nonpharmacological strategy to contol hypertension. The findings of the present study indicate that long-term aerobic exercise with HIIT is the superior nonpharmacological strategy to improve the control rate of hypertension in hypertenive elders with prescribed blood pressure medication.

The active elders

The elders included in the present study are described in detail with the overall elderly population in Norway, in regards of, average blood pressure, prevalence of hypertension and self-reported physical activity in the appendix of this report. The elders included in the present study are considered to represent the active elders, physically capable of performing aerobic exercise.

If the sample of the present study is considered to represent the active elders, and the exercise interventions, HIIT and MICT, are thought to represent supervised aerobic exercise with different training intensities. It is relevant to question whether the change in average blood

pressure in the control group accurately represent the concurrent change in the general elderly population. In the control group, blood pressure was expected to stagnate at the initial level, perhaps with a slight increase in SBP and decrease in DBP, which are the general trends associated with the progression of age.[9,22] Conversely, average SBP and DBP decreased in the control group, with 3% and 2%, respectively. One possible explanation of the observed reduction is the high adherence to the national guidelines regarding physical activity as well as the high self-reported physical activity in the control group. Thirty minutes of daily physical activity has a well-documented lowering effect on blood pressure,[16] and an accumulation of physical activity increase the blood pressure reduction even further.[151] Participation in an exercise intervention study, such as the Generation 100 study, probably enhance motivation and increase awareness of the benefits of physical activity. This in turn provide a possible explanation of the high self-reported physical activity and high adherence to the national guidelines regarding physical activity in the control group. Indeed, the control group reported a similar change in weekly physical activity as the exercise intervention group. Approximately 20% of the participating elders reported an increase in their weekly physical activity level and about 71% of the elders reported the same physical activity level pre- and postintervention. In addition, the self-reported adherence to the national recommendation regarding physical activity in the control group increased with ~15%. Furthermore, the self-reported physical activity in the control group at the 3-year follow-up of the present study, was higher than the self-reported physical activity in the general elderly population reported in connection to the invitation to the Generation 100 study.[118] Taken together, this suggest that the control group does not represent the general elderly population. The comparison between the exercise intervention groups, HIIT and MICT, and the control group, consequently compare the effect of long-term supervised aerobic exercise of different training intensities with unsupervised physical activity, on average blood pressure in active elders. This interpretation of the results of the present study indicate that 3 years of aerobic exercise of different training intensity, have the potential to reduce average blood pressure on the populational level. Average blood pressure (SBP/DBP) in the whole subsample decreased from ~137/76 mm Hg preintervention to ~132/74 mm Hg postintervention.

Prognosis of the cardiovascular risk

The results of the present study indicate that long-term aerobic exercise with different training intensity, lower blood pressure and associated cardiovascular risk status. As a vast number of clinical trials have demonstrated that pharmacological antihypertensive treatment lower blood

pressure and reduces the risk of cardiovascular and cerebrovascular events and associated mortality.[56-63] Thus, the results are in an alignment with a reduced risk of incident fatal and nonfatal cardiovascular and cerebrovascular disease. Nevertheless, the actual cardiovascular and cerebrovascular risk as well as all-cause mortality and corresponding association with high blood pressure has not been assessed. Nor has the change in blood pressure been validated with a corresponding change in morbidity and mortality. The aim of the present study was *not* to determine the effect of long-term aerobic exercise on overall morbidity and mortality, as that objective falls within the frame of the main study. In lieu the aim of the present study was to evaluate the effect of 3 years of aerobic exercise and training intensity on blood pressure. Continued collaboration within the Generation 100 study may provide essential and highly warranted information on the effect of aerobic exercise on average blood pressure and its association to the burden of cardio- and cerebrovascular morbidity and mortality in the elderly population. Noteworthy, the most recent guidelines on prevention, detection, evaluation, and management of high blood pressure in adults, by the American College of Cardiology (ACC) and American Heart Association (AHA), states that nonpharmacological interventions, reduce blood pressure and interrupt the progression towards hypertension, but clinical trials have not demonstrated that an exercise induced reduction in blood pressure is associated with a decreased cardio- and cerebrovascular risk.[17]

Antihypertensive pharmacotheraphy

In the present study, the potential confounding effect of pharmacological antihypertensive treatment during the intervention period is considered negligible, as demonstrated in the observational analysis in the appendix of this report. Firstly, it was relatively small proportion of the participating elders that altered their antihypertensive medical status, and the elders with altered antihypertensive medical status were similarly distributed between the intervention groups. Indeed, removing the elders with an altered antihypertensive medical status from the primary analysis, had no effect on the results. Secondly, the observed reduction in average blood pressure was similar in elders with and without prescribed antihypertensive medication, within all intervention groups. Thirdly, the main differences were explained by the prevailing circumstances. As the elders with prescribed blood pressure medication had a higher average blood pressure preintervention, and therefore had the potential to reduced blood pressure to a greater extent.[92]

In the control group, elders without prescribed antihypertensive medication demonstrated a greater reduction in average SBP than elders with prescribed antihypertensive medication. This

indicates that the observed reduction in average SBP, in the control group, is not a consequence of an excessive usage of antihypertensive medication. Thus, supporting the idea that a nonpharmacological intervention, underlies the observed reduction in SBP in the control group.

In the present study, the preintervention proportion of elders with prescribed antihypertensive medication was lower than the proportions reported by the national statistical institute of Norway,[121] and contemporary records from the Norwegian Prescription Database.[122] Interestingly, previous cross-sectional analyses, in young and middle-aged men, have demonstrated that the need of antihypertensive medication is reduced in relation to increased physical activity level and physical fitness.[152,153] In the present study, the proportion of elders with prescribed blood pressure medication increased within all intervention groups. There were only slight and statistically insignificant differences between the intervention groups in self-reported usage of prescribed antihypertensive medication postintervention. However, a slight alteration in the individual usage of antihypertensive medication was expected during the intervention period, because of the longevity of the study. Approximately, 5% of the participating elders initiated a novel antihypertensive treatment, whereas 2% withdrew their initial antihypertensive medication, as reported in the appendix of this report. Aerobic exercise seems to have a considerable potential as a nonpharmacological strategy to prevent, treat and control hypertension in the elderly. It remains to be investigate how aerobic exercise affect pharmacological therapy, in terms the need of antihypertensive medication, number of antihypertensive agents and subsequent medical dosage.

