Population study of physical activity and association with tissue Doppler echocardiography, left ventricular mass, hypertension, and long-term outcome

The Copenhagen City Heart Study

Alfred, Gowsini Joseph

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POPULATION STUDY OF PHYSICAL ACTIVITY AND ASSOCIATION WITH TISSUE DOPPLER ECHOCARDIOGRAPHY, LEFT VENTRICULAR MASS, HYPERTENSION, AND LONG-TERM OUTCOME

THE COPENHAGEN CITY HEART STUDY

BY
GOWSINI JOSEPH

DISSERTATION SUBMITTED 2020

AALBORG UNIVERSITY
DENMARK

Population study of physical activity and association with tissue Doppler echocardiography, left ventricular mass, hypertension, and long-term outcome:

The Copenhagen City Heart Study

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PREFACE

This thesis is based on three studies carried out during my positions at the Department of Cardiology, North Denmark Regional Hospital, Hjørring, and the Department of Clinical Medicine, Aalborg University. It has been an unpredictable journey, which took me from my comfort zone in echocardiography and left me in the middle of a challenging field of cardiovascular epidemiology, surrounded by many inspiring, talented, and dedicated colleagues whom I look forward to working with in the years to come.

I want to express my sincere gratitude to all those who have helped me directly or indirectly during the past years, keeping in mind that those things for which we are most grateful could be the most difficult to put down in words.

First, I want to thank everyone at my workplace at Hjørring Hospital. Thanks to Gitte Nielsen for believing in me and my research skills, for encouraging me and for thinking with the heart. My wonderful colleagues Asta Blaskauskaite, Jens Petersen, Holger Sejersen, Adam Plocharski, Marek Zelechowski, and Peter Stæhr admired my research and I am grateful for their support and understanding during the periods of my absence from clinical work. Special thanks to Asta for being caring, helpful and for making me feel like a star. The days I spent in clinical work were especially enlightened by Christina Skov and her staff, and I want to thank Christina for her easy-going personality, her managing skills and for her thoughtful support of me. Gitte and Christina remain for me a source of inspiration for how to create a pleasant workplace.

In Hjørring, I also had the pleasure of meeting Professor Ulrik Baandrup, whom I met for the first time many years ago at Aarhus University when I was a medical student. His passion and enthusiasm for his profession and research is true inspiration for many young researchers.

I want to thank everyone I met at the Centre for Clinical Research. Special thanks to Suzette Sørensen, Dorthe Brønnum, and Dorte Melgaard for interesting discussions, and to Lise Kristiansen for help with finding articles.

I would like to thank my former clinical supervisor Ole Eschen for inspiring me to work with cardiovascular research and for convincing me to join the Copenhagen City Heart Study. Thanks to Peter Søgaard for introducing me to clinical research in cardiac imaging. His dedication to echocardiography, research and his many ideas are inspiring. I also want to thank Peter for introducing me to the Copenhagen City

Heart Study by introducing me to Jan Skov Jensen. I am grateful to Jan for including me and for his quick, constructive, and critical feedback on my work.

Rasmus Møgelvang stood beside me from the beginning to the end of this PhD. I want to thank Rasmus for his guidance, accountability, commitment, and for finding time to address my concerns properly in a very busy schedule. I am especially grateful for his scientific enthusiasm and active presence in every stage of the process, from discussing the ideas until the publication of the articles. Working with Rasmus gave me determination, ambitions, and a faith that I will be able to achieve my professional goals.

Jacob Louis Marott was the main reason I became fascinated by both epidemiologic research and the Copenhagen City Heart Study. His knowledge of statistics and epidemiology is tremendous. I want to thank Jacob for improving the scientific quality of my studies, for making my scientific victories grander and the difficult days easier to overcome. His loyalty to the Copenhagen City Heart Study, his passion and dedication for research is contagious and admirable. Above all, Jacob is a truly kind and empathetic person caring for the people surrounding him.

I would like to thank the staff at the Copenhagen City Heart Study, Frederiksberg Hospital, where I was met with nothing but kindness, a place where I always found the doors open. I especially want to thank Gorm Boje Jensen, Peter Schnohr, Merete Appleyard, Anne-Birgitte Hjuler Ammari, and Anja Lykke Madsen for having me and helping me through the past years.

Thanks to Tor Biering-Sørensen and Eva Prescott for their help in my studies, especially for the constructive discussion of ideas and reviews of the methodology. It has been a pleasure to discuss my studies with Christian Torp-Pedersen, who contributed with immense knowledge and critical feedback. Further, I want to thank Ann-Eva Christensen and Martin Nygård Johansen for their statistical advice.

I was part of the motivating and well-organised research environment at the Department of Cardiology, Rigshospitalet, during the final year of my PhD-studies. I want to thank everyone I met here, especially the PhD-students for including me and for their friendliness. Special thanks to my colleagues from 'TeamSkrald' for creating a lovely atmosphere: Johannes Grand, Jakob Josiassen, Frederik Grund, Christoffer Vissing, Divan Topal, Katrine Myhr, and Marie Elming.

Thanks to Niels Holmark Andersen for his unbiased collegial and moral support, for being a continuous inspiration for me in cardiology, and for proving how to keep your feet on the ground when reaching for the stars.

Last, but not least, I want to thank my wonderful colleague and friend Majbritt Tang Svendsen for always being a step ahead of me, for being my greatest cheerleader, and for painting me beautiful sunny pictures when the lines in my drawings seemed like blurred clouds.

Gowsini Joseph,
Copenhagen,
December 2019

PAPERS INCLUDED IN THE PHD-THESIS

This PhD-thesis is based on the following three papers.

Publication II is selected as *High Impact Paper* by American Heart Association and Hypertension, Winter Collection 2019.

Publication II and III are currently in the top 5% of all research outputs scored by Altmetric (July 2020).

I **The association between physical activity and cardiac performance is dependent on age: the Copenhagen City Heart Study.**

Joseph G, Mogelvang R, Biering-Sørensen T, Nielsen G, Schnohr P, Sogaard P.
Int J Cardiovasc Imaging. 2019;35(7):1249-1258.
doi:10.1007/s10554-019-01566-0

II **Dose-Response Association Between Level of Physical Activity and Mortality in Normal, Elevated, and High Blood Pressure**

Joseph G., Marott J.L., Torp-Pedersen C., Biering-Sørensen T., Nielsen G., Christensen A., Johansen M.B., Schnohr P., Sogaard P., Mogelvang R.
Hypertension. 2019;74(6):1307-1315.
doi:10.1161/HYPERTENSIONAHA.119.13786

III **Level of Physical Activity, Left Ventricular Mass, Hypertension, and Prognosis**

Joseph G., Marott J.L., Biering-Sørensen T., Johansen M.N., Sævereid H.A., Nielsen G., Schnohr P., Prescott E., Sogaard P., Mogelvang R.
Hypertension. 2020;75(3):693-701.
doi:10.1161/hypertensionaha.119.14287

High Impact Papers
in *Hypertension*

Winter Collection

Editors of

Hypertension, an American Heart Association Journal

Congratulate

Gowsini Joseph

on the selection of

Dose-Response Association Between Level of Physical Activity and Mortality in Normal, Elevated, and High Blood Pressure
Hypertension. 2019;74:1307–1315

as a ***HIGH IMPACT PAPER IN HYPERTENSION*** *for*

Winter of 2019

Editor-in-Chief

American Heart Association.

ABBREVIATIONS

AMI: acute myocardial infarction
BMI: body mass index
BP: blood pressure
CI: confidence intervals
CPR: Civil Personal Register
CRS: Civil Registration System
CVD: cardiovascular disease
EF: ejection fraction
ET: ejection time
ICD: International Classification of Diseases
IVCT: isovolumetric contraction time
IVRT: isovolumetric relaxation time
LD: longitudinal displacement
LV: left ventricle
LVEF: left ventricular ejection fraction
LVH: left ventricular hypertrophy
LVM: left ventricular mass
LVMi: left ventricular mass index
METs: metabolic equivalents
MPI: myocardial performance index
TDI: tissue Doppler imaging

ENGLISH SUMMARY

Physical inactivity is one of the major causes of global death. Physical activity is associated with reduction of cardiovascular and respiratory diseases as well as malignant diseases and is considered an anti-depressive treatment. The World Health Organisation (WHO) recommends regular physical activity of a moderate amount to improve and maintain health.

Another threat to global health is the growing prevalence of hypertension. The WHO has declared hypertension to be the leading cause of death worldwide. The prevalence of hypertension is increasing, both in Western countries and in developing countries, advancing it to a major public health problem. Public health interventions with low economic cost are needed.

This thesis includes studies in the fields of physical activity, cardiac function, and hypertension. In the first study, we describe how the association between the level of physical activity and cardiac function is dependent on age. This raises several questions. Is an ageing heart capable of adapting the physiological changes induced by physical activity? Should recommendations regarding physical activity be classified according to age? Is physical activity dangerous in the elderly?

The second study describes how the association between physical activity and reduction in mortality has a dose-response pattern at all levels of blood pressure (BP) (normal BP, pre-hypertension, stage 1 hypertension, stage 2 hypertension). The reduction in cardiovascular events was independent of the level of physical activity. The most important message is that most of the health benefits are already achieved at a light level of physical activity, which is a level almost everyone can achieve. Previously, many physicians had precautions in recommending physical activity for persons in stage 2 hypertension. It is important to underscore that our main results were persistent for persons in stage 2 hypertension (≥ 160/100 mmHg) as well as the subgroup of patients with BP >180/110 mmHg. The current ESC-guidelines do not recommend physical activity in BP>180/110 mmHg.

The third study explores the impact of physical activity in a high-risk population: hypertensive patients with left ventricular hypertrophy (LVH). Patients with hypertension had significantly higher left ventricular mass (LVM) compared with persons with normal BP. Higher levels of physical activity were associated with a higher LVM in normal BP, whereas this association was not present in persons with hypertension. After a mean follow-up of 12 years, we found that higher levels of physical activity were associated with a reduction in all-cause mortality and especially cardiovascular endpoints independent of whether LVH was present.

Besides raising important questions on the association between physical activity and cardiac performance, this thesis provides new scientific knowledge on the importance of physical activity in the treatment of hypertension including the subgroups of high-risk hypertensive patients.

DANSK RESUMÉ

Fysisk inaktivitet er en af de vigtigste årsager til død på globalt plan. Fysisk aktivitet er ikke blot forbundet med mindre risiko for udvikling af hjerte-karsygdomme, men også forbundet med nedsat risiko for visse kræftsygdomme, lungesygdomme og vist at være gavnlig i behandling af depression.
Verdenssundhedsorganisationen WHO anbefaler regelmæssig fysisk aktivitet af moderat grad for at forbedre og opretholde et godt helbred.
Et andet globalt omspændende sundhedsproblem er den stigende forekomst af hypertension (forhøjet blodtryk). WHO har erklæret hypertension som værende den største risikofaktor for dødelighed verden over. Antallet af personer, der udvikler hypertension, er fortsat stærkt stigende, såvel i de vestlige lande som i udviklingslandene. Dette rejser et stort behov for behandlingstiltag med lave økonomiske omkostninger.
Aktuelle PhD-afhandling indeholder 3 studier, der undersøger sammenhæng mellem fysisk aktivitet, hjertefunktion og forhøjet blodtryk. Det første studie beskriver, hvorledes sammenhængen mellem graden af fysisk aktivitet og hjertefunktion er afhængig af alder. Dette studie giver anledning til flere spørgsmål, herunder om det aldrende hjerte er mindre i stand til at tilpasse fysiologiske ændringer forårsaget af fysisk aktivitet. Herudover, om anbefalingerne for fysisk aktivitet bør tilpasses aldersgruppe, og om fysisk aktivitet rent faktisk kan være farligt for den ældre befolkningsgruppe.
Andet studie i afhandlingen redegør for, hvordan stigende niveau af fysisk aktivitet er forbundet med tilsvarende reduktion i dødelighed og hjertekarsygdomme ved alle niveauer af blodtryk (normalt blodtryk, præ-hypertension, stadie 1 hypertension og stadie 2 hypertension). Det vigtigste budskab er, at den største del af helbredsgevinsten er opnået allerede ved let grad af fysisk aktivitet, som er et niveau, som langt de fleste personer er i stand til at opnå. Vores resultater gælder også for stadie 2 hypertension (blodtryk ≥ 160/100 mmHg), hvor læger tidligere har været tilbageholdende med at anbefale fysisk aktivitet, samt hos undergruppen af personer med blodtryk >180/110 mmHg, hvor der i aktuelt gældende europæiske retningslinjer ikke anbefales fysisk aktivitet.
Det tredje studie belyser fordelene ved fysisk aktivitet i en høj-risiko population, nemlig patienter med hypertension, der også har et tykt hjerte (venstre ventrikelhypertrofi). Venstre ventrikelhypertrofi er forbundet med stærk forværring af prognose hos patienter med forhøjet blodtryk. Patienter med forhøjet blodtryk havde ved baseline højere niveau af venstre ventrikeltykkelse ift. personer med normalt blodtryk. Stigende niveau af fysisk aktivitet var forbundet med højere venstre ventrikeltykkelse hos personer med normalt blodtryk, medens dette ikke gjaldt personer med forhøjet blodtryk. Efter mere end 12 års opfølgning kunne vi påvise, at højere niveau af fysisk aktivitet var forbundet med reduktion i død, og især en betydelig reduktion i forekomsten hjertekarsygdomme. Dette gjaldt også højrisikogruppen af personer med venstre ventrikelhypertrofi.

Udover at stille spørgsmålstegn ved sammenhæng graden af fysisk aktivitet og hjertefunktion, skaber aktuelle afhandling også ny viden om vigtigheden af fysisk aktivitets betydning for behandling af patienter med forhøjet blodtryk, herunder høj-risiko gruppen i denne patientkategori.

INTRODUCTION

'People here say there's no such thing as bad weather. Only bad clothing'.
Recently, the New York Times again published an article about the famous bicycling culture in Copenhagen, something Denmark is admired for internationally alongside its high status in the World Happiness Report [1]. However, according to the Danish National Health Profile, 28.8% of the Danish population does not fulfil the WHO recommendations for physical activity (2017: 28.2% of men and 29.4% of women) [2]. For adults 18-64 years, WHO recommends a minimum of 150 minutes physical activity of moderate intensity or 75 minutes of activity at a high intensity per week [3].
These recommendations are based on a large number of observational and experimental studies describing and verifying the health benefits of physical activity both in healthy individuals and in persons with known heart disease [4–13].
The landmark study made by Morris et al. in the 1950s introduced us to the cardiovascular benefits of regular physical activity: Active bus conductors and postmen had a 50% lower event rate from coronary heart disease compared with less active bus drivers and clerical workers in the post offices [14]. Since then, many other studies have confirmed these findings [15,16].
Physical activity promotes longevity, improves physical and mental well-being, reduces the risk of some malignancies, delays the onset of dementia and reduces the risk of depression [17–20]. In the cardiovascular field, we already know that regular physical activity reduces BP [21], improves the lipid profile [22], and increases insulin sensitivity [23,24]. In recent years, exercise has also been established as a cornerstone in cardiac rehabilitation [25].
Intense physical activity, such as marathon runs, has attracted much attention in modern time. Recent studies have questioned whether competitive physical activity might induce damage to the heart and worsen the prognosis [26–28].
Thus, exercise and physical activity remain a continuous issue in the scientific debate since the health benefits seem to be enormous and widespread, while intense levels of physical activity might be associated with cardiac alterations that might be harmful. Further studies are needed to clarify the role of physical activity in cardiovascular disease and the impact on the general population.
Besides physical inactivity, a major threat to global health is the growing prevalence of hypertension.
WHO has declared hypertension to be the leading cause of death worldwide [29]. The higher frequency of hypertension is found in Western countries as well as in the developing countries, advancing it to a major global public health problem [30]. Public health interventions with low economic cost are needed.

In the three studies included in this thesis, we studied physical activity in the general Danish population in terms of cardiac function assessed by tissue Doppler echocardiography, association with cardiac morphology, and the importance of physical activity on the prognosis in hypertension. The purpose of these studies was to acquire new knowledge of the association between physical activity, cardiac function, and the health benefits of physical activity in hypertensive persons.

OBJECTIVES

Study I

Since many previous observational studies have implied that a higher level of physical activity is associated with reduced cardiovascular outcomes [14,31–34], we wanted to study whether the benefits of physical activity were measurable on myocardial function.

Aim of study I:

a. Explore whether the level of physical activity was associated with better cardiac performance assessed by tissue Doppler echocardiography.

Study II

Physical activity is associated with a reduction in mortality and cardiovascular events. Intervention trials including persons with hypertension undergoing training protocols have documented that regular exercise reduces BP [35–38].

We wanted to study whether these two associations were linked, that is, whether physical activity improves prognosis in hypertension.

Aims of study II

a. Explore whether physical activity is associated with a reduction in mortality and cardiovascular events in hypertension.
b. Explore whether this association was present in a dose-response pattern.

Study III

LVH is a complication of hypertension and a strong predictor of cardiovascular outcome [39–44]. Physical activity is also associated with higher LVM [45–48]. Previous studies have described that physical activity is beneficial in hypertension [49,50]. The associations between physical activity, LVM, and prognosis in hypertension vs normal BP need to be clarified.

Aims of study III

a. To study whether the presence of hypertension modified the association between level of physical activity and LVM.
b. To explore whether the association between the level of physical activity and long-term prognosis in hypertension was modified by LVH.

METHODS

The Copenhagen City Heart Study (in Danish "Østerbroundersøgelsen") is a large cardiovascular prospective cohort study launched in 1976 by Dr Peter Schnohr, Dr Gorm Boje Jensen, Statistician Jørgen Nyboe, and Professor Anders Tybjærg Hansen [51]. Inspired by the Framingham Heart Study, the main purpose of the study was to explore coronary heart disease — mechanism, prognosis, and prevention [52]. However, during the past decades, many other medical areas have been added to the study: genetics, pulmonary diseases, arthrosis, echocardiography, heart failure, psychosocial factors, dementia, and more.
The study was based at Rigshospitalet from 1975 to 1997. In 1997, the study was re-located to Bispebjerg Hospital. Since 2012, the study has been housed by Frederiksberg Hospital.

Study population

As of 1st January 1976, a random sample of 19,329 men and women aged 20-93 years living within a well-defined area of the inner Copenhagen City boundary was drawn from the Central Office of Civil Registration and invited to take part in the study. The selection of the area was made by the distance of 10 wards surrounding Rigshospitalet, where the study was located. Thus, entire Østerbro and one-third of Nørrebro were included. Approximately 90,000 inhabitants were living in this area in 1976 (Figure 1 – Copenhagen) [53–55]. The sample of 19,329 men and women was stratified in 5-years age groups, and the main emphasis was on the age groups from 35 to 70 years. In total, 14,223 persons agreed to participate in the first examination (response rate 73.6%, Figure 2 — flow chart). The second survey was carried out in 1981-83, the third in 1991-94, the fourth in 2001-03, and the fifth in 2011-15. All subjects from the original sample were invited to all subsequent examinations, and a new random sample of men and women from the same area in Copenhagen was included each time. The numbers of invited persons and response rate are given in Figure 2. The present thesis included data from the first four surveys of the Copenhagen City Heart Study. All subjects gave informed consent to participate. The study was performed in accordance with the second Helsinki Declaration and approved by the regional ethics committee (KF 100.2039/91).

Figure 1.

Map of Copenhagen.

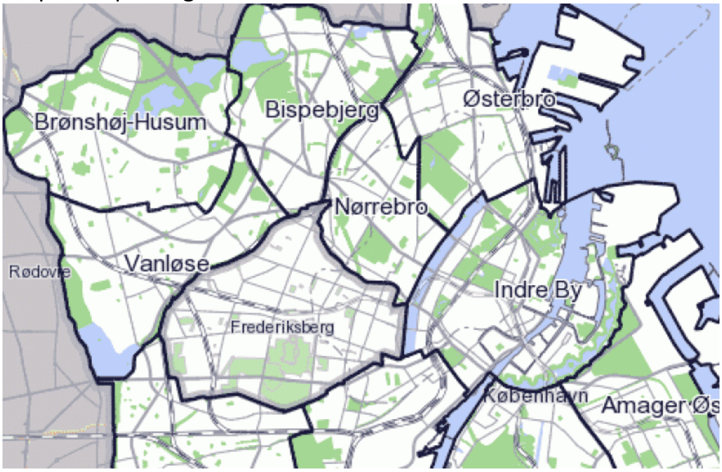
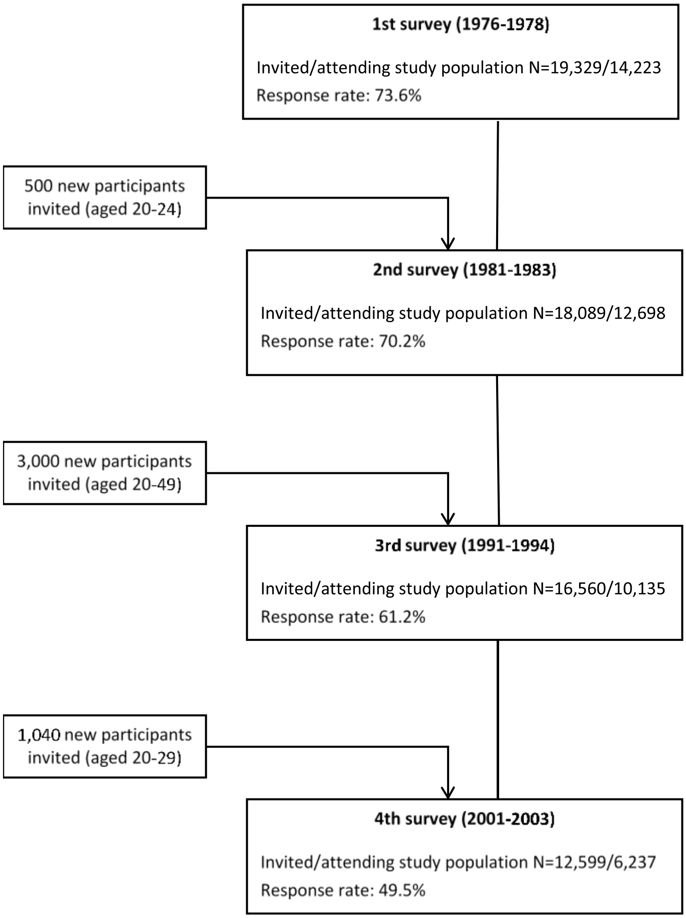


Figure 2.
Flow chart illustrating the participation in the Copenhagen City Heart Study.



Self-administered questionnaire

At each survey, all participants completed a health questionnaire regarding information on their medical history, socioeconomic status (education, income, marital status), health status, symptoms and level of physical activity in work and in leisure time [52]. The questionnaire was checked by a health professional when the participants came to the health examination.

Physical activity questionnaire

A physical activity questionnaire was a part of the self-administered questionnaire, and the same physical activity questionnaire was used in all four examinations. A single question with four categories was applied for measuring leisure-time physical activity:

Please indicate your PHYSICAL ACTIVITY LEVEL IN YOUR SPARE TIME (including transportation to and from work) over the last year (choose one option only)

I	Almost completely physically passive or physically active for less than 2 hours per week e.g., reading, watching TV, going to the cinema	
II	Light physically activity 2-4 hours per week e.g., walking, cycling, light garden work, or low-intensity workouts	
III	Light physical activity more than 4 hours per week or more strenuous activity 2-4 hours per week e.g., fast walking and/or fast cycling, heavy garden work, high-intensity workouts involving getting sweaty and short of breath	
IV	More strenuous physical activity for more than 4 hours per week or regular high-intensity workouts or sporting competitions several times per week	

In the present studies, the activity levels were categorised into the following levels according to the questionnaire:

I. Inactivity. (intensity: < 3 metabolic equivalents (METs) (Used as reference group)
II. Light activity. (intensity: 3-4.5 METs)
III. Moderate activity. (intensity: 4.5-6 METs)
IV. High-level activity. (intensity: >6 METs)

Health examination

Besides the health questionnaire, the participants underwent a physical health examination, including blood samples and an electrocardiogram, at each of the surveys.

Height and weight

Height was measured without shoes on a fixed scale to the nearest millimetre. Weight was measured without outdoor clothing and shoes on a Seco Consultation Scale, to the nearest hectogram [56]. Body mass index (BMI) was calculated by dividing weight with height^2. The classes of BMI were defined as follows: underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obesity (BMI ≥30.0 kg/m^2).

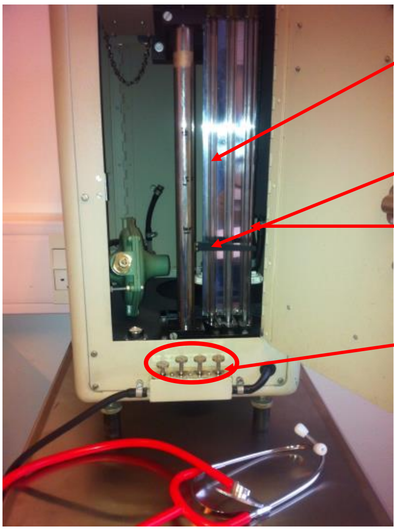
Blood pressure

The measurement of BP was performed under highly standardised circumstances and was unchanged in all four surveys. All equipment was tested at regular intervals between the surveys. The guidelines recommended by Rose & Blackburn were followed because these were the standards when The Copenhagen City Heart Study was initiated [57]. Trained technicians used a London School Hygiene Sphygmomanometer (Figure 3), which is a blind, mercury-column manometer designed to reduce observer bias and digit preference [58,59]. The subject was seated on a comfortable chair, and the back was supported. The arm was supported with the antecubital fossa at heart level. A cuff was applied to the non-dominant arm. The size of the cuff was chosen from the upper arm circumference. After 5 minutes of rest, BP was measured once. The mercury fall was 2 mm/s. The first Korotkoff sound (the sounds are first heard) defined the systolic BP. The diastolic BP was defined by the fifth Korotkoff sound (the sound disappears).
The BP levels were defined according to the seventh Joint National Committee [60]:

Normal BP: systolic BP < 120 mmHg and diastolic BP < 80mmHg.
Pre-hypertension: systolic BP between 120-139 mmHg or diastolic BP between 80-89 mmHg.
Stage I hypertension: systolic BP between 140-159 mmHg or diastolic BP between 90-99 mmHg, or receiving pharmacological treatment for hypertension with systolic BP < 160 mmHg/ diastolic BP < 100 mmHg.
Stage II hypertension: systolic BP ≥160 mmHg or diastolic BP ≥ 100 mmHg.

Figure 3

Photos of the London School of Hygiene Sphygmomanometer used in the Copenhagen City Heart Study. Explanations in Danish. Source: The Copenhagen City Heart Study, Frederiksberg Hospital.



Echocardiography

A total of 3,654 randomly selected persons from the fourth Copenhagen City Heart Study underwent conventional transthoracic echocardiogram. The tissue Doppler imaging was performed in 2,221 of these participants (Figure 4).
All participants followed the same procedure for the health examination. Echocardiographic examination was performed at the last examination station, and the sonographer was blinded to the results of the previous examinations. The collected images were stored for later analysis. In case of more than three persons waiting for the last station, the last arriving persons were sent home. None of the participants declined to undergo echocardiography [56].

Conventional echocardiography

All conventional echocardiographic measures were made by investigators blinded to other information. Recommendations from the American Society of Echocardiography were used to assess left ventricular (LV) regional and global function [61].

