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Physical fitness and exercise as prevention strategies during different stages of cardiovascular disease

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I. Preface

> „*Personally, I like to exercise, enjoy it and believe it makes us all feel better. The question, however, is simply what is the evidence that regular physical activity per se, compared with a sedentary life, lessens the likelihood of development of coronary atherosclerosis, coronary thrombosis, myocardial infarction, or death from coronary disease. Let's go over some of the evidence.*" (1)

With these words, the former president of the *American Heart Association* Dr. Oglesby Paul (2), started his writing in *The American Journal of Cardiology* in 1969 regarding the topic of „Physical Activity and Coronary Heart Disease". In this thesis, I would like to catch up Dr. Paul's wording describing current evidence on exercise and thereby improved physical fitness as prevention strategies in different stages of cardiovascular disease.

I am deeply convinced of the fact that exercise and physical fitness are highly important lifestyle parameters to sustain or even improve risk factor profile, even in later stages of prevention.

To enable individuals to actively shape their own health and risk factor profile by exercising is one of my main drivers. It is never too late to start something good.

II. Abstract/ Summary

Physical inactivity has shown to be associated with metabolic and cardiovascular diseases (CVD) e.g. metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), heart failure and chronic ischemic heart disease (CIHD). However, in specific different patient populations e.g. juvenile cancer patients, metabolic syndrome (MetS) patients and patients with T2DM and CIHD the dose of exercise as well as role of physical fitness (PF) is less clear. Therefore, in these patient populations the role of exercise capacity and exercise intervention with different intensities and volumes has been assessed in a cross-sectional and an interventional study, as well as will be investigated in a planned study design.

In the first study we have hypothesized that childhood cancer survivors (CCS) have a lower health-related PF than healthy peers due to treatment-related late sequelae, which may reveal associations to vascular function (pulse wave velocity, PWV) (MOSAIC study (CCS): cross-sectional, n=92, 47% girls, mean age 12.5 ± 4.2 years; healthy peers: unpublished "Sternstunden" cohort: n=983 Bavarian children, 50 % girls, mean age 11.8 ± 2.3 years). PF, measured by a motoric battery including strength and flexibility tasks and transformed into standardized z-scores, was significantly reduced in CCS (CCS PF z-score compared to healthy peers -0.28 ± 1.01, p=0.011). No association of PF and PWV was observed in CCS (r=0.004, p=0.972).

In the second study in patients with MetS we have hypothesized that different intensities and volumes of endurance exercise have different effects on PF (peak oxygen uptake, $\dot{V}O_2peak$) and metabolic risk factors (blood lipids, fasting glucose and insulin) after 16 weeks intervention (DZHK ExMET study, n=29, mean age 61 ± 5 years, 45% females, BMI 31.1 ± 3.7 kg/m^2, randomized 1:1:1 to high intensity interval training with two different volumes or moderate intensity continuous training). The overall PF significantly improved ($\dot{V}O_2peak$ Δ 2.7 ± 0.9 ml/min/kg, p<0.001), independent of exercise regimes. However, no significant effects on metabolic risk factors were observed.

In the third study, including patients with both T2DM and CIHD, we hypothesized in the framework of a study design that 12-months lifestyle intervention supported by telemedicine is superior than usual care on glycosylated hemoglobin reduction after six months (LeIKD study, randomized (1:1), controlled, n=1500). The design of the 12-months lifestyle intervention and its anticipated effects on metabolic control and PF is further elaborated in this dissertation.

In conclusion, neither exercise capacity in juvenile cancer patients nor 16-week exercise intervention in patients with MetS had an effect on vascular function or metabolic control, respectively. Whether 12-months lifestyle intervention in the LeIKD study in CIHD/T2DM patients will have a significant effect on metabolic control remains to be shown. However, in contrast to the general perception the significant impact of physical fitness and exercise in patients with high cardiovascular risk seems to be limited.

III. Abstract/ Zusammenfassung

Körperliche Inaktivität beeinflusst maßgeblich das Auftreten von metabolischen und Herz-Kreislauf-Erkrankungen (CVD), wie dem metabolischen Syndrom (MetS), Typ 2 Diabetes mellitus (T2DM), Herzinsuffizienz oder koronarer Herzerkrankung (KHK). Jedoch ist der Einfluss körperlicher Belastbarkeit (PF) und Training in spezifischen Patientengruppen, z.B. bei pädiatrischen Krebspatienten, Patienten mit MetS oder T2DM und KHK, weniger klar. Daher wurden in einer Quer-, einer Längsschnittstudie und einem Studiendesign der Einfluss von PF und Bewegung (Intensität und Umfang) in diesen Patientengruppen untersucht und diskutiert.

In der ersten Studie stellten wir die Hypothese auf, dass Kinder und Jugendliche nach einer Krebstherapie (CCS), aufgrund von behandlungsbedingten Spätfolgen, eine niedrigere PF, im Vergleich zu gesunden Gleichaltrigen, aufweisen (MOSAIC Studie (CCS): n=92, 47% Mädchen, Alter 12,5 ± 4,2 Jahre, Querschnittsstudie; gesunde Gleichaltrige: unveröffentlichte "Sternstunden"-Kohorte: n=983 bayerische Kinder, 50% Mädchen, Durchschnittsalter 11,8 ± 2,3 Jahre). Dies könnte in Zusammenhang mit der vaskulären Funktion (Pulswellengeschwindigkeit, PWV) stehen. Die PF, gemessen anhand von fünf Kraft- und Beweglichkeitsübungen und in standardisierte z-scores transformiert, war bei CCS signifikant reduziert (CCS-PF-Werte im Vergleich zu gesunden Gleichaltrigen -0,28 ± 1,01, p=0,011). Es wurde keine Assoziation zwischen PF und PWV bei CCS gefunden (r=0,004, p=0,972).

In der zweiten Studie, in welcher Patienten mit MetS untersucht wurden, stellten wir die Hypothese auf, dass unterschiedliche Intensität und Umfang von Ausdauertraining einen jeweils verschiedenen Einfluss auf PF (max. Sauerstoffaufnahme, V̇O2peak) und metabolische Risikofaktoren (Blutfette, Nüchternglukose und -insulin) nach 16 Wochen Intervention haben (DZHK ExMET Studie, n=29, Alter 61 ± 5 Jahre, 45% weiblich, BMI 31,1 ± 3,7 kg/m2, 1:1:1 randomisiert in hochintensives Intervalltraining mit zwei verschiedenen Umfängen oder moderat- kontinuierliches Training). Die PF verbesserte sich in allen Gruppen signifikant (V̇O2peak Δ 2,7 ± 0,9 ml/min/kg, p<0,001), ohne signifikante Gruppenunterschiede. Es wurde kein signifikanter Effekt auf die metabolischen Risikofaktoren festgestellt.

In der dritten Studie, in welche Patienten mit T2DM und KHK eingeschlossen werden, wird eine Überlegenheit der Reduktion des glykosylierten Hämoglobins nach einer sechsmonatigen Lebensstilintervention im Vergleich zur Regelversorgung (usual care) erwartet (LeIKD Studie, n=1500, 1:1 randomisiert). Das Design der 12-monatigen telemedizinischen

Lebensstilintervention und ihre angenommenen Effekte auf metabolische Risikofaktoren und PF werden im Rahmen der Dissertation ausgeführt.

Zusammenfassend hatte weder die PF bei Kindern und Jugendlichen nach Krebstherapie, noch eine 16-wöchigen Trainingsintervention bei Patienten mit MetS, einen Einfluss auf die vaskuläre Funktion bzw. metabolische Risikofaktoren. Der Einfluss nach 12-monatiger Lebensstilintervention im Rahmen der LeIKD Studie hinsichtlich der Verbesserung des Risikoprofils von Patienten mit T2DM und KHK bleibt abzuwarten. Im Gegensatz zur gegenwärtigen Auffassung scheint somit der Einfluss von PF und Bewegung bei Patienten mit hohem kardiovaskulärem Risiko begrenzt zu sein.

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List of Abbreviations

AMP	Adenosine monophosphate
ARTEMIS	Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection - study
ASCEND	A Study of Cardiovascular Events in Diabetes - trial
ASCVD	Atherosclerotic cardiovascular disease
ATP	Adenosine triphosphate
BP	Blood pressure
CI	Confidence interval
CIHD	Chronic ischemic heart disease
CCS	Childhood cancer survivor
Cm	centimeter
CPET	Cardiopulmonary exercise testing
CRF	Cardiorespiratory fitness
CRP	c-reactive protein
CVD	Cardiovascular diseases
DALY	Disability-adjusted life years
DBP	Diastolic blood pressure
DIADEM-I	Diabetes Intervention Accentuating Diet and Enhancing Metabolism - trial
DiRECT	Diabetes remission clinical trial
dl	Deciliter
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
DZHK	German Centre for Cardiovascular Research
DZHK ExMET	Substudy of the Exercise in the Prevention of Metabolic Syndrome – trial
ECG	Electrocardiogram

ENHANCE	Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression - trial
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
ESC guidelines	2020 ESC Guidelines on Sports Cardiology and Exercise
EUROASPIRE IV	European Action on Secondary Prevention through Intervention to Reduce Events IV- trial
ExMET	Exercise in the Prevention of Metabolic Syndrome - trial
FEV	Fragebogen zum Essverhalten, German Questionnaire on Eating behavior
HbA_{1c}	Glycosylated hemoglobin
HDL-C	High density lipoprotein cholesterol
HF	Heart failure
HF ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HIIT	High intensity interval training
HLS-EU-Q16	European Health Literacy Questionnaire
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HFrEF	Heart failure with reduced ejection fraction
HRPF	Health-related Physical Fitness
HRR	Heart rate reserve
HR	Heart rate
HTW	Hypertriglyceridemic waist phenotype
ICD	International Statistical Classification of Diseases
IDF	International Diabetes Federation
IL-beta	Interleukin beta
IPAQ	International Physical Activity Questionnaire
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland
Kg	Kilogram
LDL-C	Low density lipoprotein cholesterol

LeIKD	Lifestyle Intervention in Chronic ischemic heart disease and Type 2 Diabetes - trial
Look AHEAD	Action for Health in Diabetes - trial
LS	Lifestyle intervention
LTPA	Leisure time physical activity
MET	Metabolic equivalent of tasks
MetS	Metabolic syndrome
Mg	Milligram
MICT	Moderate intensity continuous training
ml	Milliliter
mmHg	Millimeters of mercury
MOSAIC	Motoric competence and arterial stiffness in children during and after chemotherapy - study
n	Number of participants
NCD	Non-communicable diseases
NO	Nitric oxide
NYHA	New York Heart Association
OR	Odds ratio
oxLDL	Oxidized low density lipoprotein
PA	Physical activity
PAD	Peripheral artery disease
PF	Physical Fitness
PWV	Pulse wave velocity
QoL	Quality of Life
RCT	Randomized controlled trial
RER	Respiratory exchange ratio
RR	Relative risk
SBP	Systolic blood pressure

Score	Systematic coronary risk evaluation
SD	Standard deviation
SF-36	Short Form Health Survey
SMCP	smooth muscle cell proliferation
TAG	Triglycerides
TEMA-HF1	Telemonitoring in the Management of Heart Failure - trial
TIM-HF2	Telemedical Interventional Management in Heart Failure II - trial
TNF	Tumor necrosis factor
TUM	Technical University of Munich
T2DM	Type 2 diabetes mellitus
UC	Usual care
$\dot{V}O_2$peak	Peak oxygen uptake
WC	Waist circumference
WTHr	Waist-to-height ratio
WHO	World health organization
WHO SEARO	World Health Organization South-East Asia Region
1HIIT	One interval- high intensity interval training/ Low volume high intensity interval training
4HIIT	Four intervals- high intensity interval training/ High volume high intensity interval training

1. Introduction

Chronic diseases[1] increase peoples' risk of dying prematurely (4, 5). People suffering from chronic diseases have increased disability-adjusted life years[2] (DALY) due to the high burden of the disease (6). This results in patients' lower quality of life (QoL) and rising public health-economic costs (3, 7). Part of chronic diseases are non-communicable diseases (NCD), defined as cardiovascular diseases, cancer, chronic respiratory diseases and diabetes[3] (9), as schematically illustrated in figure 1. NCDs are postulated as "the biggest global killers today" by the World Health Organization (WHO) (10). They account for 71.3% of all global deaths in 2015 (39.8 mio. deaths), as stated in the Global Burden of Disease study investigating data from 1980 – 2015 in 195 countries and territories (11).

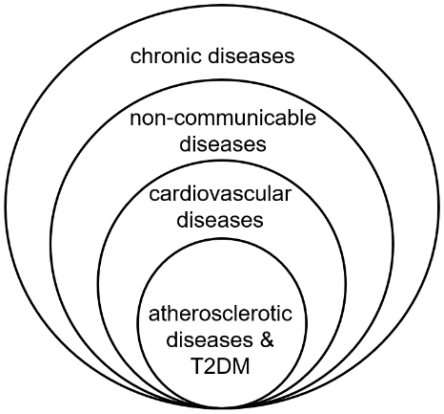

Figure 1 Overview chronic diseases - NCDs - CVDs. Authors own figure.

[1] **Chronic disease**: definition from Bernell et al. 2016 referring to the Australian Institute for Health and Welfare: "complex causality, with multiple factors leading to their onset; a long development period, for which there may be no symptoms; a prolonged course of illness, perhaps leading to other health complications; associated functional impairment or disability." 3. Bernell S, Howard SW. Use Your Words Carefully: What Is a Chronic Disease? Front Public Health. 2016;4.

[2] **Disability-adjusted life years**: "years of life lost due to death from a condition and years lived with disability due to a condition."4. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. European heart journal. 2016;37(42):3232-45.

[3] Definition **NCDs**: International Statistical Classification of Diseases (ICD-10) codes for premature death from NCDs are I00–I99, C00–C97, E10–E14, and J30–J98 8. World Health Organization. Noncommunicable diseases global monitoring framework: indicator definitions and specifications. Geneva2014 [Available from: http:// www. who.int/nmh/ncd-tools/indicators/GMF_Indicator_Definitions_Version_NOV2014.pdf..

As part of NCDs, Cardiovascular diseases[4] (CVD) and Diabetes account for more than 50% of worldwide NCDs in 2008 (5, 13). In 2015, the Global Burden of Disease study attributed 17.9 mio. and 1.5 mio. of all global deaths from CVD and Diabetes, respectively, highlighting CVD as the leading cause of death in NCDs (11). In the European Union, attributable CVD healthcare costs account for 106.000.000.000.000,00 € (106 billion) in 2009 (14). CVD incidence especially increases with aging population (5), see figure 2. Considering the increased overall global life expectancy in the past 35 years (0.27 and 0.32 years of life for males and females, respectively), this further reinforces the need to approach underlying risk factors and design prevention strategies for the affected population (11).

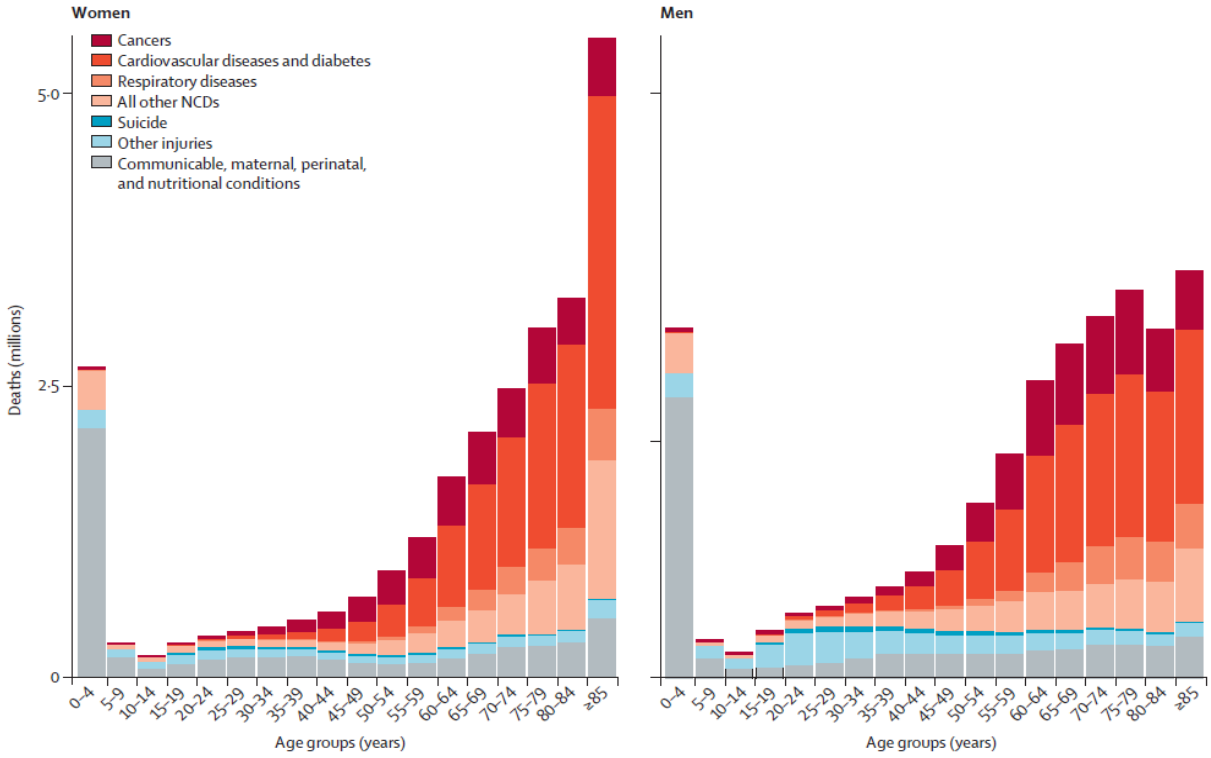

Figure 2 Number of deaths in 2016 from non-communicable diseases, injuries, and communicable, maternal, perinatal, and nutritional conditions. Figure from Bennett, 2018 (5).

[4] **Cardiovascular Disease**: "Cardiovascular diseases are a group of disorders of the heart and blood vessels and include: coronary heart disease: disease of the blood vessels supplying the heart muscle; cerebrovascular disease: disease of the blood vessels supplying the brain; peripheral arterial disease: disease of blood vessels supplying the arms and legs; rheumatic heart disease: damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria; congenital heart disease: malformations of heart structure existing at birth; deep vein thrombosis and pulmonary embolism: blood clots in the leg veins, which can dislodge and move to the heart and lungs. […]"
12. World Health Organization. Definition of cardiovascular diseases 2019 [Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/cardiovascular-diseases2/definition-of-cardiovascular-diseases.

NCDs are mainly driven by four major lifestyle risk factors: use of tobacco/ smoking, sedentariness/ physical inactivity[5], unhealthy diet/ nutrition and related exacerbated consumption of alcohol (10, 13, 16). As depicted in figure 3, there is a global shift from traditional (undernutrition, hygiene, air pollution, infectious diseases etc.) to modern risk factors (overweight, tobacco and alcohol consumption, physical inactivity etc.) in the last decades (16).

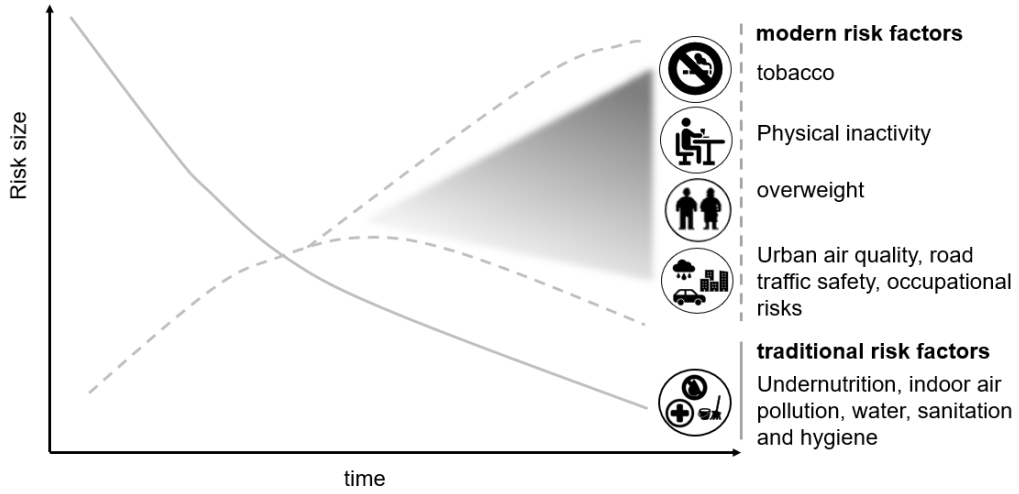

Figure 3 The risk transition from traditional to modern risk factors over time. Figure adapted from World Health Organization (2009) (16).

Reasons for decreased prevalence of traditional risk factors are public health actions, medical developments and governmental policies (16). However, the worldwide aging population, socioeconomic environment, education and individual's lifestyle choices lead to increased modern risk factors (16). If risk factor exposure accumulates, the main drivers for incident NCDs are evolving metabolic and cardiovascular disorders, based on: overweight/ obesity (17), lipid disorders / dyslipidemia (↑triglycerides, ↓high-density lipoprotein cholesterol (HDL-C)) (18, 19), chronic inflammation (20), high blood pressure/ hypertension (21), metabolic syndrome (22), insulin resistance/ type 2 diabetes mellitus (T2DM) (23) and atherosclerosis (20)/ atherosclerotic cardiovascular disease (ASCVD) (22, 24).

[5] **Physical inactivity** as defined by the WHO: "An absence of physical activity or exercise." 15. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva; 2010.

NCD and CVD incidences are therefore directly associated to behavioral decisions on risk factors, which itself presents as an option for prevention strategies (16). Every individual can be enabled to shape risk factor profile in different stages of diseases, accompanied by socioeconomic, governmental and public health interventions (16).

Especially physical activity[6] presents itself as an option to shape risk factor profile in different stages of diseases and age groups: regular exercise[7] improves physical fitness and has several health benefits with regard to reduction of metabolic risk factors, prevention or delay of disease progression (15, 26-32), which will be further discussed in the following thesis.

Individuals performing sufficient PA have a lower risk of CVDs, cancer, diabetes and hypertension and favorable impact risk factor profile, even in later stages of CVD (15, 27, 31). However, exercise as a prevention strategy is not properly installed, as low worldwide trends in general PA levels postulate (27) and primary prevention strategies in patients at risk for CVD are not as effective as foreseen (33). Prevalence of insufficient physical activity in adults (>18 years) worldwide increased from 23.4% (CI 5.8 – 57.3) in 2010 to 42.2 (CI 35.5-49.2) 2019 (34). Concluding, this clearly outlines an unfavorable risk factor management, especially regarding exercise.

Within the background of this thesis selected modifiable risk factors of NCD and CVD and the influence of exercise and physical fitness will be presented. In the framework of the authors published manuscripts populations with different risk factor profiles are examined, evaluated and options for future points of actions are outlined. Thereby, the current status quo is presented and discussed. The awareness of one of the leading risk factors worldwide must be increased and counteracted: physical inactivity kills.

[6] **Physical activity**: “Physical activity is any bodily movement produced by the skeletal muscles that uses energy. This includes sports, exercise, and other activities such as playing, walking, household chores, gardening, and dancing. Any activity, be it for work, to walk or cycle to and from places, or as part of leisure time, has a health benefit.” 25. World Health Organization. Fact files physical activity [Available from: http:// www. who.int/features/factfiles/physical_activity/en/.

[7] **Exercise** as defined by the WHO: “A subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of **physical fitness** is the objective. “Exercise” and “exercise training” frequently are used interchangeably and generally refer to physical activity performed during leisure time with the primary purpose of improving or maintaining physical fitness, physical performance, or health.” 15. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva; 2010.

2. Background

Physical inactivity is one of the most important modern risk factors and can be held accountable to cause nearly 1/3 of incident type 2 diabetes mellitus (T2DM) and coronary artery disease/ chronic ischemic heart disease (CIHD) worldwide (16). To improve risk factor profile, exercise and thereby enhanced physical fitness are major therapy options in all stages of prevention of cardiovascular and -metabolic diseases. To further evaluate this hypothesis, background on prevention, current guidelines, disorders and diseases is presented.

2.1. Stages of prevention

Different stages of prevention (35) can be identified by their specific target population (15), as defined by the German Federal Ministry of Health and the WHO, respectively:

- Primary prevention aims for disease prevention before any symptoms appear, mostly in currently healthy populations.
- Secondary prevention controls for biomedical and metabolic risk factors to prevent it from worsening, once a risk factor is evident (at risk population). This includes screening and action to delay disease progression, onset as well as severity.
- Tertiary prevention manages and tackles a disease to prevent it from worsening in a sick population. This includes the management of late sequelae from certain diseases as well as preventing from recurrence/ relapse.

With regard to the European Society of Cardiology, the definition of prevention was simplified to primary and secondary prevention only:

- primary prevention aims at promoting healthy lifestyle and elimination of CVD risk factors by individual risk stratification and categories (low-, moderate-, high- and very high risk) (14) in apparently healthy populations (36).
- “secondary prevention aims to stop and/or slow down the progress of established cardiovascular disease, to improve functional capacity, to restore quality of life and to reduce the risk of disease recurrence.” as cited by Frederix (2017) from Piepoli (2016) (14, 37).

This points out the different approaches and definitions of preventive strategies. In the framework of this thesis the definition of the WHO and German Federal Ministry of Health will be used.

With regard to the scope of this thesis, figure 4 depicts different stages of prevention referring to target populations and manifestations of diseases.