Antihypertensive effects

The present study has focused on the total effect of aerobic exercise and training intensity on blood pressure. Thus, there has been no differentiation between direct effect of aerobic exercise on blood pressure and the indirect effect through other cardiovascular risk factors. The effect through other cardiovascular risk factors has not been assessed in detail, although the data suggest that there might be indirect effects via simultaneous changes in body weight, blood lipid profile and VO_{2peak}.

The implementation of aerobic exercise

The limitation of a public health strategy promoting aerobic exercise and physical activity, as with all treatments, is the implementation and maintenance of adherence. An important aspect of maintaining individual adherence to a treatment is knowledge on what to expect from a certain intervention over time. In the present study, the adherence to the exercise interventions

were relatively high, and thus provides information on what to expect from a long-term implementation of aerobic exercise on average blood pressure on the populational level. Analyzing the data of the present study per protocol, would contribute to an estimation of the individual benefits, in terms of blood pressure reduction, to be gained from long-term adherence to aerobic exercise.

The exercise intervention groups differentiated considerably in self-reported adherence to the prescribed exercise programs. The HIIT group had a significantly lower adherence and a higher drop-out rate than the MICT group and the control group. The importance of comparing results analysed on the intend-to-treat principle and per protocol was demonstrated in another RCT, which prescribed long-term aerobic exercise of high and moderate training intensiy to middle-aged (40-65 years of age) sedentary women. The results analysed on the intend-to-treat principle, demonstrated that aerobic exercise, with moderate-intensity training, but not high-intensity training, reduced and sustained resting SBP and DBP at a lower level after 18 months.[154] Whereas the subsequent adherence analysis demonstrated that the observed reduction was predomenately associated with a higher adharance in the exercise intervention group with moderate-intenstiy training.[155] Thus, probable adharance and drop-out rate should be taken into consideration when prescribing or recommending aerobic exercise as a nonpharmacological strategy to prevent, treat and control hypertension in the elderly. In other words, the potential gains of aerobic exercise with a certain training intensity, in terms of a greater blood pressure reduction, should be weighed against the probability of maintained adherence in the long-term perspective.

Interestingly, in the present study the exercise intervention with the lowest adherence *i.e.* aerobic exercise with HIIT, demonstrated the greatest reduction in average blood pressure. This in turn suggests that the individual benefits of aerobic exercise with HIIT might be substantially greater on the individual when analyzed per protocol.

The present study demonstrated that long-term aerobic exercise with MICT or unsupervised physical activity, significantly reduce blood pressure, and can be maintained with relatively high adherence as long as 3 years in the elderly. In addition, the present study indicates that an implementation of more vigorous physical activity, in a mere fraction of the elderly population, would improve the potential of aerobic exercise as a nonpharmacological strategy to prevent, treat and control hypertension in the elderly.

In addition, the findings of the present study indicate that clinical follow-ups may improve long-term adherence to a recommended lifestyle modification. Increased adherence to aerobic

exercise in the overall population, would probably enhance the effect of aerobic exercise and training intensity on average blood pressure. Thus, public health strategies that report individual progression and provide physiological feedback outside the office of the general practitioner, may have a considerable potential to reduce average blood pressure on the populational level and lessen the associated burden of cardio- and cerebrovascular disease.

Strength and limitations

The elderly population

A major strength of the present study is the population-based study design, including a highly diverse sample, with a wide distribution of average blood pressure, and both healthy elders and elders with comorbidities.[118] The population-based sample of the present study contained normotensive and hypertensive elders with and without prescribed antihypertensive medication as well as elders with and without a previous history of diabetes, cancer, cardiovascular disease, stroke or kidney disease.

In 2012, the Generation 100 study, *i.e.* the main study of the present substudy, included approximately one fifth (22.5%) of the elderly population, 70-77 years of age, in Trondheim, Norway. As the elders included in the Generation 100 study, volunteered for participation in an exercise intervention study, it is possible that a selection bias favoring physically active elders or at least elders with a certain interest of exercise has influenced the sample included in the Generation 100 study, and subsequently the subsample in the present study as well. In addition, the sample was limited to elders physically capable of performing the supervised exercise programs, due to safety concerns of exercise with physical disabilities. Indeed, the elders participating in the Generation 100 study were generally more active, had higher educational level and had better health than the nonparticipating elders.[118] The sample of the present study is therefore regarded as a representation of the active elders, that are physically capable of performing regular aerobic exercise. Although, this might limit extrapolation to the overall elderly population, the sample can be considered to represent the proportion of the elderly population, in which aerobic exercise can be safely implemented and thus recommended as an initial nonpharmacological strategy to prevent, treat hypertension or supplement pharmacological therapy to control hypertension.

An extrapolation of the results of the present study, might suggest that a in a less active elderly population, with a higher initial level of average blood pressure, supervised aerobic exercise may provide an even greater reduction in average blood pressure. As in the present study, a

higher initial level of blood pressure was consistently associated with a greater reduction in SBP and DBP, regardless of intervention.