Assessment of left ventricular mass

In the parasternal long axis, one loop was recorded. One M-mode still frame between the tips of the mitral leaflets and the tips of the papillary muscles was also stored. Posterior wall thickness, LV diameter, and septal wall thickness were assessed in end-diastole. If it was not possible to assess the dimensions in M-mode trace, 2D images were used (Figure 5). LVM was calculated using the Devereux formula [62,63]. Left ventricular mass index (LVMi) was quantified as the anatomic mass divided by the body surface area [64]. Definition of LVH was: LVMi>115 g/m^2 for men and >95 g/m^2 for women [65].

Figure 4.

Flow chart, echocardiography in the fourth Copenhagen City Heart Study.

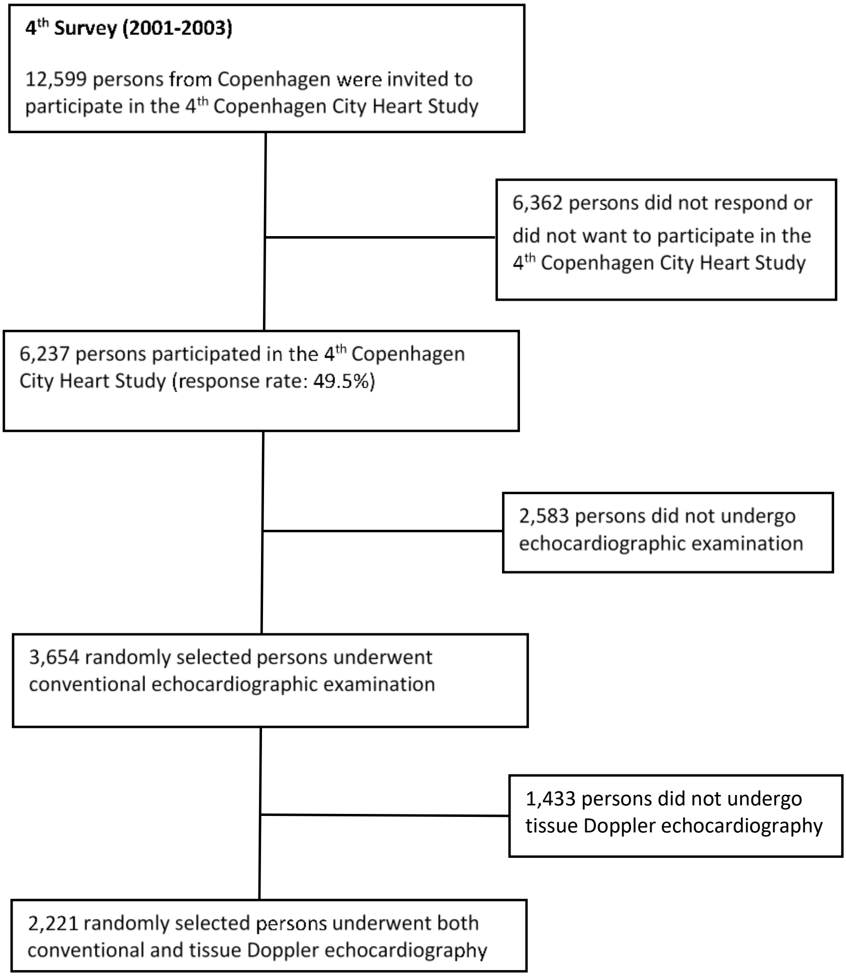
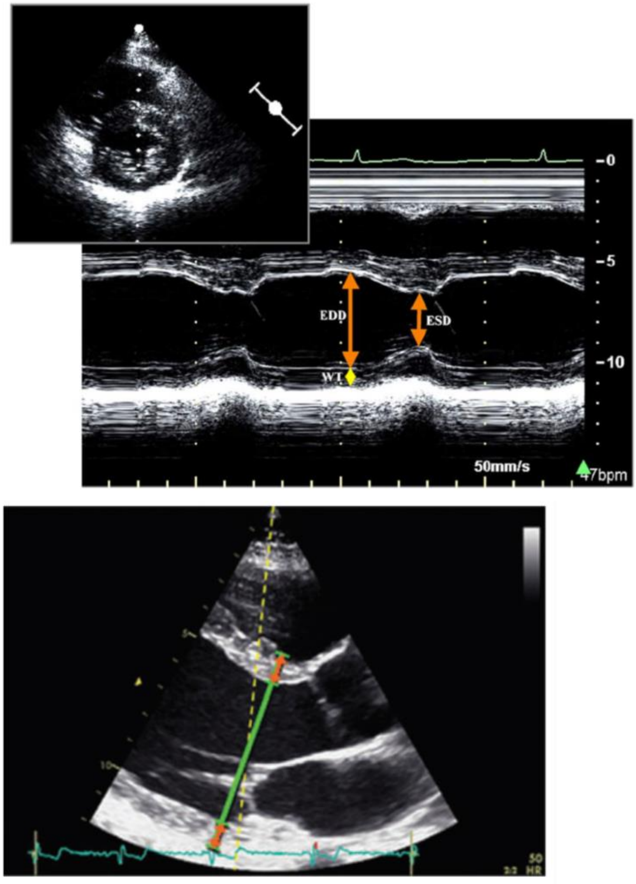


Figure 5.
Assessment of LV dimensions by M-mode (top), or 2D images (bottom).
Source: 'Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging', R.Lang et al., 2015, Journal of the American Society of Echocardiography



Tissue Doppler imaging

Colour tissue Doppler Imaging (TDI) loops were achieved at the highest possible frame rate (median 133; interquartile range 37 frames/sec) in the three apical views: 4-chamber, 2-chamber, and long axis. Investigators blinded to all other information analysed the images using ECHOPAC, GE Medical, Horten, Norway. Myocardial velocities were measured with a 6 mm circular sample volume placed at the end of ejection. Peak systolic (s´) and diastolic (e ´) mitral annular velocities were assessed (Figure 6). Longitudinal displacement (LD) was calculated as the integral of the velocity curve during ejection. Cardiac time intervals include isovolumetric relaxation time (IVRT), isovolumetric contraction time (IVCT), and ejection time (ET). Myocardial performance index (MPI) was calculated: (IVRT+ IVCT)/ET. The cardiac time intervals in the present studies were measured using colour tissue Doppler imaging M-mode line through the mitral leaflet (Figure 7).

Diastolic function evaluated by e`

In study I, we chose e` to evaluate the diastolic function of the LV. While systolic function is easily evaluated by ejection fraction (EF) or deformation techniques, evaluation of LV diastolic function remains a clinical challenge because there is no single clinical measure that quantifies LV diastolic function [66,67]. The myocardial velocity in early diastole (e') reflects LV regional lengthening and is a cornerstone in evaluating diastolic function because it covers both relaxation and restoring forces [66,68]. In heart failure, e' is less load-dependent compared with transmitral velocities [69]. In contrast to E/A-ratio in Doppler echocardiography, e' is a continuous parameter easy to interpret, where high values usually reflect normal diastolic function, except for rare conditions such as constrictive pericarditis [69,70].

Systolic function evaluated by Longitudinal Displacement

LD, also called mitral annular longitudinal displacement due to the movement of the mitral plane towards the apex, is equivalent to longitudinal systolic shortening [71]. LD differentiates myocardial dysfunction more precisely than LVEF [72,73]. Besides, LD is a sensitive and early marker of both heart failure and other structural heart diseases [74]. LD correlates with stroke volume and is, thus, also dependent on heart rate [75].

Myocardial Performance Index

MPI reflects the combined diastolic and systolic function of the LV. This is practically defined by the opening and closure of the heart valves, and has drawn attention and been measured with many different techniques: stethoscope and sphygmography in the 19th century to M-mode and pulsed Doppler echocardiography in the late 20th century to TDI echocardiography in the early 21st century [76]. The tissue Doppler method with M-mode line through the mitral leaflet has been described in detail and validated in previous studies [76–78]. In an unhealthy heart, the time from mitral valve closure to aortic valve opening (IVCT) might be prolonged due to longer time for the myocytes to achieve the pressure equal to that of the aorta. ET will be shortened because the sick myocardium will not be able to keep the systolic pressure for a long time. As diastolic dysfunction proceeds, the IVRT (time from aortic valve closure to mitral valve opening) will be prolonged due to impairment of the diastolic function. MPI will, thus, increase in a dysfunctional myocardium [78,79].

Figure 6

Myocardial velocities, TDI. Early (e') and late (a') diastolic peak is marked. LD /mitral annular displacement is calculated from the area under the curve during systole (shaded area).

Source: 'The association between physical activity and cardiac performance is dependent on age: the Copenhagen City Heart Study. ' Joseph G et al. Int J Cardiovasc Imaging [Internet]. 2019

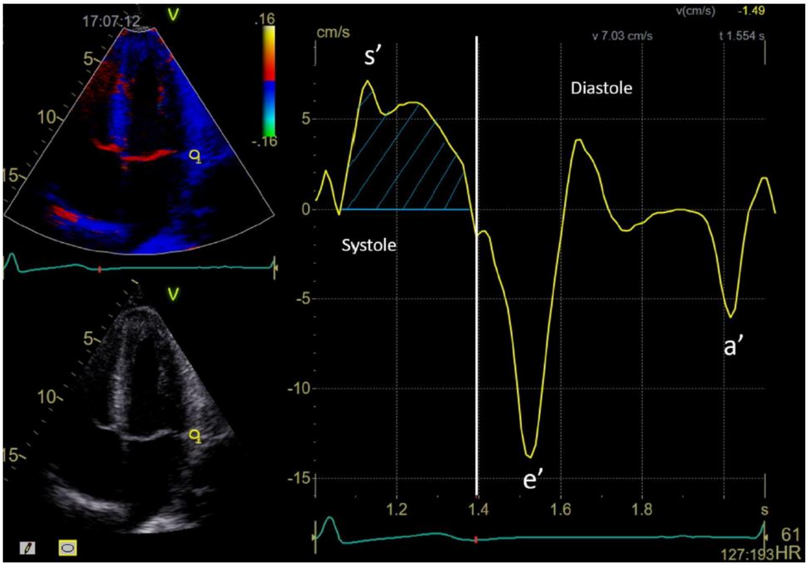
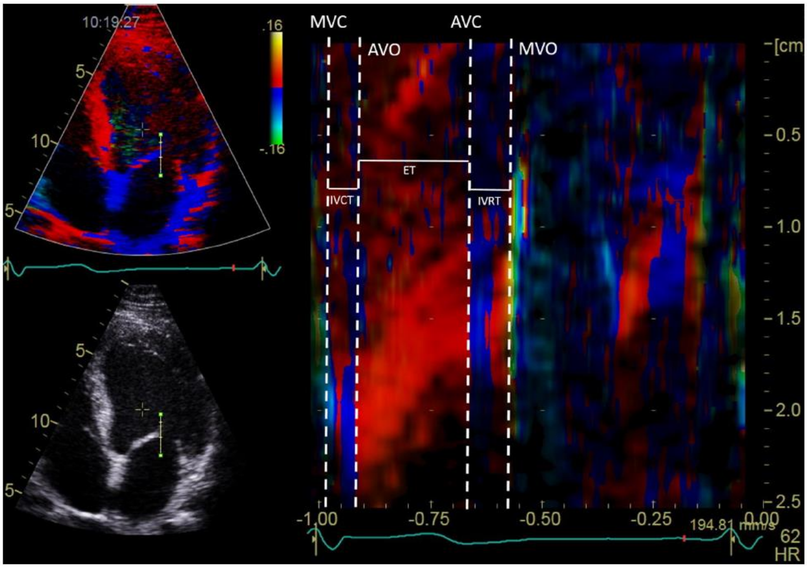


Figure 7

Cardiac time intervals assessed by colour tissue Doppler imaging M-mode line through the mitral leaflet during end-systole. MVC: mitral valve closing. AVO: aortic valve opening. AVC: aortic valve closing. MVO: mitral valve opening. IVCT: isovolumetric contraction time. IVRT: isovolumetric relaxation time. ET: ejection time.

Source: 'The association between physical activity and cardiac performance is dependent on age: the Copenhagen City Heart Study.' Joseph G et al. Int J Cardiovasc Imaging [Internet]. 2019



The Danish registries

CRS and NPR

A Civil Personal Register number (CPR) is a register linkage in all medical and administrative registers in Denmark [80,81]. A CPR-number is assigned by the Danish Civil Registration System (CRS), which provides information on the residents` migration and vital status: birth, citizenship, marital status, residence, emigration date, death date and more. Manual national registration of Danish residents was established in 1924, and the CRS in the electronic form as we know it today was established on 2 April 1968 [82]. The Danish National Patient Register (NPR) was established in 1977 and is internationally considered to be the most comprehensive of its kind [80]. In the beginning, only somatic inpatient contacts were registered. From 1969, psychiatric admissions were added, and from 1995, all emergency room contacts, as well as all outpatient contacts, were included. In 1994, Denmark adapted the International Classification of Diseases, version 10 (ICD-10).

Danish Death Cause register

It has been mandatory by law to complete a death certificate upon any case of a death occurring in Denmark since 1871 [83]. In 1970, the death causes were gathered in a central register by information collected from the manually completed death certificates. Before electronic registration, the codes were centrally validated by specially trained coding personnel in the National Board of Health. Since 2007, death certification has been submitted by an electronic form to the National Board of Health, and thus the ICD-codes are registered directly by the physical completion of the death certificate without central validation of the death causes. ICD-10 codes, as recommended by WHO, have been used since 1994.

Follow-up and outcome

All persons who participated in the Copenhagen City Heart Study were followed in the Danish registries regarding information on hospital contacts, death date, and death causes. The diagnostic information was coded according to ICD-8 until 1994, and afterwards, ICD-10. The date of death was collected from CRS and is updated daily centrally. The data on hospital admissions were collected from NPR and has a delay of two weeks on updates. The information in the Danish Death Cause Register has a delay of two years on updates. The end-date of follow-up for death date (CRS) and hospital admissions (NPR) was 19 April 2018 for study II and 13 December 2018 for study III. The end-date for follow-up for death causes was 31 December 2016 for both study II and study III.

In studies II and III in this thesis, we used the following ICD-8 codes and ICD-10 codes in NPR for defining cardiovascular events (admission or death due to acute myocardial infarction (AMI), heart failure, or stroke): ICD-8: 410-414; 42709-42711; 42719; 430-438. ICD-10: I20-I25; I50; J81; I60-I68; G45.
Previous cardiovascular disease (CVD) was defined as previous AMI or stroke reported by the participant in the questionnaire or registration of one of the above-mentioned ICD-codes in NPR before entering the Copenhagen City Heart Study for the first time.

Statistics

Study I

The association between the level of physical activity and cardiac function was analysed by linear regression models considering the level of physical activity as a categorical variable. Because tissue Doppler parameters are dependent on age, the analyses were made in the following age strata: < 50 years, 50-65 years, and > 65 years. Interaction analyses were performed in the multivariable regression models separately for each of the echocardiographic parameters to clarify whether age interacted in the association between the level of physical activity and cardiac function.
The assumptions for linear regression model were tested within each age group: Linearity, variance homogeneity, and normality. Normality was tested with plots of residuals.
We adjusted for following confounders: sex, ischemic heart disease, hypertension, BMI, and diabetes. Additionally, we also adjusted for resting heart rate (RHR) because RHR might affect TDI-values.

Study II

Cox regression model with time-dependent covariates was used to assess the association between the level of physical activity and the outcome in each of the BP groups. Thus, both exposures (level of physical activity and BP level) and confounders could potentially change over time for each of the persons included in this study. The underlying time scale was age. Besides, the following covariates were considered confounders: sex, smoking status (never smoker, former smoker, 1-14 g tobacco/day, ≥15g tobacco/day), education (<8 years, 8-10 years, ≥11 years), diabetes, previous CVD, class of BMI (underweight [BMI, <18.5 kg/m²], normal weight [BMI, 18.5–24.9 kg/m²], overweight [BMI, 25.0–29.9 kg/m²], and obesity [BMI ≥30.0 kg/m²]). Furthermore, all models were adjusted for calendar time.
When assessing cardiovascular events (admission or death due to AMI, heart failure, or stroke), death from other causes was considered as competing events.

This outcome was assessed with both Cox regression analysis and Fine-Gray subdistribution hazard regression analysis.

Study III

Linear regression models were used to assess the association between the level of physical activity and LVMi. Trend and interaction were analysed using the likelihood ratio test. All-cause mortality and cardiovascular events were assessed by cumulative incidence curves and by Cox proportional hazards regression analysis. A supplementary, Fine-Gray subdistributional hazard regression analysis was used for confirming the results for cardiovascular events considering death from other causes as a competing event. Following covariates were considered as confounders: sex, age, previous CVD, smoking status (never smoker, former smoker, current smoker), diabetes mellitus, and total cholesterol. BMI was not included as a confounder, because body surface area was used to calculate LVMi and define LVH.

RESULTS

Physical activity in the Copenhagen City Heart Study

In all four surveys, light activity was the most predominant activity level (Table 1, Figures 8-9). The percentage of moderate activity increased from 24% in survey 1 to 34% in survey 4. The percentage of persons in inactivity group decreased from 20% (survey 1) to 13% in survey 4.
This might be due to the increased health awareness over time and greater knowledge of the health benefits of physical activity.
When we study the distribution in each age group, it seems that light activity is the most predominant activity level in all age groups in all four surveys. However, in age 20–50 years, the percentage of high activity increased from 3% (survey 1) to 8% in survey 4. The percentage of inactivity increased with higher age in all four surveys; however, fewer persons were in this category in each age group over time.

Table 1.
Trend of physical activity in each of the four surveys.

	Exam 1	**Exam 2**	**Exam 3**	**Exam 4**
Inactivity, no. (%)	2,838 (20)	2,192 (17)	1,343 (13)	596 (10)
Light activity, no. (%)	7,692 (54)	6,104 (48)	5,307 (53)	3,157 (51)
Moderate activity, no. (%)	3,436 (24)	4,099 (32)	2,996 (30)	2,125 (34)
High activity, no (%)	241 (2)	294 (2)	344 (3)	295 (5)
Total, no (%)	14,207 (100)	12,689 (100)	9,990 (100)	6,173 (100)

Figure 8.
Distribution of level of physical activity in the first four surveys of the Copenhagen City Heart Study.

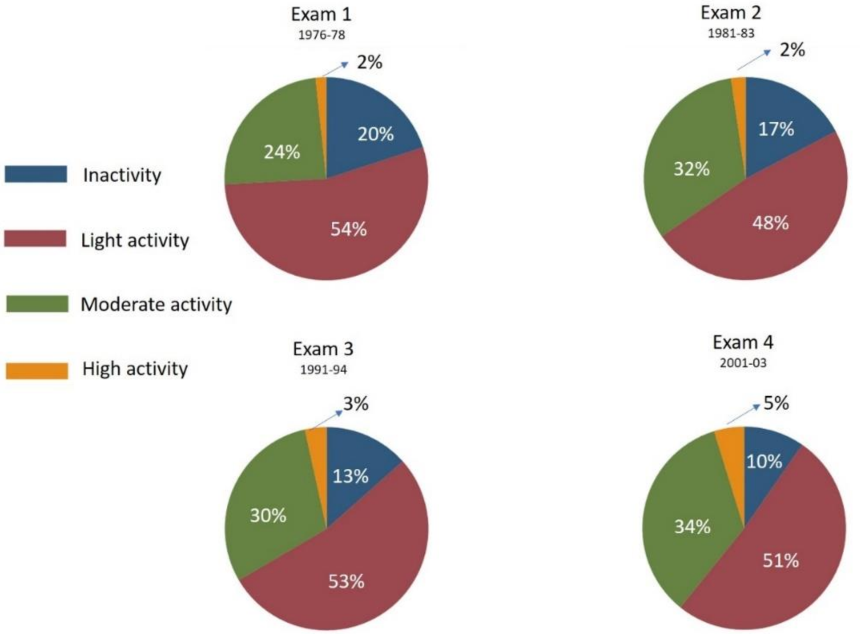
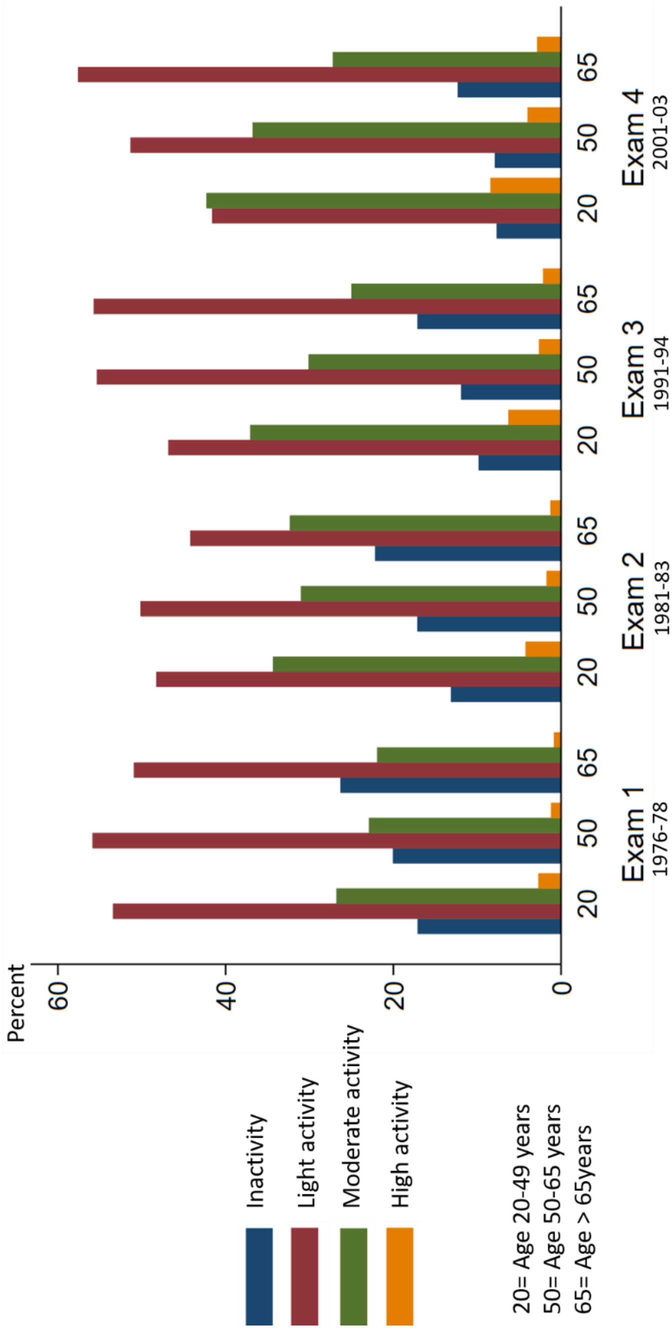


Figure 9. (next page)
Distribution of level of physical activity in the first four surveys of the Copenhagen City Heart Study, stratified by age groups.


Percent
60
40
20
0
20
50
65
Exam 1
1976-78
20
50
65
Exam 2
1981-83
20
50
65
Exam 3
1991-94
20
50
65
Exam 4
2001-03
Inactivity
Light activity
Moderate activity
High activity
20= Age 20-49 years
50= Age 50-65 years
65= Age > 65years

Study I

In all three age categories, the majority had a light activity level, and only a few had a high activity level (Table 1). Higher age group was associated with worse tissue Doppler parameters. In age< 50 years, increased levels of physical activity were associated with better cardiac performance. In age > 65 years, there seemed to be a tendency for worse cardiac function (MPI) at higher activity levels.

Table 2.
Distribution of the participants across age strata and activity levels.

	Age < 50 years	Age 50-65 years	Age >65 years	In total
I: Inactivity, no. (%)	53 (8)	47 (7)	80 (11)	180 (9)
II: Light activity, no. (%)	263 (41)	318 (48)	435 (57)	1,016 (49)
III: Moderate activity, no. (%)	261 (41)	269 (41)	223 (29)	753 (37)
VI: High activity, no. (%)	57 (9)	25 (4)	22 (3)	104 (5)
In total, no (%)	634 (100)	659 (100)	760 (100)	2,053 (100)

Figure 10.
Diastolic function.

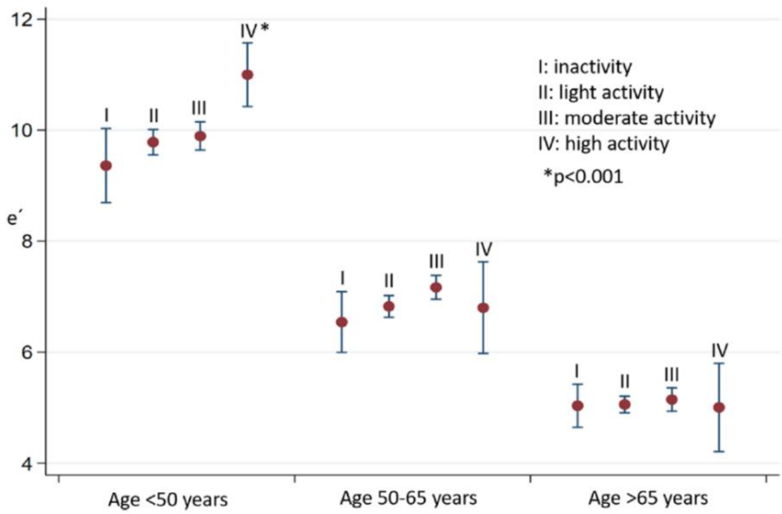


Figure 11.
Systolic function.

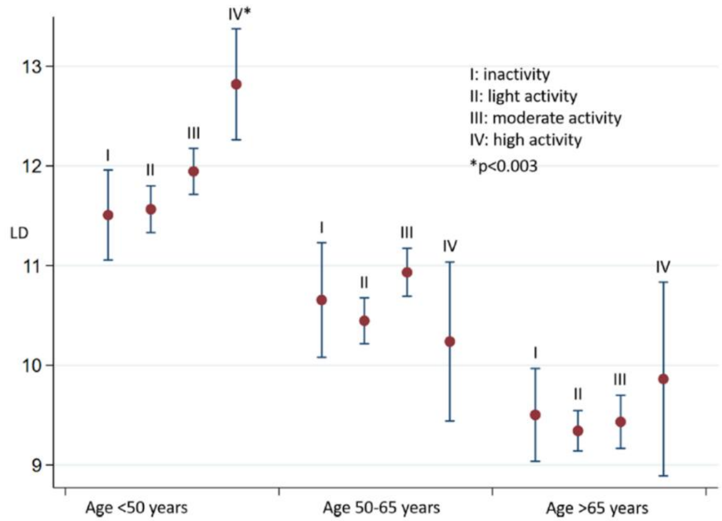
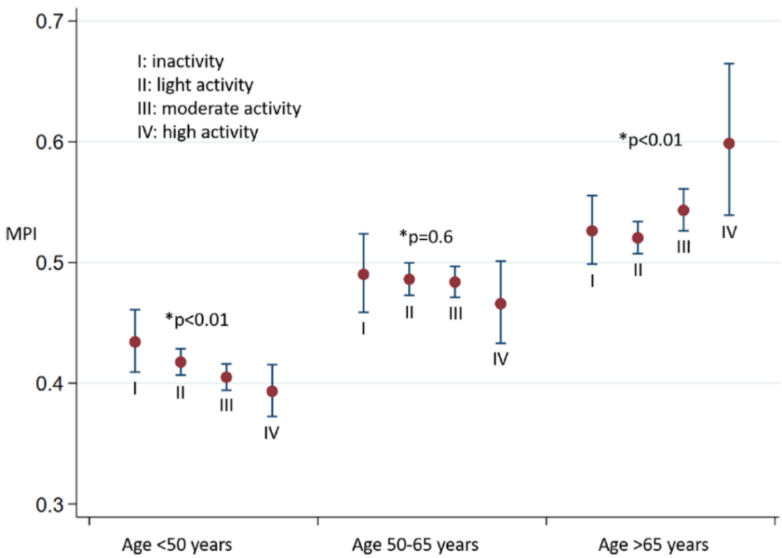


Figure 12.
Combined diastolic and systolic function.