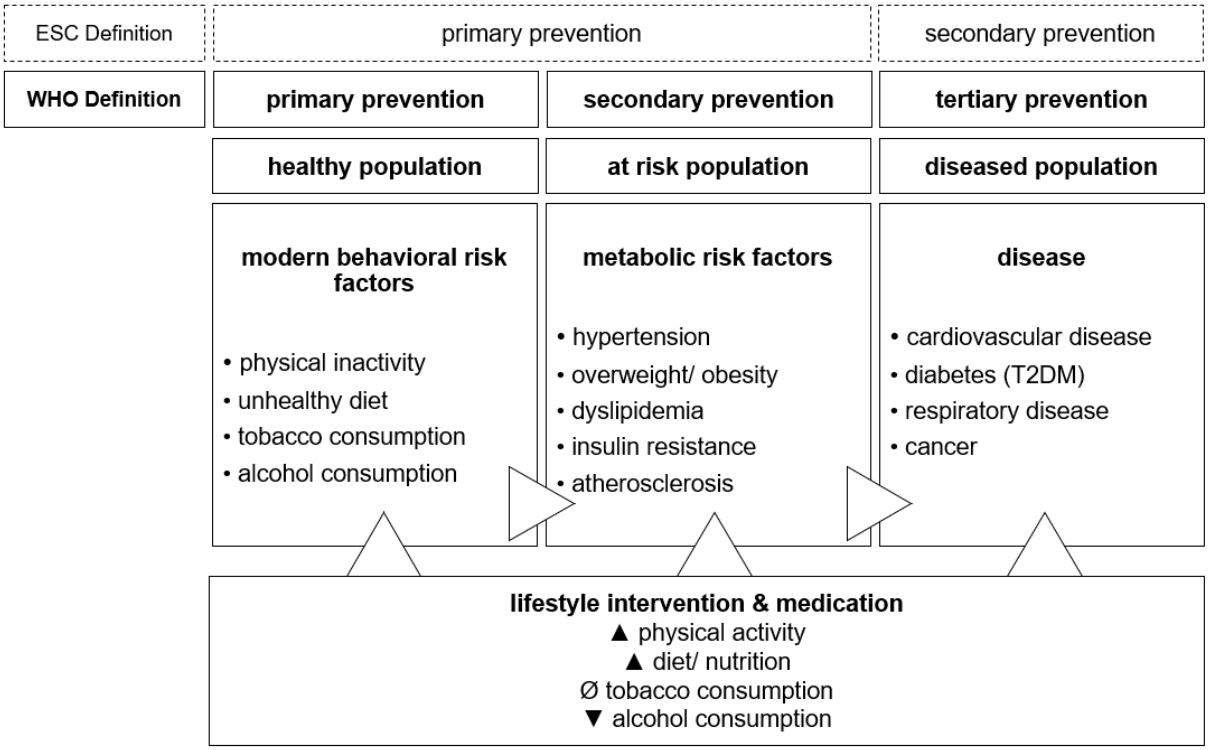

Figure 4 Risk factors, stages of non-communicable diseases, and prevention. ESC European Society of Cardiology, WHO World Health Organization. Authors own figure.

As also stated by the 2016 European Guidelines on cardiovascular disease prevention in clinical practice (14), prevention must be implemented at individual and general population level to promote healthy lifestyle and optimizing risk factors.

2.2. Guidelines on physical activity and exercise

The *Global action plan for the prevention and control of noncommunicable diseases 2013-2020* was established by the WHO in 2013, aiming at nine voluntary global targets in 2025 regarding all stages of NCD prevention (13). One of the targets is a "10% reduction from insufficient physical activity" (PA) (13), since current prevalence of physical inactivity is high (depicted in figure 5).

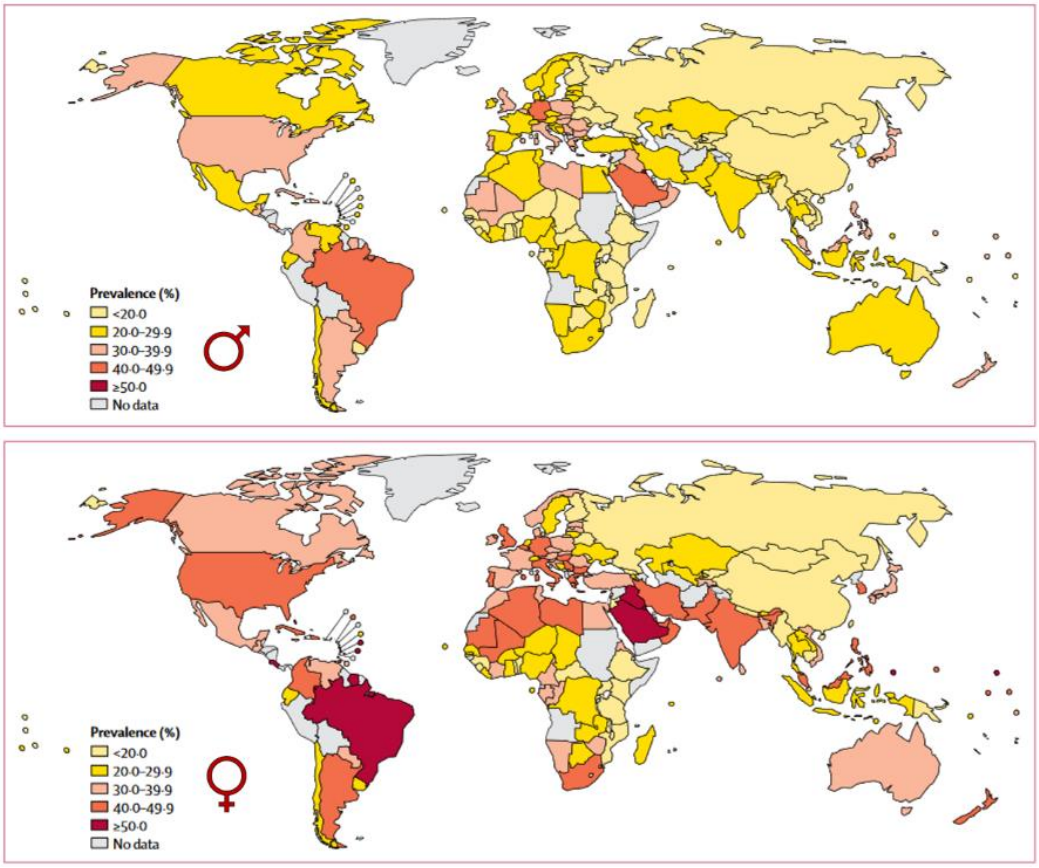

Figure 5 Prevalence of insufficient physical activity per country in men (upper figure) and women (lower figure), 2016". Figure from Guthold (2018) (27) with modified gender pictograms.

The 2018 world population fails to reach the guidelines for PA, including a negative prognosis regarding the target of the *Global action pla*n for PA (pooled analysis by Guthold et al. (2018) with 1.9 mio. participants, 2001-2016) (27). Recent prevalence of insufficient PA in high-income western countries sets at 42.3%, being twice as high as in low-income countries and stagnating over time (27). Reasons for the high prevalence of physical inactivity are lifestyle modifications over the past decades, further reinforced by changes in daily transportation, participation in leisure time PA and time spent in sedentariness (32). Physical inactivity thereby

induces physiological adaptations leading to accumulation of fat mass, unfavorable lipid and metabolic profile and endothelial function (32).

In order to promote exercise for health ("sufficient PA"), WHO Recommendations on Physical Activity for Health (WHO recommendations, 2010) state:

- "Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.
- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity.
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week." (15).

Recommendations apply to the population in leisure time, transportation, occupation and a variety of other activities. People meeting the recommendations profit from less NCDs and CVDs (15, 31). The importance of sufficient PA und PF is also underlined by the European Society of Cardiology (ESC), which released the *2020 ESC Guidelines on Sports Cardiology and Exercise* (ESC guidelines) (31).

The ESC guideline state Class I[8], Level A[9] evidence for primary prevention and are in line with the general WHO recommendations (15) on exercise intensity, volume and combination of both, but gives additional information on the importance of exercise testing and frequency (preferably daily exercise). High-intensity interval training is bespoken in the ESC guidelines to be potentially beneficial, but current concerns about safety in CVD demand for future research (31).

[8] **Class I**: "evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective."31. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). European heart journal. 2020.

[9] **Level A**: level of evidence, "data derived from multiple randomized clinical trials or meta-analyses."31. Ibid.

Regarding later prevention stages/ population at risk for CVD, the ESC guidelines recommend a risk stratification along the systematic coronary risk evaluation (SCORE) chart (19) taking age, gender, smoking, systolic blood pressure and total cholesterol into account to categorize individuals for their 10-year risk of fatal CVD events[10]. This chart gives valuable information for further evaluation and each individuals risk, but can only be used for specific populations, i.a. europids aged 40-70 years without history of CVD or T2DM (19).

The ESC guidelines (31) recommend the following for aging and diseased population:

- for cardiovascular evaluation and exercise in individuals aged >35 years:
  Class IIa[11], Level C[12]:
  - "among individuals with low to moderate CVD risk, the participation in all recreational sports should be considered without further CV evaluation. […]
  - Clinical evaluation, including maximal exercise testing, should be considered for prognostic purposes in sedentary people and individuals with high or very high CV risk who intend to engage in intensive exercise programs or competitive sports."
- For individuals with obesity, hypertension, dyslipidemia, or diabetes:
  Class I, Level A:
  - "in obese individuals (body mass index >30 kg/m² or a waist circumference >80 cm for females or >94 cm for males) resistance training ≥3 times per week, in addition to moderate or vigorous aerobic exercise (at least 30 min, 5-7 days per week) is recommended to reduce CVD risk. […]
  - Among individuals with diabetes mellitus, resistance training ≥3 times per week in addition to moderate or vigorous aerobic exercise (at least 30 min), 5-7 times

[10] "**Low risk**: calculated score <1% for 10-year risk of fatal CVD.
Moderate risk: young patients ([…], T2DM<50 years) with DM duration <10 years, without other risk factors […].
High-risk: people with: -markedly elevated single risk factor […], patients with DM without target organ damage, with DM >10 years or another additional risk factor […].
Very high-risk: people with any of the following: documented atherosclerotic cardiovascular disease, 8…], DM with target organ damage, or at least three major risk factors, [...]." Pellicia et al. (2020) 31. Ibid.

[11] **Class IIa**: "conflicting evidence and/or a divergent of opinion about the usefulness/ efficacy of the given treatment or procedure. Weight of evidence/opinion is in favor of usefulness/efficacy." Pelliccia et al. (2020)31. Ibid.

[12] **Level C**: "Consensus of opinion of the experts and/ or small studies, retrospective studies, registries." Pellicia et al. (2020) 31. Ibid.

per week) is recommended to improve insulin sensitivity and achieve a better CVD risk profile. […]"(31)

Regardless of gender, age, ethnicity and current condition, both WHO recommendations and ESC guidelines follow the basic principle of "some physical activity is better than none" (25, 31). As risk profile increases, the evidence-based exercise prescriptions are more complex and demand for evaluation. Information of exact exercise session duration, as the WHO states "bouts of at least 10 duration"(15), goes further in the 2020 ESC guideline (at least 30 min. per exercise session) (31). Data on examination of healthy (sedentary) individuals >35 years is less evidence-based, but still considerably.

In a secondary prevention setting, PA did not significantly improved by behavioral counselling in an at risk CVD population compared to a sedentary control group, as results from a meta-analysis reveal (n=32 randomized controlled trials (RCTs) including n = 19 834 patients at risk, p= 0.06) (38), which emphasized the need for targeted action including active exercise therapy. Insufficient PA therefore still contributes for (incident) CVD, NCD and chronic disease risk; therefore, exercise needs to be standard in all stages of prevention.

PA and exercise aim at maintaining or promoting components of physical fitness (PF) (15, 32). PA and PF affect CVD health benefits to the same extend (39). PF affects, amongst others, individuals' metabolism, muscles, physical functioning and cardiorespiratory function (31). By exercising and enhancing PF, various beneficial effects on physiological, cardiovascular and -metabolic risk factor profile can be noted, as concluded by Lavie et al. (2019): reduced blood pressure, improved endothelial function, improved insulin sensitivity, reduced blood viscosity, reduced systemic inflammation, maintain lean mass (improved body composition), reduced adiposity, improved psychological parameters, improved cardiac function and reduced risk for developing further NCDs (32). Individuals at risk for CVD profit from improved PF and lower their risk for further health decline (32).

Benefits from PF are induced by different modes of PA and exercise, including their determinants: frequency, volume, intensity and duration (15, 31). Improved PF by exercise must therefore be designed depending on the individuals' needs and current stage of prevention (31), because different responses are initiated.

2.3. Cardiovascular and -metabolic diseases: at risk and diseased population

In secondary prevention and at risk population, cardiometabolic diseases can be diagnosed. They can express as the metabolic syndrome (40), insulin resistance/ Type 2 diabetes mellitus and later on atherosclerotic cardiovascular disease. Figure 6 depicts the sequence of disorders from risk factor accumulation to disease. Failing prevention strategies and mismanagement of risk factors leads to, i.a. cardiometabolic and -vascular diseases, obesity or unfavorable lipid and metabolic profile, which turns into severe CVD if no preventive strategy is undertaken, even at later stages of CVD.

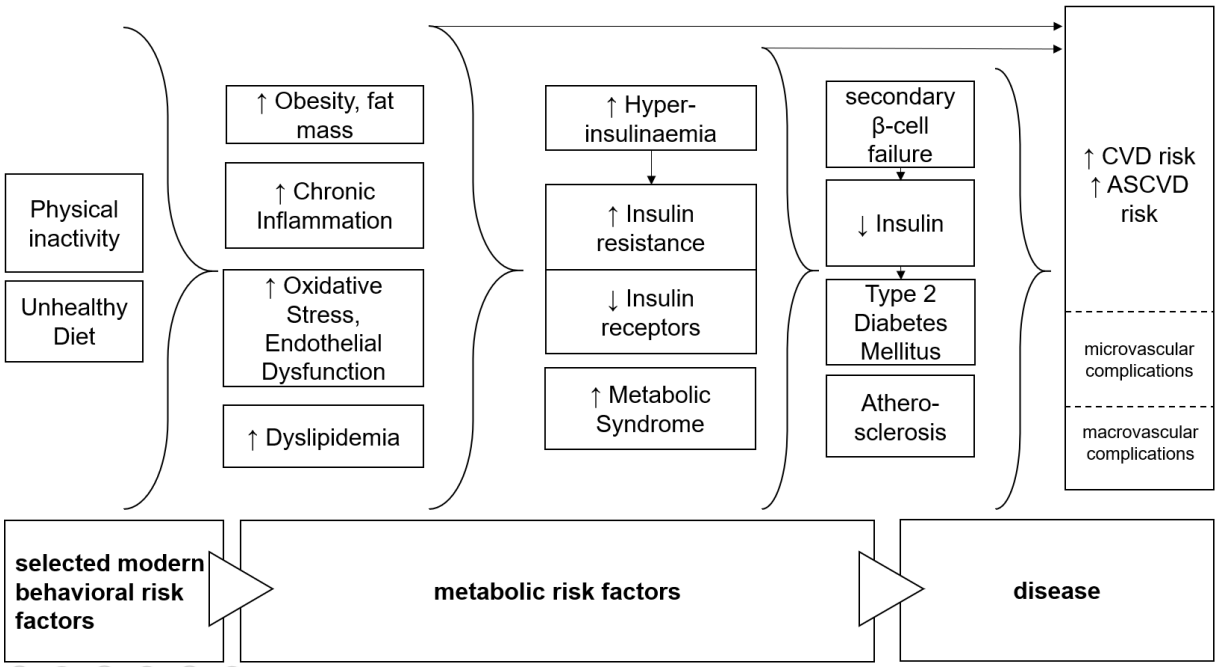

Figure 6 Turn of selected behavioral risk factors into metabolic risk factors leading to Type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD) and cardiovascular disease (CVD). Authors own figure.

2.3.1. Metabolic syndrome and exercise

The metabolic syndrome is defined by the International Diabetes Federation (IDF) as the prevalence of three of the five constitutes:

- elevated waist circumference (Europids: ≥94 cm in men, ≥80 cm in women),
- elevated triglycerides (≥150 mg/dl or on dyslipidemia medication),
- reduced HDL-C (<40 mg/dl in men, <50 mg/dl in women or on dyslipidemia medication),

- elevated blood pressure (BP) (systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg or on antihypertensive medication) and
- elevated fasting glucose (≥100 mg/dl or on glucose medication) (40).

It can therefore be characterized by the accumulation of metabolic and biomedical risk factors contributing to CVD and vascular dysfunction (e.g. ASCVD) (22, 28, 41-44). Vascular dysfunction in MetS is associated with chronic low-grade inflammation, including increased tumor necrosis factor (TNF), interleukin-beta (IL-beta) and C-reactive protein (CRP), amongst others (28, 44). Dysfunctional (ectopic) abdominal adipose tissue seems to enhance the immune- and inflammation crosstalk between several organs and is identified as one of the major contributors in MetS (28).

Patients with MetS have a 2.35-fold increase in relative risk (RR) regarding CVD (n=950.000, systematic review) (45). Insulin resistance and (abdominal) obesity are discussed as the main components of the CVD onset in MetS (22, 45), however, MetS remains a significant risk factor (RR: 1.62) for CVD even in the absence of T2DM (45). T2DM is itself a CVD risk factor, and appears with allied risk factors (44), as described in previous sections.

Still, the scientific discussion is not united about the overall risk prediction of MetS (46) or if each component's risk contributes to CVD onset (41, 47). Regardless of the scientific discussion, there is emerging evidence undermining the increased CVD risk by MetS and its components (41). Exercise in different stages of prevention contributes to MetS by improving cardiorespiratory fitness (CRF) and thereby PF, insulin resistance, inflammation, browning of adipose tissue, HDL-C and triglyceride levels (7, 26, 28, 32, 43, 44). In this patient population, the exact "dose" of exercise and its effects are less investigated; therefore, one purpose of this work is to further contribute to current evidence.

Evidence up to this point states improved PF in a substudy of the ExMET-trial (Exercise in the Prevention of MetS, NCT01676870, (48)), where three different training regimens (Moderate intensity continuous training (MICT) 60-70% Heart rate (HR) peak, 150 min/week, 4- high intensity interval training (HIIT) 50-70%/ 85-95% HRpeak, 114 min/week, 1HIIT 85-95% HRpeak, 51 min/week) have been investigated regarding the effect after 16 weeks on MetS z-score and CRF (49). All training regimens were able to reduce MetS severity (-22% MetS z-score in 4HIIT to -66% MetS z-score in 1HIIT), but without significant group differences (p=0.08) (49). CRF was significantly improved in the HIIT-groups, but also revealed "clinically significant" results in MICT, as the authors state that "a 1ml/min/kg increase in PF has been associated with a 9% reduction in CV mortality" (49). Insulin resistance by HOMA-IR was

reduced in all groups, but most preferably in MICT (-20% in all patients, -30% in MICT in patients suffering from T2DM, no significant changes between groups), in the absence of significant changes of body fat (49). There was a significant association of decrease in MetS z-score and change of HOMA-IR (49), highlighting the metabolic dimension of the syndrome moderated by insulin resistance. The similar effect of 1HIIT on PF with regard to the other training regimens can be explained by equally induced mitochondrial biogenesis and vascular function, which influence insulin sensitivity (improved oxidative capacity, glucose uptake and anti-inflammatory pathways) (49).

This study highlights the importance of exercise in MetS. Patients suffering from MetS benefit from participating in exercise with regard to insulin sensitivity and physical fitness, yet still revealing uncertainties about moderating factors and effects of different exercise modalities.

2.3.2. Type 2 Diabetes mellitus and exercise

Following unfavorable risk factor profile and later prevention stages, T2DM is one disease which can be diagnosed. It is based on increased blood glucose parameters as measured by biomarkers like glycosylated hemoglobin (HbA_{1c}) (50). The pathology of T2DM includes insulin resistance and pancreatic betacell dysfunction (50).

According to a systematic review by Magliano et al (2019) analyzing the worldwide incidence of diabetes (47 studies, data derived from cohort studies, registries or health insurance databases on clinical diagnosis, diabetic medication and self-diagnosis, 1980-2017), the global

rise of incident T2DM stagnated since 2005/2006 (51), as depicted in figure 7.

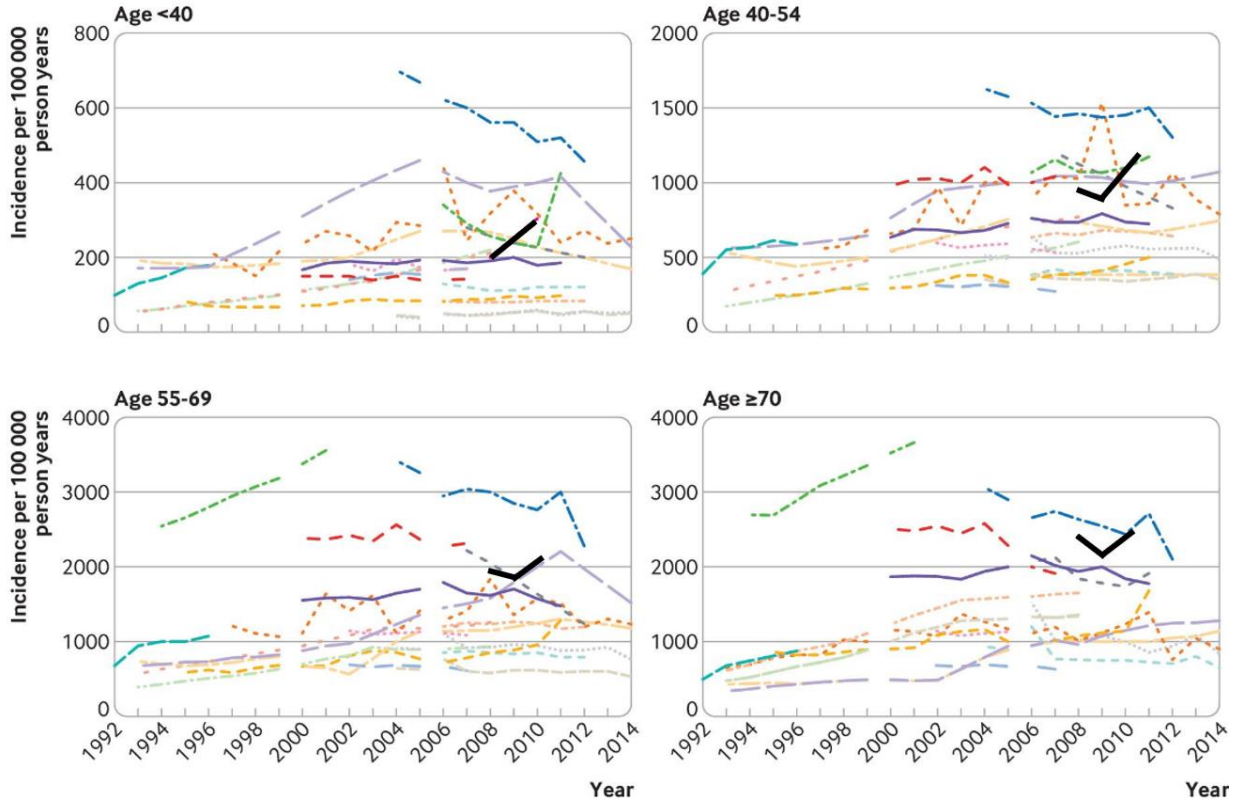

Figure 7 "Incidence of diabetes over time for populations aged under 40, 40-54, 55-69, and 70 or more", figure adapted and modified by Magliano 2019, (51), adapted: Black bar: Germany, other colors accumulated: 81% europids, 96% high-income countries.

For Germany, incident T2DM still rises in all age groups (51).

PA can delay or prevent onset of T2DM when insulin resistance is evident (pre-diabetic stage) (52). The Diabetes Prevention Study (DPS), including n=522 patients with insulin resistance (1:1 randomized, follow-up 3.2 years), revealed significant risk reductions (58%) of incident T2DM in the intervention group by changes in diet and increasing PA (52). On further notice, the Diabetes Prevention Program (DPP) randomized n=3234 participants at risk for T2DM to either medication (metformin), lifestyle or control group (placebo). Participants of the lifestyle group developed T2DM at mean four years later than participants from the placebo group and had a risk reduction of 27% of incident T2DM after 15 years and showed sex-specific differences regarding incident microvascular disease (53, 54). The lifestyle intervention and medication improved risk factors, e.g. obesity, MetS and QoL, contributing to CVD (54).

When T2DM is evident, the *Diabetes remission clinical trial* (DiRECT) even states T2DM (<six years since diagnosis) as a non-permanent disease (55). Results regarding remission of T2DM after 12 month intervention (n=306, 1:1 randomized on center-level, strict weight reduction following nutritional intake advices) state a 46% reduction of T2DM prevalence in the

intervention group, mainly driven by weight reduction (delta between groups 8.8 kg at 12 months) (55). These findings were further reinforced by the *Diabetes Intervention Accentuating Diet and Enhancing Metabolism* (DIADEM-I) study (n=147, 1:1 randomized, weight reduction by strict dietary and lifestyle change for 12 months vs. usual care), where diabetes remission was prevalent in 61% of the interventional group participants compared to 12% in the usual care group, receiving only guideline-oriented medical care (56).

Referring to DALYs and years of life lost to the disease, T2DM drives risk for premature death in both males and females tremendously by, on average in the absence of vascular disease, six years (see figure 8) (57).