Measuring blood pressure and assessing cardiovascular risk

A possible limitation of the present study is the reliance on conventional blood pressure readings. Ambulatory blood pressure is, in comparison with the conventional blood pressure assessment in the health care setting, the superior predictor of cardiovascular risk in older adults.[156] The method not only provide estimates of average blood pressure over the entire monitoring period and blood pressure variability, in addition, the automated readings are not influenced by observer bias and thus minimize the white-coat-effect.[157] The white-coat-effect is a transient rise in blood pressure during a clinical visit, which consequently leads to an inaccurate and overestimated blood pressure reading in the health care setting. The white-coat-effect is influenced by age, gender and current smoking status,[158] and is particularly prevalent in older adults.[159] White-coat-hypertension, in comparison to sustained hypertension, is not associated with an increased cardiovascular risk.[160] Consequently, one limitation of the present study is that white-coat-hypertension has not been properly screened for. In order to gain equivalent information from conventional blood pressure measurements, the measurements have to be standardized and repeated as frequent intervals, preferably at separate occasions.[161] Most contemporary health studies assessing blood pressure rely on an average blood pressure measurement obtained at a single occasion.[132] This probably result in an overestimated prevalence of hypertension compared to what would be found using the average of at least two readings taken at least two separate occasions,[162] as recommended in present and previous clinical guidelines on prevention, detection, evaluation, and management of high blood pressure.[16-19] Consequently, the method of the present study does not fulfill the criteria for a clinical diagnosis of hypertension or blood pressure categorization.[17] Nonetheless, the present method of blood pressure assessment is commonly used in national health surveys,[27,130,131] and blood pressure assessed with analogous methods have been associated with cardiovascular risk on the population level.[10] The aim of the present study is not to report the present prevalence of hypertension, but to report the effect of long-term aerobic exercise and training intensity on average blood pressure. The obtained data does *not* suggest a physiological rationale for a substantial decrease in the prevalence of white-coat-effect. On the contrary, as the prevalence of white-coat-hypertension increase with age,[158] it is more likely that a the prevalence of white-coat-hypertension has increased during the intervention period. This would consequently lead to an underestimation of the potential blood pressure reducing effect of aerobic exercise within

the intervention groups. Whereas the observed differences between the intervention groups would still be relatively accurate. However, the obtained data does *not* indicate that there has been a considerable change in the prevalence of white-coat-hypertension.

Antihypertensive pharmacotherapy

A major strength of the present study was the predetermined requirement of a complete record of the antihypertensive medical status of the participating elders. Consequently, elders with prescribed antihypertensive medication could be included and represented in the present study. In addition, the potential confounding effect of pharmacological antihypertensive treatment during the intervention period could be adequately controlled for. However, the methodological strengths are not without entailed limitations as there is no data available on the type of antihypertensive medication, number of antihypertensive agents and subsequent medical dosage have not been reported. Thus, it remains unknown whether the elderly participants have altered their antihypertensive medication, number of antihypertensive agents or medical dosage during the intervention period. Additionally, medications with an antihypertensive effect can be prescribed for other reasons than treatment of hypertension, and might therefore not have been reported as antihypertensive medication. One previous RCT, in older adults ≥ 60 years of age, demonstrated that beta-blockers do not impair the exercise induced reduction in ambulatory blood pressure in hypertensive elder adults.[107] Whether the same can be said regarding all antihypertensive medication remains to investigated.

Antihypertensive effects

Although known and plausible confounders, *e.g.* age, body weight and body composition, smoking status, alcohol consumption, usage of antihypertensive pharmacotherapy and physical activity, were controlled for in the analyses of the present study. There might still be some residual confounding. Unfortunately, there was no available data on diet and salt intake during, nor the development of novel comorbidities during the intervention period. Although the potential residual confounding can be considered as relatively small within this large RCT, it is not possible to completely preclude all confounding interferences. Nevertheless, it is reasonable to assume that the likelihood that any other interferences, besides the prescribed intervention of aerobic exercise and physical activity, have introduced substantial effects on the average blood pressure in the 237, 236 and 514 elders of the HIIT, MICT and control group, respectively.

The elderly participants with an altered antihypertensive medical status during the intervention period were removed from the secondary analyses, to avoid a potential confounding effect in smaller sample sizes. The sample sizes in the intervention groups within specific blood pressure

categories were relatively small. However, the assumption for an analysis of covariance were fulfilled as the intervention groups demonstrated similar variance and had the same preintervention level of average blood pressure.

The use of clinical guidelines

The present study used the blood pressure categorization provided in the most recent ACC/AHA guidelines on prevention, detection, evaluation, and management of high blood pressure in adults,[17] instead of the definitions provided in the corresponding European guidelines for management of arterial hypertension by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC).[34] The focus has been on the 2017 ACC/AHA guidelines, rather than the 2013 ESH/ESC guidelines, because the ACC/AHA guidelines provide a summary of more recent research and the recommendations are subsequently more up to date. The ACC/AHA guidelines derivate from observational studies investigating SBP/DBP and the associated cardiovascular risk, as well as RCTs examining the effect of different antihypertensive treatments, including different pharmacological approaches to prevent the development of cardiovascular disease, and nonpharmacological interventions to lower blood pressure.[17] The ACC/AHA and ESH/ESC guidelines both recommend that blood pressure should be categorized in order to facilitate decision making in the clinical setting and in public strategies aiming to improve health in the overall population.[17,34] The ACC/AHA blood pressure categories, *normal blood pressure*, *elevated blood pressure* and *hypertension stage 1*, based on SBP solely correspond to *optimal blood pressure*, *normal blood pressure* and *high normal blood pressure*, respectively, in the ESH/ESC guidelines. The ACC/AHA guidelines define *hypertension stage 2* as SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg,[17] which correspond to hypertension grade 1-3 in the ESH/ESC guidelines. [34] The national guidelines of Norway are based on the ESH/ESC recommendations,[140] which might be a possible explanation to why a relatively large proportion (68%) of the elderly participants with *hypertension stage 1* were without antihypertensive pharmacotherapy during the intervention portion. The corresponding proportion of the elderly participants with *hypertension stage 2* was considerably smaller (53%). The two guidelines differentiate in blood pressure categorization and implement somewhat different approaches to prevent, treat and control hypertension. Nonetheless, the general concept of a continuous, consistent and independent association between blood pressure and cardiovascular risk is well recognized in both guidelines. Using the blood pressure categorization provided by the ACC/AHA guidelines does not introduce any

physiological consequences in comparison to the ESH/ESC guidelines, as the sole purpose of the blood pressure categories are to facilitate decision making.