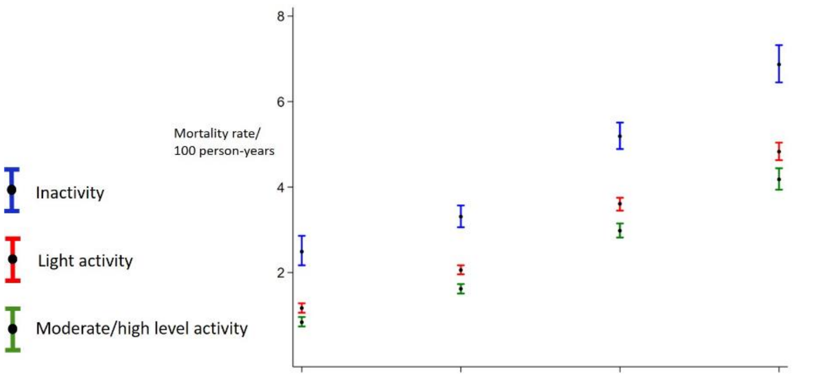
Study II

Level of physical activity was associated with a dose-response reduction in mortality at all BP levels. Compared with inactivity, any level of physical activity was associated with a reduction in cardiovascular events at all BP levels. Most of the health benefits were achieved already at the light activity level.

Table 3.
Distribution of the participants in each of the BP levels and activity levels.

	Inactivity	**Light activity**	**Moderate/ high activity**	**Total**
Normal BP, no. (%)	491 (13)	1,864 (51)	1,288 (35)	3,643 (100)
Pre-hyp., no. (%)	1,143 (17)	3,374 (51)	2,105 (32)	6,622 (100)
Stage 1 hyp., no. (%)	1,104 (21)	2,666 (51)	1,472 (28)	5,242 (100)
Stage 2 hyp, no. (%)	681 (22)	1,639 (53)	765 (25)	3,085 (100)

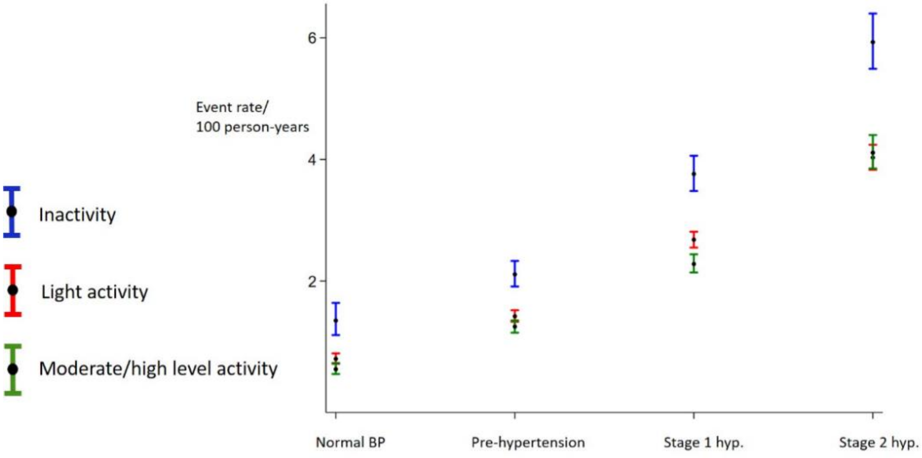
Figure 13.
All-cause mortality. Event rate. In the table below: No. of observations, and in parenthesis, no. of events.



	Normal BP	Pre-hypertension	Stage 1 hyp.	Stage 2 hyp.
In total	**6,528 (875)**	**13,733 (3,009)**	**13,460 (4,915)**	**8,793 (4,193)**
Inactivity	812 (203)	2,075 (668)	2,349 (1,097)	1,596 (945)
Light activity	3,347 (434)	6,991 (1,496)	6,957 (2,510)	4,697 (2,179)
Moderate/high level activity	2,369 (238)	4,667 (845)	4,154 (1,308)	2,500 (1,069)

Figure 14.

Cardiovascular events. Event rate. In the table below: No. of observations, and in parenthesis, no. of events.



	Normal BP	Pre-hypertension	Stage 1 hyp.	Stage 2 hyp.
In total	**6,427 (508)**	**13,420 (1,946)**	**12,719 (3,148)**	**8,306 (3,021)**
Inactivity	787 (101)	1,999 (383)	2,193 (668)	1,480 (650)
Light activity	3,296 (255)	6,839 (957)	6,546 (1,597)	4,439 (1,498)
Moderate/high level activity	2,344 (152)	4,582 (606)	3,980 (883)	2,387 (873)

Study III

1. LVMi was significantly higher in hypertension compared with normal BP (Figure 15).
2. Hypertension modified the association between the level of physical activity and LVMi. Thus, a higher level of physical activity was associated with increased LVMi in normal BP, whereas this association was not found in hypertension (Figure 15).
3. Physical activity was associated with a reduction in mortality and cardiovascular events. This association was not modified by the presence of LVH (Figure 16–17).
4. The impact of LVH on prognosis was not modified by higher physical activity levels (Figure 18).
5. BP level did not modify the impact of LVH on prognosis; thus, LVH was associated with worse outcome in both normal BP and in hypertension (Figure 19).
6. LVH remained an independent predictor of mortality and cardiovascular events (Figure 20).
7. Level of physical activity was an independent predictor of reduced outcome (Figure 20).

Table 4.
Distribution of the participants according to the BP levels and activity levels.

	Inactivity	**Light activity**	**Moderate/ high activity**	**Total**
Normal BP, no. (%)	109 (6)	764 (45)	829 (49)	1,702 (100)
Hypertension, no. (%)	129 (9)	762 (55)	485 (35)	1,376 (100)
Total, no. (%)	238 (8)	1,526 (50)	1,314 (43)	3,078 (100)

Table 5

Distribution of the participants according to presence of LVH and activity levels.

	Inactivity	**Light activity**	**Moderate/ high activity**	**Total**
No LVH, no. (%)	189 (8)	1,234 (49)	1,106 (44)	2,529 (100)
LVH, no. (%)	49 (9)	292 (53)	208 (38)	549 (100)
Total, no. (%)	238 (8)	1,526 (50)	1,314 (43)	3,078 (100)

Figure 15.

LVMi and activity level.

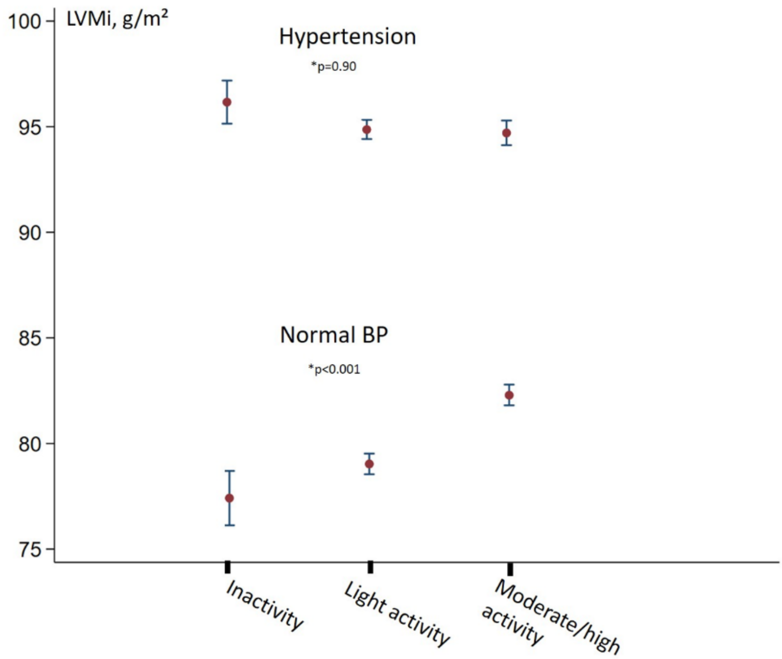


Figure 16.
Cumulative incidence of all-cause mortality and cardiovascular events, according to the presence of LVH, stratified by the level of physical activity.

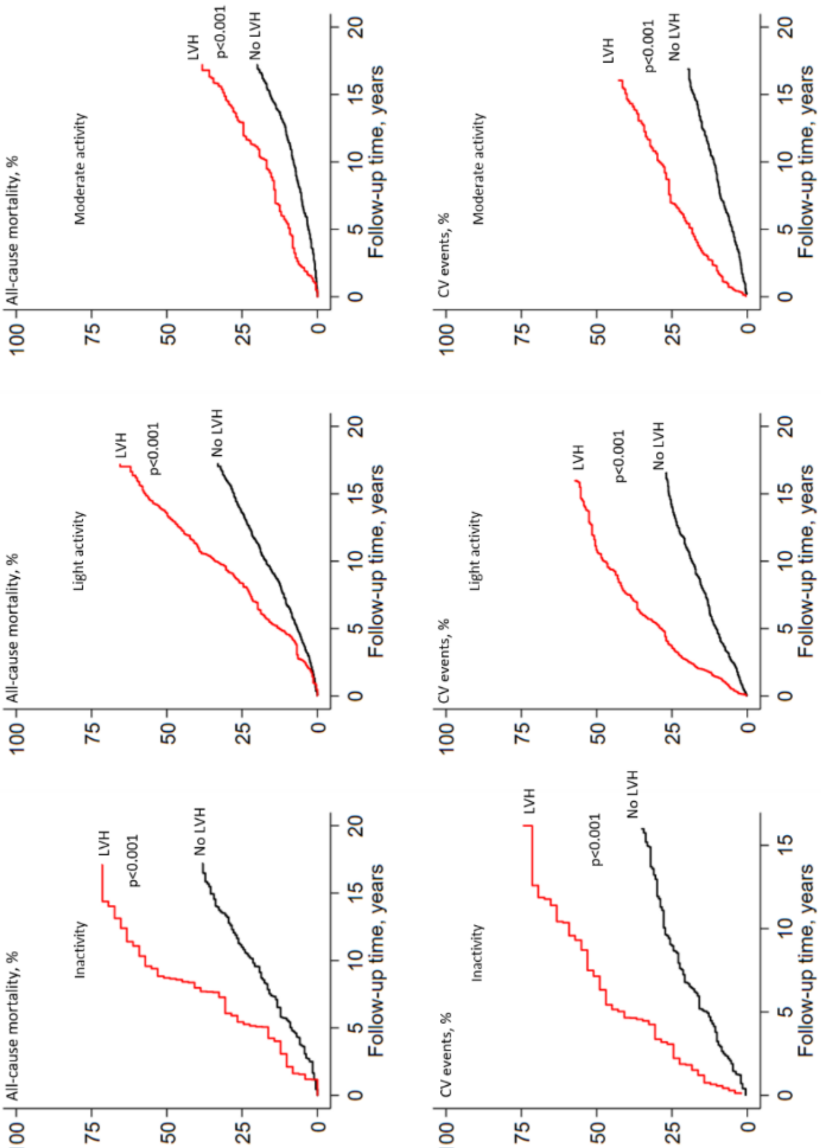


Figure 17.

LVH, physical activity, and outcome. All-cause mortality and cardiovascular events according to the level of physical activity and presence of LVH. Adjusted for age, sex, diabetes mellitus, total cholesterol, previous CVD, smoking status, and hypertension.*P<0.05; **P<0.01; ***P<0.001.

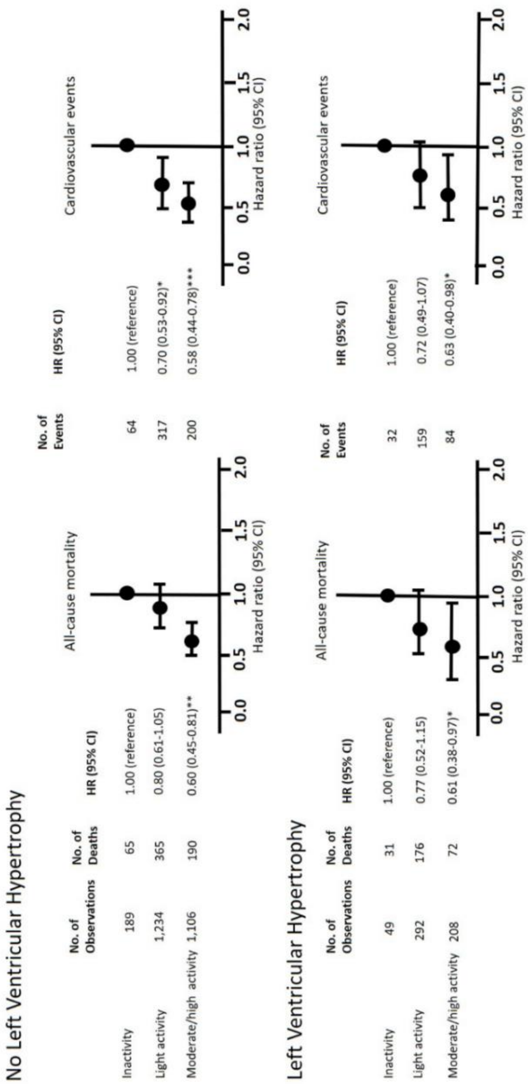


Figure 18.

Physical activity, LVH, and outcome. All-cause mortality and cardiovascular events according to the level of physical activity and presence of LVH. Adjusted for age, sex, diabetes mellitus, total cholesterol, previous CVD, smoking status, and hypertension. *P<0.05; **P<0.01; ***P<0.001.

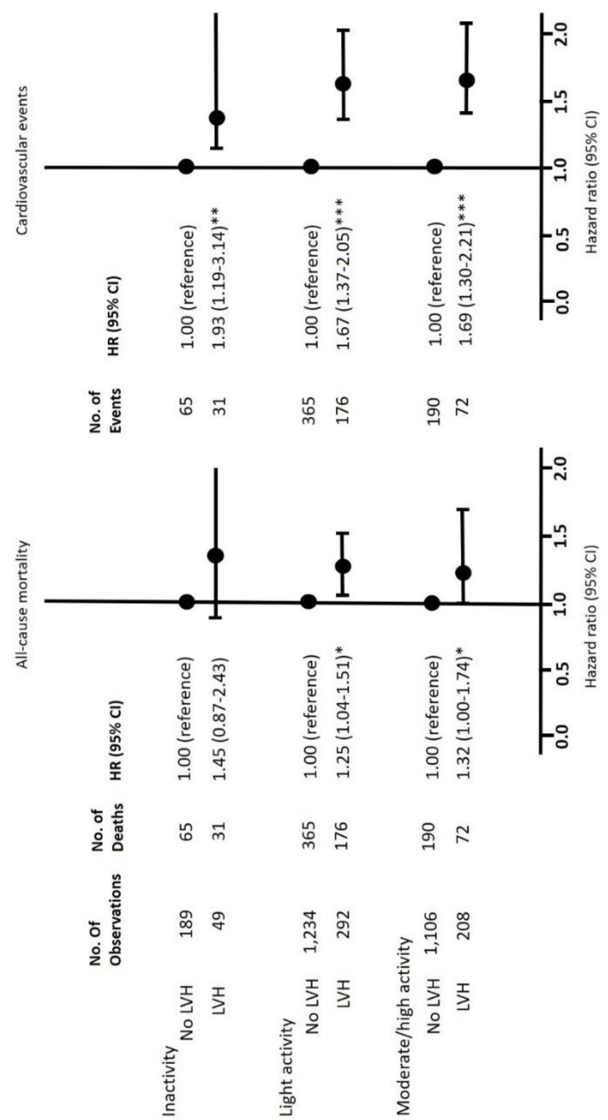


Figure 19.

BP level, LVH, and outcome. All-cause mortality and cardiovascular events according to the BP group and presence of LVH. Adjusted for age, sex, diabetes mellitus, total cholesterol, previous CVD, smoking status, and level of physical activity. *P<0.05; ***P<0.001.

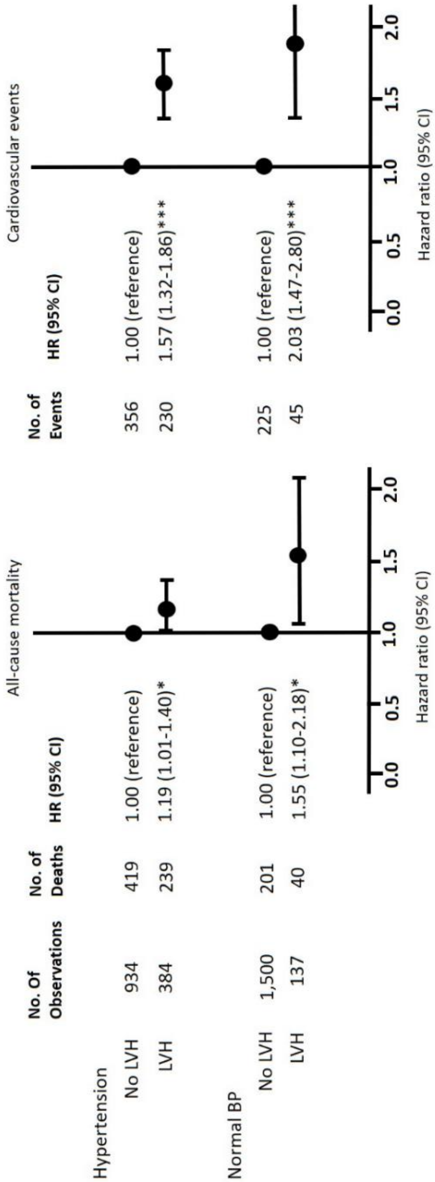
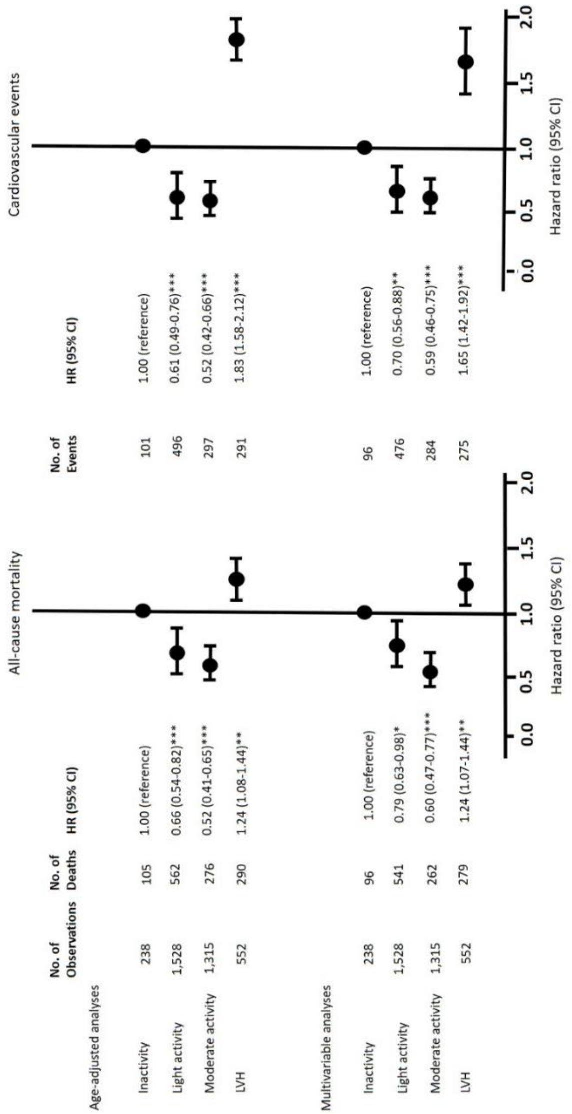


Figure 20.
All-cause mortality and cardiovascular events. Multivariable analyses are adjusted for age, sex, diabetes mellitus, total cholesterol, previous CVD, smoking status, and hypertension. *P<0.05; **P<0.01 ***P<0.001.



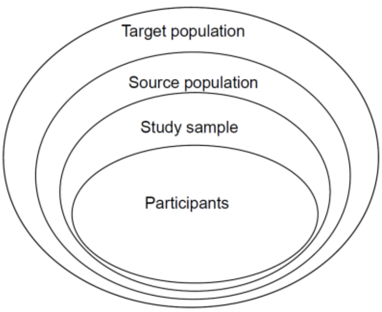
DISCUSSION OF THE METHODOLOGY

Concerns about the invited population

As illustrated in Figure 21, participants in a cohort study differ from the target population, to whom we want to address the overall study results.
There might be selection bias at different levels from planning a cohort study to the individuals who participated in the specific studies.
This was a population-based cohort-study which by its nature leads to selection bias because not everyone invited to the study will participate. Even though the persons invited to take part in the study were randomly selected, the study population consisting of persons who chose to participate might not necessarily represent a random sample. It is well-known that persons who chose to participate might be healthier than those who do not participate, leading to a systematic difference between these two groups [84]. Those who usually chose to participate in a population study might thus belong the higher social class of the community [85].

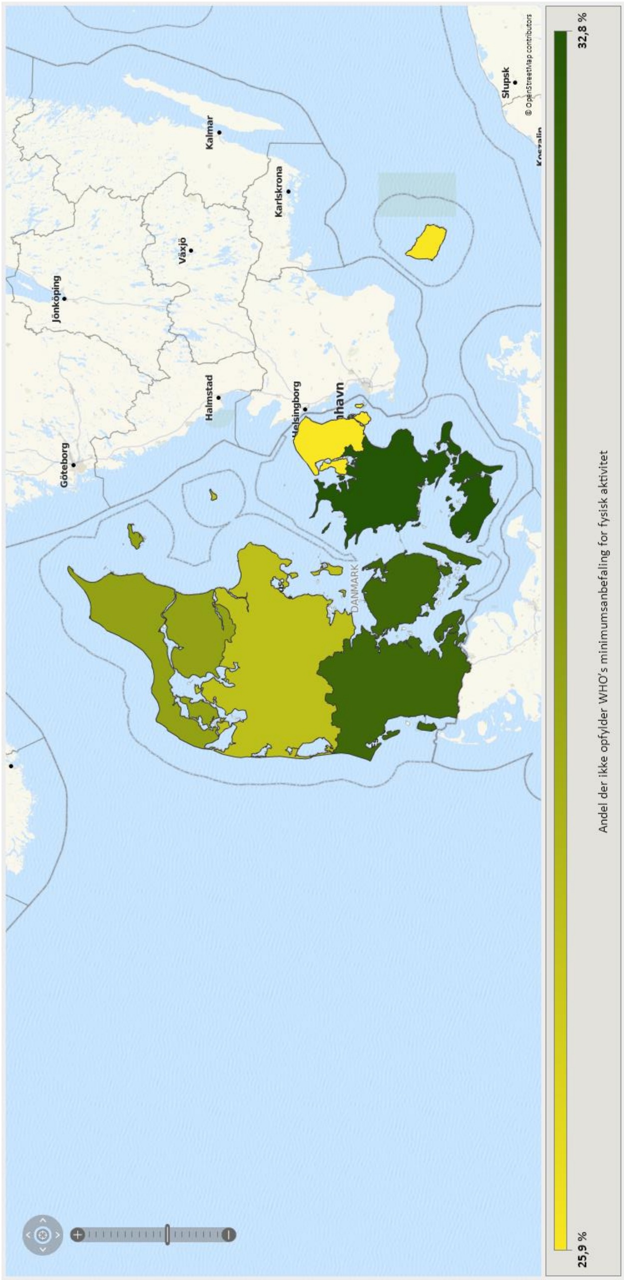
In the Copenhagen City Heart Study, the source population was inhabitants of inner Copenhagen, who were invited to take part in the surveys. The study sample (those who agreed to take part) is already a selected group. Different factors might affect who chooses to participate in a cohort study [86,87]. If this is systematically dependent on exposure or outcome, this may lead to selection bias [85,88]. However, not all exposure-outcome associations might be affected by selection bias [89]. It is already shown that the distribution of mortality rates in some Danish cohort studies, including the Copenhagen City Heart Study, differ and are higher among the non-participants compared with participants [90].

Figure 21.
The target population to whom we might want to address the results might differ from the study participants.



The population invited to take part in the Copenhagen City Heart Study was from Østerbro (2/3) and Nørrebro (1/3). Persons living in this part of Denmark, especially Østerbro, are usually healthier and wealthier compared with other parts of Denmark [2,91]. This might raise concerns about how the results could be applied to the general population. It is well-described how both the prevalence of cardiovascular diseases and survival are dependent on social, educational, and economic factors [92–95]. Physical activity, which is the main exposure in the studies included in the present thesis, is dependent on health awareness and socioeconomic status [92,96–98]. Thus, the distribution of activity levels in the current study population might differ from other populations in Denmark.
According to the Danish National Health Profile [2], the population in the Capital Region of Denmark, and especially in the areas of Østerbro and Nørrebro, has the highest adherence to the WHO recommendations on physical activity (Figure 22).

Figure 22. (next page)
Percentage of the population not fulfilling the WHO recommendation for physical activity. Source: Danish National Health Profile.
http://www.danskernessundhed.dk/


Kalmar
Karlskrona
Växjö
Jönköping
Halmstad
Helsingborg
Göteborg
Słupsk
DANMARK
© OpenStreetMap contributors
32,8 %
Andel der ikke opfylder WHO's minimumsanbefaling for fysisk aktivitet
25,9 %

Even though the study population is not representative for the whole Danish population, it should be underscored that we studied associations between physical activity and

1. cardiac performance (study I),
2. long-term prognosis in hypertension (study II), and
3. LVMi/LVH and prognosis (study III).

The distribution of both exposure (physical activity/hypertension) and outcome (death/cardiovascular events) might differ across different socioeconomic classes, but the associations between these might be the same in other study populations from Denmark and in other parts of the world.
Further, we additionally adjusted for potential confounders in the time-to-event analyses. In our analyses we included education as a measure of socioeconomic status and did not include annual income. In a Danish population, we believe, that education is a more sensitive marker of socioeconomic status than income. By this adjustment and additional adjustment for other factors which might affect the association between physical activity and cardiac function/outcome, we, therefore, hope that differences which might interfere in the association do not have a significant impact on the overall interpretation of the results.

Missing variables and non-responders

The participants in the specific studies differ further because usually only persons without missing variables on the defined exposure are included. It is important in a cohort study to clarify whether the missing information could also be a sign of bias. That means, whether persons with missing covariates have more comorbidities as this might lead to exclusion of the sickest persons in the analyses.

Another concern is the characteristics of the participants who do not attend the follow-up surveys. Once entered the Copenhagen City Heart Study, all participants were invited to the subsequent surveys, and each time a new number of participants were included (Figure 2). Those who do not participate (non-responders) might differ in both exposure and outcome, compared with those who participate in the following examinations. In selective drop-out, results might be affected dependent on associations examined [84]. Those exhibiting worse health might not participate in subsequent surveys, either because of 1) their health status or inability to participate or 2) other reasons, such as social factors, making them uninterested in participating.
A previous study has described how the non-responders in the Copenhagen City Heart Study have a worse prognosis compared with the persons who attend the subsequent examinations [99].