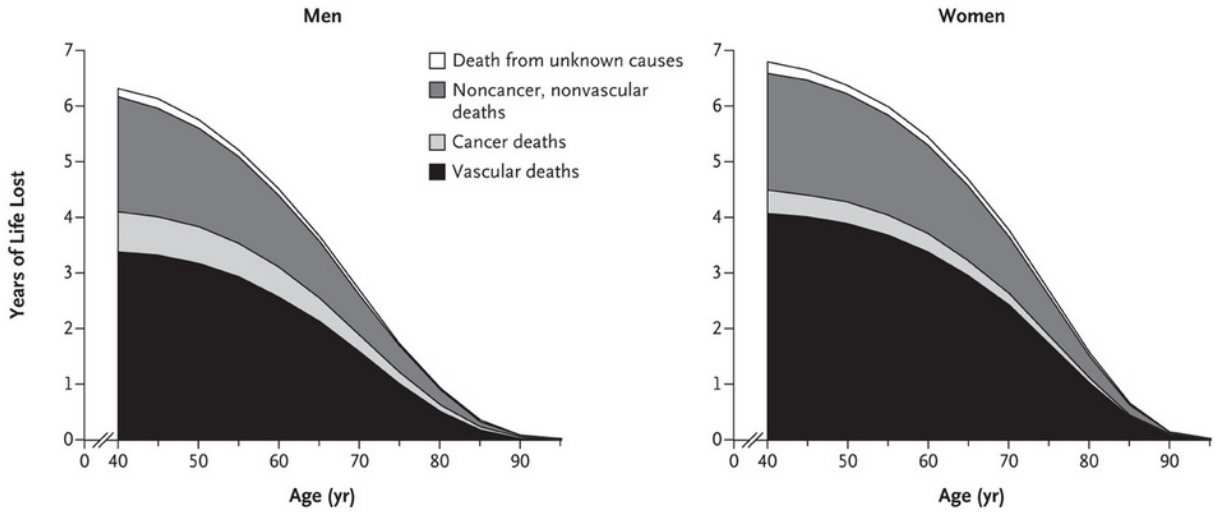

Figure 8 Years of life lost due to T2DM. Figure from Seshasai et al. 2011 (57)

Micro- and macrovascular diseases are major long-term effects of evident T2DM. The main underlying course is again ASCVD. T2DM drives CVD risk tremendously, as results from a meta-analysis (n= 698.782, 102 studies, patients with T2DM) by Sarwar et al. (2010) reveals (Hazard ratio (HR) 2.00 for CIHD, HR 2.27 for stroke, HR 1.73 for other vascular deaths) (58). It accounts for 11% of all vascular deaths (58), demonstrating an association of T2DM and ASCVD.

When treating T2DM, it is often not without limitations: results from pharmacological studies regarding dyslipidemia or hyperinsulinemia in patients suffering from T2DM (aiming at reducing major cardiovascular events (MACE)) showed major side effects. The *A Study of Cardiovascular Events in Diabetes* (ASCEND) trial including n=15480 patients suffering from T2DM, investigated the effect of aspirin medication on cardiovascular events (1:1 randomized,

placebo-controlled, follow-up 7.4 years), showing benefits in the aspirin group, but again high burden due to side effects (59).

Behavioral risk factors are major contributors of T2DM, however, medication is often prescribed to lower and ameliorate symptoms. Though, medication does not tackle the core: behavioral risk factors like sedentariness, unbalanced nutritional intake and insufficient PA in line with low physical fitness.

Evidence from large trials underlines the beneficial effects of exercise in this cohort: The *Action for Health in Diabetes* (Look AHEAD) trial, a lifestyle intervention with exercise training and dietary change for patients suffering from T2DM, reduced HbA_{1c} and CRF significantly compared with the control group (n=5145 patients with overweight and obesity and T2DM,) after one year follow up (60). The trial was stopped early (median follow up of 9.6 years) due to no significant differences between the groups regarding MACE (intervention group: Hazard ratio (HR) 0.95, p=0.51) (60).

Major effects of exercise in patients suffering from T2DM are the reduction of visceral fat (shift in body composition), glycemic control, improved insulin resistance and lipid profile (31), to possible tackle or reverse underlying risk factors. Hence, patients suffering from T2DM are below-average in PF, with worsening perspective regarding disease progression.

Contributing risk factors therefore must be counteracted in every stage of prevention. If both T2DM and CVD are already prevalent, a prevention of disease progression by lifestyle change seems to be a mandatory option after complete physical examination and risk factor assessment, as described in recent ESC guidelines (31).

When designing targeted exercise to improve cardiometabolic risk profile, recent ESC guideline suggests different effects of training volume and intensity in patients with T2DM: “Intensity of exercise seems to be of greater importance than the volume of exercise; individuals who exercise at moderate or high intensity have a lower risk of developing metabolic impairment compared with those who have a similar energy expenditure at a lower intensity. […] The optimal combination of duration and intensity is not well established.”(31). As presented, results from studies reveal possible mechanisms of action to further design interventions, as for example exercise intensities and modes may be not adapted after certain follow-up time and personal contact/ group sessions often regresses during the intervention, which may be crucial for future research. Part of the thesis is a study combining strength and aerobic exercise via telemedicine in patients suffering from T2DM and CVD (chronic ischemic heart disease), accompanied be recommendations on diet for 12 months. This wholesome

lifestyle intervention will contribute to the current evidence and reveals the underlying points of actions. Telemedicine may be an option for those patients to monitor each individuals progress and adapt exercise due to each patients needs and progress in the long term.

2.3.3. Atherosclerotic cardiovascular disease and exercise

One main function of the artery is to maintain a steady blood flow during both cardiac cycles (61). To maintain the peripheral circulation, the pulsatile flow between cardiac systole and diastole must be transformed to a steady, continuous flow by aortic distensibility and elasticity (arterial compliance by vasodilation and -contraction). During systole, the aorta dilates to buffer blood flow, while during diastole the aorta narrows to supply the circulation by continuous blood flow, as depicted in figure 9 (A) (61).

To quantify arterial compliance, *arterial stiffness* can be determined by different measurements like pulse wave velocity (PWV), arterial wall thickness or central blood pressure (14, 61, 62). As depicted in figure 9 (B), if arterial stiffness increases, the aorta is not able to buffer the pulsatile blood flow (generated by the left ventricle) by vasodilation, which results in a backward-reflected pulse wave during systole and overall increased blood pressure parameters (61). The left ventricle has to steadily increase the systolic pressure to overcome the reflected wave. This can develop into heart failure (HF) by peripheral pressure overload (61).

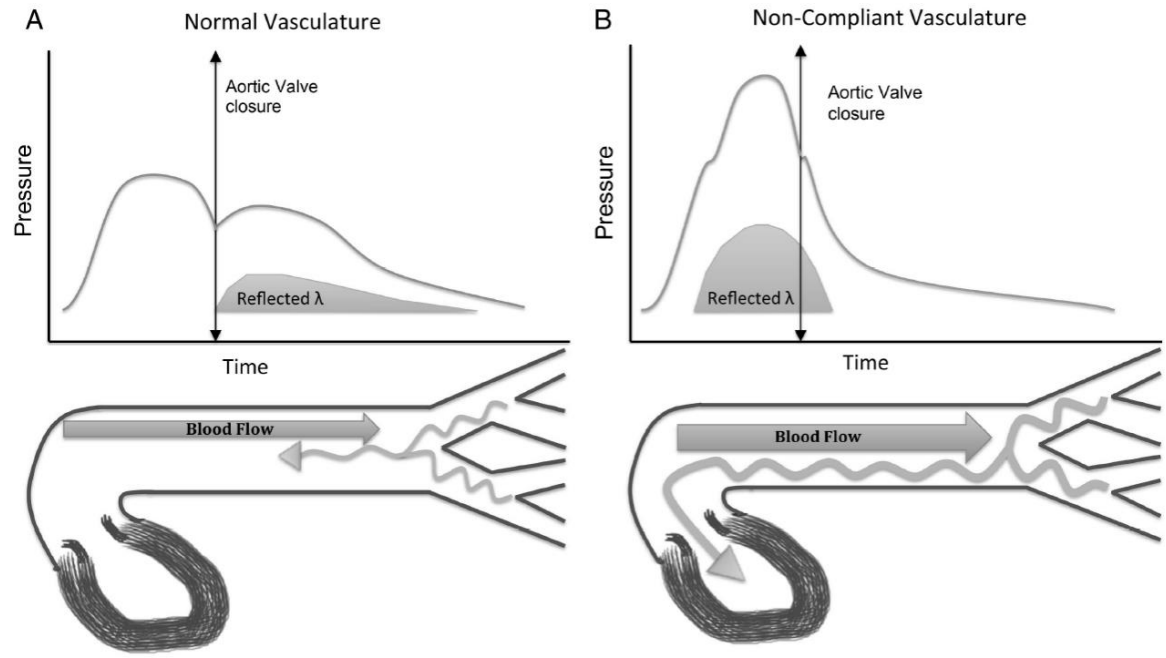

Figure 9 "Example of aortic pressure waves (lines) and reflected pressure waves (reflected λ, solid shape) from the vasculature plotted as pressure versus time. […]" Figure from Viau 2015 (63).

Arterial stiffness increases with age, but can be accelerated by early atherosclerosis[13]. It is the main contributor towards stiffening of the arteries and CVD, with allied risk factors as MetS and T2DM (64, 65). It can also be a harmful side-effect of cancer therapy, which is another common NCD, by certain cytotoxic agents like anthracyclines, who can be part of pediatric chemotherapy after cancer diagnosis (14, 66, 67). The risk for atherosclerotic and cardiometabolic diseases is elevated in those cohorts, who were administered by anthracyclines or mediastinal radiation (68-70). Adding up with several other behavioral risk factors, this can lead to increased risk of arterial stiffness (14), as we investigated in the *Motoric competence and arterial stiffness in children during and after chemotherapy* (MOSAIC) study as part of the thesis.

[13] **Atherosclerosis** as defined by Insull (2009): "[…] a disease of the arterial wall that occurs at susceptible sites in the major conduit arteries. It is initiated by lipid retention, oxidation, and modification, which provoke chronic inflammation, ultimately causing thrombosis or stenosis. Atherosclerotic lesions can cause stenosis with potentially lethal distal ischemia or can trigger thrombotic occlusion of major conduit arteries to the heart, brain, legs, and other organs." (15).

As part of failing prevention strategies and risk factor mismanagement, atherosclerosis causes and provokes severe CVDs. Atherosclerotic cardiovascular disease (ASCVD) according to the National Research Council Committee on Diet and Health/ US (1989) is defined as:

> "[…] the pathological process in the coronary arteries, cerebral arteries, iliac and femoral arteries, and aorta that is responsible for coronary heart disease [author's note: CIHD] […], stroke, and peripheral arterial disease (PAD)" (65).

Therefore, ASCVD is more specific during the late manifestations and diseases. In the framework of this work, the term *ASCVD* will be used for atherosclerotic diseases. Early research about coronary heart disease, as main manifestation of ASCVD, and its allied risk factors, was conducted in populations at risk enrolled in the Framingham Heart study by Kannel et al. (1961) (71). Hypertension and high serum cholesterol, in line with left ventricular hypertrophy electrocardiography (ECG) patterns, were presented as risk factors contributing to increased risk of coronary heart disease in secondary prevention (n=5127, follow up: 6 years) (71). ASCVD is directly accelerated by behavioral, metabolic and drug-related risk factors, as figure 10 and figure 11 depict in the disease progression in detail.

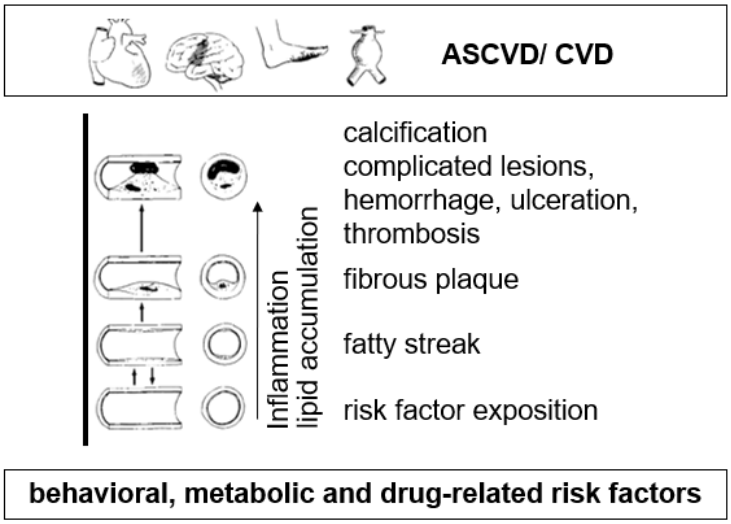

Figure 10 Risk factor transition to atherosclerotic cardiovascular disease (ASCVD) and cardiovascular disease (CVD). Figure modified from National Research Council (US) (1989) (65) as former adapted from McGill et al. (1988) (72).

In further detail of the arterial stiffening process, functional endothelial cells promote regular vascular compliance (elasticity) by the release of nitric oxide (NO), which has a direct impact on the stimulation of vascular smooth muscle cells (inside Tunica media) for vasodilation (73). NO acts as a cardio- and vasoprotective agent due to anti-inflammatory, anti-thrombotic and

anti-oxidant effects (73). During the regular ageing process and ASCVD, endothelial cells decrease their functionality leading to endothelial dysfunction (73). This results in a decreased bioavailability of NO and its cardio- and vasoprotective effect (73).

The pathology of ASCVD plaques, see figure 11, includes the intracellular accumulation of lipids (*initial lesions, foam cells* and *fatty streaks*) in the intimal layer of the artery (20, 64, 73). This is driven by increased levels of circulating low-density lipoprotein cholesterol (LDL-C) and dyslipidemia (64). Fatty streaks evolve to an *intermediate lesion* due to additional extracellular lipid accumulation, which later on develop to an *atheroma* including excessive lipid accumulation with a core of extracellular lipids (64). In the following, atheromas develop varieties of a fibrous cap with calcified layers (64).

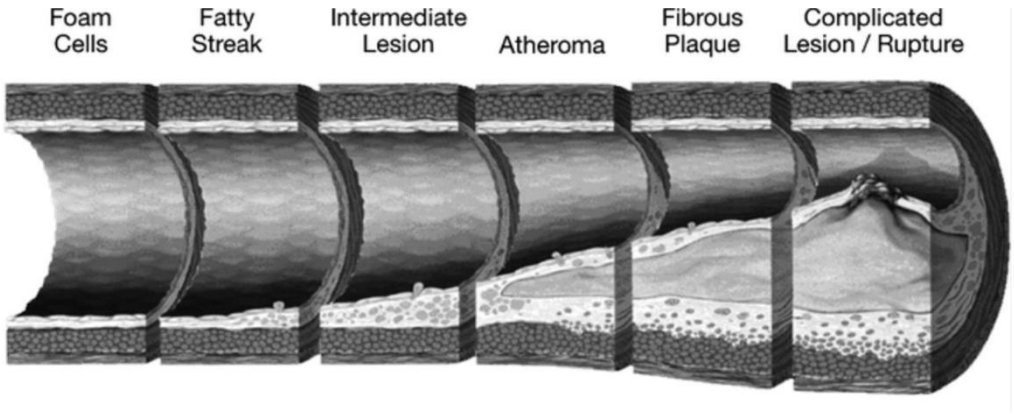

Figure 11 Atherosclerosis timeline. Figure from Lavie et al. (2008) (74) as adapted from Stary et al. (1995) (75).

ASCVD is characterized by high levels of on-site and chronic inflammation in the arterial wall. High proportion of on-side inflammation in ASCVD is multifactorial, involves several components of innate and adaptive immunity and increases CVD risk and progression (details see Supplement on *Atherosclerosis and Plaque formation* (61, 64).

Atheromas can rupture, which results, if clinically relevant, in a thrombus, hemorrhage or stenosis of the artery (64). This lead, in worst case, to an ischemic status of the affected vessel (e.g. CIHD if coronary arteries are affected, stroke if cerebral vessels are affected). If clinically silent, the plaque “heals” by forming a new fibrous cap by elastic fibers and collagen, which can result in several layers, ruptures and healings in the same plaque over time (20). In case of an acute ASCVD event, it is diagnosed as “acute coronary syndrome” versus, if asymptomatic and clinically stable, “chronic coronary syndrome” (76). It is noteworthy that the

chronic coronary syndrome can get acute at any time due to the severe nature of the disease and concomitant risk factor management (76).

If a plaque gained significant growths, it can include relevant hemodynamic changes, increased pulse wave velocity (PWV) and arterial stiffness (73). This results in functional disturbances and changed arterial compliance. Increased aortic PWV (carotid-femoral) is associated with increased CVD risk (*Framingham Heart study*, n=2232, mean age 63 years, mean follow-up 7.8 years, Hazard ratio 1.48) (62). With regard to MACE, patients with elevated aortic PWV (m/s) show increased incidence compared to patients with lower aortic PWV (62), also see figure 12.

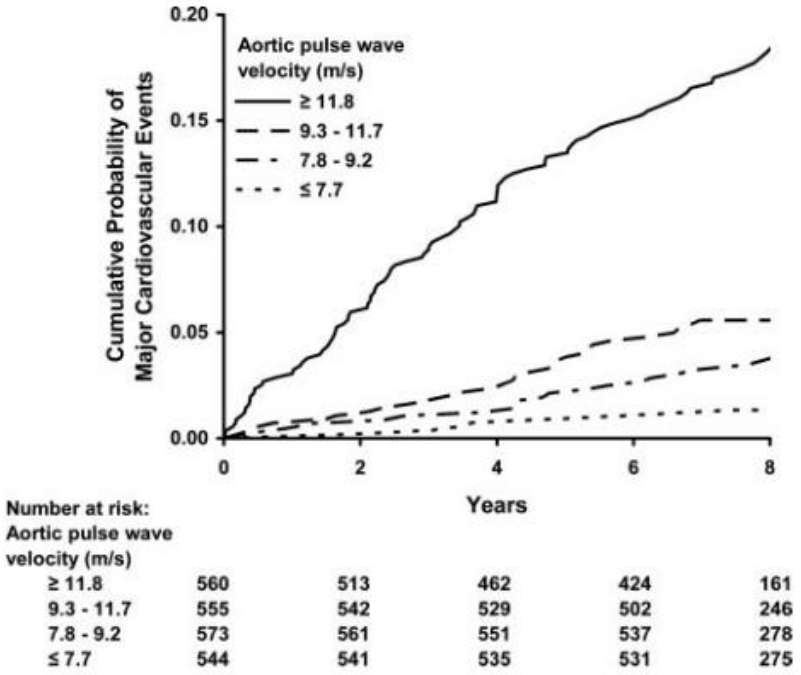

Figure 12 "Kaplan-Meier plot of cumulative probability of a first major cardiovascular event, participants grouped according to quartiles of carotid-femoral (aortic) pulse wave velocity". Figure from Mitchell et al. 2010, Framingham Heart Study (62).

The risk of clinical stability and risk of rupture depends on the morphology of the plaque, which can be influenced by lifestyle (physical activity (77, 78) and nutrition; e.g. marine n-3 fatty acids (77, 79)) and medication (statins; reduction of lipid content, increasing collagen content, reduction of oxidative stress and inflammation; stabilization of plaque) (20). Taken together, these strategies and agents indicate a coronary plaque stabilization and anti-inflammatory on-site effect (31, 77, 80), which also results in improved endothelial function.

Lifestyle modification and especially exercise is beneficial for patients suffering from atherosclerosis and severe manifestations of ASCVD. As stated in the 2019 ESC guidelines on chronic coronary syndromes, exercise and improved PF is beneficial and reduces mortality risk in those patients (76). Peak oxygen uptake (as a marker of PF) is a predictor of all-cause and cardiovascular mortality in patients suffering from CIHD (81). Taking up with exercise or PA even in later stages of prevention is associated with less angina pectoris and increased survival time (76).

In patients with only severe CVD (CIHD, n=507), and patients with both CIHD and T2DM (n=539), no leisure time PA at baseline was significantly associated with MACE events for 24 months follow up, as shown in the *Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection* (ARTEMIS) study (HR 3.41, 95% CI 1.67–6.96, p = 0.001) and depicted in figure 13 (82).

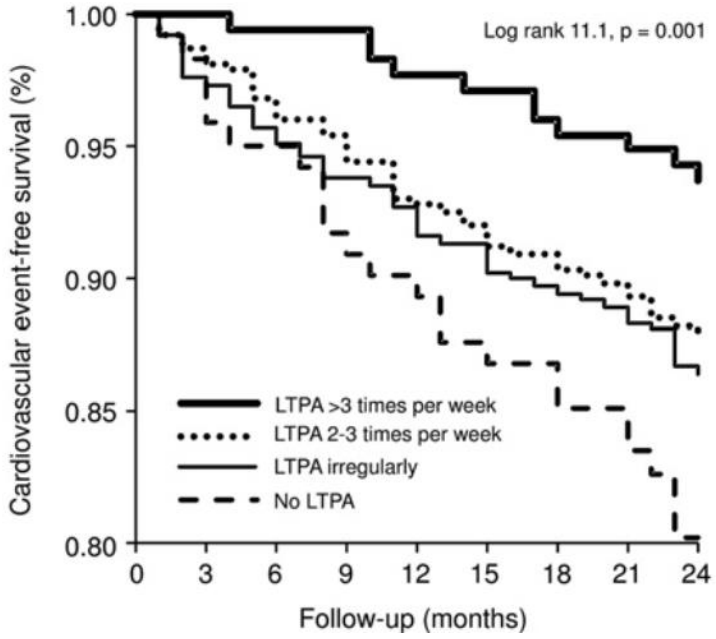

Figure 13 "Leisure time physical activity [LTPA] as predictors of a composite endpoint of CV death, acute coronary event, stroke, or hospitalization for heart failure in Kaplan-Meier survival analysis." Figure from Karjalainen et al. (2015) (82)

Following exercise intervention (home-based combined strength and aerobic exercise, 24 months, reported adherence: 81 to >100% of targeted exercise time) CIHD patients without and with T2DM did significantly improve exercise capacity (metabolic equivalent of tasks (MET) 6.7 ± 1.7 to 6.9 ± 1.6 and 8.2 ± 1.9 to 8.5 ± 1.7, p< 0.05, respectively) compared to control group (82). Both groups did not significantly change other parameters of their CVD risk profile by the applied exercise intervention(82).

As data like from the ARTEMIS study underlines, there is controversial data on long-term effects on metabolic and risk factor profile. Exercise interventions improve the major risk factor physical inactivity, but still other CVD risk factors remain untouched. This is why the design of exercise interventions must be questioned, which will be discussed in the framework of the third manuscript of the thesis. As reported by ARTEMIS, patients are “left alone” after three months exercise and six months prior to follow-up, exercise is again intensified (82). This leaves points of actions for specialists to further improve exercise interventions, steadily adapt the exercise modalities and install mechanisms to support patients throughout a wholesome lifestyle intervention.

However, results from the *European Action on Secondary Prevention through Intervention to Reduce Events IV* – survey (EUROASPIRE IV) (2016) regarding physical activity of patients suffering from CIHD show insufficient PA, stating 59.9% of the population doing no or little PA (crosssectional study, n=7998 patients with CIHD, 24 countries in europe) (83). Prevalence of other behavioral risk factors in patients with CIHD was 29.6% for smoking and 32.6% for obesity (body mass index (BMI) ≥30 kg/m²) (83). Metabolic risk factor prevalence was 77.8% for hypertension, 72.8% for dyslipidemia and 30.7% for T2DM in CIHD patients (83).

Regular exercise was significantly associated with decreased cardiovascular mortality in patients with stable CIHD (n= 15487, PA data by questionnaire, 38.7% T2DM, adjusted hazard ratio: 0.92) (84). Moreover, in the *Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training* (HF ACTION) trial, one of the largest trials addressing patients with heart failure (HF), (51.4% ischemic etiology of HF) and a high percentage of T2DM (32.1%) reveal that, after adjusting for prognostic factors, exercise training was significantly associated with cardiovascular mortality risk reduction and hospitalization (hazard ratio: 0.85, p= 0.03) (85).

With regard to designing the *Lifestyle Intervention in CIHD and T2DM*- study (LeIKD), the long-term lifestyle modification and clinical outcomes are to be monitored via telemedicine and will significantly contribute to the current understanding and evidence. CVD, ASCVD and risk factor management will be closely monitored to further design targeted exercise and conscious lifestyle modification.

Within the framework of the first publication of this thesis, the *Motoric competence and arterial stiffness in children during and after chemotherapy* - study (MOSAIC) will assess the status quo of PF and arterial stiffness and will reveal possible associations, risk factors and further evidence in this young, at risk population. All research conducted in the framework of the thesis will be presented in the following sections.

3. Aim and Hypothesis of the thesis

The aim of this thesis is to contribute to the current evidence of physical fitness and exercise as prevention strategies in different stages of CVD (at risk and diseased population, secondary and tertiary prevention).

Unifying and separate Hypotheses:

Higher PF and exercise have an impact on CVD risk factor profile in

1) the MOSAIC study.
   Children and adolescents after cancer therapy have a lower health-related fitness, which may reveal associations to arterial stiffness properties.
2) the DZHK ExMET study.
   MetS patients profit from a 16-week exercise intervention regarding metabolic risk factors and PF, including evaluation of different exercise intensities (MICT vs HIIT) and volumes (1HIIT vs 4HIIT).
3) the LeIKD study.
   Patients suffering from both T2DM and CIHD profit from a telemedical approach of a 12-months lifestyle intervention regarding metabolic risk factors and PF compared to usual care.