Summary

In summary the results of the present study indicate that aerobic exercise of different training intensities, HIIT and MICT lower average blood pressure in elders at the populational level. After 3 years, average blood pressure was significantly lower within the exercise intervention groups, HIIT and MICT, and the control group. Three years of aerobic exercise with HIIT reduced average blood pressure in comparison to aerobic exercise with MICT and control without supervised exercise. Thus, the effect of long-term aerobic exercise in the elderly population appears to be intensity dependent. In addition, aerobic exercise with HIIT, seems to be the superior nonpharmacologic strategy to treat and control hypertension in elders, at least in comparison to aerobic exercise with MICT and the control. Aerobic exercise with HIIT, demonstrated a promising potential to treat *hypertension stage 2* and prevent the progression of *hypertension stage 1* to *stage 2* in hypertensive elders without prescribed antihypertensive mediation. In addition, long-term aerobic exercise with HIIT may also provide a superior improvement in the control rate of hypertension in hypertensive elders with prescribed antihypertensive medication. Neither of the aerobic exercise interventions reduced average blood pressure in normotensive elders nor prevent the development towards hypertension in comparison to the control. The long-term effects of aerobic exercise and training intensity, on the are dependent on maintained adherence. Thus, the future nonpharmacological strategies to prevent, treat and control hypertension need to focus on the implementation of long-term adherence, to ensure the long-term effect of aerobic exercise and training intensity. In conclusion, aerobic exercise as nonpharmacological strategy to prevent, treat and control hypertension in the elderly, is dependent on training intensity and long-term adherence to the exercise intervention. Thus, the implementation of more vigorous physical activity and practices that ensure long-term adherence to aerobic exercise, have a substantial potential to not only promote healthy ageing, but also reduce the burden of fatal and nonfatal cardio- and cerebrovascular disease in the elderly population.

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Appendix

Methods: Questionnaire

GENERASJON 100

Nr [   ]

Spørreskjema 1

1. Kjønn: ☐ Kvinne ☐ Mann   2. Fødselsår: [   ]

3. Høyde: [   ] cm   4. Vekt: [   ] kg

Utdanning

5. Hva er din høyeste utdanning?
   - ☐ Folkeskole
   - ☐ Realskole
   - ☐ Yrkesskole
   - ☐ Handelsskole
   - ☐ Gymnas
   - ☐ Høgskole eller universitet, mindre enn 3 år
   - ☐ Høgskole eller universitet, mer enn 3 år

Boligforhold og venner

6. Hvem bor du sammen med? (Sett ett eller flere kryss)
   - ☐ Ingen   ☐ Ektefelle/samboer   ☐ Andre personer

Mosjon og fysisk aktivitet

Med mosjon mener vi at du for eksempel går tur, går på ski, svømmer eller driver trening/idrett. Fysisk aktivitet omfatter både fysisk aktivitet i hverdagen, planlagte aktiviteter og trening.

7. Hvor ofte driver du mosjon? (Ta et gjennomsnitt)
   - ☐ Aldri
   - ☐ Sjeldnere enn en gang i uka
   - ☐ En gang i uka
   - ☐ 2-3 ganger i uka
   - ☐ Omtrent hver dag

8. Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? (Ta et gjennomsnitt)
   - ☐ Tar det rolig uten å bli andpusten eller svett
   - ☐ Tar det så hardt at jeg blir andpusten og svett
   - ☐ Tar meg nesten helt ut

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9. Hvor lenge holder du på hver gang? (Ta et gjennomsnitt)

☐ Mindre enn 15 minutter ☐ 15-29 minutter ☐ 30 minutter – 1 time ☐ Mer enn 1 time

10. Har du vanligvis minst 30 minutter fysisk aktivitet daglig? ☐ Ja   ☐ Nei

11. Hvis du aldri eller sjelden er fysisk aktiv. Hva er det som hindrer deg:

☐ Dårlig helse/funksjonsnedsettelse

☐ Tilgjengelighet av passende aktiviteter

☐ Avstand til turområder

☐ Tilrettelegging av turområder

☐ Utrygghet

☐ Ikke interessert

☐ Annet

12. Omtrent hvor mange timer sitter du i ro på en vanlig hverdag? ☐☐

Helse og dagligliv

13. Hvordan er helsa di nå? ☐ Dårlig   ☐ Ikke helt god   ☐ God   ☐ Svært god

14. Røyker du?

☐ Nei, jeg har aldri røykt

☐ Nei, jeg har sluttet å røyke

☐ Ja, sigaretter av og til (fest/ferie, ikke daglig)

☐ Ja, sigarer/sigarillos/pipe av og til

☐ Ja, sigaretter daglig

☐ Ja, sigarer/sigarillos/pipe daglig

15 Bruker du, eller har du brukt snus?

☐ Nei, aldri

☐ Ja, men jeg har sluttet

☐ Ja, av og til

☐ Ja, daglig

16. Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av 2 uker? (Regn ikke med lettøl) (Sett 0 hvis du ikke drikker alkohol)

Antall glass: Øl: ☐☐   Vin: ☐☐   Brennevin: ☐☐

17. Bruker du medisin mot høyt blodtrykk?

☐ Ja   ☐ Nei, men jeg har brukt   ☐ Nei, har aldri brukt

18. Klarer du selv, uten hjelp av andre, i det daglige å:

Gå innendørs i samme etasje? ☐ Ja ☐ Nei

Gå på toalettet? ☐ Ja ☐ Nei

Vaske deg på kroppen? ☐ Ja ☐ Nei

Bade eller dusje? ☐ Ja ☐ Nei

Kle på og av deg? ☐ Ja ☐ Nei

Legge deg og stå opp? ☐ Ja ☐ Nei

Spise selv? ☐ Ja ☐ Nei

Lage varm mat? ☐ Ja ☐ Nei

Gjøre lett husarbeid (f.eks oppvask)? ☐ Ja ☐ Nei

Gjøre tyngre husarbeid (f.eks gulvvask)? ☐ Ja ☐ Nei

Vaske klær? ☐ Ja ☐ Nei

Gjøre innkjøp? ☐ Ja ☐ Nei

Betale regninger? ☐ Ja ☐ Nei

Ta medisiner? ☐ Ja ☐ Nei

Komme deg ut? ☐ Ja ☐ Nei

Ta bussen? ☐ Ja ☐ Nei

19. Har du i løpet av de siste 12 måneder hatt:

Anfall med pipende eller tung pust ☐ Ja ☐ Nei

Daglig hoste i perioder ☐ Ja ☐ Nei

Høysnue eller neseallergi ☐ Ja ☐ Nei

Smerter og/eller stivhet i muskler og ledd, som ☐ Ja ☐ Nei
har vart i minst 3 måneder sammenhengende

20. Hvor mange ganger har du i løpet av de siste 12 måneder vært hos:

Fastlege / allmennlege ☐☐ ganger

Annen legespesialist utenfor sykehus ☐☐ ganger

Kiropraktor ☐☐ ganger

Homøopat, akupunktur, soneterapeut, ☐☐ ganger
håndspålegger eller annen alternativ behandler

24605

78

21. Har du, eller har du noen gang hatt, noen av disse sykdommene / plagene:
(Sett ett kryss pr. linje)   Hvis ja, hvor gammel var du første gang?