Persons who underwent echocardiogram

Persons who underwent echocardiogram were randomly selected from the study population of the fourth survey. Their health status did not determine whether they underwent an echocardiogram. The technicians who performed the echocardiograms and the investigators analysing the images were blinded to the participants´ health information. The participants who underwent TDI were a random sample, as well. In Paper I, we studied the population who underwent TDI (N= 2,221), and in Paper III, we studied all persons who underwent conventional transthoracic echocardiograms (N=3,654). The population sample who underwent TDI was a random sample (N=2,221) of those who underwent conventional transthoracic echocardiogram (N=3,654) (Figure 4.) To confirm that these two echocardiographic populations were random samples, we made sensitivity analyses by performing the time-to-event analyses for those who underwent TDI vs. conventional echocardiogram only (prior to publication of Paper III). The results exhibited the same pattern.

Blood pressure

Casual BP measurement

In the present studies, a single BP measurement (casual BP) on the non-dominant arm was performed under highly standardised circumstances as described by Rose & Blackburn [57]. The circumstances were unchanged in all four surveys. Current guidelines recommend that BP is measured under standardised circumstances more than once, on both arms, and additional measurements are required if the first two readings differ by >10 mmHg [100]. Thus, casual BP is not the best method to diagnose or grade hypertension status. However, casual BP has been widely used in other large epidemiological trials and suggested by Rose & Blackburn as a feasible method. Casual BP is a reliable predictor of hypertension and risk of stroke and other CVD [101,102]. A study from Framingham also described casual BP as highly predictive of future cardiovascular events in an epidemiological setting, even though a single BP measurement does not provide a precise characterisation for each person [103].

Trends of BP in the study population

A previous study performed by Andersen et al. in 2004 showed that the study population from the Copenhagen City Heart Study had a decrease in systolic BP over time [104]. The decrease was independent of major cardiovascular risk factors and increasing alcohol intake [105]. The level of physical activity did not explain the declining population BP [106]. However, even though this trend reflected a decline in

mortality risk in the younger and middle-aged part of the population, the effect of systolic BP on mortality remained the same [107]. Women with a higher economic income had significantly lower systolic BP compared with women in a low-income group [108]. This difference seemed to increase with time. This pattern was not found among men. No income-associated differences were found in the pharmacological treatment of hypertension.
Daytime variations in both systolic and diastolic BP have also been described, but these differences were not found after adjustment for age [109]. There were also seasonal variations since there was a tendency of higher BP during winter. However, the examinations, including BP measurements, took place in all seasons, minimising the importance of seasonal variations.

Blood pressure medication

The definition of hypertension and BP levels are based on the measurement at baseline. We do not know if the persons who were diagnosed with hypertension at baseline started antihypertensive medication during the follow-up, and how this would affect the results. Especially for study III, it might be of importance, because some medications, especially medications affecting the renin-angiotensin system, might reduce LVM independent of the reduction in BP [110,111]. It would have been desirable if we applied for data from the Danish National Prescription Registry [112], which is a registry covering individual-level data on prescriptions for Danish residents. This registry was established in 1994, and detailed information on the pharmacological prescriptions have been registered since 1995. Because the Copenhagen City Heart Study started in the 1970s, we could not have medication data from the registry for study II, but for study III, it would have been possible. However, this was not made because of the well-known very long waiting time from formal application to possible granting of access to the data.

Physical activity in work time

In the present studies, we studied the physical activity only in leisure time. We did not include occupational physical activity. The main reason was that many persons, especially persons aged >60 years, had missing information on the variable determining level of physical activity in work, because many persons >60 years are usually retired from work. Besides, the levels of physical activity in leisure time and work time might not be comparable in terms of cardiovascular prognosis. Persons having high physical demands at work are at higher risk of atherosclerosis [113,114] and have higher levels of systolic BP [115]. Previous studies have described that this part of the population has a higher risk of cardiovascular events and all-cause mortality [116]. Physical activity in leisure time promotes health, while occupational physical activity impairs health, a phenomenon named the ‘physical activity paradox’ [117]. Thus, not including physical activity level in work time seems reasonable in the present studies.

Reporting bias: self-reported physical activity

The level of physical activity was self-reported. Since this is a prospective cohort study, we do not assume there is a recall bias, but there might rather be a reporting bias. The causes could be social desirability, inaccurate memory, or the inability to evaluate the absolute activity level [118]. This induces a limitation to self-reported activity concerning reliability and validity [119]. The question is, whether there is a systematic error in the ways the exposed (active) group and the unexposed (inactive) groups reported their activity level. One might suspect that most people tend to overestimate their level of physical activity. Many persons might have a desire to increase their level of physical activity, and this might affect the reporting, especially among those in the inactivity or light activity group [120].
Direct/objective measures might provide precise estimates of energy expenditure and remove reporting bias. Direct measures could be calorimetry, physiologic markers (i.e., cardiorespiratory fitness), and motion sensors/monitors (i.e., accelerometers) [121,122].
The questionnaire used in this study was described by Rose & Blackburn [57] and Saltin & Grimby [123], later used in modified versions in other Nordic countries [124], where it was found to be sufficiently reliable and valid to monitor physical activity levels in the population. Other studies comparing the association between the objectively measured level of physical activity and self-reported activity concluded that study participants reported more vigorous activity and less sedentary time compared with accelerometer data [121].
In the fifth survey of the Copenhagen City Heart Study, accelerometers were used to assess physical activity in 2,335 persons [125]. In the future, it would be possible to compare and validate the self-reported physical activity data in the study population of the Copenhagen City Heart Study.

Duration of level of physical activity

Persons having a high BP at the examination were told to contact their general practitioner to remeasure the BP and evaluate the need for medical treatment. It is possible that these persons, with time, became more aware of their health status and thus changed their health behaviour including increasing their level of physical activity afterwards. This could probably affect the results. Further, participating in a cardiovascular population study might also affect the health awareness.
In the physical activity questionnaire, the participants were asked to grade their level of physical activity for the last year. In the longitudinal studies, we assumed that these activity levels were present until the date of an event/censoring or the next survey. We cannot, of course, be sure that the persons did not change their level of activity. Previous publication from the Copenhagen City Heart Study described that more than half of the study population remained in the same activity level between two surveys [126]. Our study results are very consistent in the

association between level of activity and outcome. Additionally, previous studies with self-reported activity showed similar results [10,127,128].

STUDY-SPECIFIC DISCUSSION

Discussion study I

Study design: Analytical cross-sectional study

Cross-sectional studies are a snapshot of the study population. Cross-sectional studies, also called, prevalence studies, can either be descriptive or analytical. In the analytical study, both exposure and outcome are measured at the same time point [129]. By their nature, cross-sectional studies are not the most suitable for concluding any causality, especially because of the uncertainty of durance of the exposure [130]. Study I in this thesis is an analytical study, where exposure is the level of physical activity and outcome is cardiac function. We considered the level of physical activity as a stable exposure. However, according to the physical activity questionnaire, the participants were supposed to select the activity level that was appropriate for their physical activity during the past year. So, the actual exposure is the level of physical activity for the past year. The outcome is the cardiac function measured by tissue Doppler echocardiography.

Another important issue in cross-sectional studies is, whether the exposure or the outcome came first [131]. In the present study, it means, whether we believe that the cardiac function reflected the level of physical activity, or if better cardiac performance lead to higher physical activity level. The latter assumption would make no sense. However, we should remember, that persons in better health are able to perform higher levels of activity.

Statistics and confounders

The results presented in the figures for e`, LD, MPI, and RHR in the paper were mean and 95% confidence intervals (CI). It would have been better to present the adjusted means and 95% CI, after adjustment for all confounders. The presented p-values for the trend tests are p-values in a multivariable trend test (multivariable linear regression where physical activity was considered as a continuous variable). It would have been more appropriate to use a likelihood ratio test for trend analysis.
RHR does not fulfil the criteria for being a confounder (associated with both exposure and outcome without being an intermediate) [132]. Lower RHR might rather be a physiologic consequence of high activity level. However, we chose to adjust for RHR in the multivariable model because the tissue Doppler values are related to RHR [133,134]. Especially, cardiac time intervals are sensitive to changes in the heart rate.

It would also have been interesting and relevant to adjust for the continuous systolic/diastolic BP or mean arterial BP because this might determine the peak values of tissue Doppler parameters [135,136]. We adjusted for hypertension vs normal BP as a binary variable in the published paper. Sensitivity analyses with adjustment for continuous BP did not change the results presented in Paper I. These analyses were made after the publication.

Age, physical activity, and cardiac function

When I presented the results from study I at meetings and congresses, the older part of the audience usually chose to interpret the results, as saying that persons > 65 years do not have to be physically active. However, even if the conclusion is that the association between physical activity and cardiac function is modified by age, this cannot be a causal correlation.

First, the study is performed in a cross-sectional study design. Second, we do not know for how long a time the participants had their reported level of physical activity. Third, we do not know whether each participant`s own classification of their level of physical activity is dependent on their age. The fact, that the activity level is self-reported is also an important detail, which is addressed previously in this thesis. We should also be aware of the fact that persons still alive at age > 65 years and who are able to perform physical activity are already a selected healthy group. Their health status is not only dependent on their cardiac function but also other factors keeping them in a good life and health status. Even though MPI shows a sign of deterioration in cardiac function, it should not discourage one from exercising. Besides, the benefits of physical activity might be induced through many several physiological mechanisms apart from cardiac function, which is why the results should be interpreted with precautions. We assume that the main reason for the interaction between age and activity level is that an ageing heart and myocardium might be less capable of changes due to physical activity compared with a younger myocardium.

The echocardiograms were performed at rest. Thus, the echocardiographic parameters reflect the cardiac function at rest. It would be interesting to study the same measures during exercise to evaluate how well the measures in rest correlate with the cardiac function during stress.

In our study, we found different trends in MPI for both the younger (<50 y) and elder (>65 y) age groups. When analysing MPI, we found that the changes in these age groups were primarily driven by IVRT. Diastolic function is an important determinant of aerobic fitness and IVRT is a sensitive marker in evaluating LV diastolic function in terms of exercise. Our finding is comparable with results reported by Libonati and colleagues regarding changes in both Tei-index and IVRT [137–139].

However, from an academic point of view, this study contributes slightly to the ongoing modern discussion about the theme, if too much physical activity could be dangerous, even though this concern has mainly been raised about persons at younger age performing sports on a competitive level [26,140,141]. Concluding from our study that physical activity is dangerous would be unfair.

Discussion study II

Study design II: Observational cohort study

Study II and the second part of study III were performed in a cohort study design. The main criterion a cohort study should fulfil is that the unexposed should be similar in the characteristics to the exposed, with the exception of not having the exposure [142,143]. As in many other cohort studies, this criterion was not fulfilled for the present studies. Persons in light/moderate/high activity were the exposed groups, and sedentary persons were defined as the unexposed. These groups differed significantly from each other in terms of health profile and socioeconomic status. This was, however, an expected finding.

Physical activity is a measure of the health profile, as well as socioeconomic status. These three subjects are linked with each other and make natural differences in the description of the study populations. Controlling for confounding is therefore very important.

The differential loss to follow-up between exposed and unexposed can bias the results. Fortunately, the unique features of the Danish registries made it possible to follow every person in the cohort until end of follow-up, date of death, or event. Only 1.1% of the study population emigrated, and they were followed until the date of emigration.

Stratification on BP level

There was a dose-response association between the level of physical activity and mortality at all levels of BP. This means that there was no interaction between physical activity and BP level on the outcome. So, practically and statistically, the analyses could be performed as a pooled analysis without stratification on the BP level. However, we chose to perform the analyses in each of the BP levels. The reason was, in the case that all BP levels are pooled, the assumption would be that the confounders have the same impact on every person regardless of the BP level. This means, that e.g. BMI-class or smoking status have the same impact on the prognosis for a person in normal BP as for a person in stage 2 hypertension. This might not necessarily be the case since there might be interaction between the covariates and the levels of BP on the outcome. Because BP level is a strong prognostic marker, the most appropriate method will be stratification on BP level in the way we chose to do, even though a pooled analysis could be justified statistically.

When to stop the follow-up?

The number of years between the four surveys differed by 5 to 10 years. Not all persons continued in all subsequent surveys once they entered the study. Some of them were absent from one or more of the subsequent surveys. We decided to follow the participants until the date of an event or April 2018 once they had entered the study. When the statistical analyses were performed, the latest covariates were considered valid until the next time the participant attended a survey or until the end of follow-up if the participant did not attend further surveys. If we had decided to make censoring when a subject did not attend the following survey, this study would have a significant bias in only following a survival-cohort which is not representative of the general population. However, we made sensitivity analyses where we censored subjects who did not participate in the following surveys. This did not change the pattern of the results.

Persons with previous CVD

The main results presented in the paper included persons with previous CVD, and previous CVD was considered a confounder in the multivariable analyses. Excluding persons with previous CVD at baseline might possibly be one way to come closer to a causal association. However, this would not represent the general population (target population) to whom we want to address the results. Persons with hypertension might already have been at risk for CVD for a long time or already have suffered from CVD. However, we made sensitivity analyses with the exclusion of persons with previous CVD and found the same result pattern.

Reverse causality

When interpreting the results, a major concern was reverse causality. The question was whether the lower activity levels were a result of severe morbidity or higher age (both leading to higher mortality). Ageing is associated with higher frequencies of comorbidities, higher BP, and lower activity levels [144,145]. To exclude the possibility of reverse causation, we made two sensitivity analyses. In the first, we excluded everyone who had an event during the first three years, assuming that persons with severe comorbidities would pass away during the first three years. The follow-up time started three years later for the remaining population. In the second analysis, we excluded everyone who were older than 60 years of age. In both analyses, we found the same pattern of results for both mortality and cardiovascular events.

Time-to-event analyses with time-dependent covariates

The study population was followed since 1976, and the covariate data were collected longitudinally. Both exposure and other covariates changed over time, which is why we selected Cox regression with time-dependent covariate instead of using fixed covariates.
The time-to-event analyses made it possible to let the exposure and covariates/confounders change over time.

Persons in medical treatment for hypertension

Participants who already received pharmacological treatment were included in the study population, and they were categorised in stage 1 hypertension, unless their BP values justified stage 2 hypertension. In the published paper, we did not add sensitivity analyses only for persons already treated with antihypertensive medication. These analyses were made later, and the results confirmed a dose-response pattern between the level of physical activity and mortality with Inactivity as reference group: Light activity HR 0.86 [95% CI: 0.78 – 0.96], p=0.005; Moderate/high activity HR 0.76 [95% CI: 0.67 – 0.86], p<0.001.

Discussion study III

Study design III: Cross-sectional and cohort study

Study III consisted of both a cross-sectional study and a cohort study. The association between the level of physical activity and LVMi was evaluated in a cross-sectional study design. The impact of physical activity on prognosis was studied in a cohort study design. The cross-sectional analysis included level of physical activity as exposure and LVMi as the outcome.

Assessment of left ventricular mass

M-mode tracing was the predominant method used to assess LVM in this study. At the time of the echocardiographic examination, this method was the standard and recommended method to study LVM [146]. M-mode assessment is previously shown to overestimate LVM [65]. Besides, the single dimension image makes it representative only in normally ellipsoid shaped ventricles and is less suitable for asymmetric distribution of hypertrophy [147]. The latter issue remains a limitation in 2D measurements as well, but 2D measure of LVM facilitates more accurate measurements perpendicular to the LV long axis [65].
Further, we indexed the LVM to body surface area. This measure has previously shown to underestimate LVM in overweight and obese hypertensive subjects [148]. Dividing LVM by height to the allometric power of 1.7 or 2.7 has been suggested to minimise this limitation [149].
In our study population, a total number of N=1,134 persons (37%) were overweight (25≤BMI<30), N= 301 (10%) were obese (30≤BMI<35), and N=74 (2%) had severe obesity (BMI≥35).

Stratification on sex

To convey the study results clearly, we chose to analyse the data not stratified on sex. A previous publication from the Framingham Heart Study described that men had a positive association between level of physical activity and LVM, whereas this association was not found for women [150]. Other studies have also found that LV remodelling due to physical activity and hypertension is dependent on sex [151–153]. However, from an epidemiological and physiological point of view, it would have been reasonable to stratify on sex, even though we did not find any statistical interaction between sex and physical activity on LVMi or outcome.

Left ventricular hypertrophy in normal blood pressure

Interestingly, we found that LVH was present in N=144 persons with normal BP. We also found that LVH was associated with significantly higher mortality and cardiovascular events in normal BP. It is possible that these persons had masked hypertension, which was not discovered at the exam. Presence of LVH could also be due to other causes than hypertension, which we did not evaluate in our study [154,155].

LVH and physical activity as independent predictors of prognosis

During study III, we made some supplemental analyses, which are not included in the published paper. We made a multivariable Cox regression analysis where we included both LVH and level of physical activity, beside adjusting for already defined confounders (Figure 20). We found that both LVH and level of physical activity remained as independent predictors of prognosis; thus, LVH was associated with the worsening of the prognosis, while physical activity was associated with a better prognosis. These results underscore that LVH has a strong impact on prognosis but also that the importance of physical activity remains significant.

Duration of hypertension

At baseline, the LVMi was significantly higher in persons with hypertension. Only N=481 persons were in pharmacological treatment, and the rest N=884 were newly diagnosed with hypertension. The fact that their LVMi is higher already at baseline might indicate that the newly diagnosed hypertensive subjects have had hypertension for a longer time due to the lack of symptoms in essential hypertension [100].

Exercise testing

In recent years, there has been a focus on exercise testing as an important player in the risk assessment for hypertension and the development of LVH. The research in the field of exercise BP is growing, and the findings in this area are divergent. Previous studies have concluded that exaggerated exercise BP is related to the future development of hypertension [156] and higher LVM in normotensive persons [157,158].

Recently, Tanaka S. and colleagues published a paper describing a study comprising 143 persons in medical treatment for hypertension. All participants had maintenance of the BP<140/90 and did not have LVH on echocardiography at baseline [159]. During treadmill and cycle ergometer exercise testing, the BP response during moderate exercise was measured. After a follow-up time of 2.5 ± 1.6 years, they found that the risk of developing LVH was associated with the change in systolic BP during exercise testing; thus the persons who had the highest increase in systolic BP during exercise had the highest occurrence of LVH. Controversy exists in this field since another study reported by Mizuno R. and colleagues showed that exaggerated BP response during exercise was associated with depressed LVH regression in hypertensive patients on medical treatment [160].

PERSPECTIVES

Physical activity, cardiovascular disease, and prognosis

Studies II and III demonstrated the long-term health benefits of physical activity and added more specific knowledge about the importance of exercise in hypertension. The role of physical activity as a treatment modality in hypertension has been the focus in these studies, and the main conclusions from these studies also apply to the especially high-risk sub-groups among hypertensive patients:
1. persons with LVH, and
2. patients in stage 2 hypertension.
Meanwhile, study I went in-depth with the association between physical activity and myocardial performance. The results imply that the impact of physical activity on cardiac function might be age dependent. However, we should remember that not all benefits of physical activity are achieved through changes in cardiac function and morphology, and yet, there are many physiological mechanisms in relation to physical activity which need to be explored. Longitudinal studies with physical activity as an intervention in different age groups and repetitive echocardiograms could be a way of exploring the cardiac alterations induced by physical activity.

Future studies

All three studies give a basis for many future studies. The association between physical activity and changes on cardiac morphology and cardiac function has been studied extensively in athletes, while we need more studies of this issue in the general population who are active on a light-moderate activity level. For this population, we also need more studies on different training modalities and the impact on myocardial performance.
The role of physical activity in hypertensive patients with LVH could be supplied with echocardiograms during follow-up to explore whether the level of activity was associated with changes in LVMi. Further, it would also be interesting to study whether the prognosis has a linear association with LVMi among hypertensive patients with LVH.
Another interesting issue is whether physical activity enhances drug-efficacy in hypertension.
Further, the impact of other comorbidities, e.g. how kidney failure at different stages affects the prognosis at different levels of LVMi, is also an area for future research.
How to differentiate between physiological and pathological hypertrophy remains a clinical challenge. Especially among hypertensive patients at a high activity level, we need to clarify when pathological hypertrophy ends and physiological hypertrophy starts [161]. This also includes further exploration of the diastolic

function. Previously, tissue Doppler techniques have been used to explore this theme [162,163].
With the novel echocardiographic methods including 3D echocardiography and the development in cardiac magnetic resonance imaging, it will be possible in the future to perform studies with more detailed characterisation of cardiac morphology and function.

CONCLUSIONS

Study I
Age modified the association between the level of physical activity and cardiac performance. In age <50 years, higher activity levels were associated with better myocardial performance. In age > 65 years, higher levels of physical activity were associated with worse cardiac function.

Study II
Higher levels of physical activity were associated with reduction in all-cause mortality and cardiovascular events at all levels of BP. This association was present in a dose-response pattern for all-cause mortality.

Study III
Hypertension modified the association between level of physical activity and LVMi. In normal BP, higher levels of physical activity were associated with higher LVMi, whereas this association was not present in hypertension.
The presence of LVH did not modify the association between physical activity and reduction in mortality/cardiovascular events. Thus, physical activity was associated with reduction in mortality and cardiovascular events, independent of the presence of LVH.

The following hypothesis was written in the background paper for the Framingham Heart Study in 1952: ‘ It is assumed that these diagnoses [hypertensive and arteriosclerotic disease] do not each have a single cause (as is the case of most infectious diseases), but that they are the result of multiple causes which work slowly within the individual. ’ [164–166].

In the present studies, we studied only physical inactivity and hypertension as risk factors for cardiovascular disease, both well-described in previous studies. However, in the 21st century, we still have many unanswered questions in the field of the development and treatment of cardiovascular disease. The role of physical activity is just a small part of this.

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Appendix - Published Papers

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ORIGINAL PAPER

The association between physical activity and cardiac performance is dependent on age: the Copenhagen City Heart Study

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Abstract
This study aimed to test the hypothesis that regular physical activity is associated with improved cardiac function measured by tissue Doppler imaging (TDI) in the general population. Within a large prospective community-based population study, cardiac function was assessed in 2221 persons by TDI. Longitudinal displacement (LD), early diastolic velocity (e'), and myocardial performance index (MPI) was obtained by TDI. Linear univariable and multivariable regression analyses were performed in relation to age groups (< 50 years, 50–65 years, > 65 years) and self-reported level of physical activity: I (inactivity), II (light activity), III (moderate activity), and IV (high-level activity). Participants < 50 years in the most active group had significantly better cardiac performance when compared to all other activity levels (higher levels of e', LD, and lower levels of MPI). The findings remained with statistical significance after adjustment for sex, ischemic heart disease, diabetes, hypertension, and body mass index (e' = 11.0, 95% CI (10.4–11.6), p < 0.001; LD = 12.8 (12.3–13.4), p < 0.003; MPI: 0.40 (0.38–0.42), p = 0.02). In age > 65 years, there was a tendency of impaired cardiac function in higher levels of exercise. Interaction analysis revealed that age significantly modified the association between physical activity and cardiac function (p < 0.001). We found a positive association between higher level of physical activity and improved cardiac function in younger persons (< 50 years). In the general population, however, the association interacted with age and amongst persons above 65 years there was a negative association between higher level of physical activity and cardiac function.

Keywords Exercise · Cardiac function · Tissue Doppler imaging · Echocardiography · Population study · Cardiac time intervals · Physical activity

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Abbreviations

BMI	Body mass index
ET	Ejection time
IHD	Ischemic heart disease
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time
LAVI	Left atrial volume index
LD	Longitudinal displacement
LVEF	Left ventricular ejection fraction
MPI	Myocardial performance index
RHR	Resting heart rate
TDI	Tissue Doppler imaging

Introduction

Worldwide, health authorities recommend regular physical activity as a means of improving health. This recommendation is based on multiple studies on the beneficial association between physical activity, mortality, and the development of cardiac disease in patients with known heart disease and the general population [1–10]. However, a recent publication from the Copenhagen City Heart Study has indicated that strenuous physical activity is associated with higher mortality in healthy joggers [11]. Investigations of the association between cardiac performance and activity level in the general population are sparse.

Tissue Doppler imaging (TDI) provides a comprehensive evaluation of systolic and diastolic left ventricular function and is superior to conventional echocardiography for risk assessment in patients with heart disease and the general population [12–16]. Previous investigations have indicated that TDI not only identifies deteriorating cardiac function in the general asymptomatic population, but also provides prognostic information on cardiovascular mortality and morbidity independently of traditional risk factors [14, 17, 18]. Moreover, TDI has been used to document improvement in systolic and diastolic function following targeted dedicated exercise protocols in healthy individuals as well as in patients with cardiovascular risk [19–21]. However, most of these studies have included populations of younger age.

Cardiac time intervals are closely related to cardiac physiology, hemodynamics, and mechanics. Myocardial performance index (MPI), also known as the Tei-index, is a method that combines the systolic and diastolic phases of the cardiac cycle. MPI is calculated by dividing the sum of the isovolumic contraction time (IVCT) and the isovolumic relaxation time (IVRT) by the ejection time (ET). In individuals with impaired cardiac function, IVCT and IVRT are prolonged, and ET might be shortened. Thus, MPI is higher in individuals with heart disease than in healthy subjects. MPI has been reported to be associated with cardiovascular mortality in patients with heart disease and the general population [12, 22, 23].

Using data from the Copenhagen City Heart Study, we explored whether higher levels of habitual physical activity in the general population are associated with improved cardiac function assessed by TDI. We chose to focus on the following parameters: e' (diastolic performance), longitudinal displacement (LD, systolic performance), and MPI (combined systolic and diastolic function). Since TDI-parameters are highly dependent on age, we decided to study the population in the following three age groups: < 50 years, 50–65 years, and > 65 years.

Methods

Study population

The Copenhagen City Heart Study is a prospective cohort study of cardiovascular disease and risk factors among Danish citizens. At the first examination in 1976–1978, a random sample of citizens from a well-defined area of Copenhagen City was invited to participate in the study. This present study used data from the fourth examination in 2001–2003. The population consisted of persons who had been invited to the three previous examinations, and a random sample of persons from the younger age group (n = 1000). In total, 6237 persons participated. A total of 2221 randomly selected persons underwent echocardiography including TDI. Persons with atrial fibrillation, significant valvular stenosis, or regurgitation were excluded (n = 157). Due to missing information on physical activity level, 11 persons were excluded. A total of 2053 persons were included in the current study. All subjects gave informed consent to participate, and the study was performed in accordance with the second Helsinki Declaration and approved by the regional ethics committee.

Echocardiography

Three experienced echocardiography technicians performed all echocardiogram examinations using GE Vingmed Ultrasound's Vivid Five with a 2.5-MHz probe (Horten, Norway). All participants were examined with color TDI and two-dimensional and M-mode echocardiography in the left lateral decubitus position. All images were recorded with second-harmonic imaging at the time of end expiration. Collected data were stored on magneto-optical disks on an external hard drive (FireWire, LaCie, France) and analyzed offline with a commercially available software program (EchoPac, GE Medical). The investigator was blinded to other information about the participants.

Color tissue Doppler imaging

Color TDI loops were obtained in the apical four-chamber, two-chamber, and long-axis views at the highest possible frame rate. Myocardial velocities, including e', were measured within a 6 mm circular sample volume in the septal, lateral, inferior, anterior, posterior, and anteroseptal mitral annular positions. Longitudinal displacement (LD) was calculated from the area under the velocity curve during ejection using an automated algorithm (Fig. 1). TDI curves were smoothed by averaging myocardial velocities over 30 ms. Both LD and e' were measured in all of the six basal segments; the averages were calculated and applied in this study.