4. Methods and Results

To address the aim and hypothesis, three studies are included in the thesis. Exercise and parameters of PF are evaluated and discussed as prevention strategies in an at risk and diseased population.

- **MOSAIC** (figure 14): Motoric competence and arterial stiffness in children during and after chemotherapy.
  Population: at risk population
  Stage of prevention: secondary prevention
  design: crosssectional monocenter study
  key parameters: assessment of PF, arterial stiffness and risk factors
  short description: As cancer therapy accelerates the risk of low PF, atherosclerosis and arterial stiffening, n=92 children and adolescents after cancer therapy are evaluated in a crosssectional, monocenter study to reveal possible associations of arterial stiffness and PF status.

- **DZHK ExMET** (figure 14): The effect of exercise intensity and volume on metabolic phenotype in patients with Metabolic Syndrome: a randomized, controlled trial.
  population: at risk population
  Stage of prevention: secondary prevention
  design: randomized (1:1:1), controlled interventional monocenter study
  key parameters: intervention and assessment of PF and risk factors
  short description: MetS accelerates the risk of further CVD. Risk factor management in the at risk population includes lifestyle changes, especially exercise. As details of exercise regimens and their impact on risk factors in MetS are less investigated, n=29 patients were included into a randomized, controlled interventional trial for 16 weeks. High-intensity high-volume (4HIIT), high-intensity low-volume (1HIIT) and moderate intensity continuous training MICT) were analyzed regarding their impact on CVD risk factors and PF.

- **LeIKD** (figure 14): Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes.
  population: diseased population
  Stage of prevention: tertiary prevention
  design: randomized (1:1), controlled interventional multicenter study

short description: Patients suffering from both T2DM and CIHD most likely failed in primary and secondary prevention and risk factor management. To improve risk factor profile in this cohort at late prevention stage, a 12 month lifestyle intervention, including exercise and diet, via telemedicine, will be conducted in n=1500 individuals with both diseases. The study design includes a wholesome approach for this cohort, as i. a. health economics, QoL, risk factors and PF will shape future design of prevention strategies.

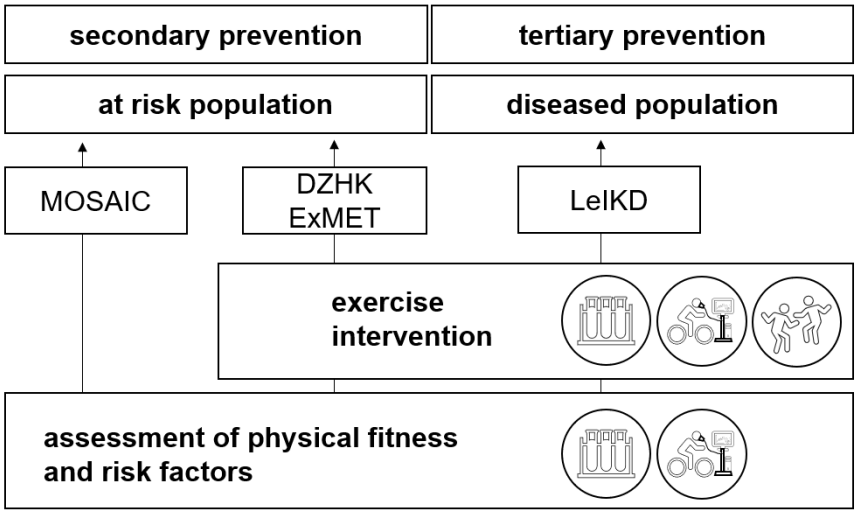

Figure 14 Context of PhD studies. Authors own figure

4.1. MOSAIC study

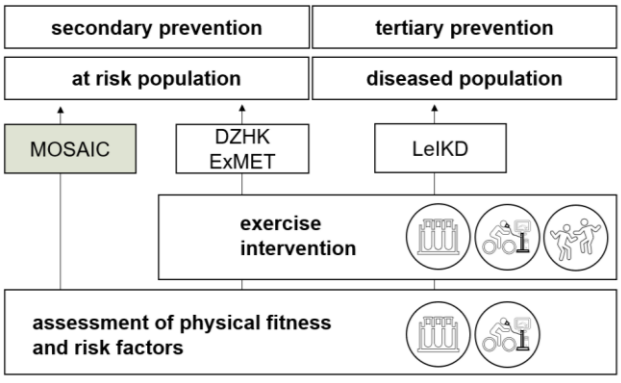

Figure 15 Context of PhD studies: MOSAIC study. Authors own figure.

Starting from an early point in childhood or adolescence, the MOSAIC cohort is to be set in tertiary prevention of cancer and secondary prevention of CVD. Prevention in this context aims at preventing the progression of initial disease but also preventing from CVD onset, as risk of late sequelae by anticarcinogenic therapy and metabolic risk factors are increased in this cohort.

Background of the study

The background was published in the framework of the first published manuscript (86):

Due to improved anticarcinogenic treatment regimens (chemotherapy and radiation) more children and adolescents are surviving a cancer diagnosis (87). As a result, there are a growing number of long-term adult survivors with multiple co-morbidities who need appropriate aftercare management. In numbers, more than 70 % of the childhood cancer survivors (CCS) suffer from chronic health conditions (88), which are often directly associated to anticarcinogenic therapy. Improved screening modalities can predict cardiovascular morbidity in the future and are therefore essential.

Health related physical fitness (HRPF) is an indicator for the development, growths and lifestyle of children and adolescents, and it is significantly reduced after acute treatment phase in CCS (89). Physical activity remains reduced in CCS for years after diagnosis, (90) and frailty, a complex syndrome of the elderly, can occur prematurely in CCS (91).

Nevertheless, especially cardiovascular issues are also of particular concern in CCS as even low-dose anthracyclines, a group of chemotherapy drugs, can damage cardiomyocytes in the heart and impair endothelial functioning of the vessels (66, 67). The relative risk for coronary heart disease is therefore 10.4 times higher in CCS as compared to healthy siblings, and overall cardiovascular morbidity and mortality is sevenfold higher in CCS as compared to the normal population (68). Arterial stiffness, the ability of the vessels to expand and recoil, is a parameter for early cardiovascular aging and has been reported to be significantly higher in CCS than in the normal population (69, 70).

Previous studies outlined the beneficial association of HRPF and aerobic capacity to arterial vessel properties (92-94), but there is a lack of evidence-based data for CCS. This study therefore investigates functional outcomes in CCS by means of HRPF and arterial stiffness to determine lifelong cardiovascular risk factors.

Collaborators

Collaborators of the study are Prof. R. Oberhoffer, MD and PD J. Müller, PhD, Department of Preventive Pediatrics, Faculty of Sports- and health science, Technical University of Munich and Prof. T. Feuchtinger, MD, and PD I. Schmid, MD., Dr. von Hauner University Children`s Hospital, Ludwig- Maximilians-University Munich, Pediatric Hematology and Oncology.

Aim and hypothesis

The aim of the MOSAIC study was to assess the children's and adolescent's vascular function (as a determinant of CVD health and status') by arterial stiffness after cancer therapy. This was evaluated with regard to the physical fitness status, as assessed by a motoric battery.

The hypothesis that childhood cancer survivors have a lower health-related physical fitness compared to healthy peers, which is associated to arterial stiffness properties.

Inclusion criteria and Recruiting

The crosssectional study's inclusion criteria for participants were oncologic disease, current age of 6-20 years, absence of fever and acute infections, no mental retardation, ability to write and communicate in German or English language without assistance, physical exercises without assistance and the physician's confirmation (86). Only patients treated at the Department of Pediatric Hematology and Oncology of the Dr. von Hauner University Children's Hospital in Munich were able to participate (86).

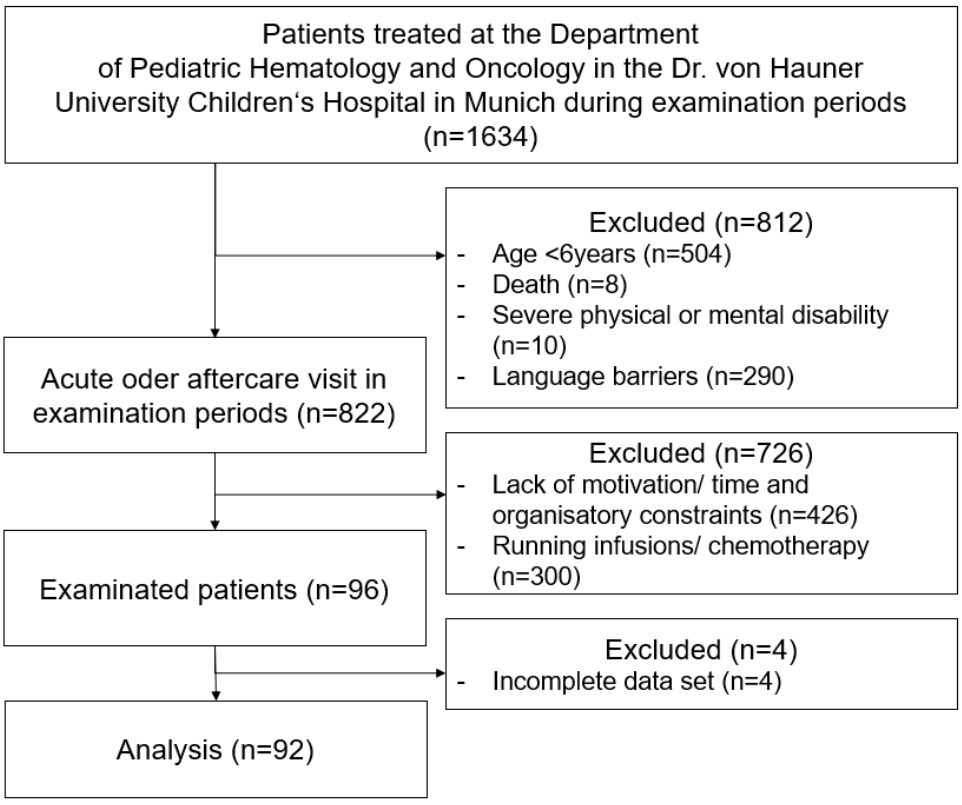

Figure 16 Flow chart MOSAIC study. Data estimated from first examination period (march to june 2016) and second examination period (february to august 2017). Authors own figure.

Key methods

Physical fitness was assessed by five tasks of the Fitnessgram® motoric battery: maximum repetitions push-ups and curl-ups for strength, shoulder stretch, sit-and-reach and trunk lift for flexibility. They were transformed and compared by standard-deviation scores (z-scores) to healthy peers from an unpublished dataset of the “Sternstunden” cohort (983 bavarian children, 498 girls, mean age 11.8 ± 2.3 years) (86).

Arterial stiffness by pulse wave velocity (PWV) and hemodynamics were assessed by oscillometric Mobil-O-Graph (I.E.M. GmbH, 114 Stolberg, Germany and HMS Client-Server Version 4.7) after a resting phase in supine position (86). Central and peripheral blood pressure as well as PWV were also transformed into z-scores referring to healthy peers from Elmenhorst et al. (n= 1445 children and adolescents, n=715 girls; mean age 13.41 ± 2.80 years) (95), the *Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland*- study (KiGGS, german children and adolescents aged 0.25 to 17.98 years, n= 17158, n=8452 girls) (96) and unpublished data from the “Sternstunden” cohort, respectively, as reference (86).

To assess differences between z-scores a one sample t-test (test value “0”) was conducted (86). Associations were analyzed using Pearson’s correlation coefficient (r). Data analysis was performed using IBM SPSS 23.0 (IBM Corp., Armonk, NY). All tests were performed two-sided at a significance level of a = 5%.

Key results

As depicted in table 1 and reported in von Korn (2019) (86), health-related physical fitness was significantly reduced in pediatric cancer survivors compared to healthy peers from the “Sternstunden” cohort (z-score: -0.28 ± 1.01, p=.011) (86).

The peripheral systolic blood pressure was significantly increased (z-score: 0.31 ± 1.11, p=.017) and the peripheral diastolic blood pressure was decreased (z-score: -0.30 ± 1.25, p=.040) (86), both in comparison to healthy peers from the KiGGS study, respectively (96). This results in an overall increased pulse pressure (high systolic and low diastolic blood pressure).

The pulse wave velocity (p=0.649), compared to healthy peers from “Sternstunden” cohort, and central systolic blood pressure (p=0.408), compared to healthy peers from Elmenhorst et al. (95), were not increased (86).

No association of health-related physical fitness to pulse wave velocity (r=0.004, p=0.972) or central systolic blood pressure (r=0.001, p=0.998) were identified (86).

Table 1 Outcomes MOSAIC study (86).

	Childhood Cancer Survivors (n=92)	
Sex (girls)	43 (47%)	
Age (years)	12.5 ± 4.2	
Height (cm)	151.0 ± 21.3	
Weight (kg)	46.3 ± 18.3	
	CCS (n=92)	**p-value**
BMI z-score*	0.21 ± 1.15	0.102
HRPF (z-score)****	-0.28 ± 1.01	0.**011**
Curl-ups (z-score)	0.22 ± 1.39	0.152
Push-ups (z-score)	-0.09 ± 0.98	0.415
Sit and Reach (z-score)	-0.32 ± 1.35	**0.032**
Shoulder Stretch (z-score)	-0.58 ± 1.44	**<0.001**
Trunk Lift (z-score)	-0.45 ± 1.69	**0.014**
Peripheral SBP (z-score)**	0.31 ± 1.11	**0.017**
Peripheral DBP (z-score)**	-0.30 ± 1.25	**0.040**
Central SBP (z-score)***	0.12 ± 1.28	0.408
PWV (z-score)****	0.07 ± 1.40	0.649

BMI: Body-Mass-Index, SBP: systolic blood pressure, DBP: diastolic blood pressure, PWV: pulse Wave velocity, HRPF: Health-related Physical Fitness
* comparison to the German reference from Kromeyer-Hauschild and colleagues (97)
** comparison to the German reference from the German KIGGS Study (96)
*** comparison to the German reference from the Elmenhorst and colleagues (95)
**** comparison to unpublished data of 916 healthy German children

4.2. DZHK ExMET study

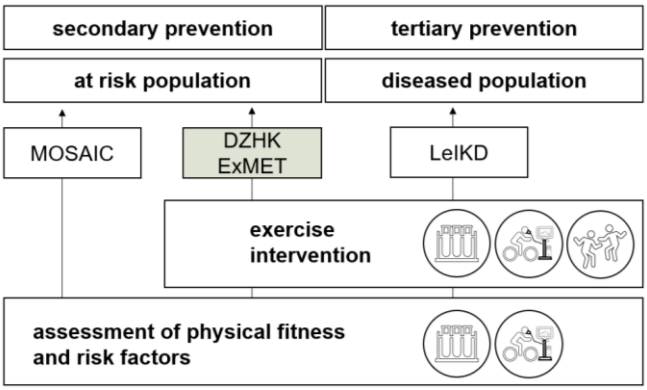

Figure 17 Context of PhD studies: DZHK ExMET study. Authors own figure.

Going along the pathway of CVD, the risk of incident MetS is increased in patients with accumulated behavioral risk factors, late sequelae of diseases or failed primary prevention strategies. It is often accompanied by subclinical vascular changes, insulin resistance and/or T2DM (98).

One major option to modify risk factor profile in patients with MetS is exercise and thereby improving physical fitness in secondary prevention of CVD (28, 98, 99).

Background of the study

The background was published in the framework of the second manuscript by von Korn et al. (2021) (100):

Metabolic Syndrome is an accumulation of acquired cardiometabolic traits including elevated waist circumference (WC), elevated levels of triglycerides (TAG) and low levels of high-density lipoprotein-cholesterol (HDL-C), fasting hyperglycemia and elevated blood pressure. MetS has reached pandemic proportions and poses a major challenge for health systems worldwide (101). Its metabolic signature is recognized as a major and prevalent risk factor for atherosclerotic cardiovascular disease by major bodies including the World Health Organization (102), the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III) (103) and the International Diabetes Federation (IDF) (104).

Traditional moderate intensity continuous exercise training (MICT) ameliorates metabolic control and reduces ASCVD risk (77) including in the subgroup of patients living with prediabetes, diabetes (105), and dyslipidemia (19). It is thus recommended as a principle therapy for risk factor management by major expert bodies and should be included in the care paths for the management of these diseases (19, 105). Exercise training instigates a coordinated response of favorable metabolic adaptations linked to cardiometabolic health (78) and has therefore been endorsed as an effective and safe strategy for prevention and management of cardiometabolic risk factors and global ASCVD risk (77). Regular aerobic exercise has been shown to reduce visceral adiposity (106, 107) and favorably impact glucose

and lipid metabolism. It is now widely accepted that central adiposity – as a marker of "dysfunctional adipose tissue" – is the most prevalent trait associated with ASCVD risk and therefore of high clinical importance (101, 108). The accumulation of dysfunctional, ectopic adipose tissue in the abdominal cavity and in visceral organs such as liver, pancreas, pericardium and skeletal muscle, instigates a coordinated set of local and systemic pathophysiological events that significantly elevate ASCVD risk (109). These include hepatic overproduction of triglyceride-rich very low-density lipoproteins (VLDL1) and increased peripheral HDL-C catabolism (i.e., atherogenic dyslipidemia), increased hepatic and muscular insulin resistance, and oxidative stress, among other factors (24, 110).

Due to a less robust evidence base for HIIT versus MICT, guidelines continue to recommend the latter for risk factor management in patients living with prediabetes, diabetes (105), and dyslipidemia (19). This underpins the need for trials comparing the metabolic adaptations of MICT and HIIT in patients with MetS.

Collaborators and Funding

Collaborators of the study are Prof. M. Halle, MD, Department of Preventive and Rehabilitative Sports Medicine, University hospital 'Klinikum rechts der Isar', Faculty of medicine, Technical University of Munich, the DZHK (German Centre for Cardiovascular Research), partner site Munich and Berlin and PD N. Kraenkel, Dr. rer. nat., Department of Cardiology, Charité - Universitaetsmedizin Berlin.

The study was funded by Deutsches Zentrum für Herz-/Kreislaufforschung (DZHK)/ German Heart Alliance, shared expertise, grant no. 81X2100238. Its acronym is DZHK ExMET. This substudy is associated to the interventional, prospective, multicenter, randomized controlled trial Exercise in Prevention of Metabolic Syndrome (ExMET, ClinicalTrials.gov identifier: NCT01676870).

Aim and hypothesis

The aim of the single-center, randomized, interventional DZHK ExMET study was to assess and compare markers of PF (e.g. $\dot{V}O_2$peak), metabolic risk factor profile and innate/adaptive immune function after 16 weeks intervention between three training regimens in patients with MetS.

Training regimens were low (one interval- high-intensity interval training, 1HIIT) or high volume high-intensity interval training (four intervals- high-intensity interval training, 4HIIT) or moderate intensity continuous training (MICT) (100).

The hypothesis is that MetS patients profit from a 16-week exercise intervention regarding metabolic risk factors and PF, including evaluation of different exercise intensities (MICT vs HIIT) and volumes (1HIIT vs 4HIIT).

Inclusion criteria and Recruiting

The study's inclusion criteria for participants were central adiposity (elevated waist circumference ♀ ⩾80 cm, ♂ ⩾94 cm) and at least two further criteria of MetS (100) according to IDF criteria (104). Only patients treated 12 months prior to recruiting start and archived at the database of the outpatient clinic of the Department of Preventive and Rehabilitative Sports Medicine, TUM, were assessed for eligibility, see figure 18. The aim was to recruit n=30 patients.

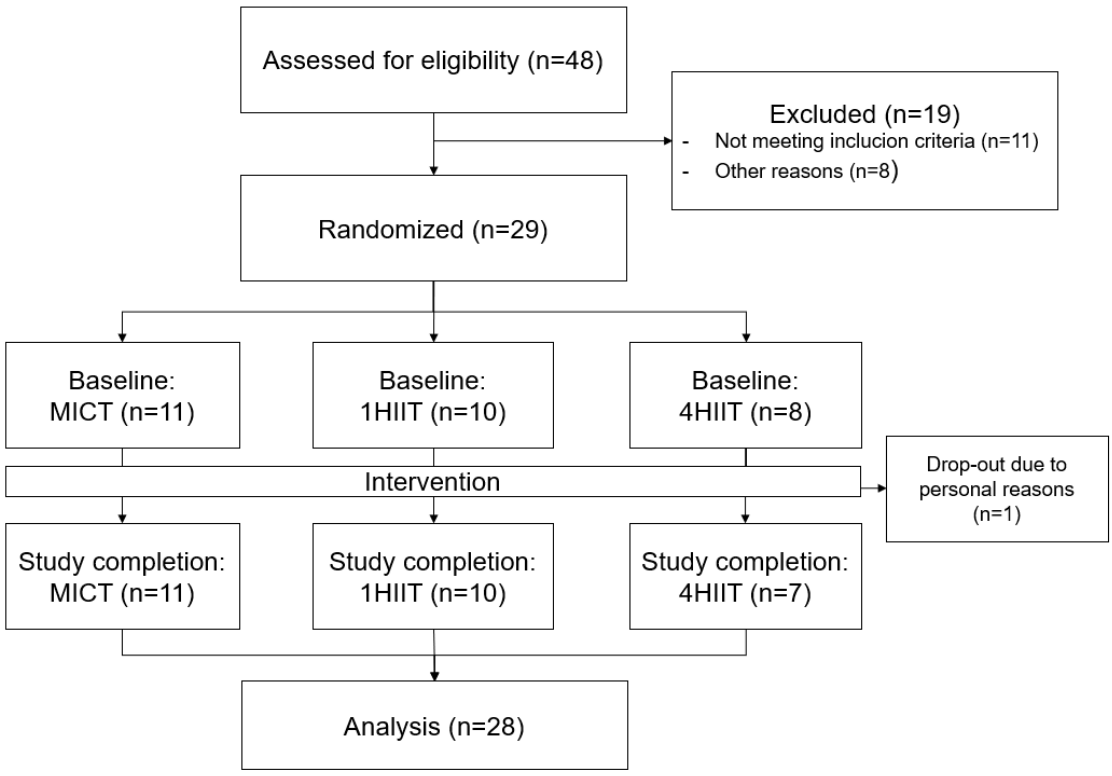

Figure 18 Flow chart DZHK ExMET study, consort, MICT moderate intensity continuous training, 1HIIT high-intensity interval training with low volume, 4HIIT high-intensity interval training with high volume. Authors own figure as published in von Korn et al. (2021) (100).

Key methods

Metabolic risk factor profiling (sex-specific waist circumference (WC), waist-to-height-ratio (WTHr, WC/height), hypertriglyceridemic waist phenotype (HTW phenotype, prevalence of both increased triglycerides (TAG) and WC), fasting glucose and insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR, fasting insulin x fasting glucose/ 405), atherogenic dyslipidemia (both increased TAG and decreased HDL-C)) was conducted by blood surrogates and anthropometric measures at baseline and follow-up (100).

Regarding PF, a symptom-limited cardiopulmonary exercise test (CPET) was conducted to, amongst others, define the peak oxygen uptake ($\dot{V}O_2$peak) and respiratory exchange (RER) ratio during warm-up phase (100). Patients were 1:1:1 randomized to:

(1) MICT (5x30 min/week, 35-50% heart rate reserve (HRR)

(2) 1HIIT (3x17min/week incl. 4min @80-90%HRR)

(3) 4HIIT (3x38 min/week incl. 4x4min @80-90%HRR) (100).

Examinations were conducted at baseline and after 16 weeks intervention, as depicted in figure 19.

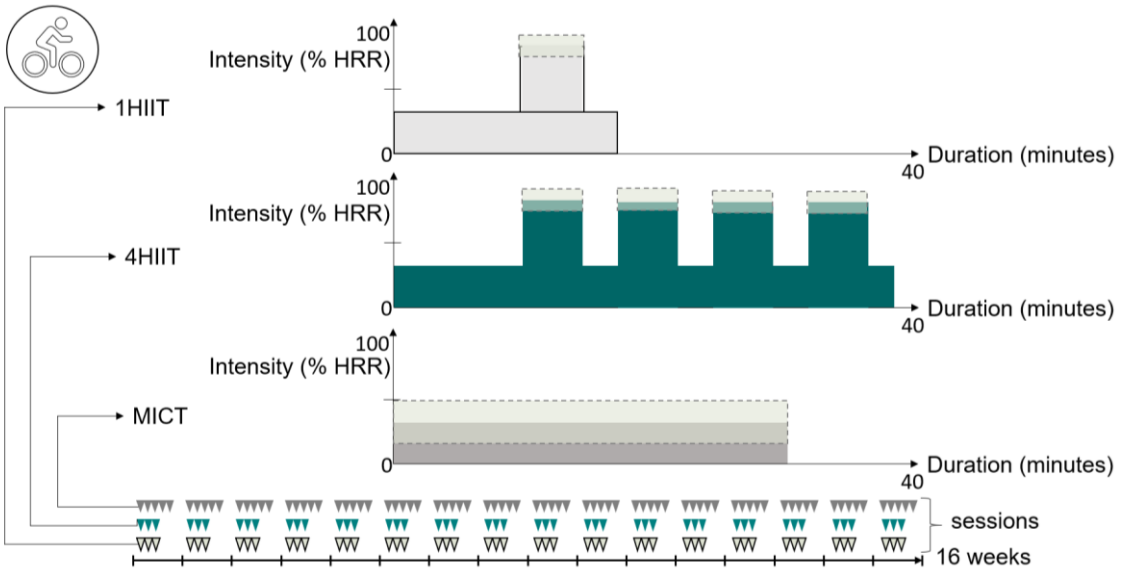

Figure 19 DZHK ExMET training regimens. Style adapted from Kraenkel (unpublished). 1HIIT one interval high intensity interval training, 4HIIT four intervals high intensity interval training, MICT moderate intensity continuous training, HRR heart rate reserve.