Hjerteinfarkt	☐ Ja	☐ Nei	[ ]	år
Angina pectoris (hjertekrampe)	☐ Ja	☐ Nei	[ ]	år
Hjertesvikt	☐ Ja	☐ Nei	[ ]	år
Atrieflimmer	☐ Ja	☐ Nei	[ ]	år
Annen hjertesykdom	☐ Ja	☐ Nei	[ ]	år
Hjerneslag/hjerneblødning	☐ Ja	☐ Nei	[ ]	år
Nyresykdom	☐ Ja	☐ Nei	[ ]	år
Astma	☐ Ja	☐ Nei	[ ]	år
Kronisk bronkitt, emfysem, KOLS	☐ Ja	☐ Nei	[ ]	år
Diabetes (sukkersyke)	☐ Ja	☐ Nei	[ ]	år
Psoriasis	☐ Ja	☐ Nei	[ ]	år
Eksem på hendene	☐ Ja	☐ Nei	[ ]	år
Kreftsykdom	☐ Ja	☐ Nei	[ ]	år
Epilepsi	☐ Ja	☐ Nei	[ ]	år
Leddgikt (reumatoid artritt)	☐ Ja	☐ Nei	[ ]	år
Bechterews sykdom	☐ Ja	☐ Nei	[ ]	år
Sarkoidose	☐ Ja	☐ Nei	[ ]	år
Beinskjørhet (osteoporose)	☐ Ja	☐ Nei	[ ]	år
Fibromyalgi	☐ Ja	☐ Nei	[ ]	år
Slitasjegikt (artrose)	☐ Ja	☐ Nei	[ ]	år
Psykiske plager som du har søkt hjelp for	☐ Ja	☐ Nei	[ ]	år
Lavt stoffskifte (hypotyreose)	☐ Ja	☐ Nei	[ ]	år
Høyt stoffskifte (hypertyreose)	☐ Ja	☐ Nei	[ ]	år
Katarakt (grå stær)	☐ Ja	☐ Nei	[ ]	år
Glaukom (grønn stær, høyt trykk i øyet)	☐ Ja	☐ Nei	[ ]	år

**Takk for at du tok deg tid til å svare på spørsmålene,
og husk å sende inn svarene dine!**

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Results: Medical history and prevalence of previous disease

Table A1: Preintervention prevalence of previous disease.

Prevalence of previous disease [Counts (%)]	HIIT n = 237	MICT n = 236	Control n = 514	Group differences (*p-value*):
Cancer	38 (16.2)	41 (17.5)	70 (13.8)	*0.379*
Cardiovascular disease	31 (13.4)	32 (14.0)	53 (10.6)	*0.342*
· Myocardial infarction	11 (4.7)	11 (4.7)	18 (3.6)	*0.688*
· Angina pectoris	6 (2.5)	6 (2.6)	16 (3.2)	*0.853*
· Heart failure	4 (1.7)	1 (0.4)	1 (0.2)	**0.048*
· Atrial fibrillation	18 (7.6)	16 (6.9)	26 (5.1)	*0.358*
· Other heart disease	5 (2.2)	4 (1.7)	17 (3.4)	*0.368*
Stroke	11 (4.7)	19 (8.1)	19 (3.8)	**0.042*
Kidney disease	7 (3.0)	12 (5.2)	18 (3.6)	*0.436*
Hypothyroidism	19 (8.2)	22 (9.4)	36 (7.2)	*0.561*
Hyperthyroidism	0 (0.0)	3 (1.3)	4 (0.8)	*0.247*

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; *n*: sample size.
*The frequency is statistically different between the intervention groups ($p < 0.05$).

Results: Antihypertensive medical status

A clear majority (93%) of the participating elders had an unaltered antihypertensive medical status during the whole intervention period. The study included 287 (29%) participants [HIIT: 57 (24%); MICT; 71 (30%); Control: 159 (31%)] *with* and 628 (64%) participants [HIIT: 160 (68%); MICT; 156 (68%); Control: 315 (61%)] *without* prescribed antihypertensive medication during the whole 3-year intervention period. Whereas, only 72 of the 987 participants, altered their antihypertensive medical status during the intervention period, including 53 (5%) participants [HIIT: 14 (6%); MICT: 9 (4%); Control: 30 (6%)] that *initiated* pharmacological antihypertensive treatment, and 19 (2%) participants [HIIT: 6 (3%); MICT: 3 (1%); Control: 10 (2%)] that *withdrew* their antihypertensive medication during the intervention period. The alterations in antihypertensive medical status did not differ between groups ($p = 0.402$).

Results: The effect of antihypertensive medication

The observed change (Δ) in average blood pressure differed between elders with an altered medical status, *i.e.* elders that either initiated a pharmacological antihypertensive treatment or withdrew their antihypertensive medication during the intervention period, and elders with an unchanged medical status, *i.e.* elders with or without prescribed antihypertensive medication during the whole the intervention period (Table A2).

Table A2: Observed change in average blood pressure in elders with an altered antihypertensive medical status, *i.e.* elders that either initiated treatment with antihypertensive medication or withdrew their antihypertensive medication during the intervention period. The observed change is compared with the change observed in elders with an unaltered medical status, *i.e.* elders with or without prescribed antihypertensive medication during the whole intervention period.