Previous studies have suggested LD and e' as being sensitive markers of changes in cardiac function when studying the effect of physical activity. We therefore chose to focus on LD and e' in the evaluation of myocardial function in our study [19–21].

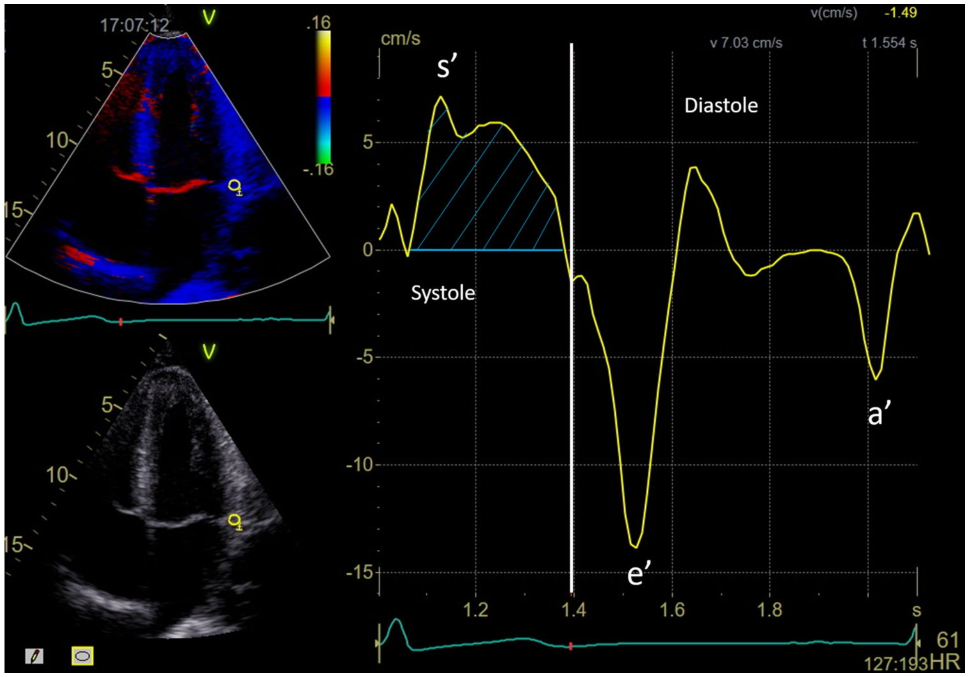

Fig. 1 Example of myocardial velocity curve by tissue Doppler imaging. The yellow circle shows the place where the sample is obtained (lateral region of the mitral annulus). Y-axis: myocardial velocity (cm/s). X-axis: time (seconds). The positive peak during systole is marked by s’ on the velocity curve. During diastole, early (e’) and late (a’) diastolic peak is marked. Mitral annular displacement (longitudinal displacement) is calculated from area under the curve during systole (shaded area)

The cardiac time intervals were obtained in the apical four-chamber view at the highest possible frame rate. A 2–4 cm straight M-mode line was placed through the septal half of the mitral leaflet in closed position in end-systole (Fig. 2). Cardiac time intervals were measured based on the color M-mode diagram. The method has been described in detail in a previous publication from the Copenhagen City Heart Study [24].

Physical activity

All participants filled in the Copenhagen City Heart Study Questionnaires containing questions on previous medical history, lifestyle, and sociodemographics. The physical activity questionnaire included information about activity level both at work and during leisure time. The activity level was scored from 1 to 4 in the questionnaire with increasing activity level (physical activity questionnaire included in the

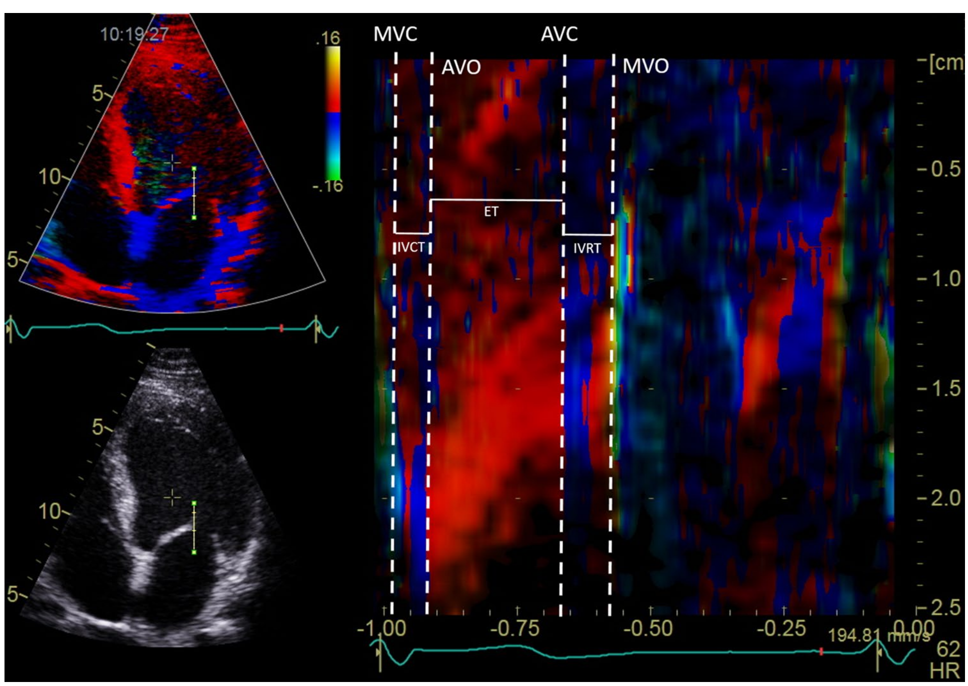

Fig. 2 (Left) Four-chamber gray-scale (bottom) and color tissue Doppler imaging (top) views in end-systole showing the position of the M-mode line used for measurement of cardiac intervals. (Right) Color diagram of the tissue Doppler imaging M-mode of the anterior mitral leaflet. *AVC* aortic valve closing, *AVO* aortic valve opening, *MVC* mitral valve closing, *MVO* mitral valve opening, *IVRT* isovolumic relaxation time, *IVCT* isovolumic contraction time, *ET* ejection time

electronic supplementary material). Leisure-time physical activity levels were defined as follows: Group I—almost entirely sedentary, group II—light physical activity for 2 to 4 h per week, group III—light physical activity for more than 4 h per week or more vigorous physical activity for 2 to 4 h per week, and group IV—high vigorous physical activity for more than 4 h per week or regular heavy exercise or competitive sports several times per week. According to the activity level from the questionnaire, participants were divided into four groups: I (inactivity), II (light activity), III (moderate activity), and IV (high-level activity).

Statistical analyses

For demographics, Pearson's Chi square test was used for categorical covariates and one-way analysis of variance (ANOVA) for continuous covariates. If the data were not normally distributed (MPI), transformation to natural logarithm was made, and geometric mean was calculated. The Kruskal–Wallis rank test was used instead of ANOVA when data were not normally distributed. Linear regression models in the following age strata were used to examine the associations between activity level and TDI parameters: < 50 years, 50–65 years and > 65 years. Activity level was considered as a categorical variable and TDI measurements were plotted on a continuous scale. In the multivariable analyses, we adjusted for the following pre-specified potential confounders: sex, ischemic heart disease, hypertension, body mass index (BMI), and diabetes. Since resting heart rate (RHR) might affect values of TDI-parameters, we performed a separate analysis where we additionally adjusted for RHR [25]. Interaction analyses were performed to clarify whether interactions between age and physical activity level affected the results. The analyses were performed separately for each TDI parameter. Linearity, variance homogeneity, and the assumption of normality were tested with plots of residuals in each age stratum. P-values < 0.05 on two-sided tests were considered statistically significant. Values in parentheses are 95% confidence intervals unless stated otherwise.

All analyses were performed by STATA Statistics/Data Analysis version 14.1.

Results

Characteristics of the study population are displayed in Tables 1 and 2. BMI was lower in the highest activity groups. Frequencies of hypertension, diabetes, and ischemic heart disease were lower in higher activity levels. In the highest activity groups, we found higher left atrial volume index

Table 1 Baseline characteristics of study population in relation to level of physical activity

	The total population (N = 2053)	Inactivity (N = 180)	Light activity (N = 1016)	Moderate activity (N = 753)	High level activity (N = 104)	p-value
Age, years	58.3 ± 16.0	60.6 ± 16.8	60.8 ± 15.5	55.8 ± 15.3	48.0 ± 18.6	< 0.01
Male sex, %	42.7	48.3	37.7	46.1	56.7	< 0.01
Body Mass Index, kg/m^2	25.5 ± 3.9	26.3 ± 4.4	25.7 ± 4.1	25.0 ± 3.6	24.9 ± 3.2	< 0.01
Resting HR/bpm	67.1 ± 11.3	70.0 ± 10.8	67.6 ± 11.3	66.3 ± 10.9	62.1 ± 12.4	< 0.01
Hypertension, %	43.3	55.3	47.6	36.8	26.9	< 0.01
Diabetes mellitus, %	10.1	11.2	11.2	9.0	3.9	< 0.01
IHD, %	13.9	19.4	16.4	10.2	5.8	< 0.01
Smoking, %						< 0.01
Never smoked	32.4	23.9	31.3	35.2	37.5	
Current smoker	33.4	50.6	35.9	27.0	27.9	
Former smoker	33.5	25.6	32.2	37.5	32.7	
LVEF, %	59.7 ± 2.1	59.8 ± 1.1	59.6 ± 2.6	59.8 ± 1.4	60.0 ± 0.4	NS
LAVI, ml/m^2	19.3 ± 6.5	17.9 ± 5.5	19.4 ± 7.3	19.3 ± 5.6	21.3 ± 5.8	< 0.01
e' (cm/s)	7.2 ± 2.7	6.7 ± 2.7	6.8 ± 2.6	7.5 ± 2.6	8.8 ± 3.3	< 0.01
LD (mm)	10.6 ± 2.3	10.4 ± 2.1	10.3 ± 2.2	10.8 ± 2.2	11.6 ± 2.5	< 0.01
MPI (median, in parenthesis: 25% and 75% percentiles)	0.47 (0.40–0.56)	0.48 (0.43–0.55)	0.48 (0.41–0.56)	0.47 (0.39–0.55)	0.44 (0.39–0.51)	< 0.01

HR heart rate/ beats per minute, *IHD* ischemic heart disease, *LVEF* left ventricular ejection fraction, *LAVI* left atrial volume index, *LD* longitudinal displacement, *MPI* Myocardial Performance Index, MPI = (IVCT + IVRT)/ET, *IVCT* isovolumic contraction time, *IVRT* isovolumic relaxation time. Mean and standard deviations, unless specified otherwise. *NS* non-significant

Table 2 Number of persons in each age stratum and activity group

	Age < 50 years	Age 50–65 years	Age > 65 years	In total
I: Inactivity	53	47	80	180
II: Light activity	263	318	435	1016
III: Moderate activity	261	269	223	753
IV: High activity	57	25	22	104
In total	634	659	760	2053

(LAVI), and lower resting heart rate (RHR). Left ventricular ejection fraction (LVEF) was similar in all activity groups.

To adjust for confounding concerning age, the population was divided into three age strata when we analyzed the tissue Doppler parameters: <50 years, 50–65 years, and > 65 years.

Cardiac function and physical activity

Linear regression analysis was performed in each age group to clarify whether the level of physical activity was associated with myocardial performance. Figures 3, 4, and 5 illustrate the associations between activity level and cardiac function in each age group.

All of the echocardiographic parameters e', LD, and MPI were strongly associated with age, regardless of activity levels. In the following, we describe the associations within each age group.

Age < 50 years

In this age group, we found improved systolic and diastolic function with increased activity level. Both LD and e' were significantly higher in high level activity (group IV) compared to the three other activity levels. This pattern remained significant after adjusting for sex, diabetes, hypertension, BMI, and ischemic heart disease (e' $p < 0.001$, LD: $p < 0.003$, MPI: $p = 0.02$). Even after Bonferroni correction, activity group IV had a significantly higher values of LD and e'. Trend tests were made with activity level as a continuous variable. Here, we found that activity levels were significantly associated with improved cardiac function (higher e' ($p = 0.001$), LD ($p = 0.004$) and lower MPI ($p < 0.002$)). The decrease in MPI was primarily due to a decrease in IVRT/ET ($p < 0.001$) in higher activity levels.

Age 50–65 years

In this age group, we did not find any significant association between level of physical activity and systolic or diastolic myocardial performance (e' $p = 0.17$; LD: $p = 0.16$; IVRT/ET: $p = 0.92$; IVCT/ET: $p = 0.83$; MPI: $p = 0.58$).

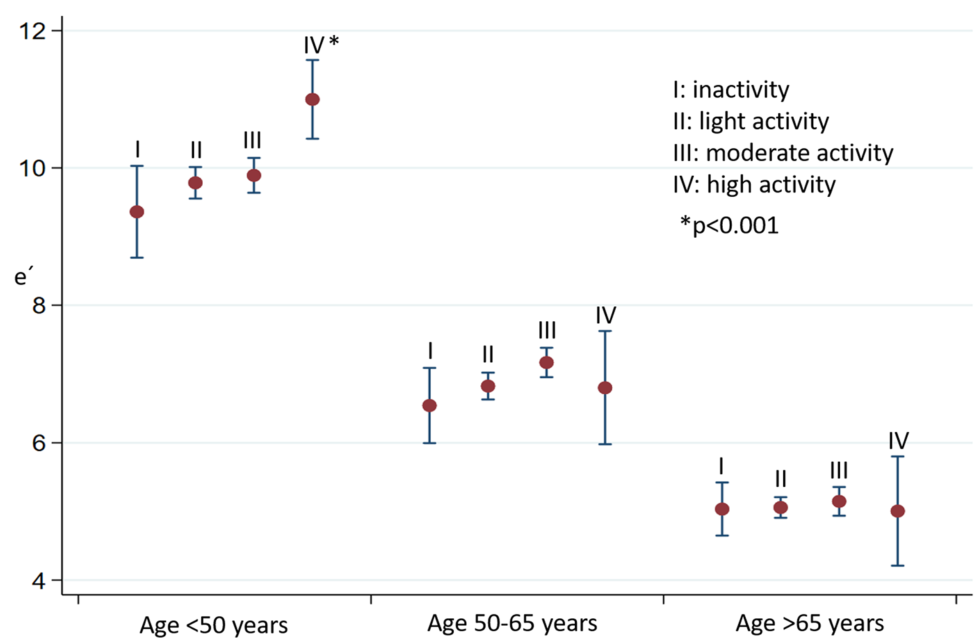

Fig. 3 Early diastolic velocity e' in relation to age group and activity level. Mean and 95% confidence intervals

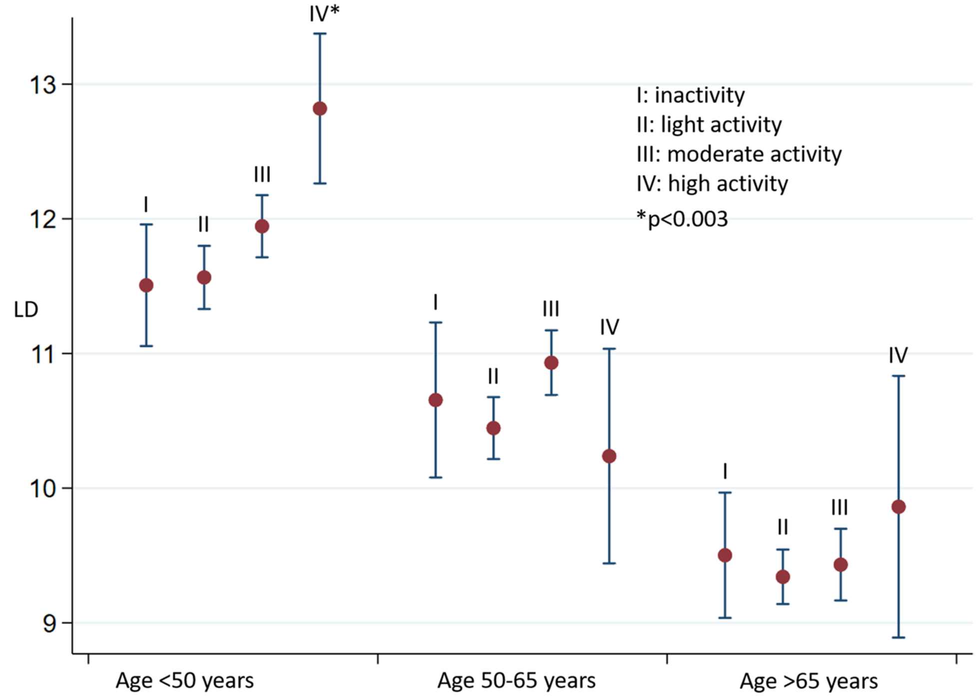

Fig. 4 Longitudinal displacement (LD) in relation to age group and activity level. Mean and 95% confidence intervals

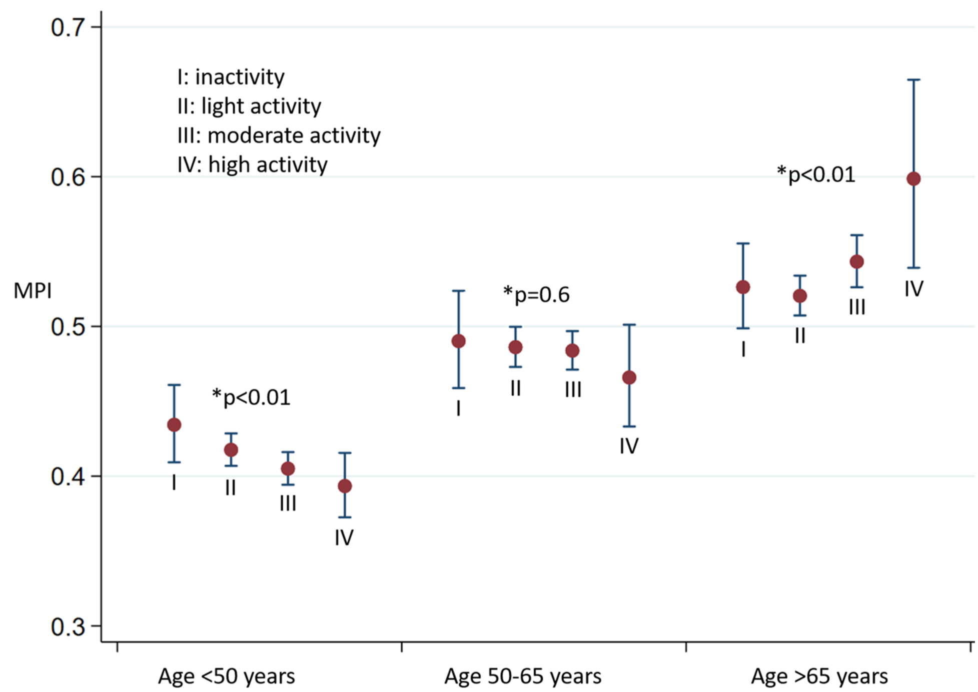

Fig. 5 MPI (geometric mean and 95% confidence intervals) in relation to age group and activity level. MPI=(IVRT + IVCT)/ET. *MPI* myocardial performance index, *IVRT* isovolumic relaxation time, *IVCT* isovolumic contraction time, *ET* ejection time. *The p-values in trend analysis for MPI within each age group

Age > 65 years

In age > 65 years, both systolic and diastolic myocardial function seemed to be similar in all four activity levels when activity levels were analyzed as a categorical variable. The trend test (activity levels as a continuous variable) revealed a significant tendency towards reduced myocardial function with increased activity level independent of sex, ischemic heart disease, hypertension, BMI, and diabetes (an increase of MPI by 0.02 (0.006–0.038) for each higher activity level, $p < 0.01$). No significant changes in e' and LD were found (e': $p = 0.402$; LD: $p = 0.452$).

Adjustment for RHR

We performed separate analyses where we additionally adjusted for RHR. Adjusting for RHR did not change any of the results.

Interaction analyses

Interaction analyses with adjustment for potential confounders revealed interaction between age group and activity level when studying e' ($p<0.008$). This means that the association between cardiac function and activity level is changed by aging; physical activity in young age was associated with higher levels of e' compared with the older age groups. For LD, we did not find any significant interaction ($p=0.182$).

Interaction analyses revealed a significant interaction between activity level and age when studying MPI ($p<0.001$).

Resting heart rate and level of physical activity

We studied the RHR in relation to age group and level of physical activity (Fig. 6). There was a tendency towards a lowering of the RHR in higher activity levels when studying age groups < 50 years, and 50–65 years. For individuals aged < 50 years, we found a drop in heart rate of 2.4 beats/min (95% CI 0.7–3.6) for each increased level of activity ($p<0.001$). A decrease of 2.0 beats/min (95% CI 0.7–3.4) was found for trend analysis in persons aged 50–65 years ($p<0.01$). Both findings were statistically significant. For persons aged > 65 years, we did not find any association between the level of physical activity and the heart rate ($p=0.39$).

Discussion

This large community-based study investigated the association between cardiac function and level of physical activity. To the best of our knowledge, this is the first study to examine this association in relation to age. Our results indicate that a better myocardial performance in relation to higher levels of physical activity is achieved only when age is below 50 years. In age > 65 years, there seems to be a tendency for impairment of myocardial performance at higher activity levels.

The parameter e' is a sensitive and frequently used echocardiographic measure in studies on the diastolic function in relation to physical activity including sports [20, 26–28]. Moreover, e' has been shown to be significantly higher in endurance and strength athletes. LD is associated with stroke volume and ejection fraction [29–31]. The studies including LD as a measure of systolic function found significant changes in relation to physical activity [19, 20].

Studies of the athlete's heart have revealed structural and functional changes towards higher systolic and diastolic performance assessed by TDI when compared with age-matched non-athletes [26–28]. Usually, athletes belong to a young age group. Our results support these findings; thus we also find a high level of physical activity to be associated

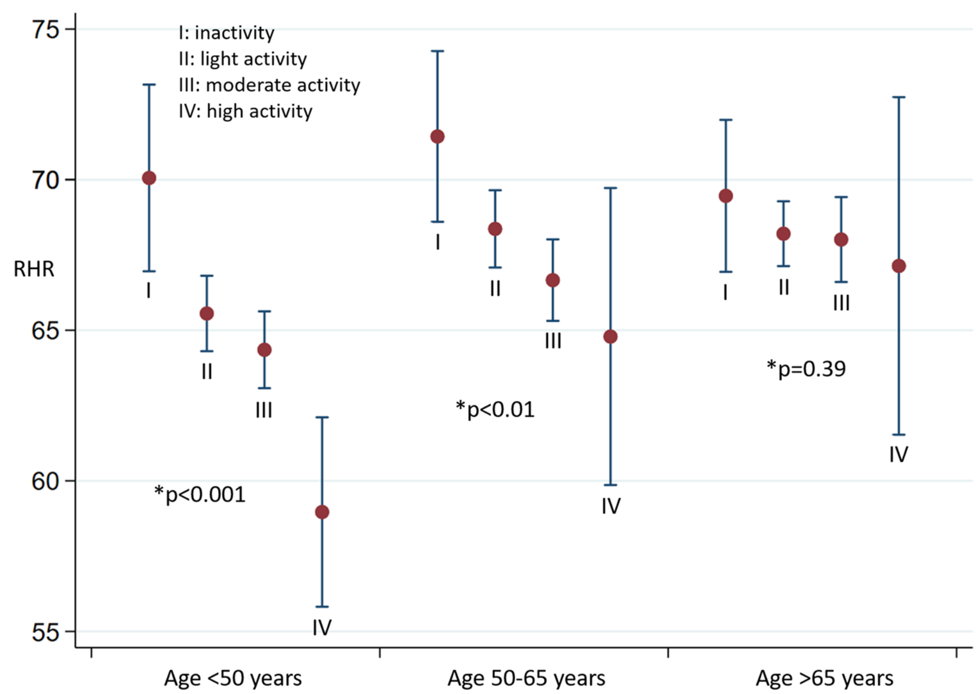

Fig. 6 Resting heart rate (RHR, beats per minute) in relation to age group and activity level. *The p-values in trend analysis for RHR within each age group

with improvement in myocardial performance in the younger age group.

Andersen et al. described improved systolic and diastolic myocardial function in sedentary women less than 50 years of age (36.5 ± 8.2 years) undergoing 16 weeks of regular physical training [20]. These findings suggest that cardiac adaptations are easily achieved in the younger age group. However, changes in cardiac function in older age groups in relation to physical activity require further investigation.

A few studies have investigated the association between cardiac time intervals and the level of physical activity. In 1999, Libonati et al. described how systolic time intervals were prolonged and isovolumic relaxation time shortened in long-distance runners in comparison to short-distance runners [32]. They also found lower levels of MPI in long-distance runners. Seismocardiography was used to determine the cardiac time intervals, which is different from the method we used in our study. Despite differences in the study population, our study confirms the findings by Libonati et al.

From a physiological point of view, it is reasonable to assume that a younger heart might be more sensitive to changes in myocardial performance in relation to exercise. One of the reasons could be that this age group has a low frequency of medical conditions that affect cardiac function such as hypertension, diabetes, and IHD. In addition, aging is associated with molecular and cellular alterations including increased interstitial myocardial fibrosis [33–35]. These changes cause altered myocyte contractile function, stiffness of the myocardium, and thus impairment of systolic as well as diastolic function in the aging population.

The interaction analyses in our study show that age might be an effect modifier when studying the association between physical activity and myocardial performance. These findings emphasize the importance of age when studying cardiac adaptations in relation to physical activity. Effect modification in this context means that younger age groups have a greater impact on improving cardiac function when exercising. In age groups < 50 years and 50–65 years, the resting heart rate decreased in higher levels of activity, whereas the heart rate was unchanged in those aged > 65 years. A decrease in resting heart rate during physical activity is a basic physiological change. In our study population, this correlation was seen only in those aged < 65 years. This is in line with the findings by TDI, revealing that improved myocardial performance was associated with increasing levels of activity in age groups < 65 years, but not in those aged > 65 years.

Our results raise the question of whether myocardial performance is reversed by aging regardless of exercise. There may be a cut-off point in age, a "point of no return," where the beneficial effects of physical activity on myocardial performance might no longer exist.

One of the limitations of our study is that we do not have data for how many years the participants have had the reported physical activity level, and whether their activity level changed during their lifetime. We assume that the reported activity level has been the most dominant level during their adult lifetime. Thus, we assume that the participants in the two highest age groups have had a high level of physical activity for many years, if reported as such.

In defining the groups according to their level of activity, we primarily focused on the self-reported activity level in leisure time. In 792 persons, we did not have data on their activity level during working hours, so the analyses could not be performed with classification of activity levels at work only.

However, in this study, physical activity was not an intervention, and the results reflect associations, and no causal inference can be assessed. Previous studies on physical exercise as an intervention reported improvement in cardiac function measured by TDI. More studies of this kind are needed, especially studies including persons > 50 years of age.

Previous studies comparing aerobic interval training with continuous endurance training found better myocardial performance after interval training [20]. How aging affects this association thus requires further exploration.

The current recommendations concerning regular physical activity do not distinguish between differences in age. Even though several studies have shown a reduction in cardiovascular disease and mortality in those who are physically active, the effects on myocardial performance are sparsely studied. It is scientifically interesting whether a reduction in mortality and cardiovascular disease in relation to physical activity in the general population is associated with improved myocardial performance. Schnohr et al. found that long-term moderate or high levels of physical activity were associated with significantly lower all-cause mortality and death from coronary heart disease in an observational study design [4]. Physical activity induces physiological benefits such as increased insulin sensitivity, lower blood pressure, and improved lipid profile, which could partly explain these findings. However, persons capable of participating in moderate to high levels of physical activity have good physical health, so the increased survival time for these individuals might therefore be explained by factors other than only physical activity.