Patients randomized to the HIIT groups trained three times per week in a supervised setting, whereas the MICT group was engaged to increase leisure time physical activity as recommended by the WHO guidelines (15) and trained two times supervised per week (100).

The statistical analysis was performed according to the published section in von Korn et al. (2021) (100): Statistical analysis was performed using paired t-test (main effect of time) and repeated measurement analysis of variance (including group-by-time-interaction). Analysis of covariance was performed to additionally control for covariates (metformin, insulin, and statin medication). Pearson's correlation coefficient (r) was used to quantify strength of association between continuous variables. All tests were performed two-sided at a significance level of a = 5%. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY).

Key results

The results have been published in the framework of the second manuscript of von Korn et al. (2021) (100). Twenty-nine patients with MetS aged 61 ± 5 years were included into the study (nine females, BMI 31.1 ± 3.6 kg/m2, WC ♀ 102.2 ± 10.6 cm, ♂ 108.5 ± 8.6 cm, WTHr ♀ 0.62 ± 0.07, ♂ 0.62 ± 0.06) with no significant differences between groups.

Descriptive characteristics of the DZHK ExMET cohort at baseline and follow-up are depicted in table 2.

Table 2 Baseline and follow-up descriptive characteristics of DZHK ExMET participants (100).

	Pre (n=29)	**Post (n=28)**
Age (years)	61 ± 5	
Sex (male/female)	20/9	19/9
Metabolic syndrome (n)	29	21
Hypertriglyceridemic waist phenotype (n)	12	9
Medication (n)		
Metformin	3	3
Insulin	2	2
Statin	14	11
Beta blocker	8	8
Angiotensin receptor blocker	15	16

Calcium antagonist	7	6
Acetylsalicylic acid	9	8
Medical history (n)		
History of Myocardial infarction	4	
History of Type 2 Diabetes mellitus	5	
History of Coronary artery bypass	2	
History of percutaneous coronary intervention	6	
History of Atrial fibrillation	1	
History of Hypertension	22	
History of smoking	16	

There were no significant group x time interactions between groups in WC (p=0.590), fasting glucose (p=0.773), fasting insulin (p=0.509), HOMA-IR (p=0.158), atherogenic dyslipidemia (TAG p=0.468, HDL-C p=0.665, TAG/HDL-C p=0.502), $\dot{V}O_2$peak (p=0.999) or RER (p=842) after 16 weeks intervention (100), as depicted in table 3.

In the whole study population, irrespective of allocated group, there was a time effect: while metabolic markers did not significantly change, $\dot{V}O_2$peak significantly improved by a clinically meaningful amount (Δ 2.7 ± 0.9ml/min/kg; p<0.001) and RER at warm-up significantly decreased (Δ-0.03 ± 0.06, p=0.039) (100). The overall MetS prevalence decreased by -28% (initial n=29 to n=21 after intervention).

Table 3 Outcomes DZHK ExMET study (100).

	All			**1HIIT**	**4HIIT**	**MICT**	
	Pre, n=29 **Mean** ± SD	**Post, n=28** **Mean** ± SD	p value (time)	Delta ± SD (n=10)	Delta ± SD (n=7)	Delta ± SD (n=11)	p value (group x time)
BMI (kg/m²)	31.1 ± 3.7	30.8 ± 3.8	0.121	-0.40 ± 1.08	-0.21 ± 0.88	0.24 ± 0.97	0.903
Body fat[a] (%)	28.4 ± 5.3	27.8 ± 6.1	0.137	-0.3 ± 3.7	-0.3 ± 2.3	-1.6 ± 2.2	0.518
WC (cm)	106.5 ± 9.6	106.1 ± 10.3	0.506	0.7 ± 5.4	-1.6 ± 4.6	-1.1 ± 4.4	0.590
Resting HR (bpm)	68 ± 13	66 ± 12	0.359	-4 ± 11	0 ± 9	0 ± 9	0.671
SBP (mmHg)	134 ± 13	133 ± 13	0.766	6 ± 12	-4 ± 9	-5 ± 13	0.107
DBP (mmHg)	85 ± 9	83 ± 9	0.269	-1 ± 8	-4 ± 15	-2 ± 9	0.881
PWV (m/s)	8.8 ± 0.8	8.7 ± 0.9	0.626	-0.1 ± 0.2	-0.1 ± 0.4	0.3 ± 0.3	0.076
TAG (mg/dl)	141.7 ± 53.8	131.8 ± 60.7	0.291	-4,7 ± 63.1	-29.3 ± 25.7	-2.4 ± 42.2	0.468
HDL-C (mg/dl)	50.0 ± 10.5	51.4 ± 11.8	0.177	1.3 ± 6.0	0.1 ± 5.0	2.6 ± 5.4	0.665
TAG/HDL-C ratio	3.0 ± 1.4	2.8 ± 1.8	0.446	0 ± 1.9	-0.7 ± 0.6	0 ± 1	0.502
LDL-C (mg/dl)	129.4 ± 36.5	131.3 ± 35.8	0.595	-10.5 ± 12.9	14.1 ± 29.2	6.6 ± 22.4	0.067
Total cholesterol (mg/dl)	195.2 ± 44.1	204.5 ± 46.9	0.177	1.9 ± 38.3	28.9 ± 41.5	5.0 ± 33.6	0.310
Fasting glucose (mg/dl)	112.2 ± 19.8	111.3 ± 21.3	0.712	0.8 ± 11.2	0.6 ± 9.8	-4.1 ± 23.8	0.773
Fasting insulin (µU/ml)	12.8 ± 7.6	14.5 ± 16.5	0.551	-4.5 ± 19.4	-3.1 ± 8.4	-0.17 ± 8.8	0.509

Hb	15.1 ± 1	14.8 ± 1.1	**0.045***	0 ± 0.5	-0.6 ± 1.1	-0.3 ± 0.7	0.326
HOMA-IR	3.7 ± 2.5	4.2 ± 5.1	0.586	2.4 ± 6	1.2 ± 3	-1.1 ± 1.9	0.158
$\dot{V}O_2$peak (ml/min/kg)	22.7 ± 6.1	25.4 ± 7	**0.001****	2.2 ± 3.7	2.2 ± 2.4	2.3 ± 3.7	0.999
RER at warm-up	0.83 ± 0.1	0.81 ± 0.1	**0.039***	0 ± 0.1	0 ± 0.1	0 ± 0.1	0.842

Means ± standard deviation. BMI body mass index, WC waist circumference, resting HR resting heart rate, SBP systolic blood pressure, DBP diastolic blood pressure, PWV pulse wave velocity, TAG triglycerides, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, HOMA IR Homeostasis Modell Assessment, Hb hemoglobin, $\dot{V}O_2$peak peak oxygen uptake, [a]7-site skin-fold caliper method, SD standard deviation, * P<0.05, **P<0.01

No alterations of metabolic results were found after adjustment for medication (100), as depicted in table 4.

Table 4 Outcomes DZHK ExMET study adjusted for baseline medication (100).

		1HIIT	**4HIIT**	**MICT**	
		delta ± SD (n=10)	delta ± SD (n=7)	delta ± SD (n=11)	p value (group x time)
Adjusted for metformin, insulin and statins	**TAG** (mg/dl)	-1.7 ± 17.1	-34.6 ± 20.5	-1.4 ± 15.1	0.416
	TAG/HDL-C ratio	0.1 ± 0.5	-0.8 ± 0.6	0 ± 0.5	0.485
	Fasting glucose (mg/dl)	2.4 ± 5.6	-3.7 ± 7.1	-2.9 ± 5.3	0.733
	Fasting insulin (µU/ml)	5.2 ± 4.5	-4.8 ± 5.7	0.3 ± 4.3	0.413
	HOMA-IR	2.5 ± 1.5	1.1 ±1.7	-1.1 ± 1.2	0.173
Adjusted for statins	**LDL-C** (mg/dl)	-9.2 ± 6.7	11.4 ± 8.1	7.1 ± 6.3	0.115
	Total cholesterol (mg/dl)	1.7 ± 12.1	29.3 ± 14.7	4.9 ± 11.5	0.332

TAG triglycerides, LDL-C low density lipoprotein cholesterol, HOMA IR Homeostasis Model Assessment, SD standard deviation

4.3. LeIKD study

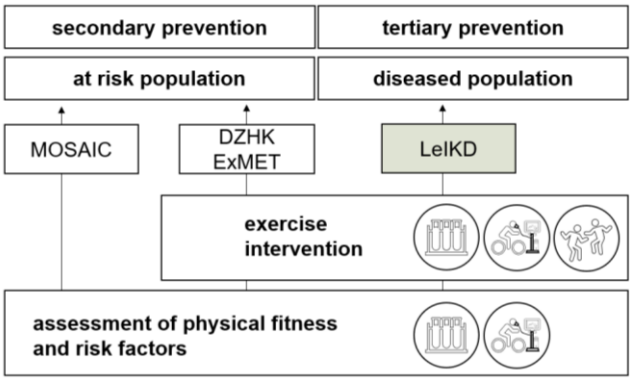

Figure 20 Context of PhD studies: LeIKD study. Authors own figure.

Referring to the pathway of CVD, chronic ischemic heart disease (or coronary artery disease) grounds on atherosclerotic disease and increases the likelihood of a severe cardiovascular event. T2DM again accelerates the risk for ASCVD. Patients suffering from both diseases have a high burden of disease and thereby higher DALYs. Health-economic burden by intensive late prevention strategies and medical support defines these conditions. Exemplarily, the costs for T2DM only globally tripled from 2003 to 2013 up to US$ 827 billion, as the Global Report on diabetes (2019) by the WHO states (111).

The *Lifestyle Intervention in Chronic ischemic heart disease and Type 2 Diabetes* – study (LeiKD) will contribute to further evidence on exercise and diet in a 12 months interventional setting by telemedicine and its effect on metabolic control, PF and CVD risk factors in a randomized, controlled, multicenter, prospective design (tertiary prevention).

Background of the study

The background of the study was published in the framework of the third published manuscript by von Korn et al. (2021) (112):

Patients with both, chronic ischaemic heart disease (CIHD) and type 2 diabetes mellitus (T2DM), have a high morbidity and mortality (50). Results from the *European Action on Secondary Prevention through Intervention to Reduce Events IV* (EUROASPIRE-IV) survey (n=7998), assessing the implementation of current guidelines in secondary prevention, show that 26.8% of patients with CIHD also suffer from T2DM (83). Combining the diagnosis of T2DM and CIHD exponentially increases the risk of impaired quality of life (QoL) and mortality (50, 58).

Recommendations for lifestyle intervention are included in current guidelines in CIHD (50) as well as T2DM (113). Both have received Ia classifications, which is based on evidence from

randomized controlled intervention trials. The largest trial (Look AHEAD) in T2DM (14% with former cardiovascular event) has revealed that lifestyle intervention including exercise training in combination with a hypocaloric diet improved glycosylated hemoglobin (HbA_{1c}) over one-year, as compared to usual care (60). Moreover, results from the ENHANCE trial in patients with T2DM (1:1 randomized, n=296, behavioural intervention, increasing diabetes self-care by monitoring software) have shown a trend towards a mean reduction of HbA_{1c} of 0.4% after six months, although this was non-significant due to improvements in both experimental and control groups (114). Furthermore, results of the DiRECT study in an outpatient general practitioner setting have demonstrated a 46% remission of T2DM through weight reduction by meal replacement therapy and exercise counselling after twelve months intervention (115).

Evidence from a recent study in patients with stable CIHD (n=15,487, physical activity (PA) data by questionnaire, 38.7% T2DM) has revealed that habitual exercise is significantly associated with lower cardiovascular mortality (adjusted hazard ratio= 0.92) (116). Moreover, in patients with heart failure with reduced ejection fraction (HFrEF) the HF-ACTION study (51.4% ischaemic aetiology of heart failure, prevalence of T2DM 32.1%), has revealed that, after adjusting for prognostic factors, exercise training significantly reduced rehospitalisation rate (hazard ratio: 0.85, p=0.03) (117).

However, in all of these trials adherence to intervention has been the key challenge (60, 117). Telemedical applications may support implementation of and adherence to lifestyle measures, as demonstrated by the ENHANCE trial (114). A recent review by Zhu et al. (2019) has underlined the effectiveness of telemedical interventions in heart failure patients (10981 patients with HFrEF, NYHA I-IV, 29 randomized controlled trials) by revealing significant reductions in hospitalisation rate, all-cause mortality, and length of hospitalisation in the intervention group (118). The TIM-HF2 trial investigated the efficacy of a remote patient management in n=1571 heart failure patients (NYHA II-III, 1:1 randomisation) on morbidity and mortality (40% ischaemic cause of heart failure, 45% T2DM) (119) and revealed a significant difference in days lost to cardiovascular hospital admissions (4.9% in remote patient management vs. 6.6% in usual care, p=0.046).

Collaborators and funding

The study committee is led be Prof. M. Halle, MD, Department of Preventive and Rehabilitative Sports Medicine, University hospital ‘Klinikum rechts der Isar’, Faculty of medicine, Technical University of Munich, Munich, Germany. Members of the committee are Techniker Krankenkasse. Dr. S. Neubauer. Bramfelder Straße 140. 22305 Hamburg, the Privates Institut

für angewandte Versorgungsforschung GmbH (inav). Univ.-Prof. Dr. V. Amelung. Friedrichstraße 95. 10117 Berlin and IDS Diagnostic Systems AG. Dr. med. B. Hackenberg. Karlsburgstraße 2. 76227 Karlsruhe.

It is funded by the Federal Joint Committee (Innovationsfond des gemeinsamen Bundesausschuss G-BA), grant no. 01NVF17015.

Study design

The randomized, controlled, multicenter study will include n=1500 patients suffering from both CIHD and T2DM and insured at the collaborating Techniker Krankenkasse (health insurance company) (112). Patients will be randomized into lifestyle intervention (LS) or usual care (UC) for 12 months, as depicted in figure 21. The LS consists of exercise via telemedicine, diet recommendations and regular feedback from experts. After six months intervention, the regular feedback and exercise monitoring is reduced in the LS group. Visits will be conducted at baseline, after six and 12 months.

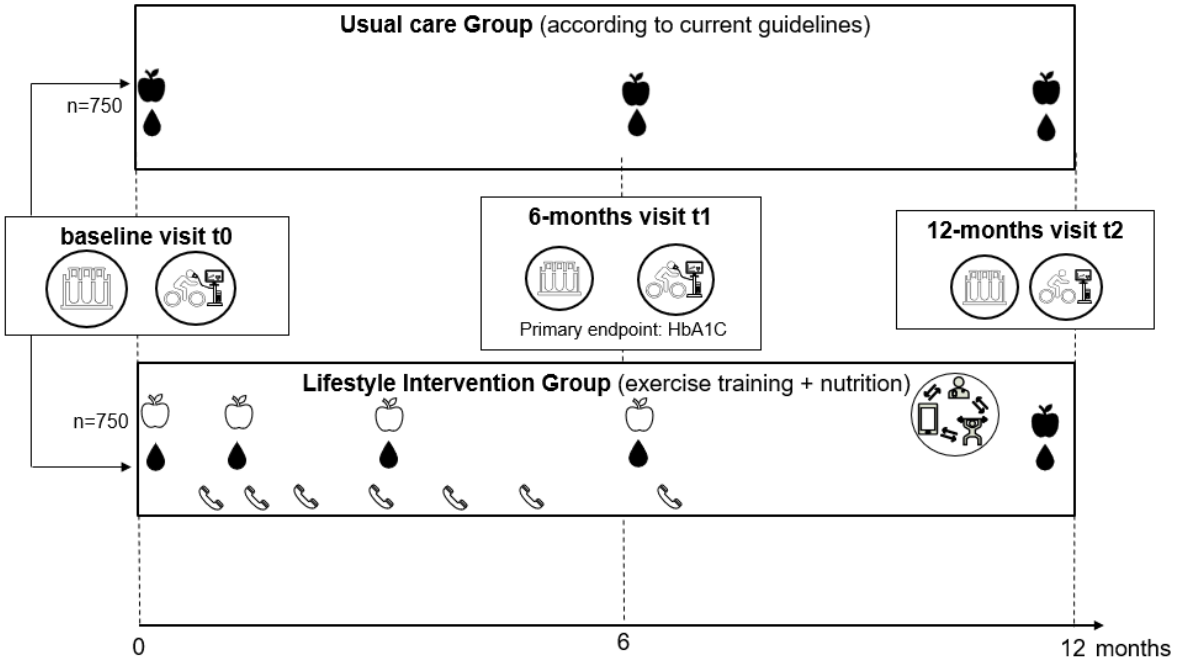

Figure 21 LeIKD study design (112). Apple black: food diary without feedback, apple white: food diary with feedback, blood drop: blood glucose profile without feedback, phone: feedback training from core lab. Authors designed figure as published in (112).

Aim and hypothesis

As the approach of lifestyle intervention via telemedicine and its effect on adherence, risk factor profile, PF, motivation and education remains unclear in patients suffering from both CIHD and

T2DM, the LeIKD trial will contribute to further evidence. Data on health economics will add valuable information for possible future implementation into standard of care.

The primary endpoint is change in HbA_{1C} levels from baseline to 6 months of lifestyle intervention (LS) compared with usual care (UC) (reduction of HbA_{1C} −0.4% from baseline level) (112). Secondary endpoints include health literacy, quality of life and cost-effectiveness after six and twelve months (112).

The hypothesis is that patients suffering from both T2DM and CIHD profit from a telemedical approach of a 12-months lifestyle intervention regarding metabolic risk factors and PF compared to usual care.

Inclusion criteria and Recruiting

Patients will be able to participate in LeIKD if they are insured at Techniker Krankenkasse and diagnosed with both Ischemic heart disease (ICD-10: I20-I25) and Diabetes mellitus (ICD-10: E11) and $HbA_{1c} \geq 6.5$ or anti-diabetic medication at the time of screening (112). Patients have to be adult and if willing to participate, a physician's permission must be obtained. Further details of the stepwise recruiting process are obtained in figure 22.

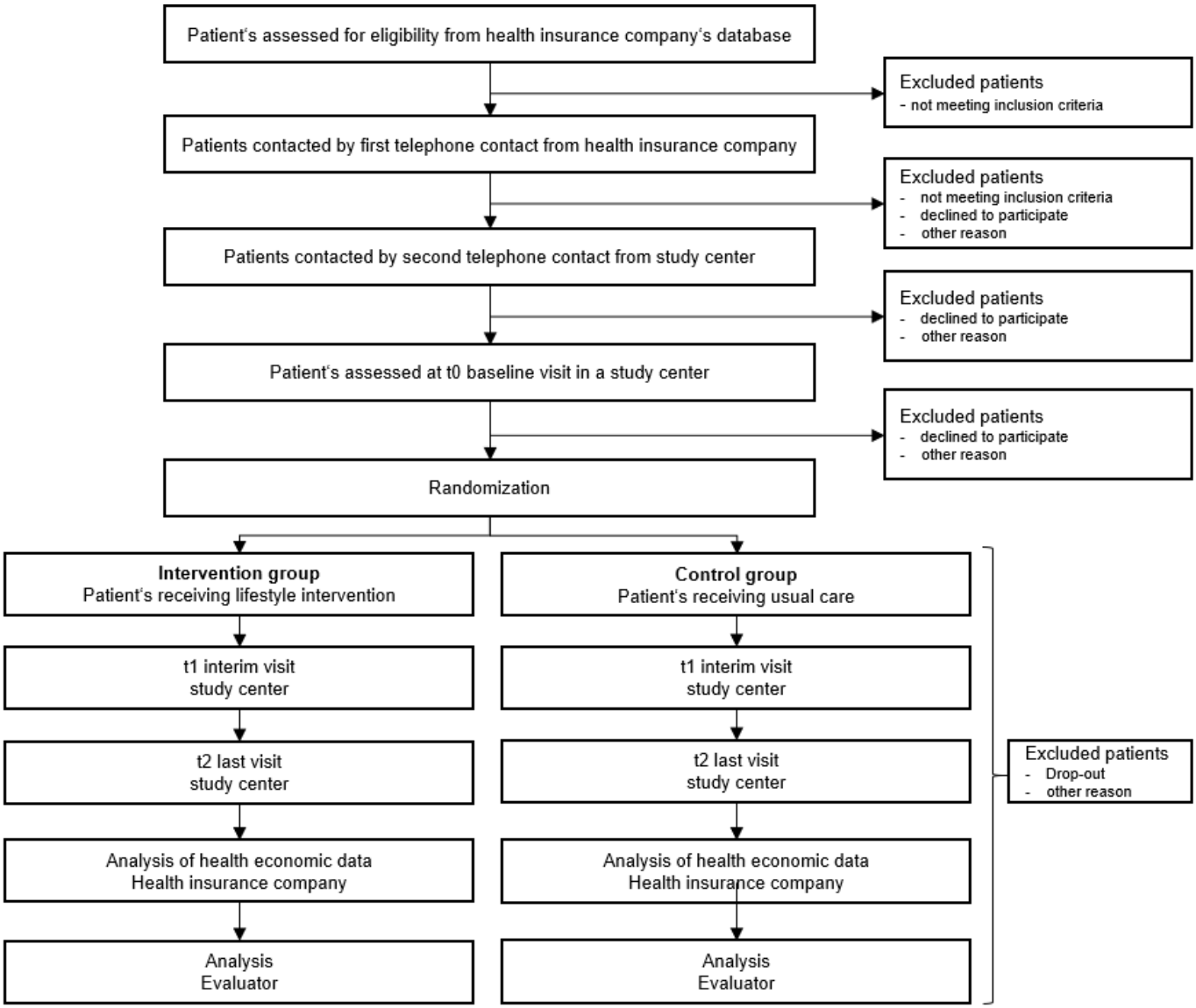

Figure 22 Flow chart LeIKD recruiting and inclusion. Authors own figure.

Methods

Methods have been published in the framework of the third manuscript by von Korn et al. (2021) (112):

Anamnesis including medical history, medication, physical examination, anthropometry and resting electrocardiogram (ECG) will be performed. Blood samples will be taken and analyzed

for standard laboratory values (HbA_{1c}, blood count, blood lipids, N-terminal pro-brain natriuretic peptide) in a local laboratory.

Health literacy, eating behavior, daily PA and QoL will be assessed by the European Health Literacy Questionnaire (HLS-EU-Q16), a German questionnaire on eating behavior ('Fragebogen zum Essverhalten', FEV), the International Physical Activity Questionnaire (IPAQ) and the Short Form Health Survey (SF-36), respectively. These examinations will be repeated after 6 (t1) and 12 months (t2).

Furthermore, a symptom-limited maximal cardiopulmonary exercise test (CPET) on a stationary cycle ergometer will be performed according to current recommendations at baseline and after 6 months (120). An exercise stress test (including exercise ECG) will be performed after 12 months. Breath-by-breath CPET data will be transferred to and analyzed by the CPET core laboratory at Technical University of Munich (TUM).

To monitor daily PA and blood glucose levels, all patients (both groups) will receive a pedometer (AS80/AS87, Beurer GmbH, Ulm, Germany) and blood glucose meter (GL50evo, Beurer GmbH, Ulm, Germany), which are connected to an app (Beurer Health manager, Beurer GmbH, Ulm, Germany). While the pedometer should be worn throughout the entire duration of the study, patients are asked to measure 3-day blood glucose profiles at three different points in the study: during week 1 (after t0), the week after t1 and the week before t2. Randomized patients are equipped with relevant smartphone applications (apps). If necessary, a smartphone will be provided free of cost for the duration of the study.

Furthermore, 7-day paper-based food diaries corresponding to these three points in time will be recorded by the study participants and evaluated by nutrition specialists at TUM.

For safety monitoring and analysis, adverse events will be obtained and immediately forwarded to the study site at TUM to be revaluated by a safety committee.

5. Discussion

Cardiovascular and -metabolic diseases, mainly caused by modern behavioral risk factors, account for ~30% of all deaths worldwide (16). As in Europe 72% of cardiovascular deaths are attributable to eight risk factors (alcohol and tobacco consumption, ↑blood pressure, ↑BMI, ↑ cholesterol, ↑blood glucose, ↓fruit/ vegetable intake and physical inactivity (16)), there still is

an urgent need for prevention strategies. Sufficient exercise inducing improved PF can counteract the overall CVD risk and thereby improves risk factor profile, like blood glucose levels or BMI (31). Therefore, in the framework of the thesis, three studies were presented to evaluate the role and influence of exercise and PF in different stages of CVD.

5.1. MOSAIC study

In secondary prevention of CVD due to accumulated risk factors in a relatively young “at risk” cohort, we found significant differences in health-related physical fitness and pulse pressure compared to healthy peers.