	HIIT		MICT		Control	
Initiated treatment with antihypertensive medication:						
Sample size:	*n = 14*		*n = 9*		*n = 30*	
ΔSBP (mm Hg)	-21.3 ± 3.9*	*	-7.8 ± 4.9^{NS}	NS	-19.7 ± 2.8*	*
ΔDBP (mm Hg)	-6.6 ± 2.0*	NS	-3.3 ± 2.5^{NS}	NS	-7.4 ± 1.5*	*
Withdrew antihypertensive medication:						
Sample size:	*n = 6*		*n = 3*		*n = 10*	
ΔSBP (mm Hg)	+14.8 ± 5.9^{NS}	*	+7.7 ± 8.4^{NS}	NS	+6.7 ± 4.9^{NS}	*[1]NS[2]
ΔDBP (mm Hg)	+9.0 ± 3.0*	*	+8.8 ± 4.4^{NS}	*	+1.7 ± 2.6^{NS}	NS

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training
ΔSBP: Change in systolic blood pressure; ΔDBP: Change in diastolic blood pressure.
ΔSBP and ΔDBP are presented as *mean ± SE*.
*The observed change is statistically *significant* ($p < 0.05$)
^{NS} The observed change is statistically *insignificant* ($p > 0.05$)
* The observed change is statistically *different* from the observed change in elders with an unaltered medical status ($p < 0.05$)
NS The observed change is statistically *indifferent* from the observed change in elders with an unaltered medical status ($p > 0.05$)
*[1]NS[2]: The observed change is statistically *different* from the observed change in elders without prescribed antihypertensive medication ($p < 0.05$) but statistically *indifferent* from the observed change in elders with prescribed antihypertensive medication ($p > 0.05$).

In general, elders initiating a pharmacological antihypertensive treatment during the intervention period demonstrated a decrease in average SBP and DBP. Whereas elders that withdrew their antihypertensive medication demonstrated an increase in average SBP and DBP (Table A2).

A significant reduction in SBP was observed in elders with and without prescribed antihypertensive medication in both exercise groups ($p < 0.022$). The observed reduction in SBP was slightly larger in elders with prescribed antihypertensive medication than in elders without (Figure A1A), but the difference was statistically insignificant in both exercise groups ($p > 0.228$). On the other hand, elders in the control group with prescribed antihypertensive

medication demonstrated a small but statistically insignificant reduction in SBP ($p = 0.126$), whereas elders without antihypertensive medication demonstrated a slightly larger and statistically significant reduction in SBP ($p < 0.001$). However, the mean difference between elders with and without prescribed antihypertensive medication was not statistically significant ($p = 0.458$) in the control group either (Figure A1A).

Preintervention SBP was significantly higher ($p < 0.001$) in elders with prescribed antihypertensive medication, 140.5 ± 1.0 mm Hg, than in those without, 134.1 ± 0.7 mm Hg (Table A3A), and postintervention SBP remained higher in elders with antihypertensive medication than in elders without (Table A3B). Adjusting the change in SBP with preintervention SBP, diminished the differences between elders with and without antihypertensive medication in the two exercise groups ($p > 0.713$), but not in the control group, in which the antihypertensive effect remained significantly larger ($p = 0.006$) in elders without prescribed antihypertensive medication (Figure A1B).

Table A3: Pre- and postintervention average systolic (SBP) and diastolic (DBP) blood pressure in elders with an unaltered antihypertensive medical status, *i.e.* elders with and without prescribed antihypertensive medication in the exercise intervention groups, and control group.

A: Preintervention SBP (mm Hg)	HIIT		MICT		Control	
Elders with prescribed antihypertensive medication	141.9 ± 2.3	*	140.0 ± 2.0	NS	140.6 ± 1.4	*
Elders without prescribed antihypertensive medication	133.2 ± 1.2		135.1 ± 1.9		134.0 ± 0.9	
B: Postintervention SBP (mm Hg)						
Elders with prescribed antihypertensive medication	133.9 ± 2.2	*	135.1 ± 1.9	NS	138.0 ± 1.3	*
Elders without prescribed antihypertensive medication	127.9 ± 1.3		132.0 ± 1.4		130.6 ± 1.0	
C: Preintervention DBP (mm Hg)						
Elders with prescribed antihypertensive medication	76.5 ± 1.3	NS	77.6 ± 1.2	*	76.8 ± 0.9	
Elders without prescribed antihypertensive medication	75.7 ± 0.7		75.0 ± 0.7		75.3 ± 0.5	NS
D: Postintervention DBP (mm Hg)						
Elders with prescribed antihypertensive medication	72.2 ± 1.4	NS	77.4 ± 1.1	*	75.3 ± 0.8	NS
Elders without prescribed antihypertensive medication	72.7 ± 0.8		73.2 ± 0.8		74.2 ± 0.5	