Our study results reveal that aging could reverse the benefits of physical activity on cardiac function. These findings need to be confirmed in future studies.

Conclusion

In the general population, the association between increased levels of physical activity and improved cardiac function, assessed by TDI, was found only in persons < 50 years of age. In persons aged > 65 years, higher levels of physical activity were associated with reduced myocardial performance. Our results suggest that the beneficial associations between myocardial performance and physical activity are altered and reversed by aging. Myocardial performance measured by TDI decreases with age, independent of the level of physical activity. Additional studies are needed to explore more associations between physical activity and myocardial performance in relation to age and exercise modalities and training protocols.

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Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest.

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Electronic supplementary material

The association between physical activity and cardiac performance is dependent on age: The Copenhagen City Heart Study

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Supplementary material

A. The physical activity questionnaire

Information on activity level at work as well as in leisure time was included. The activity level was scored from 1 to 4 in the questionnaire with increasing activity level.

Question 1

Please indicate your PHYSICAL ACTIVITY LEVEL DURING WORK over the last year (students, home-makers and the unemployed should fill out the answers while retirees without work should proceed to question 2) (choose one option only)

I	Primarily seated while working e.g. deskwork, home-maker with no children and with domestic help	
II	Sitting or standing, sometimes walking e.g. clerk, teacher, home-maker washing and cleaning without small children	
III	Walking, lifting once in a while e.g. postal worker, caretaker, home-maker washing and cleaning with one or more small children	
IV	Heavy physical work e.g. construction worker, furniture remover	

If options III or IV were chosen. Do you often lift heavy weights? YES ____ NO ____

Question 2

Please indicate your PHYSICAL ACTIVITY LEVEL IN YOUR SPARE TIME (including transportation to and from work) over the last year (choose one option only)

I	Almost completely physically passive or physically active for less than 2 hours per week e.g. reading, watching TV, going to the cinema	
II	Light physically activity 2-4 hours per week e.g. walking, cycling, light garden work or low-intensity workouts	

III	Light physical activity more than 4 hours per week or more strenuous activity 2-4 hours per week e.g. fast walking and/or fast cycling, heavy garden work, high-intensity workouts involving getting sweaty and short of breath	
IV	More strenuous physical activity for more than 4 hours per week or regular high-intensity workouts or sporting competitions several times per week	

Dose-Response Association Between Level of Physical Activity and Mortality in Normal, Elevated, and High Blood Pressure

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Abstract—It has been a challenge to verify the dose of exercise that will produce the maximum health benefits in hypertension. This study aimed to explore the association between level of daily physical activity, all-cause mortality and cardiovascular outcome at different blood pressure levels. A random sample of 18 974 white men and women aged 20 to 98 years were examined in a prospective cardiovascular population study. Self-reported activity level in leisure-time was drawn from the Physical Activity Questionnaire (level I: inactivity; II: light activity; and III: moderate/high-level activity). Blood pressure was defined as normal blood pressure: <120/<80 mm Hg; Prehypertension: 120–139/80–89 mm Hg; Stage I hypertension: 140–159/90–99 mm Hg; Stage II hypertension ≥160/≥100 mm Hg. The mean follow-up time was 23.4±11.7 years. At all levels of blood pressure, higher levels of physical activity were associated with lower all-cause mortality in a dose-response pattern. The pattern remained unchanged after adjustment for following confounders: sex, age, smoking status, education, diabetes mellitus, previous cardiovascular disease, body mass index, and calendar time. Compared with inactivity, following hazard ratios were found for stage I hypertension: light activity, hazard ratio 0.78 (0.72–0.84; *P*<0.001), moderate/high-level activity, hazard ratio 0.69 (0.63–0.75; *P*<0.001). At all levels of blood pressure, the risk of cardiovascular events was significantly reduced independent of the level of physical activity. In conclusion, the association between physical activity and all-cause mortality was present in an inverse dose-response pattern at all levels of blood pressure. Physical activity was associated with reduction in cardiovascular events independent of the level of physical activity. **(*Hypertension*. 2019;74:1307-1315. DOI: 10.1161/HYPERTENSIONAHA.119.13786.)**

Key Words: blood pressure ■ cardiovascular diseases ■ exercise ■ hypertension ■ mortality ■ physical activity

Hypertension kills 9.4 million people annually worldwide—about as many as all infectious diseases combined.[1] The World Health Organization has declared hypertension to be the leading risk factor for global death in rich as well as developing countries bringing it to be a major public health problem.[2–4] Its prevalence has an epidemic growth, and the disastrous consequences are well described.[3–9] The warning of the upcoming magnificent burden of disease and death worldwide is calling for public health interventions with low healthcare cost.

Elevated blood pressure (BP) is modifiable by non-pharmacological interventions such as regular physical activity.[10–12]

We know from previous epidemiological studies that regular physical activity is associated with lower mortality in the general population.[13,14] Intervention studies in patients with hypertension have granted us the knowledge on how regular physical activity resulted in a significant reduction in BP values.[10,15–18]

However, there is a missing link and lack of evidence in the association between BP-reducing effect of regular exercise and the assumption on this association being directly correlated with reduced mortality and cardiovascular disease (CVD).

Besides, it has been a great challenge to verify the dose of exercise that will produce maximum health benefits at different levels of hypertension.

The aim of this study was

1. To test the hypothesis that daily physical activity is associated with mortality and cardiovascular outcome in persons with hypertension

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2. To investigate whether this association is present in a dose-response pattern

Methods

Data Availability

This study used data based on human persons. The data used in this study are governed by the Danish Data Protection Agency. Any additional researcher who wants access to these data is required to file a formal application to the Danish Data Protection Agency. Therefore, the authors cannot grant access to the data used in this study.

Study Population

The Copenhagen City Heart Study is a longitudinal cardiovascular population study initiated in 1976. A random sample of 19 329 white men and women aged 20 to 98 years was drawn from the Danish civil registration system as of 1 January 1976. The sample was stratified by age and sex (5-year age strata from the age of 20 years). A total number of 14 223 participated in the first examination. The population sample went through 4 examinations (1976–1978, 1981–1983, 1991–1994, and 2001–2003). All subjects from the original sample were invited to all subsequent examinations, and a new random sample of men and women was included each time. The inclusion criteria were age ≥20 years. There were no exclusion criteria. To the first examination in 1976–1978, in total 19 329 persons were invited and 73.6 % (N=14 223) of them participated.[19] For the subsequent examinations, the response rates were: second examination (1981–1983): 12 698/18 089 (70.2%); third examination (1991–1994): 10 135/16 560 (61.2 %); fourth examination (2001–2003): 6237/12 599 (49.5%).

In total, 18 974 persons were included in the current study and followed until the outcome of interest or April 2018. Only 214 persons were lost to follow-up due to emigration.

The study was approved by the Committee of Biomedical Research Ethics for the Capital Region in Denmark. All participants gave written, informed consent, and the study was performed in accordance with the second Helsinki Declaration.

Survey Methods

Established procedures and examinations for cardiovascular epidemiologic surveys were used (Rose & Blackburn).[20] A self-administered questionnaire concerning previous medical history, cardiovascular risk factors, socio-economic status (income, education, marital status), medication, and family history was completed and checked by the staff. All participants also fulfilled a questionnaire including questions on physical activity at work and in leisure-time.

Physical Activity Questionnaire

The same self-administered physical activity questionnaire was used in all 4 examinations. A single question with 4 categories was applied for measuring leisure-time physical activity: "Which description most precisely covers your pattern of physical activity during leisure-time?"

1. Inactivity. Being almost entirely sedentary (eg, reading, watching television or movies, engaging in light physical activity such as walking or biking for less than 2 h/wk). (Intensity: <3 metabolic equivalents (METs), used as reference group; Score 1
2. Light activity. Engaging in light physical activity for 2 to 4 h/wk. (Intensity: 3–4.5 METs; Score 2)
3. Moderate activity. Engaging in light physical activity for more than 4 h/wk or more vigorous activity for 2 to 4 h/wk (eg, brisk walking, fast biking, heavy gardening, sports that cause perspiration, or exhaustion). (Intensity: 4.5–6 METs; Score 3)
4. High-level activity. Engaging in highly vigorous physical activity for more than 4 h/wk or regular heavy exercise or competitive sports several times per week. (Intensity: >6 METs; Score 4]

Because of very few persons (n=570) in the highest category of leisure-time physical activity (score 4), the variable was categorized into: score 1= Inactivity, score 2= Light activity, and score 3 to 4= Moderate/high level activity.

Clinical Examination

Clinical examination included the measure of BP, lung function, height, weight, resting heart rate, electrocardiogram, and blood samples.

BP Measurements

The World Health Organization guidelines recommended by Rose & Blackburn were followed in all 4 surveys.[20] The recommendation suggested that epidemiologists measure BP once under highly standardized circumstances. The result is called a casual BP and is adopted by several epidemiological studies. Casual BP is shown to predict hypertension and cardiovascular disease very well.[21,22]

The subject was seated in a comfortable chair designed for BP measurements. The back was comfortably supported, and the arm was supported with the antecubital fossa at heart level. BP was measured once on the non-dominant arm after a minimum 5 minutes rest with the subject in the sitting position. A cuff was applied evenly to the upper arm. The size of the inflatable part of the BP cuff was 12×22 cm in survey 1, 12×26 cm in surveys 2, 3, and 4. For subjects with an upper arm circumference >46 cm, a cuff measuring 15×37 cm was used. Specially trained technicians using a standardized method and a London School of Hygiene Sphygmomanometer performed the measurements. The London School of Hygiene is a blind, mercury-in-glass Sphygmomanometer designed to reduce observer bias. The fall of the mercury column was set to 2 mm/s. The Korotkoff sounds were auscultated through a stethoscope placed over the brachial artery. Systolic BP was defined as the pressure at which the sounds were first heard. The fifth Korotkoff sound (the sounds disappear) defined the diastolic BP. The measurement of BP was performed once. In all 4 surveys, the technicians were instructed in the same way, and all conditions during the measurements were identical in the 4 surveys. All equipment was examined at regular intervals.

The BP-levels were defined as following[23]:

1. Normal BP: systolic BP <120 mm Hg and diastolic BP <80 mm Hg
2. Prehypertension: systolic BP between 120 and 139 mm Hg or diastolic BP between 80 and 89 mm Hg
3. Stage I hypertension: systolic BP between 140 and 159 mm Hg or diastolic BP between 90 and 99 mm Hg or receiving pharmacological treatment for hypertension with systolic BP <160 mm Hg/diastolic BP <100 mm Hg
4. Stage II hypertension: systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg

Potential Confounders

Potentially confounding factors for the association between leisure-time physical activity and outcomes were defined as following: sex, age, smoking status (never smoker, former smoker, 1–14 g tobacco per day, ≥15 g tobacco per day), education, diabetes mellitus, previous CVD, class of body mass index (BMI; underweight [BMI, <18.5 kg/m^2], normal weight [BMI, 18.5–24.9 kg/m^2], overweight [BMI, 25.0–29.9 kg/m^2], severe overweight [BMI ≥30.0 kg/m^2]), and calendar time.

Follow-Up and Outcome

Subjects were followed in the Danish national registers from the date of their first examination until 19 April 2018 or death.

Data on hospital admission, date of death, and death cause were drawn from the Danish National Patient Register[24,25] and the Danish Register of Causes of Death.[26] In Denmark, every person has a unique identification number which is linked to the Danish registers.[27] By this identification number, it is possible to gather information on exact dates and diagnoses for all citizens' hospital contacts, death date, and death causes.

1. Primary end point: all-cause mortality.
2. Secondary end point: cardiovascular events defined as admission for acute myocardial infarction, heart failure, or stroke, or death of the same causes.

Statistical Analysis

For demographics, Pearson's χ^2 test was used to compare categorical variables and one-way analysis of variance to compare continuous variables between physical activity groups.

Mortality rates and rates for cardiovascular events were calculated as the number of events/100 person-years. The associations between physical activity, all-cause mortality, and cardiovascular events were assessed using Cox proportional hazards regression analyses with time-dependent covariates. Associations were investigated with stratification according to the BP categories. The Cox models were performed with age as the underlying time scale and age at baseline as the entry time. All adjusted models included the following additional covariates: sex, smoking status (never smoker, former smoker, 1–14 g tobacco per day, ≥15 g tobacco per day), education, diabetes mellitus, previous CVD, BMI-class, and calendar time. The covariates were revised each time an individual participated in a new examination. The subjects were censored at emigration or the end of follow-up. None of them was lost to follow-up. If a participant did not participate in a subsequent examination, the covariates were revised the next time the person was examined using the last observation carried forward principle.

Competing Risk

Cardiovascular events (admission for acute myocardial infarction, heart failure, stroke, or death of the same causes) were assessed using Cox proportional hazards. Death from other causes was considered a competing risk. We also assessed the same outcomes by Fine and Gray's subdistributional hazards model with death from other causes as a competing risk.

Sensitivity Analyses

Sensitivity analyses were performed to investigate whether censoring at the time of absence from one or more examinations at the subsequent surveys changed the results. Further, sensitivity analyses were also made to explore whether excluding persons with previous CVD changed the results.

To clarify whether reverse causality could confound the results, we made 2 additional sensitivity analyses: in the first one, we excluded everyone who had an event during the first 3 years after inclusion in the study and let the follow-up time start 3 years later for the remaining study population. In the second analysis, we excluded everyone aged >60 years.

Interaction Analyses

We tested whether physical activity modified the prognostic value of BP for both all-cause mortality and cardiovascular events. Interaction analyses were also performed to explore whether sex modified the association between activity level and mortality. To clarify if being young had different effect on the association between physical activity and mortality, we divided the population into 2 age-groups (≤60 years and >60 years) and assessed if the age groups induced effect modification.

Results

Individuals in the inactive group had higher systolic BP, diastolic BP, resting heart rate, and BMI. We also found a higher frequency of diabetes mellitus and hypertension in this group.

Table illustrates the population characteristics for the participants at their first examination. The mean follow-up time was 23.4±11.7 years. A total of 214 persons (1.1%) were lost to follow-up due to emigration and were censored at the date of emigration.

All-Cause Mortality

During the follow-up, 13 355 persons died. In all BP groups, the level of physical activity was associated with lower mortality in a dose-response pattern. Both the mortality rates and Cox regression analyses showed the same pattern (Figures 1 and 2). The results remained highly statistically significant after adjustment for confounders. There was no interaction between activity level and BP-level on all-cause mortality (hazard ratio [HR], 1.00 [95% CI, 0.98–1.04], *P*=0.68). This means that physical activity had the same effect on mortality in all levels of BP. There was no effect modification of sex on the association between physical activity level and mortality except for prehypertension (HR, 0.88 [95% CI, 0.79–0.98], *P*=0.02). Being in young (≤60 years) versus older age group did not modify the association between activity level and mortality in any of the BP-levels (eg, for stage 1 hypertension: HR, 1.07 [95% CI, 0.97–0.18], *P*=0.17).

Cardiovascular Events

The number of cardiovascular events was 9470. This number included 1198 persons who had acute myocardial infarction, heart failure, or stroke and 8272 persons who died of one of these causes. Any level of activity was, compared with inactivity, associated with reduced cardiovascular events, as illustrated in Figures 3 and 4. Both mortality rates (Figure 3) and Cox regression with time-dependent covariates (Figure 4) showed this pattern. Competing risk analyses with Fine and Gray' subdistribution hazards model showed the same pattern (Figure 5). There was no interaction between activity level and BP-level on cardiovascular events (HR, 1.01 [95% CI, 0.97–1.05], *P*=0.62).

Persons with BP >180/110 mm Hg

Persons with BP >180/110 mm Hg are usually not encouraged to perform regular exercise.[28] We, therefore, assessed both all-cause mortality and cardiovascular outcome particularly in this group. We found, that the result pattern remained unchanged for both outcomes. For all-cause mortality, following hazard ratios were found: Inactivity HR=1 (reference); light activity, 0.93 [0.82–1.07], *P*=0.32; moderate/high level activity, 0.82 [0.71–0.96], *P*=0.02. For cardiovascular events: light activity 0.81 [0.69–0.94], *P*=0.006; moderate/high level activity, 0.80 [0.67–0.95], *P*=0.01.

Sensitivity Analyses

Sensitivity analyses were performed to investigate whether censoring the participants who had an absence from one or more of the subsequent surveys would have changed the results. These persons were censored at the time of the subsequent survey they did not attend. The same univariable and multivariable analyses were performed with censoring at the time of absence. The results did not change pattern compared with the results without censoring at the time of absence. We performed the same statistical analyses with exclusion of persons with previous CVD, so the cohort consisted only of persons without known cardiac disease. The results for all-cause mortality and cardiovascular outcome remained the same.

Table. Population Characteristics for the Participants in Relation to the 3 Activity Levels at Their First Examination

Characteristics	Inactivity, N=3483	Light Activity, N=9692	Moderate/High Level Activity, N=5715	*P* Value
Age at examination, y	54.4±12.7	51.1±12.8	47.0±14.4	*P*<0.001
Male sex, No. (%)	1628 (46.7)	4025 (41.5)	3123 (54.6)	*P*<0.001
Treated with antihypertensive, No. (%)	307 (8.9)	613 (6.3)	243 (4.3)	*P*<0.001
Diabetes mellitus, No. (%)	151 (4.6)	260 (2.8)	114 (2.1)	*P*<0.001
Systolic blood pressure, mm Hg	139±23	136±22	133±21	*P*<0.001
Diastolic blood pressure, mm Hg	84±13	82±13	81±13	NS*
Body mass index, kg/m^2	25.8±4.8	25.0±4.1	24.5±3.7	*P*<0.001
Previous CVD,† No. (%)	196 (5.6)	291 (3.0)	163 (2.9)	*P*<0.001
Smoking, No. (%)				*P*<0.001
Never smoked	613 (17.7)	2085 (21.6)	1446 (25.4)	
1–14 g tobacco/d	849 (24.5)	2611 (27.0)	1462 (25.7)	
>14 g tobacco/d	1509 (43.6)	3278 (34.0)	1725 (30.3)	
Former smoker	494 (14.3)	1682 (17.4)	1054 (18.5)	
Resting heart rate, bpm	76±14	74±13	71±13	*P*<0.001
Cholesterol, mmol/L	6.1±1.3	6.0±1.3	5.7±1.3	NS
Cardiac medication, No. (%)	184 (5.3)	289 (3.0)	119 (2.1)	*P*<0.001
Education, No. (%)				*P*<0.001
<8 y	1945 (56.1)	3956 (40.9)	1865 (32.7)	
8–10 y	1075 (31.0)	3684 (38.1)	1957 (34.3)	
≥11 y	447 (13.0)	2042 (21.1)	1882 (33.0)	

Mean and standard deviation, unless specified otherwise.
*NS indicates non-significant.
†CVD indicates cardiovascular disease.

We also made sensitivity analyses to clarify whether reverse causality could explain the results. In the first analyses, we excluded all who had an event <3 years after inclusion in the study and let the follow-up time start 3 years later for those remained in the study population. In the second analyses, we excluded all who were aged >60 years. In both analyses, the pattern of results was unchanged for both all-cause mortality and cardiovascular events.

Discussion

To date, this is the first study to show long-term associations between daily levels of leisure-time physical activity,

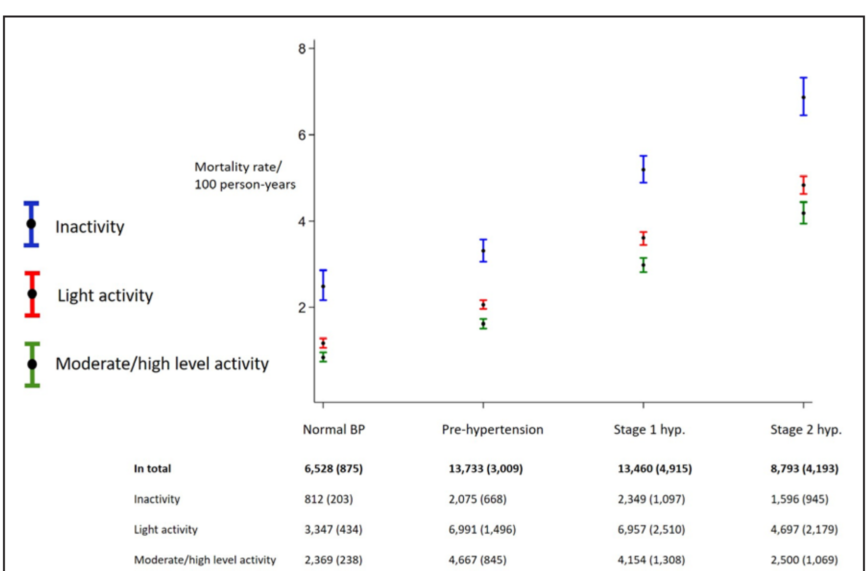


Figure 1. All-cause mortality. Mortality rates (no. of deaths/100 person-years) for all-cause mortality in relation to activity level and blood pressure (BP) level. In the table below: No. of observations, and in parenthesis, no. of events is given.

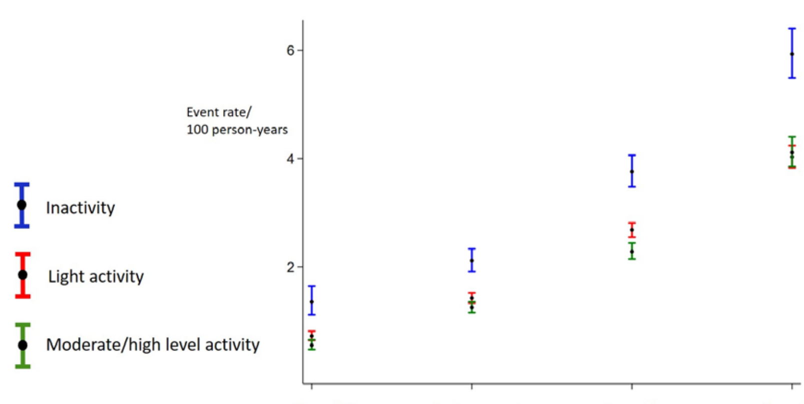
Covariates	No. of Observations	No. of Deaths	Age-adjusted analyses: Hazard ratio (95% CI)	Multivariable analyses: Hazard ratio (95% CI)
Normal blood pressure	**6,528**	**875**		
Inactivity	812	203	1.00 (reference)	1.00 (reference)
Light activity	3,347	434	0.61 (0.52-0.72)***	0.76 (0.64-0.91)**
Moderate/high activity	2,369	238	0.55 (0.46-0.67)***	0.68 (0.56-0.84)***
Pre-hypertension	**13,733**	**3,009**		
Inactivity	2,075	668	1.00 (reference)	1.00 (reference)
Light activity	6,991	1,496	0.66 (0.60-0.73)***	0.84 (0.77-0.93)**
Moderate/high activity	4,667	845	0.60 (0.54-0.66)***	0.76 (0.69-0.85)***
Stage 1 hypertension	**13,460**	**4,915**		
Inactivity	2,349	1,097	1.00 (reference)	1.00 (reference)
Light activity	6,957	2,510	0.66 (0.61-0.70)***	0.78 (0.72-0.84)***
Moderate/high activity	4,154	1,308	0.59 (0.55-0.64)***	0.69 (0.63-0.75)***
Stage 2 hypertension	**8,793**	**4,193**		
Inactivity	1,596	945	1.00 (reference)	1.00 (reference)
Light activity	4,697	2,179	0.70 (0.65-0.76)***	0.82 (0.75-0.89)***
Moderate/high activity	2,500	1,069	0.63 (0.58-0.69)***	0.72 (0.66-0.80)***

Figure 2. All-cause mortality. Cox regression with time-dependent covariates showing hazard ratios and 95% CIs for all-cause mortality for each of the blood pressure levels according to the level of physical activity. **Left**, Age-adjusted analysis. **Right**, After adjustment for sex, age, calendar time, smoking status, BMI-class, diabetes mellitus, previous cardiovascular disease, and education. *P<0.05; **P<0.01; and ***P<0.001.

all-cause-mortality, and cardiovascular outcome in all levels of BP in the general population. This study addresses many unanswered questions and has 3 main findings. First, higher levels of physical activity were inversely associated with all-cause mortality at all levels of BP. Second, this finding was dose-dependent regardless of BP-level. Third, cardiovascular outcome (admissions for acute myocardial infarction, heart failure, stroke, or death of same causes) was significantly reduced by physical activity independent of the BP-level. For both all-cause mortality and cardiovascular events, most of the health benefits are achieved already at the light activity level which was related to significant reduction in outcome compared with inactivity.

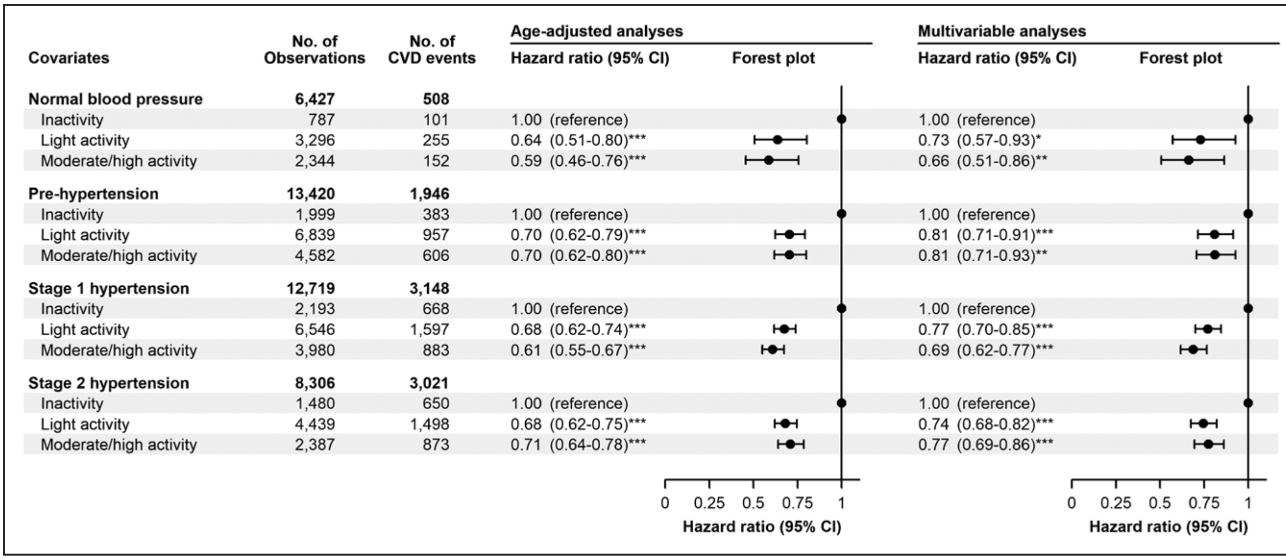
We did not find any interaction between the level of physical activity and BP groups. This means that the levels of physical activity have the same effect on outcome independent of the level of BP. Thus, recommendations on physical activity should not be modified by the level of BP but should be the same in all BP-levels to achieve maximum health benefits.