Health-related physical fitness

We found significantly decreased health-related physical fitness in children and adolescents after cancer therapy, which is in line with previous studies and further discussed in von Korn et al. (2019) (86). For CCS, it is seven times more likely to die from CVD than healthy peers, which is driven by higher risk of obesity, T2DM and underlying cardiovascular and -metabolic diseases with ageing (121). As stated in the *Childhood Cancer Survivor Study* by Meacham et al. (2010) (122) (n=8599 CCS and n=2939 healthy siblings, retrospective analysis 1970-1986 of 5-year survivors and their cardiovascular risk factors), CCS have significantly higher odds of taking cardiometabolic medication (hypertension odds ratio (OR) 1.9, T2DM OR 1.7, dyslipidemia 1.6) than their siblings, although no difference in obesity or cardiovascular risk factor prevalence was found. As a surrogate for MetS, “cardiovascular risk factor clustering” revealed physical inactivity (OR 1.7) and older age at examination (OR 8.2) as two of the significant contributors (amongst total (OR 5.5.), chest and abdomen (OR 2.3) irradiation) (122). Sufficiently physically active CCS have a significantly ($p<0.05$) lower %fat mass, lower abdominal subcutaneous and visceral fat, higher lean body mass and higher insulin sensitivity than physically inactive CCS (121). Compared to healthy siblings, the association of CVD risk factors (waist circumference, abdominal subcutaneous and visceral fat, %fat mass) on PA was stronger in CCS (121). Regarding exercise as a prevention strategy, this implies a stronger effect of PA and PF on CVD risk factor profile in CCS than healthy siblings (121), when exercise is targeted and sufficiently applied to the needs of CCS.

When referring to our results, they must be interpreted with caution because the measurement of health-related fitness was based on one physical functioning measurement by motoric battery. On the one hand, this does not relate to a direct measurement of PF by cardiorespiratory /physiological parameters, but refers to an indirect measurement of previous physical activity and motoric development. On the other hand, the motoric test battery is easy

to apply and a well-established instrument, assessing different dimensions of PF than “just” laboratory parameters. Overall, this depicts a basic clinical overview on assessed motor skills of health-related physical fitness.

Hemodynamics

Regarding the MOSAIC results on hemodynamics, only pulse pressure was significantly increased. These results are also in line with previous studies and act as risk factors for early-onset vascular ageing and underline the increased cardiovascular risk in this cohort (123-125). As also stated by Slater et al. (2015) (121), the vascular health must be seen as a “continuum”. The measurement of arterial stiffness can therefore be discussed as being too crude to diagnose early vascular changes, as the PWV of CCS in our cohort does not reveal the early, subtle vascular changes in short term after cancer diagnosis (mean time between diagnosis to examination: 3.6 ± 2.8 years). The significant change of hemodynamics by pulse pressure, which is sensitive to vascular changes (123), can be interpreted as an indicator for early stage of CVD late sequelae. The progress of vascular pathologies into adulthood will therefore get more prominent in a later stage, when other risk factors additionally contribute to the overall CVD risk, e.g. aging process, unfavorable sedentary lifestyle (121). The measurement of arterial stiffness may therefore add further information and gain importance in later stages of the aftercare, since the overall effect of arterial stiffness measures in early prevention stage is discussable due to publication bias (Tzoulakis et al. meta-analysis including n=15 studies on Aortic PWV, observed to expected studies ratio= 25.00, excess significance $p<0.001$) (14, 126).

Due to the lacking association of HRPF and hemodynamics in the MOSAIC study, CVD risk factors may be interpreted as independent risk factors, which can be targeted by different interventions (medication, lifestyle intervention). Still, physical inactivity is one major independent risk factor for CVD in CCS (121, 122). As a further hypothesis and research need, it could be tested how diminishing physical inactivity in CCS could be counteracted in one sweep: exercise most likely improves PF, which again has beneficial effects on risk factor profile. When applying targeted exercise to each individual, regarding their special need (motor skills, possible therapy induced side effects etc.) and personal aim, the risk of comorbidities may be reduced. Long-term effects of risk factor management and exercise in CCS are though still missing.

With regard to the hypothesis, this study fosters the current status of risk factor profiling of CCS. Due to the lacking association of HRPF and arterial stiffness in the early aftercare phase

in MOSAIC, it underlines the need for further research on exercise and PF in secondary and tertiary prevention of CVD or interventional trials. Although no association was found between vascular health and physical fitness, children and adolescent will most likely not improve their risk factor profile with ageing, which it is the utmost important to implement an active lifestyle and regular screening methods in this cohort. If children and adolescents after cancer therapy remain inactive or fail to implement a low “lifestyle risk-factor profile”, the risk for CVD will increase with ageing. To counteract this unfavorable lifestyle, prevention strategies in secondary and tertiary prevention must include physical activity, exercise and an improved physical fitness level, as current evidence demands.

Limitations

The sample of MOSAIC is relatively small, crosssectional and heterogenous, included a variety of different cancer diagnosis, ages at diagnosis and ages at examination (see von Korn et al. (2019) (86)). It represents the regular prevalence of cancer diagnosis in Germany, but results have to be interpreted with caution due to different treatment regimens, radiation and administered drugs. The cohort is recruited from a single-center. Data on long-term effects and further association of PF and CVD risk in childhood cancer survivors should be added in future research.

5.2. DZHK ExMET study

In secondary prevention, we evaluated three different training regimens in patients with MetS (at risk/ diseased cohort). We found no significant differences in physiological and metabolic changes between the groups, but an overall favorable effect of exercise (HIIT and MICT) on PF.

Physical fitness and exercise

There was no significant difference between exercise regimens (1HIIT, 4HIIT and MICT), but the DZHK ExMET patients globally profited from the intervention (MICT and HIIT) with regard to their PF status. Patients with MetS were able to overall improve their PF status, as also stated in populations with dyslipidemia, T2DM and obesity (31, 99): the sole improved PF generates a beneficial effect on overall risk factor profile. Interestingly, there was no significant difference between the 1- and 4-HIIT groups, which evokes further questions regarding the importance of volume in high-intensity training regimens in patients with MetS.

All groups performed exercise according to the WHO guidelines of sufficient physical activity (MICT: five sessions of 30 min. moderate PA per week, 1HIIT: three sessions of 17 min. moderate-to-vigorous intensity training per week, 4HIIT: three sessions of 38 min. moderate-to-vigorous intensity training per week). As also stated in the ESC guidelines, different effects of HIIT and MICT are anticipated in populations with CVD risk factors: moderate to high intensity training affects metabolic diseases more effectively than low intensity, whereas the volume of training seems to have less relevance (31).

Aerobic exercise or combined aerobic and resistance training are discussed to be favorable with regard to lower inflammation, improved glycemic control, functional adaptations (muscle strength, CRF) (127, 128). High intensity training, longer protocols and additional lifestyle adaptations lead to improved body weight and composition in patients with evident T2DM (128). Regarding the results of the DZHK ExMET study, we did not control for additional lifestyle change (e.g. aerobic PA during leisure time) and intervention lasted just 16 weeks, as further research on a more wholesome approach may reveal further insights into different results induced by high-intensity training than moderate intensity training. Therefore, our results present a global favorable effect of exercise, but we were not able to differentiate between exercise regimens within 16 weeks of intervention, and not controlling for diet and further lifestyle change.

Additional strength training, which is recommended in chronic diseases and at risk population to foster long-term lifestyle change and benefits regarding risk factor profile (31), was not included in our intervention. A combined approach of exercise would have added relevant information on cardiovascular and -metabolic effects (28, 99), which may be induced by improved body composition following strength training (↑muscle mass). On contrast, in the meta-analysis be Wewege et al. (2018) (n=16 randomized controlled interventional trials including n=588 patients with MetS), strength training in patients with MetS is expected to have a minor impact compared to aerobic exercise (n=4 studies), but evidence from several, well-controlled large trials is lacking (99). As it is evident from recent literature, the effect of different exercise regimens on MetS is of highest interest in research. As discussed by Kraenkel et al. (2019), the metabolic phenotype, medication, genetic background, sex and age contribute to the overall effect of exercise- on top of different exercise regimens addressing a variety of possible effects (44). Therefore, it can be concluded that the expression of metabolic phenotype at baseline must be included into designing the individual “best fit”-approach for patients with MetS. This has not been conducted in the framework of the DZHK ExMET trial due to independent randomization at baseline, regardless of metabolic phenotype.

However, future research needs to define individual approaches for lifestyle and exercise, to apply targeted interventions based on each patients' health and risk factor status. The DZHK ExMET study did not show differences between the exercise regimens, as the length of the intervention and sample size must be questioned. Changing the risk factor profile may takes longer than enhancing exercise for 16 weeks, as a long-term lifestyle change must be prioritized in this cohort.

Myers et al. (2019) review improved CRF by increased PA and exercise as a future "standard therapy" for patients with MetS or those at high risk (28), which was further reinforced by the ESC 2020 guideline by Pelliccia et al. (2020) (31). The authors view the WHO recommendation as minimum requirements addressing risk factors of the MetS (28). The DZHK ExMET study proofed exercise as a valuable prevention strategy with regard to improved PF and favorable risk factor profile, but details on exercise volume and intensity must be further evaluated and remain unclear. Improved PF alone contributes to lower risk of MetS severity and therefore acts as a successful prevention strategy, which can be reinforced with our results (reduced prevalence of MetS after 16 weeks) (28). Further investigation of the DZHK ExMET cohorts profiling and clustering may add further information on more targeted approaches. It underlines the demand for real-world implementation strategies based on larger trials investigating the effect of different exercise regimens and metabolic phenotypes. Designing targeted exercise to evoke significant effects on risk factor profile, despite PF, is still challenging in patients suffering from MetS (28).

Cardiovascular and -metabolic risk factors

Different to our expectations and current evidence, we found no significant effect on metabolic parameters in this cohort after 16 weeks intervention, which has to be interpreted with caution due to limitations like sample size. Controversially, the overall prevalence of MetS in the DZHK ExMET was reversed by one third.

When addressing metabolic traits, our study contributes to the current knowledge, but is not conclusive in all studied cases: we found no significant effect on TAG, TAG/HDL, LDL, HOMA, fasting insulin and glucose, which arouses further discussions. Hence, the DZHK ExMET study was able to detect slight shifts of metabolic phenotypes in all groups. It is controversial to other ExMET substudies by Ramos et al. (2016, 2017), which were able to detect differences in glucose and metabolic risk factor profile in a similar, but a slightly larger cohort (49, 129). Wewege et al. (2018) also state beneficial effects of aerobic exercise on lipid and glucose profile, CRF and waist circumference, with greater benefits if exercise is constantly adapted

and conducted thrice weekly for more than three months (99). Our intervention was conducted in a well-controlled setting for 16 weeks thrice weekly, too, but the sample size and lacking power calculation may contribute to the non-consistent results.

Despite lacking difference between exercise regimens, one third of the patients reversed their MetS after 16 weeks, which underlines the improved overall risk factor profile and is in line with previous evidence (28, 129). As reported by the Australian substudy of the ExMET trial, all exercise groups (1HIIT n=23, 4HIIT n=22 and MICT n=21) were able to modify different risk factors and overall PF after 16 weeks of exercise (129). However, despite lacking significant differences between the groups, the overall effect of exercise on the severity of MetS was decreased after 16 weeks intervention: MetS z-score 1HIIT 2.48 ± 3.38 to 0.84 ± 2.98, 4HIIT 2.75 ± 2.56 to 2.17 ± 2.71 and MICT 1.80 ± 1.93 to 0.90 ± 1.93 (49). Still, the presented results from DZHK ExMET point out inconsistencies with regard to exact mechanisms, and why no significant difference between the groups was evident. Nevertheless, as one third of the cohort was able to shift evident MetS, the uptake of exercise (regardless of intensity) and improved PF, has ameliorated risk factor profile.

As also stated by Kraenkel et al. (2019), exercise induces a variety of beneficial effects on CVD risk profile in patients with MetS and T2DM, like body weight and insulin sensitivity, but further details on choice of training regimen and exact mechanisms are lacking evidence (31, 44). Referring to supplementary figure 23, exercise induces different physiological responses, which is beyond affected by modifiable and non-modifiable risk factors like diet, age, sex, use of drugs/ medication and genetic background (28, 44). Future studies may be able to solve these gaps of knowledge, which are at current state not resolvable and also discussed in reviews to be inconclusive (28). Hypothesis about the exact mechanisms on different effects of training regimens on metabolic risk profile can therefore be not affirmed or rejected by the DZHK ExMET study, but underline the need for further research. In our case, it is noteworthy to have a closer look on e.g. diet, immune function and related metabolic risk factors for further analysis. Future research will contribute to this gap in knowledge, how e.g. immune function and activation contributes to lipid lowering by exercise (130) or how metabolic phenotype at baseline affects response to different exercise intensities and volumes. Nevertheless, the effect of exercise and PF alone are favorable and beneficial on each modifiable risk factor in patients suffering from MetS (28), as the overall effect on decreased MetS prevalence in DZHK ExMET underlines.

Regarding further details of training regimen in patients with MetS, HIIT, irrespective of volume, not significantly differed to MICT in improving PF or metabolic health (100). This is in line with

previous results from an ExMET substudy (49). It could be discussed, if the exercise “per se” improved the risk factor profile over 16 weeks in the relatively physically unfit population, and further shaping of the training regimen would be of higher importance in later stages of exercising (>16 weeks of exercising).

HIIT training is mentioned have stronger effects on metabolism (28, 31), which we cannot confirm or reject in our population. With regard to the position paper of Kemps et al (2019) (44) and the following editorial by Scherrenberg and Dendale (2019) (127) addressing exercise in T2DM, the authors further strengthen the favorable effect of exercise on metabolic, functional and structural dimensions. Still, in patients suffering from MetS T2DM is not mandatory, but glucose level abnormalities and the vicious cycle leading to T2DM is often not counteracted in MetS. As reinforced by the *Diabetes Prevention Study* (n=522 overweight patients with insulin resistance, (52)) and the *Diabetes Prevention Program* (n=2776, (53, 54)), lifestyle intervention including exercise/ PA ameliorated the prevalence of MetS, T2DM and improved glucose tolerance (prevention of T2DM where insulin resistance is evident) (DPP, reduction of T2DM prevalence after 15 years lifestyle intervention vs metformin vs placebo: HR 0.73, 95% CI 0.65-0.83; p<0.001, (54)). On top of that, a change of lifestyle for patients suffering from MetS, as indicated by Myers et al (2019), should include dietary consultation and additional strength training (28).

As a target outcome for future research; controlled weight loss if overweight (↓abdominal visceral and subcutaneous fat), improved glucose tolerance and muscle gain should be added in lifestyle trials, as these are major contributors to improved risk factor profile in patients along the pathway of T2DM, CVD and MetS (28). Thereby, different pathways of metabolic and functional dimensions would be addressed to make a more wholesome approach. To reach for a sustained lifestyle change in patients suffering from MetS, a well-controlled and powered, RCT must include an intervention of more than 16 weeks, including combined aerobic and resistance training. In the meta-analysis including nine RCTs in patients with MetS by Sequi-Dominguez et al. (2020), lifestyle and PA advice via telemedical approach lead to significant mean changes of BMI (p=0.03), WC (p=0.005), SBP (p=0.02), fasting glucose (p<0.001) and HDL-C (p<0.001) (duration of intervention 8-48 weeks) (131). To address latest technologies like telemedicine, exercise monitoring and recommendations regarding lasting lifestyle-change and diet should be introduced, to offer a wholesome approach including all dimensions of prevention in these patients. Considering trials following DZHK ExMET, this should be integrated into an intervention to strive for targeted exercise as a prevention strategy in patients with MetS.

Limitations

Beneath the small sample size, we did not control effectively for diet or further lifestyle change and PA in leisure time. It could be discussed, if all included patients were able to improve LTPA diet over the study course and the differences of exercise thrice weekly were therefore ameliorated. A food diary or pedometers to assess LTPA could have add valuable information on this hypothesis.

As our MICT group acted as the control group (treated according to usual care), they were technically not sedentary. The MICT group was engaged to exercise, too, as they were also able to improve risk factor profile during the intervention. Nevertheless, the training regimen for MICT included exercise according to the current guidelines, which we decided to offer to the MICT group for ethical reasons.

Regarding laboratory parameters, due to the less accurate parameter LDL-C than apoB or LDL particle number, our results must be interpreted with caution. We conducted measurements at two visits, and did not control for dietary intake the day before the examination. Long-term data may have given a closer insight into relevant changes of cardiovascular and -metabolic effects, as our intervention duration of 16 weeks revealed short-term effects without follow-up.

5.3. LeIKD study

In patients suffering from manifested T2DM and CIHD in tertiary prevention of CVD, a telemedical lifestyle intervention for 12 months will be implemented including nutritional counselling, increasing PA and health literacy. Aiming at improved metabolic risk profile by HbA_{1c} after 6 months, also parameters of PF and PA will add valuable information on exercise prescriptions, long-term adherence, cost-effectiveness and telemedical approach feasibility.

Telemedical approach

The telemedical approach has been performed in individuals suffering from severe CVD, but the LeIKD interventional data on both CIHD and T2DM will be a novelty and therefore contributes to a current gap in evidence.

In patients with severe, acute heart failure, a six-months telemedical intervention (n=160) in rehabilitation reduced all-cause mortality (p=0.014), as demonstrated by Dendale et al. (2012) in the *Telemonitoring in the Management of Heart Failure* (TEMA-HF 1) study (132). The effect of telemedicine on health economics has been evaluated in the TEMA-HF1 study, as reductions in hospitalization (p=0.934) and hospitalization costs (1,458 ± 3,420 € in control

group vs 902 ± 2,277 € in intervention group, p=0.23) demonstrated – however, the decrease in hospitalization costs was not significant (132). As promising as these results are, however, long-term data in telemedical lifestyle interventions are lacking, as LeIKD will contribute to further evidence on health economics' perspective. If the telemedical approach will positively shape patients risk factor profile in the LeIKD study, the applied intervention may influence future standard of care and recommendations in patients suffering from both CIHD and T2DM.

Another positive aspect is that the LeIKD intervention is set in patient's daily routine and home, as it is more time-efficient than travelling to a training site and items of the household (e.g. water bottle as weights) or area nearby (e.g. steps in a park) can be implemented in exercise routine. It therefore contributes to each individuals' preferences and is independent of weather, training facilities or presence of a trainer. As stated by the HF-ACTION study group, barriers for long-term adherence in CVD patients were low motivation, barriers related to comorbidities and the condition itself (85). As comorbidities of CVD diseased are often reinforced by unfavorable risk factor profile, exercise and improved PF ameliorate these contributing barriers in the long-term (e.g. weight/ fluid loss improves compression-induced body pain and shortness of breath) (31). Though patients are free to design their preferred exercise mode, exercise sessions are monitored by experts. Frequent feedback calls from experts will again motivate and inform patients, but decrease over time to enable the patient. This reinforces the patients' education, self-awareness and health literacy, which is demanded to be addressed by experts to overcome barriers in CVD prevention (133). The intervention therefore contributes to high safety and support mechanisms, but will empower patients to shape their own lifestyle. This may improve long-term adherence towards a more beneficial risk factor profile in diseased populations with a high proportion of modifiable risk factors.

On top of that, as reported from the ARTEMIS trial (n=267, 1:1 randomized to exercise training or usual care, 24 months intervention, CIHD patients with and without T2DM, drop-out rate 39%), patients in long-term interventions must not only be engaged to perform regular exercise, but also to increase daily PA for an active lifestyle (82). Both PA and exercise sessions will be monitored and recorded by telemedicine in the LeIKD study, which is a novelty. The telemedical approach will record consecutively (by pedometers and training app) and add by far more information on both parameters than paper-based diaries and questionnaires. Individual goals regarding PA are steps per day, which are set by experts and increase over time, based on patients individual PF level. The count of steps per days by pedometer therefore acts as a daily incentive.

The additional monitoring of blood glucose levels by telemedicine will add to further information on glucose control, which has been performed beforehand as e.g. in the ENHANCE trial by Sevick et al. (2012) (114). Patients with T2DM (n=263) were randomized to either intervention group (monthly decreasing group counselling sessions on diet and healthy lifestyle, individual energy intake targets) or attention control group for 12 months. The effect on glycemic control, irrespective of baseline HbA_{1c} level, showed no significant differences between groups after six months intervention (HbA_{1c} <8% Δ 0.1, 95% CI -0.1 – 0.4, p=0.28, HbA_{1c} ≥8% Δ 1.0, 95% CI -0.2 – 2.1, p=0.10) (114). All participants were supplied with blood glucose meters, pedometers and educational seminars. This is why the authors speculate that the improvement in the usual care group lead to non-significant differences, aside to the overall significant effect, on metabolic and glycemic control (114). Unfortunately, the PA (measured by pedometers/ steps per day) has not been reported in the framework of Sevick et al.'s manuscript (114), concluding that the association to PA cannot be drawn. It is noteworthy to also discuss the influence of PA on glycemic control, as the LeIKD study will contribute to this gap in research. The effect of exercise and PA measures is a must with regard to improvements in lifestyle-associated glycemic improvements, accompanied by diet/ energy intake.

Regarding feasibility, the telemedical approach has been performed, next to the TEMA-HF1, in the framework of the *Telemedical Interventional Management in Heart Failure II* (TIM-HF2) trial (heart failure with reduced ejection fraction (HFrEF), NYHA II-III, n=1571, randomized to usual care or additional telemedical management, maximum follow-up 393 days) (119). Tim-HF2 showed promising results on percentage of days lost to hospital admission or all-cause death (IG 4.88 % 95% CI 4.55 – 5.23 vs. UC 6.64 % 95% CI 6.19 – 7.13; ratio 0.80, p=0.046), accompanied by very good technical support and data handling (83% of transmitted data were accurately) (132). The additional personal support and guidance may contribute to the success of the intervention (132), which will be analyzed by the comparison of the first vs. the second half of the LeIKD intervention, where no personal support is foreseen. The LeIKD study will therefore not only analyze the possible influence of a feedback/ personal guidance system in comparison to only app-guided instructions on motivation, but also on adherence and recording quality. This will further shape the mode of exercise prescriptions, allow to control for general acceptance and telemedical + personal support vs. only telemedical support, which has not been done before. On top of that, the cost-effectiveness ratio, presented by association to health economics, will contribute to urgently demanded evidence in the field (14).

Cardiovascular and -metabolic risk factors

The benefit of PA and PF by exercise in at risk and diseased patients on ASCVD and T2DM is undisputed, as mirrored by guidelines on chronic coronary syndrome, T2DM and exercise in CVD (31, 76, 113, 134).

Effects on CVD risk factors in patients suffering from both T2DM and CIHD has been reported by Karjalainen et al. (2015), as results from the ARTEMIS substudy on CVD morbidity, mortality and risk factors state (82). Exercise comprised of endurance and strength training, constantly increasing from only moderate to moderate-to-vigorous intensity and HIIT training. Physical activity was associated with significantly lower CVD morbidity and mortality after two years, as presented in the background section 1.3.3. (82). Exercising more than three times weekly has a beneficial effect on risk factors and mortality, compared to no PA (hazard ratio: 2.68, 95% CI 1.06–6.75; p= 0.037) (82). The effect on exercise capacity and waist circumference was minor, but greater in patients with both CIHD and T2DM in the intervention group than in patients without T2DM ($p<0.05$), but further effects on metabolic risk factor profile were not significant. As discussed by the authors, they assume a future combination of exercise and diet to be more effective, than exercise alone (still, both combined explain 9% of the variability of CVD risk factors) (82). No effect on metabolic and lipid profile following intervention was evident in the ENHANCE trial, too, where no significant treatment x time effect between IG and UC after six months was found (LDL-C p=0.42, HDL-C p=0.25, Triglycerides p=0.38, SBP p=0.79, BMI p=0.18, WC p=0.86) (114). As the authors speculate the UC group to have profited from the study participation as well, the overall (but not significant) results tend in favorable direction. The impact and association PA in the study cohort was not discussed, which additionally might explain the overall favorable tendency and accounts for lacking significance between the groups. Lacking impact on metabolic profile was also addressed be Scherrenberg and Dendale, 2019, who demand a more personalized approach in patients with T2DM (127).

In LeIKD, exercise, PA and diet will be addressed, which will reveal further insights in change of risk factor profile in patients suffering from both T2DM and CIHD. Lacking effects on cardiometabolic risk factors in the ARTEMIS trial may also arise from less monitoring during the intervention, as patients may have overestimated their exact PA and exercise in the underlying questionnaires. With regard to the ENHANCE trial, PA was assessed by pedometers, but not considered when interpreting the results. In LeIKD, the telemedical approach, constant adaptation of exercise and feedback from experts may contribute to a different result with regard to metabolic and CVD risk factors. Further, the influence of exercise and PA will be evaluated.

Exercise

With regard to PF, we expect the LS group to be in favor compared to the usual care group, due to the constantly increasing, adapting combined exercise intervention, close monitoring and incentives to enhance daily PA. Every 1 ml/min/kg body weight increase in $\dot{V}O_2$peak is associated with a decrease in all-cause and cardiovascular mortality by 14-17% (n=2812 acute CIHD patients, median follow-up 4.9 years, males HR 0.83, 95% CI (0.80 – 0.86, p<0.001, females HR 0.86, 95% CI 0.80 – 0.93, p<0.001) (81). As in both males and females, diagnosis of T2DM (males HR females HR 2.70 95% CI 1.64-4.46, p<0.001) was significantly associated with increased risk for all cause and cardiovascular death (81), the LeIKD study contributes to further data on the importance of PF and its association to survival.