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training.
SBP and DBP are presented as *mean ± SE*.
Sample size (*n*) in elders with [HIIT: *57*; MICT; *71*; Control: *159*] and without prescribed antihypertensive medication [HIIT: *160*; MICT; *153*; Control: *315*].
* The observed mean in elders with prescribed antihypertensive medication is statistically *different* from the observed mean in elders without prescribed antihypertensive medication ($p < 0.05$).
NS The observed mean in elders with prescribed antihypertensive medication is statistically *indifferent* from the observed mean in elders without prescribed antihypertensive medication ($p > 0.05$).
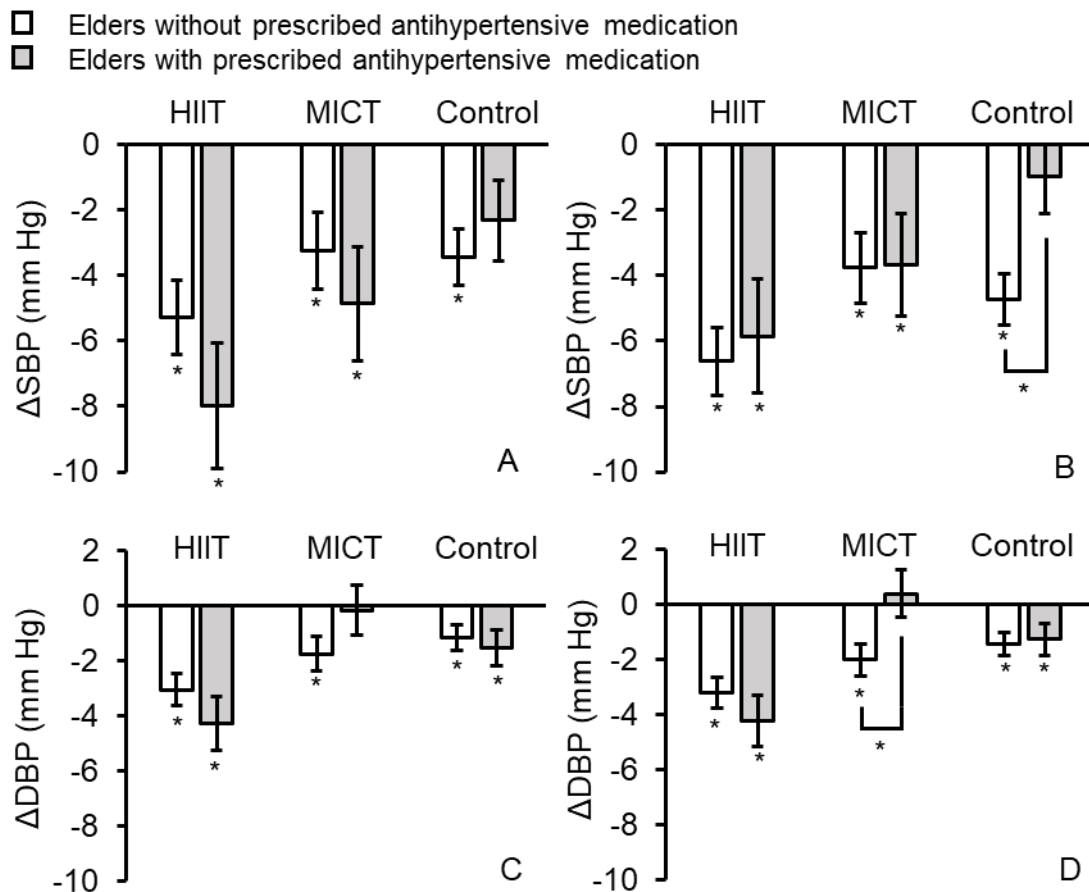
Figure A1: Observed change in average blood pressure in elders with and without prescribed antihypertensive medication, within the exercise intervention groups, high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT), and the control group, respectively. **A**: Observed change in systolic blood pressure (ΔSBP). **B**: Observed ΔSBP in elders with the same initial level of SBP [HIIT: 136.5 mm Hg; MICT: 136.7 mm Hg; Control: 137.1 mm Hg]. **C**: Observed change in diastolic blood pressure (ΔDBP). **D**: Observed ΔDBP in elders with the same initial level of DBP [HIIT: 76.3 mm Hg; MICT: 75.8 mm Hg; Control: 76.1 mm Hg]. *The white and grey bars represent average change in blood pressure in elders with and without prescribed antihypertensive medication, respectively, whereas the error bars represent the standard error of the mean. Sample size (n) in elders with [HIIT: 57; MICT; 71; Control: 159] and without prescribed antihypertensive medication [HIIT: 160; MICT; 153; Control: 315]. * Represents a statistically significant change or difference between elders with and without antihypertensive medication ($p < 0.05$).*

A significant reduction in average DBP was observed in elders without prescribed antihypertensive medication in both exercise groups ($p < 0.004$), and in elders with prescribed antihypertensive medication in the HIIT group ($p < 0.001$). Whereas there was no observed change in average DBP in elders with prescribed antihypertensive medication in the MICT group ($p = 0.872$), nevertheless, the observed reduction in DBP in elders without prescribed antihypertensive medication was statistically indistinguishable ($p = 0.147$) from the unnoticeable change in elders with prescribed antihypertensive medication (Figure A1C). The observed reduction in DBP was slightly higher in elders with prescribed antihypertensive

medication than in elders without in the HIIT group, but the difference was not supported statistically ($p = 0.277$). A significant ($p < 0.042$) reduction in average DBP was observed in elders with and without antihypertensive medication in the control group (Figure A1C), and the reductions were of similar extent ($p = 0.632$).

In general, there was no difference in preintervention DBP between in elders with and without prescribed antihypertensive medication. However, elders in the MICT group, with prescribed antihypertensive medication had a significantly higher preintervention DBP than elders without (Table A3C). The same tendency was observed postintervention, as postintervention DBP in the HIIT and control group did not differ between elders with and without prescribed antihypertensive medication. Whereas in the MICT group postintervention DBP was significantly lower in elders without prescribed antihypertensive medication than in elders with prescribed antihypertensive medication (Table A3D). Adjusting the change in DBP with preintervention DBP, did not affect the differences between elders with and without antihypertensive medication in the HIIT ($p = 0.322$) and control group ($p = 0.825$). Whereas in the MICT group, the observed reduction in DBP in elders without prescribed antihypertensive medication becomes statistically different ($p = 0.020$) from the unnoticeable change in elder with prescribed antihypertensive medication, when the change in DBP was compared between elders with the same initial level of DBP (Figure A1D).

The change in SBP (ΔSBP) is negatively correlated with preintervention SBP [$r = -0.473$; $p < 0.010$], and the change in DBP (ΔDBP) is negatively correlated with preintervention DBP [$r = -0.388$; $p < 0.01$]. Consequently, preintervention SBP explain 22.4% of the observed variance in ΔSBP, and preintervention DBP explain 15.1% of the observed variance in ΔDBP.

Adjusting the observed ΔSBP and ΔDBP with preintervention SBP and DBP, respectively, allows a comparison of the average change in SBP and DBP in elders with the same initial level of blood pressure. The adjusted ΔSBP and ΔDBP in elders with an altered medical status is compared to the adjusted ΔSBP and ΔDBP in elders with an unchanged medical status in Table A4.