Further, the association between physical activity and outcome in stage 2 hypertension (BP >160/100 mm Hg) is the same as in the other BP groups. This is an important finding, since many clinicians usually have precautions in recommending physical activity in patients with stage 2 hypertension. According to the European Society of Cardiology/European Society of Hypertension guidelines 2018, physical activity is not recommended in persons with BP >180/110 mm Hg.[28] Our results do not imply any dangerous effect of exercise in this patient group; the highest level of physical activity in stage 2 hypertension is also associated with lower mortality and cardiovascular outcome compared with both inactivity and light activity. The additional analysis we made in only persons with BP >180/110 confirmed this conclusion.



	Normal BP	Pre-hypertension	Stage 1 hyp.	Stage 2 hyp.
In total	**6,427 (508)**	**13,420 (1,946)**	**12,719 (3,148)**	**8,306 (3,021)**
Inactivity	787 (101)	1,999 (383)	2,193 (668)	1,480 (650)
Light activity	3,296 (255)	6,839 (957)	6,546 (1,597)	4,439 (1,498)
Moderate/high level activity	2,344 (152)	4,582 (606)	3,980 (883)	2,387 (873)

Figure 3. Cardiovascular events. Event rates (no. of events/100 person-years) for cardiovascular events in relation to activity level and blood pressure (BP) level. Cardiovascular events are defined as admissions due to acute myocardial infarction, heart failure, stroke, or death of one of the causes. In the table below: No. of observations, and in parenthesis, no. of events is given.



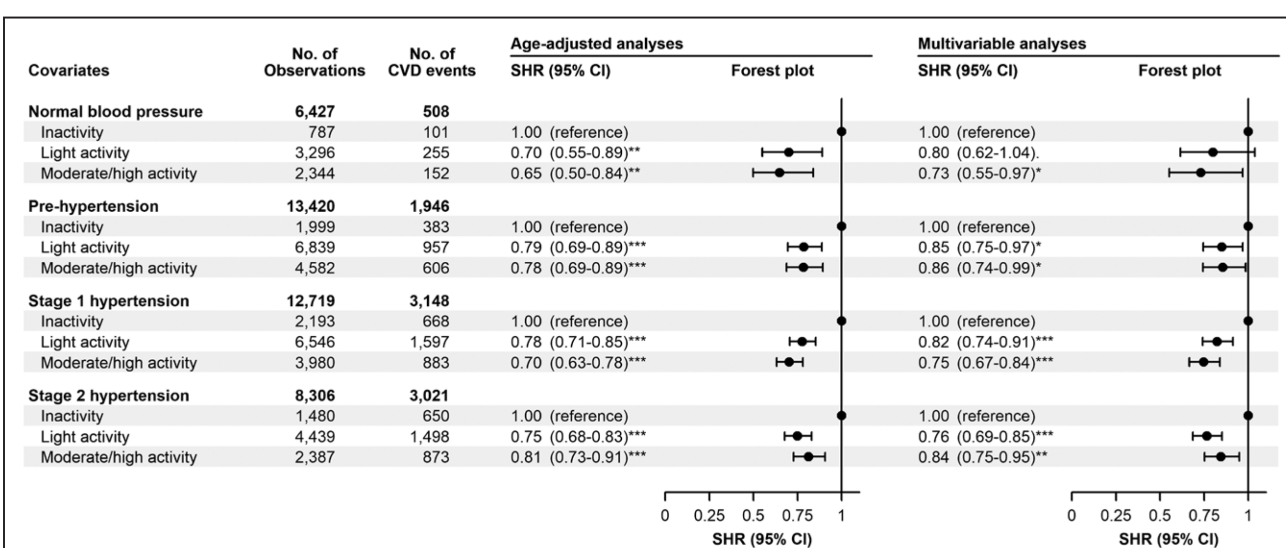
Covariates	No. of Observations	No. of CVD events	Age-adjusted analyses Hazard ratio (95% CI)	Multivariable analyses Hazard ratio (95% CI)
Normal blood pressure	**6,427**	**508**		
Inactivity	787	101	1.00 (reference)	1.00 (reference)
Light activity	3,296	255	0.64 (0.51-0.80)***	0.73 (0.57-0.93)*
Moderate/high activity	2,344	152	0.59 (0.46-0.76)***	0.66 (0.51-0.86)**
Pre-hypertension	**13,420**	**1,946**		
Inactivity	1,999	383	1.00 (reference)	1.00 (reference)
Light activity	6,839	957	0.70 (0.62-0.79)***	0.81 (0.71-0.91)***
Moderate/high activity	4,582	606	0.70 (0.62-0.80)***	0.81 (0.71-0.93)**
Stage 1 hypertension	**12,719**	**3,148**		
Inactivity	2,193	668	1.00 (reference)	1.00 (reference)
Light activity	6,546	1,597	0.68 (0.62-0.74)***	0.77 (0.70-0.85)***
Moderate/high activity	3,980	883	0.61 (0.55-0.67)***	0.69 (0.62-0.77)***
Stage 2 hypertension	**8,306**	**3,021**		
Inactivity	1,480	650	1.00 (reference)	1.00 (reference)
Light activity	4,439	1,498	0.68 (0.62-0.75)***	0.74 (0.68-0.82)***
Moderate/high activity	2,387	873	0.71 (0.64-0.78)***	0.77 (0.69-0.86)***

Figure 4. Cardiovascular events. Cox regression with time-dependent covariates showing hazard ratios and 95% CIs for cardiovascular events for each of the blood pressure levels according to the level of physical activity. **Left**, Age-adjusted analysis. **Right**, After adjustment for sex, age, calendar time, smoking status, BMI-class, diabetes mellitus, previous cardiovascular disease, and education. Cardiovascular events are defined as admissions due to acute myocardial infarction, heart failure, stroke, or death of one of the causes. Death from other causes was considered as a competing event. *P<0.05; **P<0.01; and ***P<0.001.

An important point is, that majority of the health benefits is achieved by light activity, which is an activity level most persons can perform. For persons at inactivity level, this might be a unique motivation to increase their activity level slightly.

This study has several strengths. The study population encompass a randomly selected large sample from the general population, and only a limited number of participants (n=214) were lost to follow-up. We had detailed information on the potential confounding variables. The long follow-up time and complete follow-up data from the Danish National Patient registers made it possible to measure specific outcome and event dates. Cox regression with time-dependent covariates made it possible to incorporate updated covariate values, including information from health examinations, activity levels, medical history, and changes in confounders for each of the individuals. The sensitivity analyses excluded reverse cause causality as a possible explanation for the associations found in this study.

The physical activity questionnaire used in this study is well-established, described by Rose & Blackburn, and has been shown to discriminate between sedentary persons and more active counterparts concerning maximal oxygen uptake.[20] According to the METs calculation due to the activity levels presented in the questionnaire, all activities having more than 3 METs effort daily is advantageous for reducing CVD and mortality. The new guidelines from European Society of Cardiology/European Society of Hypertension recommend



Covariates	No. of Observations	No. of CVD events	Age-adjusted analyses SHR (95% CI)	Multivariable analyses SHR (95% CI)
Normal blood pressure	**6,427**	**508**		
Inactivity	787	101	1.00 (reference)	1.00 (reference)
Light activity	3,296	255	0.70 (0.55-0.89)**	0.80 (0.62-1.04).
Moderate/high activity	2,344	152	0.65 (0.50-0.84)**	0.73 (0.55-0.97)*
Pre-hypertension	**13,420**	**1,946**		
Inactivity	1,999	383	1.00 (reference)	1.00 (reference)
Light activity	6,839	957	0.79 (0.69-0.89)***	0.85 (0.75-0.97)*
Moderate/high activity	4,582	606	0.78 (0.69-0.89)***	0.86 (0.74-0.99)*
Stage 1 hypertension	**12,719**	**3,148**		
Inactivity	2,193	668	1.00 (reference)	1.00 (reference)
Light activity	6,546	1,597	0.78 (0.71-0.85)***	0.82 (0.74-0.91)***
Moderate/high activity	3,980	883	0.70 (0.63-0.78)***	0.75 (0.67-0.84)***
Stage 2 hypertension	**8,306**	**3,021**		
Inactivity	1,480	650	1.00 (reference)	1.00 (reference)
Light activity	4,439	1,498	0.75 (0.68-0.83)***	0.76 (0.69-0.85)***
Moderate/high activity	2,387	873	0.81 (0.73-0.91)***	0.84 (0.75-0.95)**

Figure 5. Cardiovascular events. Cardiovascular events assessed by Fine and Gray subdistributional hazard. Left, age-adjusted analyses. Right, adjusted for age, sex, calendar time, smoking status, BMI-class, diabetes mellitus, previous cardiovascular disease, and education. Cardiovascular events are defined as admissions due to acute myocardial infarction, heart failure, stroke, or death of one of the causes. Death from other causes was considered as a competing event. SHR indicates subdistributional hazard ratio. *P<0.05; **P<0.01; and ***P<0.001.

30 minutes activity 5 to 7 d/wk for persons with hypertension.[28] The recommended level matches with the light activity level in our study.

What Is Already Known?

Although it is well-established that regular physical activity has a BP-reducing effect and well-known that physical activity is associated with better survival, reports on long-term outcome in hypertension due to a habitual level of physical activity are scarce.

We performed a systematic literature search in Embase and Medline for the period January, 1985 to October, 2018. We found some studies that aimed to investigate the association between physical activity and outcome in hypertension in other settings than ours.

A Swedish study by Engström et al followed 642 persons with hypertension for 25 years. Perhaps due to the limited number of persons, they chose to include both inactivity and light activity in the reference group (non-vigorous) and measured the CVD death compared with the vigorous activity group. They had a somewhat peculiar finding that hypertensive physically active persons had lower CVD mortality than normotensive non-active persons, which is not consistent with several previous studies investigating the association between leisure-time physical activity and long-term outcome in the general population.[29,30] They explain it by the fact of exclusion of persons with symptomatic atherosclerotic disease, different smoking habits, and lipid levels in the study population.

Vatten et al[31] studied a population consisting of 4766 persons who had never used BP medication and without a history of CVD. The cohort was examined once. In the analyses, the systolic and diastolic BP were categorized into 7 categories. Their results support our findings since they found higher relative risk in higher BP and lower activity level. However, their statistical analyses were based on relative risk, which is a cumulative risk rate at the time-point at the end of follow-up and does not consider the time to each of the events.

Sui et al[32] also published an interesting study about the association between fitness level and outcome in hypertension. One of the strengths in their study was that cardiorespiratory fitness was measured by treadmill exercise test. However, their measure of outcome was based on self-reported mail-back surveys, which might be less robust for measuring hard end point outcomes.

Another relevant study originating from Scandinavia included only hypertensive individuals and found that physical activity reduced cardiovascular mortality. The study, which was performed by Hu et al,[33] had several strengths, among others a long follow-up time of 19.9 years. One of the limitations in their study was that they did not have data on changes in physical activity, BP, or other covariates during follow-up. Also, they included only hypertensive persons without a previous history of CVD and diabetes mellitus, which may not represent the usual population cohort of persons with hypertension in the general community.

Fang et al[34] also found protective effects of physical activity in hypertensive subjects but could not show the same association among normotensive and pre-hypertensive subjects, perhaps due to lack of power.

As a sub-study of the well-designed LIFE-trial (Losartan Intervention For End point reduction in hypertension), Fossum et al described all-cause mortality and cardiovascular end points in a cohort consisting of 9193 patients with hypertension in relation to their physical activity level (never exercise, exercise ≤30 minutes twice per week, exercise >30 minutes twice per week).[35,36] The mean follow-up time was 4.8 years. They found a similar reduction in BP and heart rate among the physical activity groups, but only those with the highest level of activity had a significant reduction in the end points compared with the inactive patients. Because they studied a high-risk population with concurrent risk factors, the frequency of cardiovascular events was higher than in a general population. Despite that, they did not find any significant association between moderate activity (exercise ≤30 minutes twice per week) and cardiovascular end points. Also, they did not consider the level of hypertension in their analyses.

Does the Physical Activity Level Reflect the Health Profile?

The level of daily physical activity depends on the person's ability to perform activities. Further, a higher exercise level might be a marker of a better health profile. In our study population, we found lower BMI, frequency of diabetes mellitus, medication for hypertension, and cardiac medication in the highest activity group. The percentage of heavy smokers (>14 g tobacco/d) was also highest in the inactivity group. Even though some of the covariates might have a causal association to the level of physical activity (eg, diabetes mellitus and BMI), it seems fair to conclude that persons who are in the highest activity group might have a better health profile due to, for example, better health awareness.

Study Limitations

This study has some limitations. The physical activity level was self-reported and not objectively measured. The participants' answers might be influenced by their future wishes on their exercise level and not reflect the actual level. There might also be a probability that they changed their activity level during the time between surveys. A previous study from The Copenhagen City Heart Study showed that most of the participants kept their activity level during the repetitive surveys.[37]

If the persons had an absence from one of the following surveys, all the covariates from the previous survey were considered to be valid until the next time the person took part in a survey or until an event or end of follow-up. It would have been better if all persons participated in all the subsequent surveys once entered in the study. However, this is not a realistic condition to make in a population study. As mentioned above, the sensitivity analyses did not show any significant change in the results.

The BP was measured as a casual BP measurement, which has been validated before and known to be a good predictor of outcomes in large epidemiological trials.[21,22] We are aware of the fact that casual BP is not the best method to diagnose hypertension. Repeated home BP measurement and ambulatory BP monitoring are better to detect the presence of hypertension.[28] In a large epidemiological trial such as ours, the best method is so far the casual measurement.

Clinical Impact

Our results justify the importance of regular physical activity in the treatment of persons with hypertension and prehypertension. The most important point is that light level of physical activity, which almost everyone can perform, is responsible for most of the health benefits at all levels of BP, including stage 2 hypertension. Doctors and other health professionals should encourage patients with hypertension and prehypertension to being physically active at the level of the patient's capability. The recommendation to each patient should be individual under consideration of the individual patient's medical history, other risk factors, capability, and ability to perform exercise.

Perspectives

Randomized clinical trials are needed to confirm our findings. The level of daily physical activity should be studied as an intervention in patients with hypertension, especially patients with stage 2 hypertension, to determine the long-term effects of physical activity on prognosis in this patient group. Ongoing medical treatment and the interaction with physical activity should be taken into consideration.

Conclusions

In conclusion, this study contributes with new knowledge on long-term outcomes at all levels of BP. Physical activity is associated with lower mortality and cardiovascular events in both hypertension and prehypertension. Light level of physical activity is responsible for most of the measurable and significant health benefits, and the benefits are even better in higher levels of physical activity. The dose-response association between physical activity and mortality in hypertension should further encourage patients with hypertension to keep their physical activity level high. We suggest that all health professionals recommend patients with hypertension to be physically active and increase their activity level if it is low.

We suggest, that regular physical activity should be recommended as a prescribed treatment in all persons with elevated BP.

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Disclosures

Dr Torp-Pedersen has declared following conflict of interests: grants and personal fees from Bayer, outside this submitted work. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- Higher levels of physical activity are associated with better health benefits in a dose-response pattern at all levels of blood pressure.

What Is Relevant?

- Light level of physical activity, which almost everyone can perform, is responsible for most of the health benefits at all levels of blood pressure

Summary

In this population-based cohort study comprising 18 974 persons, there was a dose-response association between level of daily activity and all-cause mortality at all levels of blood pressure: normal blood pressure, prehypertension, stage 1 hypertension, stage 2 hypertension. Compared with inactivity, any level of physical activity was associated with a reduction in cardiovascular outcomes independent of the blood pressure level. Light-moderate physical activity is beneficial in persons with hypertension. Compared with inactivity, even a light level of daily physical activity is associated with significant health benefits in hypertension.

Level of Physical Activity, Left Ventricular Mass, Hypertension, and Prognosis

Gowsini Joseph, Jacob Louis Marott, Tor Biering-Sørensen, Martin Nygård Johansen, Hans A. Saevereid, Gitte Nielsen, Peter Schnohr, Eva Prescott, Peter Søgaard, Rasmus Mogelvang

Abstract—Left ventricular hypertrophy is a strong predictor of prognosis in hypertension. Physical activity is associated with higher left ventricular mass but also reduced risk of cardiovascular outcomes. The aims were to explore whether (1) presence of hypertension modifies the association between physical activity and left ventricular mass; (2) the beneficial association between physical activity and prognostic outcome is modified by left ventricular hypertrophy. Randomly selected number of 3078 persons from the general population underwent echocardiogram. Left ventricular mass was indexed to body surface area. Level of physical activity was self-reported: inactivity, light activity, and moderate/high activity. Blood pressure was measured in rest: normal BP (<140/90 mm Hg) and hypertension (≥140/90 mm Hg or in pharmacological treatment for hypertension). Presence of hypertension modified the association between physical activity and left ventricular mass index significantly (test for interaction: P=0.01): in normal BP, higher levels of physical activity were associated with significantly higher left ventricular mass index (P<0.001), but this was not present in hypertension (P=0.90). Level of physical activity was associated with reduction in mortality and cardiovascular outcome independent of the presence of LVH (Persons with LVH: light activity HR, 0.77 [0.52–1.15], moderate/high activity HR, 0.61 [0.38–0.97]; test for interaction between LVH and level of physical activity P=0.71). In conclusion, persons with normal BP had higher left ventricular mass index at increased levels of physical activity, whereas this association was not present among persons with hypertension. Level of physical activity was associated with better prognosis independent of whether left ventricular hypertrophy was present or not. **(*Hypertension*. 2020;75:693-701. DOI: 10.1161/HYPERTENSIONAHA.119.14287.)** • **Online Data Supplement**

Key Words: blood pressure ■ exercise ■ hypertension ■ hypertrophy, left ventricular ■ mortality

Hypertension is a leading risk factor for death globally and is often diagnosed late due to the lack of symptoms before end organ damage.[1,2] Left ventricular hypertrophy (LVH) is a well-known complication to hypertension. It is a risk factor independent of the level of arterial pressure.[3] Its role as an independent major risk factor for cardiovascular disease and mortality has long been recognized in both electrocardiographic, echocardiographic, and cardiac magnetic resonance studies.[4–11] Lowering of the blood pressure (BP) usually leads to regression of LVH and improved prognosis.[12] Diminishing LVH is an established goal of treatment in hypertension.[13] Beside pharmacological treatment, nonpharmacological treatment such as regular physical activity has shown to reduce LVH in patients with hypertension.[14–16]

Regular physical activity is generally associated with lower mortality and cardiovascular events in persons with normal BP as well as in persons with hypertension.[17–20] However, regular physical activity is also associated with physiological cardiac adaptations leading to higher left ventricular mass (LVM) across the age spectrum.[21–24] The increase in LVM induced by hypertension is physiologically and histologically different from the exercise-induced increase in LVM.[25,26] We wanted to study if the association between level of physical activity and LVM was different in persons with normal BP and in persons with hypertension; in other words, if hypertension modified the association between level of physical activity and LVM. As LVH is associated with worse prognosis, we also wanted to study if the benefits of physical activity on prognosis was present independent of the presence of LVH.

The 2 aims of this study were therefore to assess:

1. Whether hypertension modifies the association between level of physical activity and LVM.
2. Whether LVH modifies the impact of physical activity on prognosis

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Methods

Data Availability

This study is based on human persons. The Danish Data Protection Agency governs the data used in the present study. Any researcher who wants to get access to these data must file a formal application to the Danish Data Protection Agency. Therefore, the authors cannot provide access to the data used in this study.

Population

The description in this paper follows the STROBE guidelines (Strengthening the Reporting of Observational studies in Epidemiology) for cohort studies.[27]

The Copenhagen City Heart Study is a longitudinal cardiovascular cohort study initiated in 1976. Persons of both sexes aged 20 and above were randomly selected from the civil register of people living in a well-defined area of Copenhagen. The sample was stratified by age and sex (5-year age strata from the age of 20 years). The population sample went through 4 examinations (1976–78, 1981–83, 1991–94, 2001–03). All subjects from the original sample were invited to all subsequent examinations, and a new random sample of men and women was included each time. Echocardiogram was performed in the fourth examination (2001–03). The present study is based on data from the fourth examination (4th Copenhagen City Heart Study). All participants fulfilled a self-administered questionnaire covering questions on previous medical history, lifestyle, and sociodemographic information and underwent a health examination. A total number of 6237 persons participated in the 4th Copenhagen City Heart Study, and a randomly selected number of 3078 persons who underwent echocardiogram are included in the current study (Please see online-only Data Supplement). Whether or not a participant underwent echocardiography was completely independent of his or her health status, BP, and other risk factors. All persons gave informed consent to participate. The study was undertaken in accordance with the Second Helsinki Declaration and approved by the regional ethics committee.

Measurement of BP

BP was measured according to standardized protocols as recommended by Rose and Blackburn.[28] The subject was in the sitting position, and after 5 minutes of rest, specially trained technicians using a London School of Hygiene Sphygmomanometer auscultated BP once on the nondominant arm. The mercury column was set to fall by 2 mm/second. A stethoscope was placed over the brachial artery. The first Korotkoff sound indicated systolic BP. The fifth Korotkoff sound (when the sounds disappear) signified diastolic BP. Hypertension was defined as systolic BP≥140 mmHg or diastolic BP ≥ 90mmHg or if the participant was currently treated with antihypertensive medication.[29]

Level of Daily Physical Activity

Level of daily physical activity was drawn from the self-administered questionnaire. A single question with 4 categories was applied for measuring leisure time physical activity: Which description most precisely covers your pattern of physical activity during leisure time?[30,31]

1. Almost completely passive or physically active for <2 hours/week (eg, reading, watching television, going to cinema, engaging in light physical activity such as walking or cycling; intensity: <3 metabolic equivalents)
2. Light physical activity 2 to 4 hours per week (eg, walking, cycling, light garden work, or low-intensity workouts; intensity: 3.0–4.5 metabolic equivalents)
3. Engaging in light physical activity for >4 hours per week or more vigorous activity 2 to 4 hours per week (eg, brisk walking, fast cycling, heavy gardening, physical activities that cause perspiration or exhaustion; intensity: 4.5–6.0 metabolic equivalents)
4. More strenuous physical activity for >4 hours per week or regular heavy exercise or competitive sports several times per week (intensity: >6.0 metabolic equivalents)

Because of few persons in category 4 (n=297), persons who answered 3 or 4 were included in the same category. The variable was hereby categorized into: inactivity, light activity, or moderate/high activity.

Echocardiogram

Three echo technicians using GE Vingmed Ultrasound's Vivid Five with 2.5 MHz probe (Horten, Norway) performed all echocardiograms. All images were recorded using second harmonic imaging at the time of end-expiration. All echocardiograms were stored on magneto-optical disks and an external FireWire hard drive (LaCie, France) and analyzed offline with commercially available software (EchoPac, GE Medical, Horten, Norway) by investigators who were blinded to all other information about the participants. Further details on the echocardiograms in The Copenhagen City Heart Study have been published previously.[32–34]

Analysis of Echocardiogram

The following measures were quantified in end diastole: posterior wall thickness, left ventricular end diastolic diameter, septal wall thickness. LVM was calculated using Devereux formula.[35,36] Left ventricular mass index (LVMi) was calculated as the anatomic mass divided by the body surface area.[35,37,38] LVH was defined as LVMi >115 g/m^2 for men and >95 g/m^2 for women according to current guidelines.[36] Concentric LVH was defined as presence of LVH and relative wall thickness >0.42. Eccentric LVH was presence of LVH and relative wall thickness <0.42. Relative wall thickness was calculated using the formula: relative wall thickness=2× posterior wall thickness/left ventricular end diastolic diameter.[36]

Follow-Up and Outcome

All participants were enrolled from 2001 to 2003 and followed until death or 13 December 2018. Danish citizens have a unique civil registration number, which is linked to the Danish Civil Registration System, Danish National Patient Register, and Danish Register of Causes of Death.[39–41] From these registers, information on hospital admissions, death date, and cause of death was obtained. None of the participants was lost to follow-up. During follow-up, 1.3 % of the study population (n=40) emigrated from Denmark, and they were followed in the registries until the date of emigration. The primary outcome was all-cause mortality. The secondary outcome was cardiovascular events defined as hospital admission or death due to acute myocardial infarction, heart failure, or stroke.

Statistics

For demographics, comparisons between groups were performed by Pearson χ^2 test for categorical variables and 1-way ANOVA for continuous covariates. Linear regression models were used to assess the association between physical activity and LVMi and whether hypertension modified this association. Means and CIs in each of the activity groups were estimated in the multivariable linear regression analysis. Activity level was considered as a categorical variable. Linearity, variance of homogeneity, and the assumption of normality were tested with plots of residuals. Likelihood ratio test was performed when testing for interaction and trend.

Time to Event Analyses

Cox proportional hazards regression models were used to assess the association between LVMi, cardiovascular events, and all-cause mortality. The underlying time scale was follow-up time since health examination. Subjects were followed until death or, if still alive December 13, 2018. For cardiovascular events, subjects were followed until their first cardiovascular event (admission or death due to acute myocardial infarction, heart failure, or stroke). Death from other causes was considered as a competing risk. A Fine and Gray subdistribution hazards model with death from other causes as a competing risk was performed. Interaction analyses were performed to explore whether LVH modified the association between physical activity and the defined outcomes.

The *P* values for the differences between the cumulative incidence curves were assessed by log-rank test (all-cause mortality) and Fine and Gray analysis (cardiovascular events).

In all multivariable analyses, the following covariates were considered as confounders: sex, age, previous cardiovascular disease, smoking status (never smoker, former smoker, current smoker), diabetes mellitus, and total cholesterol. Additional adjustment for hypertension was made when the study population was not stratified on normal BP versus hypertension. Body mass index was not included as a confounder because body size was included in the calculation of LVMi and LVH.

Two-sided *P* values <0.05 were considered statistically significant. Values in parentheses are 95% CIs unless stated otherwise.

Stata Statistics/Data Analyses version 15.1 was used for all analyses.

Sensitivity Analysis

Thyroid status is associated with alterations in cardiac morphology including LVMi.[42,43] Diet might also affect LVMi.[44,45] Therefore, we made sensitivity analyses with additional adjustment for both thyroid status and diet (low fat intake, medium fat intake, high fat intake). Definition of thyroid status: euthyroid (thyrotropin/TSH ≥0.3 and ≤4.0 µIU/L), hyperthyroid (TSH<0.3 µIU/L), hypothyroid (TSH>4.0 µIU/L).

Results

Population Characteristics

Persons with normal BP were younger and had better health status than the group with hypertension: lower body mass index, lower frequency of diabetes mellitus, previous cardiovascular disease, and smoking (Table). In both groups, higher activity levels were associated with better health profile. In both BP groups, we found lower resting heart rate and lower body mass index among the activity groups. Left ventricular diastolic function assessed by è was reduced in persons with hypertension and was better in higher activity levels among persons with normal BP. LVH was more frequent in persons with hypertension, and among them, concentric LVH was the predominant LVH type in the inactivity group.

Outcome and Follow-Up

During a mean follow-up of 12.5±5.4 years, 941 deaths occurred, and the majority were identified among persons with hypertension (N=687 [73%]). In total, 894 cardiovascular events occurred (214 cardiovascular deaths; 680 admissions due to stroke/heart failure/acute myocardial infarction). Most of the events (N=613 [69%]) occurred among persons with hypertension at baseline.