LeIKD combines aerobic and strength training over 12 months, accompanied by general instructions to increase daily steps and dietary advice, and therefore pursues the ESC guideline (2020) (31). The guidelines indicate a lack of evidence regarding detailed prescription on exercise intensity and volume, but mention training intensity to be more important in improved metabolic risk factor profiles. As demanded by practitioners (135), further shaping of exercise training recommendations in patients suffering from T2DM and CIHD is mandatory. Jacob et al. (2020) following Schwaab et al. (2020) mentions low to moderate training, compared to higher intensities, as potentially superior to ameliorate after-work out blood glucose levels in T2DM (135, 136). As addressed by Scherrenberg and Dendale (2019) (127) following the Position Paper from Kemps et al. (2019) regarding exercise in CVD and T2DM (128), exercise mode must be grounded on each individuals targets, capabilities and current health status. The Position Paper refers to three targets, which can be modified by exercise: metabolic (inflammation, dyslipidemia and glycemic control), functional (vascular function, muscle strength, blood pressure, CRF and autonomic regulation) and structural (body weight and composition) adaptations (128). Each of those dimensions can be addressed when aerobic and/ or resistance training is performed, with different volumes causing different responses, displaying a complex synergy of intensity, mode and volume of exercise (127, 128).

As displayed by this example, there is indeed a great need for further research and long-term data on exercise prescriptions in diseased populations. Following our analyzes, more data on exercise programming and preferences of patients will be available and foster scientific evidence about training mode, intensity and volume on clinical parameters.

Limitations

In LeIKD, a variety of technical skills is necessary to record data from home-based training, blood glucose monitoring and PA, which is then transferred via app to the study server. If patients are unable to use telemedicine or report issues on data safety, the study participation is therefore more difficult and challenging for them. The constant feedback and technical support are provided by the TUM, but still patients need to be willing to use telemedicine and conquer possible challenges.

We assume patients with limited technical background, experience and skills to be discouraged by the intervention. Still, patients of all technical skills levels are engaged to participate and may benefit from the intervention.

On top of that, only patients insured at the participating health insurance company will be randomized, which can be seen as a strength, but also bias to the evaluation. It allows the intervention to include a distinct health economics perspective, where additional data from other health insurances would broaden the data. Therefore, the LeIKD study may initiate other stakeholders for future research, which joins the evidence.

6. Conclusion

The purpose of the thesis was to address current evidence of PF and exercise in different stages of CVD and to evaluate their influence on risk factor profile, which was presented in the framework of three studies. Therefore, we hypothesized exercise and PF to be beneficial and affecting different parameters of risk factor profile in at risk and diseased cohorts.

Regarding the first study, the association between risk factors and PF status' is not mandatory in CCS short period after the cancer therapy, as non-significant results were found.

Prevention by PF and exercise in different stages of CVD is complex, as data from the DZHK ExMET study revealed. Despite the overall favorable effect on PF and MetS prevalence, no relation of exercise volume or intensity towards metabolic risk factors or PF could be drawn. As evidence from former studies suggest, different training regimens seem to target different risk factors, but we were not able to differentiate between exercise regimens, which again arouses further research need. Both results may ground on methodological aspects and study design, but it underlines the importance of well-designed, further studies to well address the needs of CVD patients.

The LeIKD study will be one of the well-designed, large RCTs, which will include patients at a late stage of CVD and T2DM, with telemedical approach and long-term intervention. This study

design includes a wholesome approach on lifestyle and will certainly contribute to further insights on e.g. telemedicine and health economics/ cost-effectiveness of exercise as a prevention strategy.

Regarding further research and practice, it is about extracting scientific evidence into policies and prevention strategies, which work in reality. So, what's the point of first action; where to start? Reviewing the pathway of risk factor exposition into disease and the investigated cohorts, the answer must be: start, wherever you are, and strive for a lower risk factor profile. Since health and risk can be seen as a continuum (14) and our results are partly controversial, we cannot set a "perfect match-threshold" to administer exercise like medication: we need to take account each individuals status quo, recommendations from guidelines and adapt continuously. This must include each individuals risk factor profile, preferences on exercise and comorbidities, to strive for a best-fit, lasting, motivating prevention strategy – even in later stages of CVD. Even if not every dimension of a risk factor profile can be significantly addressed or associated to exercise and PF, the overall beneficial effect speaks for itself and the thesis contributes to further evidence.

Up until now and further on, exercise and PF are key strategies to improve risk factor profile, as it should be promoted and addressed in every stage of CVD. This work underlines the importance and constant need for further evidence on a "never resting" field of research.

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Supplement

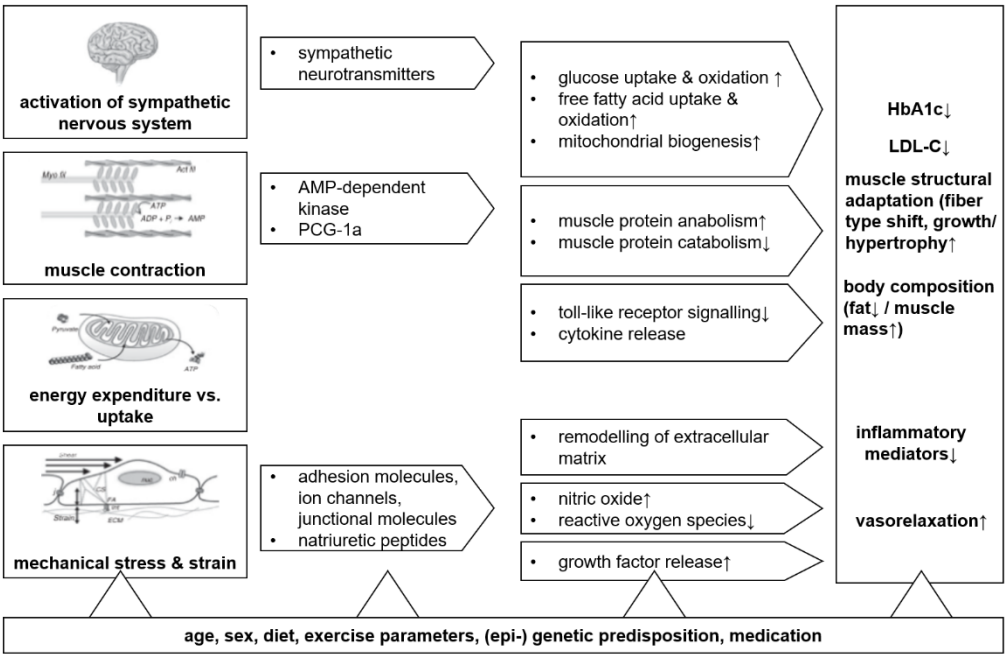

Figure 23 "Exercise-induced stimuli [...]. AMP: adenosine monophosphate, ATP: adenosine triphosphate, LDL: low-density lipoproteins." Figure and caption adapted and modified from Kraenkel et al. (2019) (44).

"Systemic inflammatory status is improved by reducing circulating levels of fatty acid metabolites and glycated end-products and altered paracrine spectra of myocytes and immune cells. Mechanical forces initiate muscle and vascular remodeling and vascular nitric oxide availability. Jointly, those mechanisms lead to reduced plasma levels of low-density lipoproteins, glucose and inflammatory mediators and to improved vascular function. Depending on the individuals age, sex, the parameters of the exercise program, genetic background and medication, each of the listed mechanisms may be modulated, affecting the individual effect of exercise." Kraenkel et al. (2019) (44)

Atherosclerosis and Plaque formation

LDL-C migrates to the Tunica intima, is being oxidized (oxLDL) and activates endothelial cells to express receptors for white blood cells on their surface (61). This leads to the adhesion of monocytes and T-helper cells on the receptors. As monocytes enter, they transform to macrophages which take up oxLDL; becoming foam cells (20, 61). Atherosclerosis is evident, if extracellular lipid pools and -cores appear, showing decreased cell density (plaques) (20).

Another proinflammatory process includes the expression of cytokines and reactive oxygen species by foam cells inside the plaque (61). Reactive oxygen species inactivate NO expression from endothelial cells, leading to increased oxidative stress (61).

During the apoptosis of foam cells, their lipid content and DNA is being released. This again attracks neutrophils and increases inflammation (61).

T-helper cells also act as major culprits to inflammation, due to their migration to the lipid core and receptor-increasing stimulation for further immune cells on the endothelial layer (61).

As the plaque progresses over time from fatty streaks to atheromas, foam cells promote the migration of smooth muscle cells from the Tunica media to the Tunica intima (smooth muscle cell proliferation/ SMCP) (61). SMCP triggers the synthesis of collagen and elastic fibers in the plaque, formatting to a fibrous cap as an outside layer over the lipid-rich core (20).

Taken together, atherosclerotic processes are determined by high inflammation, endothelial dysfunction (and therefore arterial stiffness) and a vicious cycle leading to CVD risk elevation (61).

Individual Contribution

MOSAIC

published manuscript:

von Korn, P., Müller, J., Quell, C., Tenius, L., Oberhoffer, R., Feuchtinger, T., & Schmid, I. (2019). Health-Related Physical Fitness and Arterial Stiffness in Childhood Cancer Survivors. Frontiers in Cardiovascular Medicine, 6(63). doi:10.3389/fcvm.2019.00063

Pia von Korn is the main author of the manuscript and was responsible for coordination, recruiting, examination and collecting data, analyzing and processing of the data and drafted the manuscript. Jan Mueller was responsible for conception and design of the study, analyzing and processing the data and gave important input for drafting and revising the manuscript. Christina Quell and Lisa Tenius coordinated examinations, C. Quell recruited and collected part of the data. Renate Oberhoffer and Tobias Feuchtinger gave important input for study design, drafting and revising the manuscript. Irene Schmid performed medical examinations, analyzed documented medication and gave important input for drafting and revising the manuscript.

Parts of this study were described in the master thesis of Christina Quell entitled “Motorische Leistungsfähigkeit und Gefäßsteifigkeit bei Kindern und Jugendlichen in der onkologischen Nachsorge“ and Pia von Korn „Motorische Leistungsfähigkeit, Körperzusammensetzung und Gefäßsteifigkeit bei Kindern und Jugendlichen nach Krebstherapie“.

DZHK ExMET

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Pia von Korn is the main author of the manuscript and was responsible for recruiting, examination, conducting the exercise intervention and collecting data, analyzing and processing of the data and drafted the manuscript. Katharina Lechner conducted the medical

assessments and supervised the manuscript writing, interpretation and analysis. Sophia Dinges assisted in laboratory examinations, where Nicolle Kraenkel was responsible for further laboratory assessments. Stephan Mueller reviewed the cardiopulmonary exercise tests analysis. Bernhard Haller reviewed and gave important input with regard to statistical analysis. Shelley Keating, Stephan Mueller, Sophia Dinges, Nicolle Kraenkel, André Duvinage, Johannes Scherr, Arnt Erik Tjønna, Ulrik Wisløff and Martin Halle assisted in interpreting the analysis, gave important input for drafting and critical revised the manuscript.

Results from the DZHK ExMET study, which are not presented here, were used for the PhD studies of Sylvia Kia, Berlin study site, under the supervision of Nicolle Kraenkel.

LeIKD

published manuscript:

von Korn, P., Sydow, H., Neubauer, S., Duvinage, A., Mocek, A., Dinges, S., Hackenberg, B., Weichenberger, M., Schoenfeld, J., Amelung, V., Mueller, S. and Halle, M. (2021). Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes (the LeIKD study): study protocol of a prospective, multicentre, randomised, controlled trial. *BMJ Open, 11*(2), e042818. doi:10.1136/bmjopen-2020-042818

Pia von Korn is the main author of the manuscript and drafted the manuscript. Stephan Mueller, Hanna Sydow, Anja Mocek, Sarah Neubauer and Martin Halle contributed to the writing process. All authors contributed to the complex conception and design or planned the analysis of the LeIKD study, and they critically revised the manuscript and study protocol.

Parts of the LeIKD study will be included in Felix Gass' future PhD Thesis entitled "Adherence to lifestyle interventions – the potential of telemedicine in preventive cardiology".

Affidavit

Eidesstattliche Erklärung

Ich erkläre an Eides statt, dass ich die bei der promotionsführenden Einrichtung
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der TUM zur Promotionsprüfung vorgelegte Arbeit mit dem Titel:
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in Fakultät für Sport- und Gesundheitswissenschaften, Lehrstuhl und Poliklinik für Präventive und Rehabilitative Sportmedizin
Fakultät, Institut, Lehrstuhl, Klinik, Krankenhaus, Abteilung

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München, 01.06.2021, Unterschrift

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
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Health-Related Physical Fitness and Arterial Stiffness in Childhood Cancer Survivors

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Introduction: Despite decreasing mortality in pediatric oncology as a result of standardized treatment protocols, the high number of functional and cardiovascular late sequelae due to anticarcinogenic therapy remains unchanged. The aim of this study was to further assess functional limitations in Health-related Physical Fitness (HRPF) and cardiovascular risk by means of markers of arterial stiffness in Childhood Cancer Survivors (CCS).

Materials and Methods: Between March 2016 and August 2017 a total of 92 CCS (Age 12.5 ± 4.2 years, 43 girls) were recruited from their routine follow-up outpatient visit. HRPF was assessed using five Fitnessgram® tasks. Pulse Wave Velocity (PWV) along with peripheral and central blood pressure were assessed using oscillometric measurements performed by Mobil-O-Graph. Z-scores were used to compare the test results either to German reference values or to a recent healthy reference cohort.

Results: In CCS, the HRPF was significantly reduced (z-score: −0.28 ± 1.01, $p = 0.011$) as compared to healthy peers. The peripheral Systolic Blood Pressure (pSBP) was significantly increased (z-score: 0.31 ± 1.11, $p = 0.017$) and the peripheral Diastolic Blood Pressure (pDBP) was decreased (z-score: −0.30 ± 1.25, $p = 0.040$), resulting in an increased pulse pressure. The PWV ($p = 0.649$) and cSBP ($p = 0.408$), were neither increased nor showed any association to HRPF.

Discussion: CCS showed functional limitations in HRPF and an increased pulse pressure, which acts as an early onset parameter of arterial stiffness. Both a low HRPF and impaired hemodynamics are independent cardiovascular risk factors and needs to be taken into consideration in tertiary prevention of CCS.

Keywords: health-related physical fitness, arterial stiffness, pulse wave velocity, childhood cancer survivors, cardiovascular health, prevention

INTRODUCTION

Due to improved anticarcinogenic treatment regimens (chemotherapy and radiation) more children and adolescents are surviving a cancer diagnosis (1). As a result, there are a growing number of long-term adult survivors with multiple co-morbidities who need appropriate aftercare management. In numbers, more than 70% of the childhood cancer survivors (CCS) suffer from chronic health conditions (2), which are often directly associated to anticarcinogenic therapy. Improved screening modalities can predict cardiovascular morbidity in the future and are therefore essential.

Health related physical fitness (HRPF) is an indicator for the development, growths, and lifestyle of children and adolescents, and it is significantly reduced after acute treatment phase in CCS (3). Physical activity remains reduced in CCS for years after diagnosis (4), and frailty, a complex syndrome of the elderly, can occur prematurely in CCS (5).

Nevertheless, especially cardiovascular issues are also of particular concern in CCS as even low-dose anthracyclines, a group of chemotherapy drugs, can damage cardiomyocytes in the heart and impair endothelial functioning of the vessels (6, 7). The relative risk for coronary heart disease is therefore 10.4 times higher in CCS as compared to healthy siblings, and overall cardiovascular morbidity and mortality is seven-fold higher in CCS as compared to the normal population (8). Arterial stiffness, the ability of the vessels to expand and recoil, is a parameter for early cardiovascular aging and has been reported to be significantly higher in CCS than in the normal population (9, 10).

Previous studies outlined the beneficial association of HRPF and aerobic capacity to arterial vessel properties (11–13), but there is a lack of evidence-based data for CCS. This study therefore investigates functional outcomes in CCS by means of HRPF and arterial stiffness to determine lifelong cardiovascular risk factors.

PATIENTS AND METHODS

Study Subjects

The study was conducted over two examination periods (March to June 2016 and February to August 2017) at the Department of Pediatric Hematology and Oncology in the Dr. von Hauner University Children's Hospital in Munich. Eligibility criteria were oncologic disease, current age of 6–20 years, absence of fever and acute infections, no mental retardation and the ability to write and communicate in German or English language without assistance. All participants could walk and do physical exercises without assistance. Physicians had to confirm the patients study participation. The study protocol (project number 724-16) was approved by the local Ludwig Maximilian University ethical board. Participation was voluntary and informed consent was obtained from the patients and parents after provision of oral and written information about the study procedures.

In total, 92 CCS (43 girls, age 12.5 ± 4.1 years) were examined for their HRPF and arterial stiffness.

The mean age at diagnosis was 8.8 ± 4.8 years and 54 of the patients were initially diagnosed with Leukemia, 28 with solid tumors and 10 with Lymphomas. This roughly correspond to the general prevalence of cancer diagnosis in children (1). Eighty-nine children were treated with chemotherapy, and 73 received anthracyclines with a mean dosage of 225 ± 83 mg/m² body surface area. Ten children received radiotherapy where the mean radiation dosage was 28.4 ± 19.9 Gray (gy). Four Children were exposed to both chemotherapy including anthracyclines (248.0 ± 89.9 mg/m²), and radiation (18.4 ± 8.5 gy). Finally, three Children received neither chemotherapy nor radiotherapy (treated with surgery only or watch-and-wait).

All children were recruited during their regular post-acute treatment phase outpatient visit, 3.6 ± 2.8 years after primary cancer diagnosis.

Anamnestic and Anthropometric Data

Participant's anthropometric data like height (System Dr. Keller I, Längenmesstechnik GmbH, Limbach-Oberfrohna, Germany) and weight (SECA GmbH & Co KG, Hamburg, Germany) were assessed by the study investigator. BMI was calculated by dividing weight in kilograms (kg) by the height squared in meters. Reference values for BMI in children were drawn from the German reference values from Kromeyer-Hauschild et al. (14).

Anamnestic data were obtained from the patients file (original cancer disease and date of diagnosis, treatment regimens, comorbidities). A physician retrospectively computed the amount of administered anthracyclines (mg/m² body surface) and mediastinal irradiation (Gray, gy).

Health-Related Physical Fitness (HRPF)

The Fitnessgram® is a valid and reliable method to assess HRPF (15). The test battery consists of five motor tasks:

- maximum repetitions in Push-Ups (upper body strength and muscular endurance)
- maximum repetitions in Curl-Ups (abdominal strength and muscular endurance)
- Sit-and-Reach (hamstring flexibility) recorded separately on both sides
- Shoulder Stretch (upper arm and shoulder girdle flexibility) recorded separately on both sides
- trunk extensor strength and flexibility was assessed with the trunk lift (prone position, lifting Shoulders as far from the ground as possible) which was performed twice, but just the better value was recorded.

One valid Push-Up counted when the body was lifted and lowered in a prone position with an elbow flexion ≤90°. Curl-Ups are complete upper body elevations out of a supine position, without the use of the arms (knees are flexed, feet are flat on the floor). Sit-and-reach was assessed in a sitting position, one leg straight and the other one flexed, as distance from fingertips to toes at maximal stretch. For Shoulder Stretch, the participants had to stretch one hand up the back and the other hand from above down the back. The distance between both hands was measured. For statistical analysis the mean value of both sides was calculated. A detailed description of these tasks is available in the online supplement of our recent article (16).

For all of the five tasks, individual z-scores (standard deviation-scores) were calculated using data from the "Sternstunden" cohort of 983 children (498 girls), with a mean age of 11.8 ± 2.3 years. This project was designed to estimate several health outcomes in healthy children in multiple Bavarian schools.

Hemodynamics and Arterial Stiffness

Blood pressure and arterial stiffness were assessed after 5 min rest in the supine position with a single measurement on the left upper arm using the oscillometric Mobil-O-Graph (I.E.M. GmbH, Stolberg, Germany and HMS Client-Server Version 4.7). Cuff size was adjusted to the upper arm circumference. Based on the recorded brachial pulse, central Systolic Blood Pressure (cSBP) and Pulse Wave Velocity (PWV) were indirectly calculated with the ARCSolver Algorithm.

All raw values were also transformed into z-scores according to established German References. For peripheral systolic and diastolic blood pressure the national German cohort (Kiggs Study) (17) values were used and for PWV, central systolic and diastolic blood pressure the values from Elmenhorst et al. (18) were taken.

Data Analyses

All descriptive data was expressed as mean values and standard deviation (mean ± SD) or as absolute numbers and percentages if appropriate.

BMI, SBP, DBP, cSBP, PWV were expressed in terms of standard deviation scores (z-scores) according to the references mentioned above. The LMS values and z-scores for the five HRPF motor tasks were smoothed out with a Box-Cox-transformation using R-Studio (version 0.99.879, RStudio Inc.) and the module extensions gamlss (version 3.4-8) and AGD (version 0.34). The total HRPF-score represents the mean of the five motor tasks. Normal distribution of the primary outcome parameter (HRPF z-score) was proven with a Kolmogorov–Smirnov test.

For statistical analysis, a one sample t-test with test value "0" was conducted to asses significant differences in z-scores from the appropriate reference. Pearson correlation was used to calculate possible associations between HRPF and arterial stiffness. Unpaired Student's t-test were performed to assess differences in the 73 CCS that received anthracycline-containing chemotherapy to those who did not.

Data analysis was performed using IBM SPSS 23.0 (IBM Corporation, Armonk, NY, USA). $P < 0.05$ were considered to be significant.

RESULTS

CCS showed significant reduced HRPF (z-score: −0.28 ± 1.01, $p = 0.011$) in comparison to healthy peers (**Table 1**). Most prominent were reductions in flexibility by means of sit-and-reach (z-score: −0.32 ± 1.35, $p = 0.032$), shoulder stretch (z-score: −0.58 ± 1.44, $p < 0.001$), and trunk lift (z-score: −0.45 ± 1.69, $p = 0.014$). 20 (21.7%) of the CCS showed a reduction in HRPF z-scores < 1 standard deviation.

TABLE 1 | Study subjects.

	Childhood cancer survivors ($n = 92$)	
Sex (girls)	43 (47%)	
Age (years)	12.5 ± 4.2	
Height (cm)	151.0 ± 21.3	
Weight (kg)	46.3 ± 18.3	
	CCS ($n = 92$)	***p*-value**
BMI z-score*	0.21 ± 1.15	0.102
HRPF (z-score)****	−0.28 ± 1.01	**0.011**
Curl-ups (z-score)	0.22 ± 1.39	0.152
Push-ups (z-score)	−0.09 ± 0.98	0.415
Sit and Reach (z-score)	−0.32 ± 1.35	**0.032**
Shoulder Stretch (z-score)	−0.58 ± 1.44	**<0.001**
Trunk Lift (z-score)	−0.45 ± 1.69	**0.014**
Peripheral SBP (z-score)**	0.31 ± 1.11	**0.017**
Peripheral DBP (z-score)**	−0.30 ± 1.25	**0.040**
Central SBP (z-score)***	0.12 ± 1.28	0.408
PWV (z-score)*****	0.07 ± 1.40	0.649

BMI, Body-Mass-Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, Pulse Wave velocity; HRPF, Health-related Physical Fitness.
**Comparison to the German reference from Kromeyer-Hauschild et al. (14).*
***Comparison to the German reference from the German KIGGS Study (17).*
****Comparison to the German reference from the Elmenhorst et al. (18).*
*****Comparison to unpublished data of 916 healthy German children (see section Patients and Methods).*

The peripheral SBP of CCS was increased (z-score: 0.31 ± 1.11, $p = 0.017$) and the peripheral DBP decreased (z-score: −0.30 ± 1.25, $p = 0.040$), resulting in an increased blood pressure amplitude (pulse pressure). However, the more direct measures of arterial stiffness from the pulse wave analysis; PWV ($p = 0.649$) and central SBP ($p = 0.408$), were not increased.

Moreover, higher HRPF scores were neither associated with lower PWV ($r = 0.004$, $p = 0.972$) or cSBP ($r = 0.001$, $p = 0.998$), nor beneficially associated with peripheral blood pressure.

There was no significant difference in any of the measured functional parameters when the 73 patients that received anthracycline-containing chemotherapy were compared to those that did not receive cardiotoxic therapy.

DISCUSSION

This study showed impairments in HRPF in CCS. It also demonstrated an increased pulse pressure as a result of increased pSBP and decreased pDBP in CCS. These findings may result from subtle early changes of the arterial wall stiffness, which cannot yet be detected by the arterial stiffness parameters PWV and cSBP. Both of which were still within the expected range in our study.

Pioneering studies in CCS from the end of the last millennium already outlined deficits in fine and gross motor skills during and after cessation of cancer treatment (19–21). They also claimed that these limitations were linked to the neurotoxic effects of anthracycline (vincristine). However, these limitations were

not only limited to motor skills. Physical movement skills like balance, jumping, running as well as muscle strength were also found to be impaired (22, 23). Therefore, the results of deficits in HRPF line up with these previously noted functional and physical impairments (24). The reasons for such impairments are manifold and range from drug neurotoxicity to developmental delay during long periods of hospital admission, sedentary behavior, limited opportunity for active play and overprotection (3, 20, 25). Unfortunately, limitations in motor ability have shown to be a predictor of lower physical activity (25). These low levels of physical activity tend to persist into adulthood such that and CCS are more likely to be inactive and unhealthy adults. As a result their often already increased cardiovascular burden is further reinforced by their unfavorable lifestyle preferences (26). Thus, the establishment of a healthy and active lifestyle is an important treatment goal in order to improve long-term morbidity in these patients (26).

While inactivity is a predictor of cardiovascular morbidity and mortality *per se* (27), reduced physical activity also leads to diminished physical fitness. Both parameters have been shown to be strongly associated with cancer mortality in adults (28) and also improving both, must be part of a successful rehabilitation programs in CCS. It is unlikely that these limitations will normalize without treatment, although Hartman and colleagues reported on normalization in HRPF in CCS 5 years after treatment (4).