Table A4: Observed change in average blood pressure in elders with an altered medical status, *i.e.* elders that either initiated treatment with antihypertensive or withdrew their antihypertensive medication during the intervention period. The observed change is compared with the change observed in elders with an unaltered medical status, *i.e.* elders with or without prescribed antihypertensive medication during the whole the intervention period. The observed change in average blood pressure is adjusted with preintervention blood pressure and comparisons are made between elders with the same initial level of systolic (SBP) and diastolic (DBP), respectively.

	HIIT		**MICT**		**Control**	
Initiated treatment with antihypertensive medication:						
Sample size:	*n = 14*		*n = 9*		*n = 30*	
ΔSBP (mm Hg)	-13.7 ± 3.6*	NS^{1*2}	-7.8 ± 4.4^{NS}	NS	-12.0 ± 2.6*	*
ΔDBP (mm Hg)	-5.4 ± 1.9*	NS	- 3.3 ± 2.4^{NS}	NS	-5.0 ± 1.4*	*
Withdrew antihypertensive medication:						
Sample size:	*n = 6*		*n = 3*		*n = 10*	
ΔSBP (mm Hg)	+12.3 ± 5.3^{NS}	*	+5.7 ± 7.6^{NS}	NS	+3.3 ± 4.4^{NS}	NS
ΔDBP (mm Hg)	+9.5 ± 2.8*	*	+8.7 ± 4.1^{NS}	*	- 0.9 ± 2.3^{NS}	NS

HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training.

ΔSBP: Change in systolic blood pressure in elders with the same preintervention of SBP [HIIT: 136.5; MICT: 136.7 mm Hg; Control: 137.1 mm Hg]. ΔDBP: Change in diastolic blood pressure in elders with the same preintervention level of DBP [HIIT: 76.3 mm Hg; MICT: 75.8 mm Hg; Control: 76.1 mm Hg].

ΔSBP and ΔDBP are presented as *mean ± SE*.

*The observed change is statistically *significan*t ($p < 0.05$)

^{NS} The observed change is statistically *insignificant* ($p > 0.05$)

* The observed change is statistically *different* from the observed change in elders with an unaltered medical status ($p < 0.05$)

NS The observed change is statistically *indifferent* from the observed change in elders with an unaltered medical status ($p > 0.05$)

NS^{1*2} The observed change is statistically *different* from the observed change in elders with prescribed antihypertensive medication ($p < 0.05$) but statistically *indifferent* from the observed change in elders without prescribed antihypertensive medication ($p > 0.05$).

Discussion: The active elders in comparison to the overall elderly population

The elders participating in the Generation 100 study were generally more active and had better health than the nonparticipating elders.[118]

The notion that the sample of the present study represent particularly active elders, is supported by the slightly lower than expected level of average systolic blood pressure (SBP) preintervention, which was 136.8 ± 0.9 mm Hg. The Nord-Trøndelag Health (HUNT) Study, an independent longitudinal health study, conducted in a county north of Trondheim, reported that the average SBP for elders, 70-79 years of age, was 141.7 ± 0.4 mm Hg.[22] However, the study samples are certainly independent and a comparison would presume that the data provided by the HUNT study accurately represent the overall elderly population. In contrast to the present exercise intervention study, the observational HUNT study was probably not limited by physical disabilities, at least not to the same extent as the present study, and consequently less prone to the possible selection bias of favoring the most active elders. It is therefore reasonable to assume that the HUNT study, including 4940 elders, 70-79 years of age, provide a sufficiently accurate estimation of the average blood pressure level in the Norwegian elderly population. Nevertheless, the difference might be slightly overestimated as the reported estimations are assessed at least four years apart, 2012-2013 in the present study and 2006-2008 in the HUNT study, and a downward trend in average SBP have been reported, both in the overall population and in the elderly as well. In 1995-1997, the HUNT study reported that average SBP in elders, 70-79 years of age, was 156.4 ± 0.4 mm Hg. [22]

In contrast to average SBP, average diastolic blood pressure (DBP) preintervention was higher than expected. Average DBP in the present 76.1 ± 0.3 mm Hg in the present study compared to the most resent average reported by HUNT study 74.2 ± 0.2 mm Hg.[22] Nevertheless, this difference can be explained by the somewhat narrower age span or slightly higher proportion of men in the present study in comparison to the HUNT study. Average DBP was higher in men than in women, both in the present study sample and in the sample included in the HUNT study. The present study included elders, 70-77 years of age at preintervention, and 51% of the participating elders were men, whereas the HUNT study reported blood pressure for elders within the age span of 70-79 years of age, and 46% of the elders within the selected age span were men.[22]

In Norway, hypertension is defined as an average $SBP \geq 140$ mm Hg or average $DBP \geq 90$ mm Hg,[140] in accordance to the European guidelines for management of arterial hypertension by the European Society of Hypertension (ESH) and the European Society of

Cardiology (ESC).[34] In the present study, 43% of the 987 elders, 70-77 years of age, had an average blood pressure above the European hypertensive threshold preintervention. Postintervention the proportion decreased to 33%. The preintervention proportion was considerably lower than the proportion reported by the HUNT study, which in 2006-2008, reported that 52% of the 4937 included elders, 70-79 years of age, had an average blood pressure above the European hypertensive threshold.[22] In addition, the HUNT study reported that 48% percent of the elders with hypertension had prescribed antihypertensive medication,[22] whereas the corresponding proportion from the present study was 38% preintervention.

A substantial proportion of the older adults of Norway engage in physical activity, as demonstrated in a national survey on living conditions.[163] The survey was performed by the national statistical institute of Norway in 2016, and reported that around three quarters of the Norwegian older adults engage in physical activities with the intention to exercise at least once a week.[163] Upon invitation to the Generation 100 Study, a total of 2928 elders responded to the invitation and filled out the attached questionnaire regarding health, daily life, education level, social environment, exercise and physical activity. A pooled analysis of all respondents to the invitations survey of the Generation 100 study reported that more than four fifths of the elderly population, engage in physical activities with the intention to exercise at least once a week.[118] The proportion of elders that never engage in physical activity was approximately 12%, according to the Generation 100 survey and the survey by the national statistical institute of Norway.[118,163]In summary, sample of the present study sample is considered to represent active elders, physically capable of performing regular aerobic exercise.