Table. Population Characteristics

		Normal BP					Hypertension				
Characteristic	Total Normal BP (N=1702)	Inactivity (N=109)	Light Activity (N=764)	Moderate/ High Activity (N=829)	*P* Value	Total Hypertension (N=1376)	Inactivity (N=129)	Light Activity (N=762)	Moderate/ High Activity (N=485)	*P* Value	*P* Value for Comparison Between the 2 BP Groups
Age, y	49±15	48±16	52±15	47±15	<0.001	67±12	68±13	68±12	64±12	<0.001	<0.001
Male sex, no., %	719 (42)	48 (44)	289 (38)	382 (46)	0.004	551 (40)	58 (45)	262 (34)	231 (48)	<0.001	0.22
Systolic BP, mm Hg	120±11	118±12	120±11	119±11	0.01	154±18	153±18	155±18	154±17	0.78	<0.001
Diastolic BP, mm Hg	72±9	72±10	73±9	72±9	0.22	85±12	83±13	84±12	86±12	<0.01	<0.001
BMI, kg/m^2	24.5±3.5	25.3±3.9	24.7±3.7	24.1±3.2	<0.001	26.6±4.3	27.8±5.1	26.6±4.3	26.2±3.9	<0.001	<0.001
RHR/bpm	65±10	69±11	66±10	64±11	<0.001	69±12	72±12	70±13	67±12	<0.001	<0.001
Diabetes mellitus, no., %	27 (2)	2 (2)	9 (1)	16 (2)	0.47	113 (8)	19 (15)	64 (8)	30 (6)	0.007	<0.001
Previous CVD, no., %	86 (5)	7 (6)	46 (6)	33 (4)	0.14	234 (17)	38 (29)	140 (18)	56 (12)	<0.001	<0.001
Smoking, no., %											
Never	587 (35)	31 (28)	230 (31)	326 (40)		434 (32)	27 (22)	245 (33)	162 (34)		
Former	510 (31)	23 (21)	244 (33)	243 (30)	<0.001	499 (37)	38 (31)	269 (36)	192 (40)	<0.001	0.001
Current	570 (34)	55 (50)	271 (36)	244 (30)		417 (31)	59 (48)	233 (31)	125 (26)		
LVEF<50%, no., %	12 (0.7)	1 (1)	6 (0.8)	5 (0.6)	0.88	20 (1.5)	1 (0.8)	13 (2)	6 (1)	0.62	0.04
Cholesterol, mmol/L	5.2±1.1	5.3±1.2	5.3±1.1	5.1±1.1	<0.001	5.7±1.2	5.7±1.2	5.7±1.2	5.7±1.2	0.93	<0.001
Thyroid status, no., %											
Euthyroid	1578 (94)	105 (96)	698 (93)	775 (93)		1228 (91)	108 (87)	666 (89)	454 (95)		
Hyperthyroid	22 (1)	1 (1)	11 (1)	10 (1)	0.56	31 (2)	4 (3)	21 (3)	6 (1)	0.01	0.001
Hypothyroid	73 (4)	3 (3)	39 (5)	31 (4)		92 (7)	12 (10)	60 (8)	20 (4)		
LVMi, g/m^2	80±19	77±17	79±20	82±19	<0.001	94±25	96±24	94±25	94±24	0.69	<0.001
è	8.6±2.6	8.4±2.7	8.3±2.4	8.9±2.6	<0.001	5.7±1.9	5.7±2.0	5.6±1.9	5.9±2.1	0.19	<0.001
LVH, no., %	144 (8)	4 (4)	61(8)	79 (10)	0.10	405 (29)	45 (35)	231 (30)	129 (27)	0.14	<0.001
Type of LVH, no., %											
Eccentric LVH	97 (67)	3 (75)	42 (69)	52 (66)		225 (59)	20 (44)	126 (55)	79 (61)		
Concentric LVH	47 (33)	1(25)	19 (31)	27 (34)	0.9	180 (44)	25 (56)	105 (45)	50 (39)	0.13	0.01

The participants are grouped according to their BP level (normal BP/ hypertension) and their level of physical activity. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; and RHR, resting heart rate.

Physical Activity and LVMi

At baseline, the mean LVMi in the hypertensive group (n=1376) was significantly higher as compared with the nonhypertensive group (n=1702; 94±25 versus 80±19 g/m^2; *P*<0001). Presence of hypertension modified the association between physical activity and LVMi (test for interaction: *P*=0.01). In persons with normal BP, higher levels of physical activity were associated with significantly higher LVMi (*P*<0.001), whereas in persons with hypertension, there was no significant association between physical activity and LVMi (*P*=0.97). Figure 1 illustrates the adjusted means of LVMi according to level of physical activity in persons with hypertension and in persons with normal BP, respectively, after adjustment for age, sex, previous cardiovascular disease, smoking status, diabetes mellitus, and total cholesterol. Additional adjustment for thyroid status and diet did not change the result pattern.

Impact of LVH and Physical Activity on Outcome

Physical activity was associated reduction in mortality and cardiovascular events (for persons with LVH: inactivity (reference); light activity HR, 0.77 [0.52–1.15]; moderate/high activity HR, 0.61 [0.38–0.97] for all-cause mortality). This association was not modified by LVH (test for interaction: *P*=0.71; Figures 2 and 3). Additional adjustment for thyroid status and diet did not change the impact of physical activity on outcome (cardiovascular events for persons with LVH: inactivity [reference]; light activity HR, 0.76 [0.51–1.15]; moderate/high activity HR, 0.65 [0.41–1.04]).

The Prognostic Importance of LVH

Presence of hypertension did not modify the association between LVH and prognosis (Figure 4). The prognostic importance of LVH did not differ between the activity levels (Figure 5).

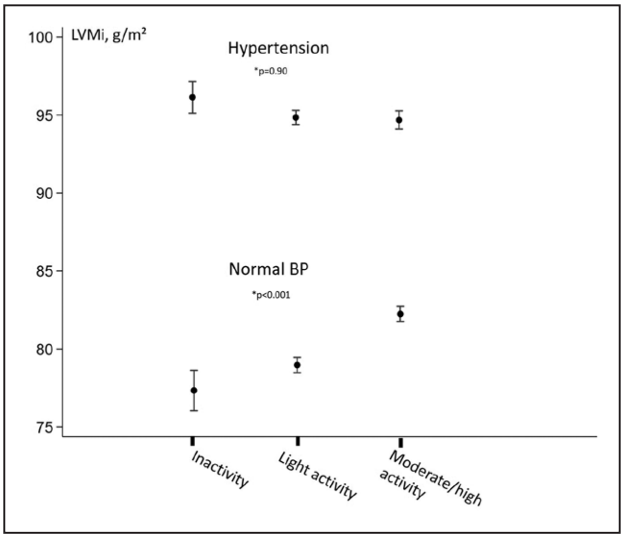

Figure 1. Left ventricular mass and physical activity. Adjusted means of left ventricular mass index (LVMi) according to the activity levels and blood pressure (BP) groups after adjustment for age, sex, previous cardiovascular disease, smoking status, diabetes mellitus, and total cholesterol. **P* values for trend test for the association between LVMi and level of physical activity in each of the BP groups after adjustment for confounders.

Persons in Medical Treatment for Hypertension

A subgroup analysis only including persons who received antihypertensive medication at baseline showed the same pattern of results: level of physical activity was not associated with LVMi (*P*=0.97). Level of physical activity was associated with a corresponding reduction in outcome independent of the presence of LVH (test for interaction: *P*=0.78).

Discussion

This study had 3 main findings: first, LVMi was significantly higher at increased levels of physical activity among persons with normal BP, whereas this association was not found among persons with hypertension. Second, physical activity was associated with better prognosis despite the presence of LVH. This means that being physically active with hypertension was not associated with further increase in LVM. Furthermore, being physically active even in the presence of hypertension and LVH was associated with better prognosis compared with inactivity.

LV Mass, LVH, and Physical Activity in Hypertension

LVH induced by hypertension is known as a pathological hypertrophy and is a result of increased systemic pressure and volume overload leading to increased workload on the left ventricle.[25] Physiological hypertrophy refers to the cardiac adaptation of the left ventricle due to high workload, for example, pregnancy and physical activity. Physiological hypertrophy regresses quickly when training is discontinued,[46] while regression of hypertension induced LVH might occur slowly after normalization of BP.[12]

Cardiovascular events including sudden cardiac death are more frequent in patients with LVH.[3]

As physical activity is associated with a further elevation in BP and afterload during exercise, it could be a concern if the combination of hypertension, LVH, and moderate/high level of physical activity might be harmful. Our study does not imply any harmful associations with prognosis when persons with both hypertension and LVH have increased activity levels.

Although we did not find a significant change in LVMi in higher activity levels among persons with hypertension, previous studies found that physical activity in persons with hypertension was associated with decrease in LVM.[14,15,47–49] The reason we did not find any association between LVMi and level of physical activity could be due to lack of power. Besides, factors like duration of hypertension and duration of the reported level of physical activity might also play a role.

The benefits of physical activity on hypertension and LVH was already described in 1995 by Kokkinos et al[48] who performed a well-designed randomized intervention trial showing how regular exercise reduced both BP and LVH in black men with severe hypertension, who were already treated with antihypertensive medication.

The impact of physical activity on LVM was later confirmed in 2009 by Palatini et al[50] studying 454 Italian habitants with hypertension in a prospective longitudinal study design. None of them had LVH at baseline and the echocardiograms were repeated during the follow-up of 8 years.

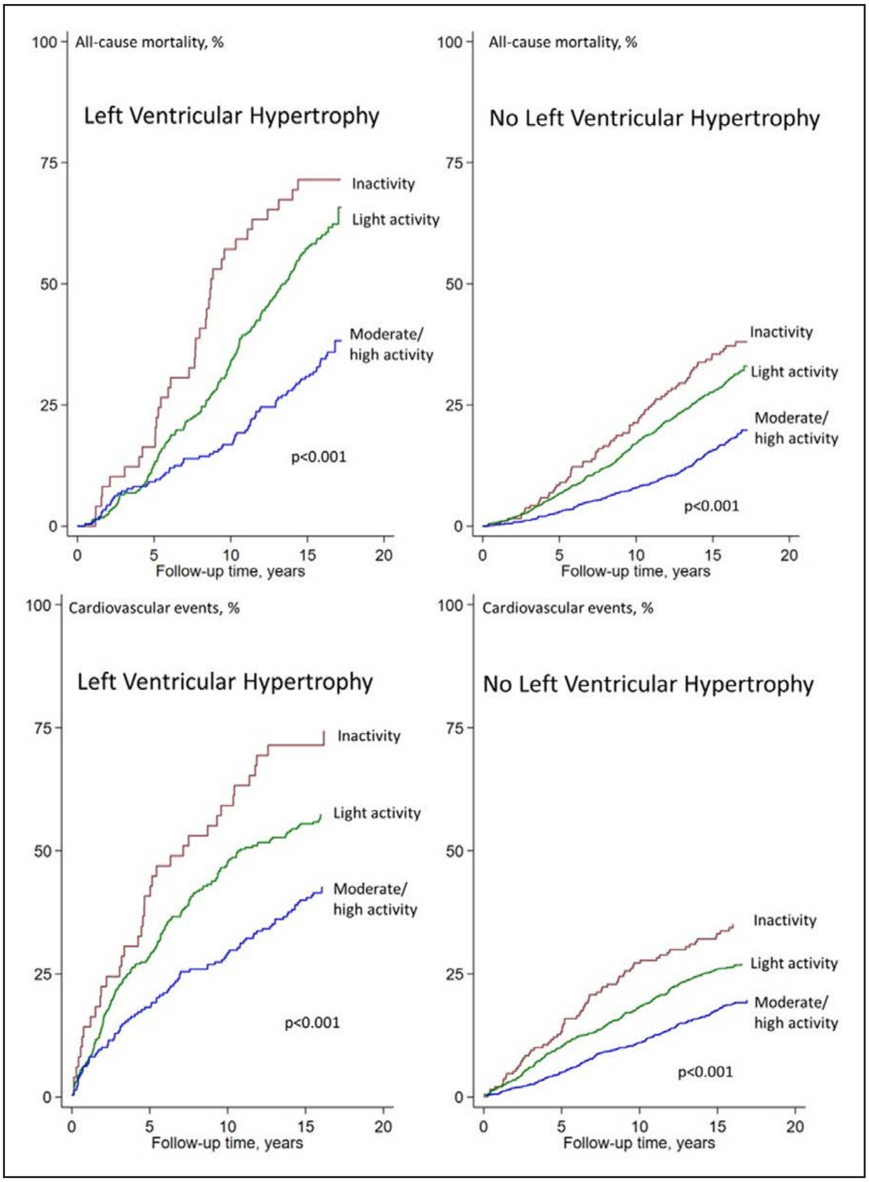

Figure 2. Left ventricular hypertrophy (LVH), physical activity, and outcome. Cumulative incidence of all-cause mortality (top) and cardiovascular events (bottom) according to the activity levels. Stratified on the presence of LVH. Cardiovascular events defined as admissions or death due to heart failure, stroke, or acute myocardial infarction.

The activity level was self-reported and categorized into Sedentary or Active. They concluded that performing regular physical activity was associated with a lower risk of LVH. The impact of physical activity on the development of LVH was independent of changes in BP and body weight. In 2011, Pitsavos et al published a study including 52 men with mild hypertension and without previous cardiovascular disease. Half of the study population was assigned to 16 weeks training programme, and the other group was allocated to a nonexercise arm.[51] They found a significant reduction in

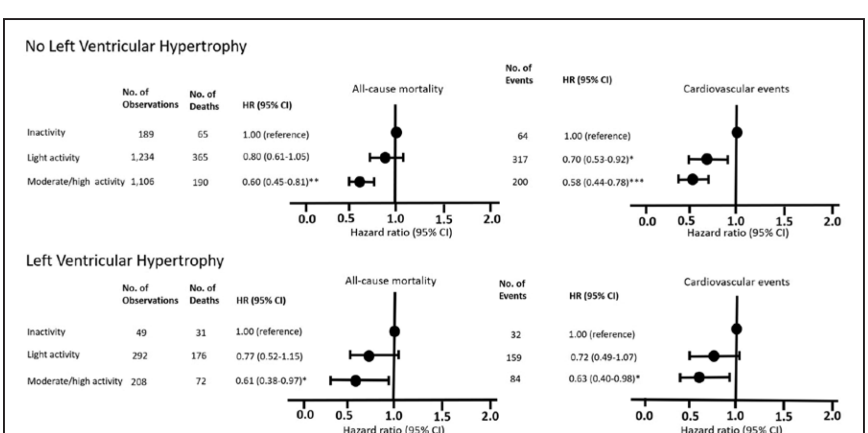

Figure 3. Left ventricular hypertrophy (LVH), physical activity, and outcome. Forest plot. Top, all-cause mortality (left) and cardiovascular events (right) according to the level of physical activity for persons without LVH. Bottom, all-cause mortality (left) and cardiovascular events (right) according to the level of physical activity for persons with LVH. Multivariable analyses. Adjusted for age, sex, diabetes mellitus, total cholesterol, previous cardiovascular disease, smoking status, and hypertension. Test for interaction between LVH and level of physical activity for all-cause mortality: $P=0.95$. Test for interaction between LVH and level of physical activity for cardiovascular events: $P=0.97$. *$P<0.05$; **$P<0.01$; ***$P<0.001$.

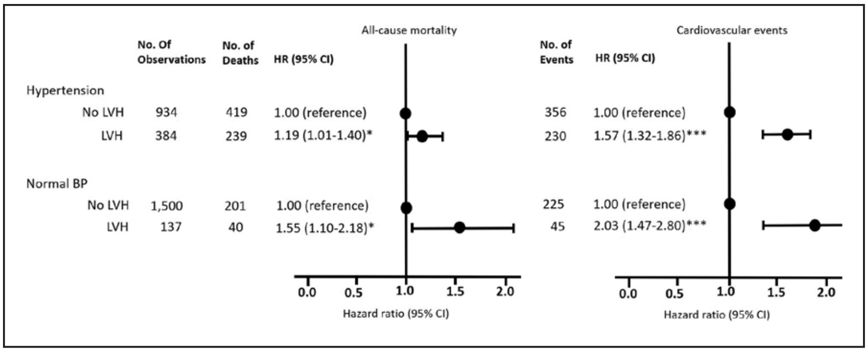

Figure 4. Blood pressure (BP) level, left ventricular hypertrophy (LVH), and outcome. Forest plot. All-cause mortality (left) and cardiovascular events (right) according to the BP group and presence of LVH. Multivariable analyses. Adjusted for age, sex, diabetes mellitus, total cholesterol, previous cardiovascular disease, smoking status, and level of physical activity. Test for interaction between LVH and hypertension for all-cause mortality: P=0.16. Test for interaction between LVH and hypertension for cardiovascular events: P=0.16. *P<0.05; ***P<0.001.

resting and exercise BP levels, lower RHR, and lower LVM in the training group. However, in both studies, only persons without LVH on echocardiography were included. Thus, conclusions cannot be drawn for a high-risk hypertensive population who already has LVH at baseline.

The impact of physical activity on the prognosis in a high-risk population with both hypertension and LVH was explored in the interesting study performed by Fossum et al[52] as part of the well-conducted LIFE-trial (Losartan Intervention for End point Reduction in Hypertension). The level of physical activity was self-reported and categorized into never exercise, ≤30 minutes twice per week, and ≥30 minutes twice per week. After a mean follow-up of 4.8 years, they found that both physical activity levels were associated with reduction in several cardiovascular end points and all-cause mortality. The findings were mostly significant for the modest activity level (≥30 minutes twice per week). Thus, our study supports their findings, as both studies explored the association between self-reported activity level and outcome in person with both hypertension and LVH.

In our study, we found that persons already in medical treatment did not have higher LVMi with increased activity levels. This finding is supported by Ketelhut et al[53] in a study investigating changes in LVM in medically treated athletes with hypertension. They were compared with hypertensive sedentary controls treated with medication. The results showed that LVM at baseline was higher in hypertensive athletes compared with the controls. The athletes continued performing regular aerobic training during follow-up. LVM decreased in both groups after end of follow-up. They explained this finding as the effect of antihypertensive medication. However, in athletes with hypertension, physical activity might also induce regression of pathological hypertrophy.

Impact of Physical Activity and LVH on Prognosis

The reason why we should draw attention to the association between level of physical activity and LVH in hypertension is, that several previous studies have shown that regression of LVH is associated with reduction in cardiovascular morbidity and mortality.[12,54,55] In these studies, regression of LVH was achieved by pharmacological treatment. However, more studies are needed on the association between level of physical activity, change in LVM and its impact on long-term prognosis.

Increased level of physical activity was associated with reduced outcome independent of the presence of LVH. This underscores the importance of physical activity in determining the prognosis as concluded in other studies.[18,20]

Persons already receiving optimal medical treatment might be in another risk category than persons with newly diagnosed hypertension. Physical activity might thus have a different impact on their LVM as well as their prognosis. The echocardiographic parameters including LVMi might also be affected by the treatment. The subgroup analyses we conducted in this study did not imply that this group differed from the rest of the persons with hypertension regarding neither the association between level of physical activity and LVMi, nor the impact of LVH and physical activity on the prognosis.

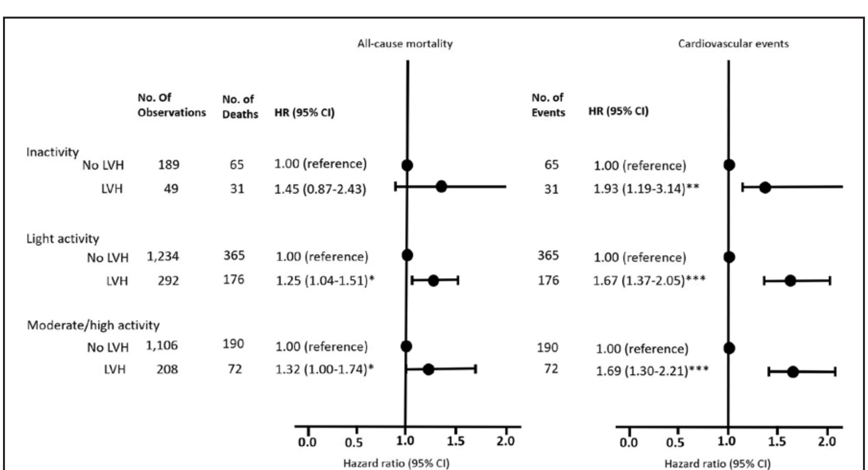

Figure 5. Physical activity level, left ventricular hypertrophy (LVH), and outcome. Forest plot. All-cause mortality (left) and cardiovascular events (right) according to the level of physical activity and presence of LVH. Multivariable analyses. Adjusted for age, sex, diabetes mellitus, total cholesterol, previous cardiovascular disease, smoking status, and hypertension. Test for interaction between level of physical activity and LVH for all-cause mortality: P=0.95. Test for interaction between level of physical activity and LVH for cardiovascular events: P=0.97. *P<0.05; **P<0.01; ***P<0.001.

Strengths and Limitations

The large number of persons included in the study and the long follow-up time without any missing participants at the end of follow-up are valuable qualities of this study. The standardized BP measurement (casual BP) has also been validated in previous epidemiological trials.[56,57] One of the limitations is that level of physical activity is self-reported and does not necessarily represent the actual activity level for each of the individuals. Further, we do not know if the participants changed their level of physical activity during the follow-up.

Another limitation is that we do not have information on the type of medication prescribed to the persons already in pharmacological treatment at baseline. Neither do we have information on initiation of antihypertensive drugs during follow-up in persons categorized in the hypertensive group at baseline. Beyond the effects of BP reduction, some of the drugs, especially blockers of renin-angiotensin-aldosterone system, have favorable effect on regression of LVH, and might interfere with the prognosis associated with LVH.[58–60]

Clinical Implication

This study shows that higher levels of physical activity is not associated with further increase in LVM in persons with hypertension. A patient with hypertension and LVH should without concerns be encouraged to increase the level of activity due to the patient's clinical condition and capability.

Conclusions

Increased level of physical activity was associated with higher LVMi in persons with normal BP. This association was not present among persons with hypertension. Compared with inactivity, higher levels of activity were associated with better prognosis, and this association was independent of the presence of LVH.

Perspectives

Further studies are needed to confirm that physical activity is not harmful in persons with both hypertension and LVH, and that physical activity might rather induce beneficial alterations in left ventricular morphology. Randomized trials including specific training programmes for hypertensive subjects with and without LVH, respectively, might provide more knowledge about changes in cardiac morphology and long-term prognosis in this patient group. Interaction between the effects of medical treatment and physical activity also needs to be explored in future studies. However, it is notable that we now have more studies indicating that physical activity is beneficial for persons with hypertension, including patients with LVH, who comprise a high-risk population.

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Disclosures

Dr T. Biering-Sørensen has declared following conflict of interest outside the submitted work: Steering Committee member of the Amgen financed GALACTIC-HF (Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure With Reduced Ejection Fraction) Advisory Board: Sanofi Pasteur; Advisory Board: Amgen; Speaker Honorarium: Novartis; Speaker Honorarium: Sanofi Pasteur. Dr Saevereid has declared following conflict of interest outside the submitted work: currently, full-time employed at Novo Nordisk A/S. The other authors declare no conflicts.

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Novelty and Significance

What Is New?

- Increased levels of physical activity are associated with higher left ventricular mass in persons with normal blood pressure, and this association is not present in persons with hypertension. The health benefits of physical activity on prognosis is present in both persons with left ventricular hypertrophy and in persons without left ventricular hypertrophy.

What Is Relevant?

- It is not harmful to perform physical activity in the presence of both hypertension and left ventricular hypertrophy.

Summary

In this population-based cohort study comprising 3078 persons, higher levels of physical activity were associated with increased left ventricular mass in persons with normal blood pressure, whereas this association was not present in persons with hypertension. Compared with inactivity, higher levels of physical activity were associated with corresponding reduction in mortality and cardiovascular outcome. This association was present independent of whether left ventricular hypertrophy was present or not.

Online supplement

Level of Physical Activity, Left Ventricular Mass, Hypertension and Prognosis

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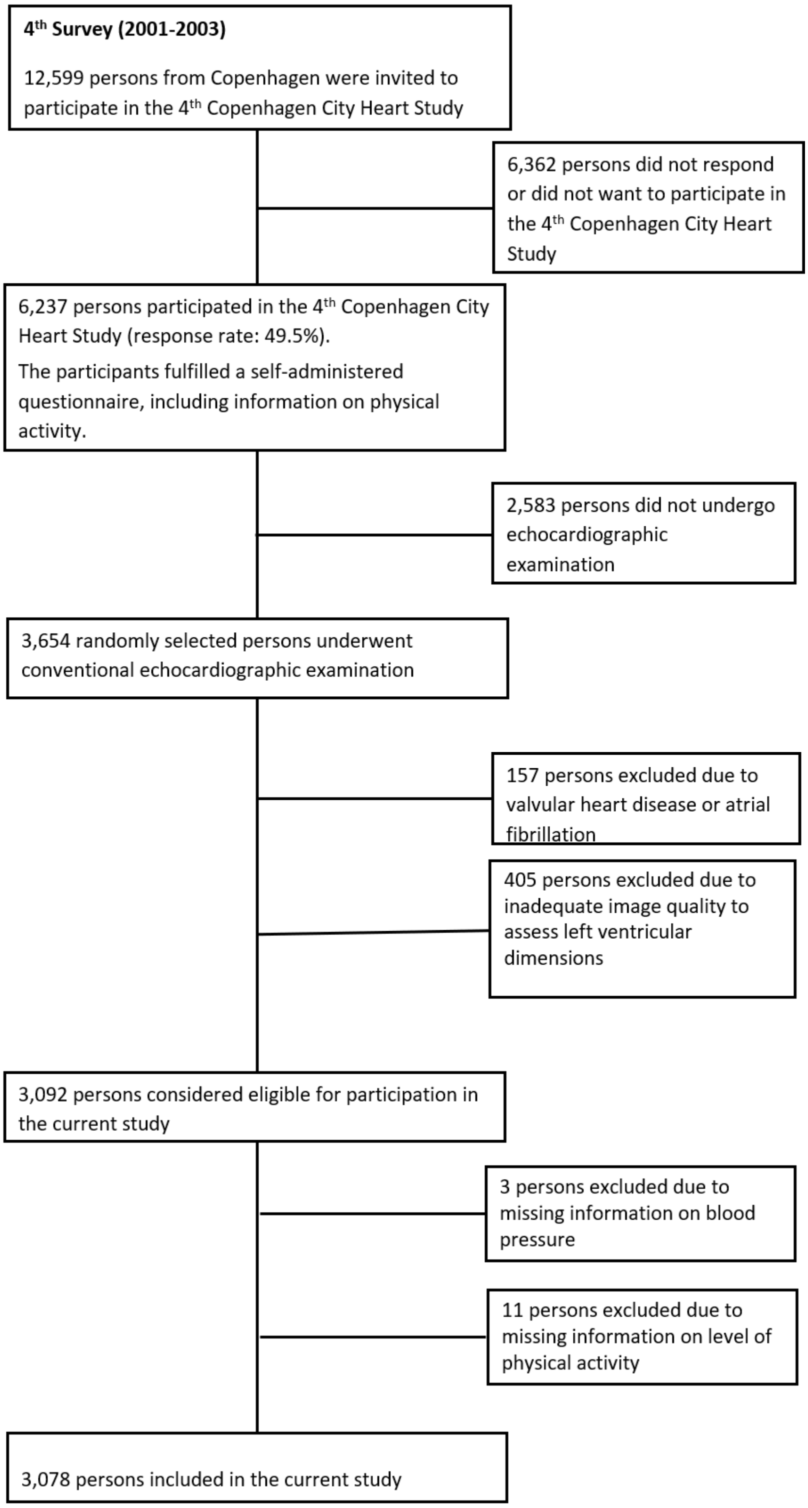

Figure S1. Flow chart for the present study at baseline.

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