- Our finding of an elevation of the pSBP in CCS demonstrates that early signs of chemotherapy-induced cardiovascular damage can already be detected in early childhood. Our results are consistent with recent studies which have demonstrated elevated pSBPs and (pre) hypertension as late complications of cancer treatment regimens (29, 30).
- In addition, the significantly decreased pDBP in combination with the increased pSBP results in a high pulse pressure, which is a known risk factor for CVD and is mentioned in the current guidelines for arterial hypertension (31, 32). In the elderly, every 10 mmHg increase in pulse pressure increases the risk of cardiovascular events by 13–22% (33). Unfortunately, this has not being translated into z-scores. Increased pulse pressure has also been reported in male acute lymphoblastic leukemia survivors by van Waas et al. (29).

Surprisingly, arterial stiffness (as measured by PWV and cSBP), an early, subtle marker for CVD (31), was still within the normal range according to these measurements in our CCS cohort. This is even though a higher risk for early vascular (endothelial damage/ higher arterial stiffness) and biological aging has previously been reported for such patients (9, 10). The major culprits involved in this premature aging are anthracyclines. These chemotherapy drugs have both cytotoxic and cardiotoxic effects (34). Two research groups clearly state the influence of anthracyclines on increased arterial stiffness and impaired endothelial function (9, 10, 35). Another paper reported only a significant influence of radiation, but not chemotherapy, on arterial stiffness parameters (36). Our findings are in line with the results from the SurFF program. This program only found a significant increase in the PWV in CCS older than 18 years as compared to controls. They, like us, did not find a significant increase in this measurement in children. Therefore, the authors suggested an exponential worsening of the PWV with increasing age in CCS (37). However, all these results have to be handled with caution because our current knowledge about the detection of markers for early subclinical cardiovascular damage and their changes over time in CCS is complicated as a result of a number of factors including: heterogeneous study groups, variation in applied methods, use of differing surrogates for measuring arterial stiffness, and varying lifestyle habits between the CCS.

From the hemodynamic point of view, only the increased pulse pressure possibly reveals early vascular aging in our CCS cohort, whereas the limitations in HRPF were manifest. Regular physical activity has a pivotal role to play in the prevention of both of these factors. Not only does it improve the HRPF, it also improves endothelial function and NO synthesis by the creation of shear stress. Several studies underline this theory and the importance of physical activity as part of successful rehabilitation (3, 4). However, this is a multifactorial approach where physicians, physiotherapists, psychologists and family have to work together.

CONCLUSION

In accordance with previous studies we found the HRPF to be slightly impaired in CCS. We also found the pulse pressure, but not the PWV, to be elevated in CCS. This combination of reduced HRPF and impaired vascular parameters may raises the likelihood of an increased long-term CVD risk in these patients. This should be taken into consideration when planning tertiary prevention measures for CCS.

LIMITATIONS

The cohort presented in this study differ widely in number of ways including cancer types, treatment regimens and doses used, age at diagnosis, and time since diagnosis. However, the approach used to assess the questions asked seems reasonable when taking into account recent studies/reviews, which also report similar findings in similarly heterogeneous CCS cohorts (38). Patients were tested under non-fasting conditions what might have influence on vascular assessment.

DATA AVAILABILITY

The datasets for this study will not be made publicly available because Data safety and protection act.

ETHICS STATEMENT

The study protocol (project number 724-16) was approved by the local Ludwig Maximilian University ethical board.

AUTHOR CONTRIBUTIONS

PvK was responsible for coordination, examination and collecting data, analyzing and processing of the data and

drafted the manuscript. JM was responsible for conception and design of the study, analyzing and processing the data and gave important input for drafting and revising the manuscript. CQ and LT coordinated examinations and collected data. RO and TF gave important input for drafting and revising the manuscript. IS performed medical examinations and gave important input for drafting and revising the manuscript. All authors have read and approved the final version of the manuscript.

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The Effect of Exercise Intensity and Volume on Metabolic Phenotype in Patients with Metabolic Syndrome: A Randomized Controlled Trial

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Abstract

Background: Moderate intensity continuous training (MICT) ameliorates dysmetabolism in patients with metabolic syndrome (MetS). The impact of low- (1HIIT) versus high-volume high-intensity interval training (4HIIT) versus MICT on central adiposity, insulin resistance, and atherogenic dyslipidemia in patients with MetS has not yet been reported.

Methods: Twenty-nine patients with MetS according to International Diabetes Federation criteria (nine females, age 61 ± 5 years, body mass index 31.1 ± 3.7 kg/m^2, waist circumference (WC) ♀ 102.2 ± 10.6 cm, ♂ 108.5 ± 8.6 cm) were randomized (1:1:1) to 16 weeks of (1) MICT (5 × 30 min/week, 35%–50% heart rate reserve (HRR), (2) 1HIIT (3 × 17 min/week incl. 4 min @80%–90% HRR), and (3) 4HIIT (3 × 38 min/week incl. 4 × 4 min @80%–90% HRR). Peak oxygen uptake ($\dot{V}O_{2peak}$), WC and anthropometric/metabolic indices indicative of MetS, fasting glucose/insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), dyslipidemia, and respiratory exchange ratio (RER) at warm-up were quantified at baseline and study completion. Analysis of variance and paired t tests were used for statistical analysis. Analyses were performed after checking for parametric distribution.

Results: There were no significant differences between groups in waist-to-height ratio (♀: Δ −0.10 ± −0.05, ♂: Δ −0.08 ± −0.06, $P = 0.916$), WC (♀: Δ −1.4 ± −0.1 cm, ♂: Δ 0.1 ± 0.9 cm, $P = 0.590$), fasting glucose (Δ −1.18 ± 16.7 μU/mL, $P = 0.773$), fasting insulin (Δ 0.76 ± 13.4 μU/mL, $P = 0.509$), HOMA-IR (Δ 0.55 ± 4.1, $P = 0.158$), atherogenic dyslipidemia [triglycerides (TAG) Δ −10.1 ± 46.9 mg/dL, $P = 0.468$, high-density lipoprotein cholesterol (HDL-C) Δ 1.5 ± 5.4, $P = 0.665$, TAG/HDL-C −0.19 ± 1.3, $P = 0.502$], $\dot{V}O_{2peak}$ ($P = 0.999$), or RER ($P = 0.842$). In the entire group, waist-to-height-ratio and $\dot{V}O_{2peak}$ significantly improved by a clinically meaningful amount (Δ 2.7 ± 0.9 mL/min/kg; $P < 0.001$) and RER at warm-up significantly decreased (Δ −0.03 ± 0.06, $P = 0.039$).

Conclusion: In patients with MetS, there was no significant difference between HIIT, irrespective of volume, to MICT for improving exercise capacity or metabolic health.

Keywords: exercise training, high intensity interval training, visceral adiposity, atherogenic dyslipidemia, metabolic syndrome, free fatty acid oxidation

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Introduction

METABOLIC SYNDROME (METS) IS an accumulation of acquired cardiometabolic traits, including elevated waist circumference (WC), elevated levels of triglycerides (TAG) and low levels of high-density lipoprotein cholesterol (HDL-C), fasting hyperglycemia, and elevated blood pressure. MetS has reached pandemic proportions and poses a major challenge for health systems worldwide.[1] Its metabolic signature is recognized as a major and prevalent risk factor for atherosclerotic cardiovascular disease (ASCVD) by major bodies, including the World Health Organization,[2] the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III),[3] and the International Diabetes Federation (IDF).[4]

Traditional moderate intensity continuous exercise training (MICT) ameliorates metabolic control and reduces ASCVD risk,[5] including in the subgroup of patients living with prediabetes, diabetes,[6] and dyslipidemia.[7] It is thus recommended as a principle therapy for risk factor management by major expert bodies and should be included in the care paths for the management of these diseases.[6,7] Exercise training instigates a coordinated response of favorable metabolic adaptations linked to cardiometabolic health[8] and has therefore been endorsed as an effective and safe strategy for prevention and management of cardiometabolic risk factors and global ASCVD risk.[5] Regular aerobic exercise has been shown to reduce visceral adiposity[9,10] and favorably impact glucose and lipid metabolism. It is now widely accepted that central adiposity—as a marker of "dysfunctional adipose tissue"—is one of the most prevalent trait associated with ASCVD risk and therefore of high clinical importance.[1,11] The accumulation of dysfunctional, ectopic adipose tissue in the abdominal cavity and in visceral organs such as liver, pancreas, pericardium, and skeletal muscle, instigates a coordinated set of local and systemic pathophysiological events that significantly elevate ASCVD risk.[12] These include hepatic overproduction of triglyceride-rich very low-density lipoproteins (VLDL1) and increased peripheral HDL-C catabolism (*i.e.*, atherogenic dyslipidemia), increased hepatic and muscular insulin resistance, and oxidative stress, among other factors.[13,14]

Due to a less robust evidence base for HIIT versus MICT, guidelines continue to recommend the latter for risk factor management in patients living with prediabetes, diabetes,[6] and dyslipidemia.[7] This underpins the need for trials comparing the metabolic adaptations of MICT and HIIT in patients with MetS.

The aim of this study was to evaluate the effect of exercise intensity (MICT vs. HIIT) and volume [high-intensity interval training with low volume (1HIIT) vs. high-intensity interval training with high volume (4HIIT)] on the expression of central adiposity, insulin resistance, and atherogenic dyslipidemia in patients with MetS. Further to that, respiratory exchange ratio (RER) at warm-up as a surrogate for energy substrate partitioning/free fatty acid oxidation was measured.

Methods

This study is a substudy from the prospective randomized controlled ExMET trial (ClinicalTrials.gov identifier: NCT01676870), which aimed to evaluate the optimal exercise dose and feasibility in patients living with MetS, presenting data collected at the Munich site. The study protocol has been previously published.[15]

Study design and population

Men and women aged 55–70 years were eligible to participate in the study if they had central adiposity (elevated WC ♀ ≥80 cm, ♂ ≥94 cm) and at least two further criteria of MetS according to IDF criteria.[4] All participants were asked for detailed medical history.

Patients were randomized (1:1:1) after giving informed consent to 16 weeks of (1) moderate intensity continuous training (MICT, 5×30 min/week, 35–50% heart rate reserve (HRR = HR_{max} − HR_{rest})), (2) 1HIIT (3×17 min/week incl. 4 min @80%–90% HRR), and (3) 4HIIT (3×38 min/week incl. 4×4 min @80%–90% HRR). HIIT regimens started with a 10-min warm-up at 35%–50% HRR followed by interval phase of 4 min high interval at 80%–90% HRR with 3 min low interval at 35%–50% HRR, repeated once in 1HIIT and four times in 4HIIT. All training sessions were supervised by exercise scientists. Heart rate was monitored continuously (Polar, Kempele, Finland). Rate of perceived exertion was assessed by BORG scale (aiming for low interval 11–13, high interval 15–17).

Peak oxygen uptake ($\dot{V}O_{2peak}$), RER at warm-up, WC, fasting glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and markers for atherogenic dyslipidemia (TAG, HDL-C, TAG/HDL-C ratio) were quantified at baseline and upon study completion, as described in detail below.

Laboratory measurements

Venous blood samples were drawn under standardized conditions from an antecubital vein after at least 12 hr of fasting (just water, no caffeine, no meal), 24 hr absence from alcohol and vigorous exercise, and 10 min of rest in supine position. Medication (if any) was taken as the usual time before testing. Samples were analyzed for fasting glucose, fasting insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, and TAG. HOMA-IR was calculated as follows:

HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dL)/405.

The TAG/HDL-C ratio is the quotient of TAG and HDL-C.

The waist-to-height ratio is the quotient of WC and height.

Cardiopulmonary exercise testing, anthropometry, and other variables

Cardiopulmonary exercise testing (CPET) (Cortex, Leipzig, Germany) was performed by experienced medical staff on a stationary cycle ergometer (ergoselect 100, ergoline GmbH, Bitz, Germany). Starting with a 3 min resting period and 3 min warm-up at 20 W, we used a personalized ramp protocol to reach the predicted maximal load (adjusted to sex, age, height, and weight)[16] after 10 min. Breath-by-breath CPET data were averaged over 10 sec. First ventilatory threshold (VT1) was set using the V-slope method.[17] $\dot{V}O_{2peak}$ was defined as the highest 30 sec average before peak exercise. RER at warm-up was calculated as the average of the last 30 sec of the warm-up period.

Height and weight were measured in light clothing according to standard techniques. WC, as a surrogate for central adiposity, was measured on bare skin at the widest circumference of the waist between upper hip bone and rib cage. Waist-to-height ratio, an anthropometric index, which has been shown to be superior in informing cardiovascular risk stratification compared to body mass index (BMI) and/or WC alone, is defined as the quotient of WC and height.[18–20] Hypertriglyceridemic waist phenotype (HTW phenotype), a metabolic index that has been linked to the presence of high-risk atherosclerosis, is defined by the presence of both elevated TAG and WC.[21,22] Blood pressure was measured in supine position after 2 min of resting. Furthermore, a 12-channel-resting electrocardiography was performed. Pulse wave velocity for assessing arterial stiffness was measured by Mobil-O-Graph (I.E.M. GmbH, Stolberg, Germany and HMS Client-Server Version 4.7).

Ethics

This trial complies with the Declaration of Helsinki and principles of Good Clinical Practice. The responsible Ethics Committee approved the study protocol of ExMET(Regional Committee for Medical Research Ethics [REK 2011/2150]). All participants gave written informed consent before undergoing any study-related procedures.

Statistical analysis

Statistical analysis was performed using paired *t*-test (main effect of time) and repeated measurement analysis of variance (including group-by-time-interaction). Analysis of covariance was performed to additionally control for covariates (metformin, insulin, and statin medication). Pearson's correlation coefficient (r) was used to quantify strength of association between continuous variables. All tests were performed two-sided at a significance level of $\alpha = 5\%$. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY).

Results

Baseline characteristics are depicted in Tables 1 and 2. Twenty-nine patients with MetS aged 61 ± 5 years were included into the study (nine females, BMI 31.1 ± 3.6 kg/m^2, WC ♀ 102.2 ± 10.6 cm, ♂ 108.5 ± 8.6 cm, waist-to-height ratio ♀ 0.62 ± 0.07, ♂ 0.62 ± 0.06) with no significant differences between groups. As depicted in Fig. 1, one patient was lost to follow-up due to personal reasons not related to the exercise intervention.

Adherence (attendance) to the exercise intervention was 82.3% ± 16% over 16 weeks, with no significant differences between groups (MICT 82.3% ± 8.9%, 1HIIT 85.4% ± 11.1%, 4HIIT 77.3% ± 28.2%, $P = 0.605$).

$\dot{V}O_{2peak}$ significantly improved from baseline to study completion for the whole study population (from 22.7 ± 6.1 mL/min/kg to 25.4 ± 7.0 mL/min/kg; $P = 0.001$), with no significant differences between the groups (MICT Δ 2.3 ± 3.7 mL/min/kg, 1HIIT Δ 2.2 ± 3.7 mL/min/kg, 4HIIT Δ 2.4 ± 2.4 mL/min/kg, $P = 0.999$). $\dot{V}O_2$/kg at VT1 changed significantly in the whole study population (from 13.7 ± 3.6 mL/min/kg to 16.4 ± 4.2 mL/min/kg; $P < 0.001$), with no significant differences between the groups (MICT Δ 2.3 ± 1.9 mL/min/kg, 1HIIT Δ 2.7 ± 2.4 mL/min/kg, 4HIIT Δ 2.8 ± 2.7 mL/min/kg, $P = 0.883$). The submaximal and maximal load significantly improved in the whole study population (Watts at VT1: from 95 ± 32 to 117 ± 51 W, $P = 0.001$, Watts at $\dot{V}O_{2peak}$: from 183 ± 56 to 195 ± 59 W, $P = 0.003$), with no significant differences between the groups (Watts at VT1: MICT Δ 16 ± 42 W, 1HIIT Δ 23 ± 22 W, 4HIIT Δ 28 ± 24 W, $P = 0.732$/W at $\dot{V}O_{2peak}$: MICT Δ 5 ± 17 W, 1HIIT Δ 17 ± 21 W, 4HIIT Δ 20 ± 22 W, $P = 0.235$).

RER at warm-up significantly decreased in the whole study population (0.83 ± 0.1 to 0.81 ± 0.1, $P = 0.039$), with no significant differences between the groups (MICT Δ 0 ± 0.1, 1HIIT Δ 0 ± 1, 4HIIT Δ 0 ± .1, $P = 0.842$).

The waist-to-height ratio significantly decreased (0.62 ± 0.06 to 0.53 ± 0.06, $P < 0.001$), with no significant differences between the groups (MICT Δ –0.09 ± 0.03, 1HIIT Δ –0.08 ± 0.07, 4HIIT Δ –0.09 ± 0.06, $P = 0.916$). We did not observe significant changes or differences in other metabolic or anthropometric indices indicative of metabolic phenotype, including WC, HTW phenotype, fasting glucose, fasting insulin, HOMA-IR, or expression of atherogenic dyslipidemia (TAG, HDL-C, TAG/HDL-C ratio) following the intervention (Tables 1 and 2). Adjustment for medication did not alter our findings as depicted in Table 3.

As outlined in Table 1, of the 29 patients with MetS at the beginning of the training intervention, upon study completion, only 21 patients fulfilled the criteria for MetS according to the IDF definition[4] and the number of patients with HTW phenotype was reduced by one-fourth.

BMI showed the largest change in the 1HIIT group (–0.40 ± 1.08 kg/m^2, $P = 0.269$), whereas the greatest WC and TAG change was found in the 4HIIT group (WC –1.6 ± 4.6 cm, $P = 0.403$, TAG –6 ± 46 mg/dL, $P = 0.743$).

No significant correlation between RER at warm-up and markers of atherogenic dyslipidemia were observed (TAG Pearson's $r = 0.123$, $P = 0.557$, HDL-C $r = 0.112$, $P = 0.595$, TAG/HDL-C ratio $r = 0.049$, $P = 0.816$, HOMA-IR $r = 0.405$, $P = 0.055$).

TABLE 1. BASELINE CHARACTERISTICS

	Pre (n = 29)	*Post* (n = 28)
Age (years)	61 ± 5	
Sex (male/female)	20/9	19/9
Metabolic syndrome (*n*)	29	21
Hypertriglyceridemic waist phenotype (*n*)	12	9
Medication (*n*)		
Metformin	3	3
Insulin	2	2
Statin	14	11
Beta blocker	8	8
Angiotensin receptor blocker	15	16
Calcium antagonist	7	6
Acetylsalicylic acid	9	8
Medical history (*n*)		
History of myocardial infarction	4	
History of type 2 diabetes mellitus	5	
History of coronary artery bypass	2	
History of percutaneous coronary intervention	6	
History of atrial fibrillation	1	
History of hypertension	22	
History of smoking	16	

TABLE 2. OUTCOMES

	All			1HIIT	4HIIT	MICT	
	Pre (n=29) *Mean±SD*	*Post* (n=28) *Mean±SD*	*P value (time)*	*Delta±SD* (n=10)	*Delta±SD* (n=7)	*Delta±SD* (n=11)	*P value (group×time)*
BMI (kg/m^2)	31.1±3.7	30.8±3.8	0.121	−0.40±1.08	−0.21±0.88	0.24±0.97	0.903
Body fat[a] (%)	28.4±5.3	27.8±6.1	0.137	−0.3±3.7	−0.3±2.3	−1.6±2.2	0.518
WC (cm)	106.5±9.6	106.1±10.3	0.506	0.7±5.4	−1.6±4.6	−1.1±4.4	0.590
WHtR	0.62±0.06	0.53±0.06	<0.001	−0.08±0.07	−0.09±0.06	−0.09±0.03	0.916
Resting HR (bpm)	68±13	66±12	0.359	−4±11	0±9	0±9	0.671
sys BP (mmHg)	134±13	133±13	0.766	6±12	−4±9	−5±13	0.107
dia BP (mmHg)	85±9	83±9	0.269	−1±8	−4±15	−2±9	0.881
PWV (m/s)	8.8±0.8	8.7±0.9	0.626	−0.1±0.2	−0.1±0.4	0.3±0.3	0.076
TAG (mg/dL)	141.7±53.8	131.8±60.7	0.291	−4,7±63.1	−29.3±25.7	−2.4±42.2	0.468
HDL-C (mg/dL)	50.0±10.5	51.4±11.8	0.177	1.3±6.0	0.1±5.0	2.6±5.4	0.665
TAG/HDL-C ratio	3.0±1.4	2.8±1.8	0.446	0±1.9	−0.7±0.6	0±1	0.502
LDL-C (mg/dL)	129.4±36.5	131.3±35.8	0.595	−10.5±12.9	14.1±29.2	6.6±22.4	0.067
Total cholesterol (mg/dL)	195.2±44.1	204.5±46.9	0.177	1.9±38.3	28.9±41.5	5.0±33.6	0.310
Fasting glucose (mg/dL)	112.2±19.8	111.3±21.3	0.712	0.8±11.2	0.6±9.8	−4.1±23.8	0.773
Fasting insulin (µU/mL)	12.8±7.6	14.5±16.5	0.551	−4.5±19.4	−3.1±8.4	−0.17±8.8	0.509
Hb	15.1±1	14.8±1.1	0.045*	0±0.5	−0.6±1.1	−0.3±0.7	0.326
HOMA-IR	3.7±2.5	4.2±5.1	0.586	2.4±6	1.2±3	−1.1±1.9	0.158
$\dot{V}O_2$peak (mL/min/kg)	22.7±6.1	25.4±7	0.001**	2.2±3.7	2.2±2.4	2.3±3.7	0.999
RER at warm-up	0.83±0.1	0.81±0.1	0.039*	0±0.1	0±0.1	0±0.1	0.842

Means±standard deviation.
[a]Seven-site skin-fold caliper method.
*$P<0.05$, **$P<0.01$.
1HIIT, high-intensity interval training with low volume; 4HIIT, high-intensity interval training with high volume; BMI, body mass index; dia BP, diastolic blood pressure; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HR, resting heart rate; LDL-C, low-density lipoprotein cholesterol; MICT, moderate intensity continuous training; PWV, pulse wave velocity; RER, respiratory exchange ratio; resting sys BP, systolic blood pressure; SD, standard deviation; TAG, triglycerides; $\dot{V}O_{2peak}$, peak oxygen uptake; WC, waist circumference; WHtR, waist-to-height ratio.

Discussion

This study examined the effects of exercise volume and intensity on anthropometric indices (WC, waist-to-height ratio and HTW phenotype) and biochemical markers indicative of metabolic function/the central adiposity phenotype in patients with MetS.

Across the entire study population, cardiorespiratory fitness and submaximal and maximal load improved significantly by a clinically meaningful amount. Waist-to-height ratio, an anthropometric index, which has been shown to add predictive value in informing cardiovascular risk stratification compared to BMI and/or WC alone,[18–20] significantly decreased across the entire study population. This indicates

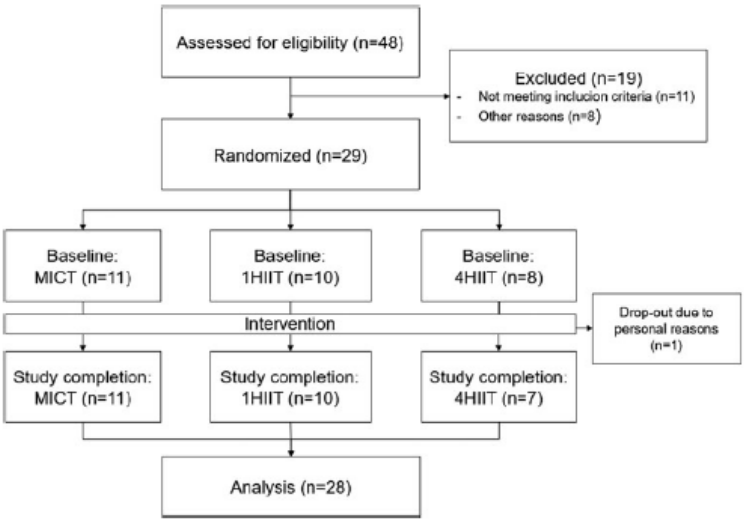

FIG. 1. Consort flowchart. 1HIIT, high-intensity interval training with low volume; 4HIIT, high-intensity interval training with high volume; MICT, moderate intensity continuous training.

TABLE 3. OUTCOMES ADJUSTED FOR BASELINE MEDICATION

	1HIIT	4HIIT	MICT	P value
	Delta ± SD (n = 10)	Delta ± SD (n = 7)	Delta ± SD (n = 11)	(group × time)
Adjusted for metformin, insulin, and statins				
TAG (mg/dL)	−1.7 ± 17.1	−34.6 ± 20.5	−1.4 ± 15.1	0.416
TAG/HDL-C ratio	0.1 ± 0.5	−0.8 ± 0.6	0 ± 0.5	0.485
Fasting glucose (mg/dL)	2.4 ± 5.6	−3.7 ± 7.1	−2.9 ± 5.3	0.733
Fasting insulin (μU/mL)	5.2 ± 4.5	−4.8 ± 5.7	0.3 ± 4.3	0.413
HOMA-IR	2.5 ± 1.5	1.1 ± 1.7	−1.1 ± 1.2	0.173
Adjusted for statins				
LDL-C (mg/dL)	−9.2 ± 6.7	11.4 ± 8.1	7.1 ± 6.3	0.115
Total cholesterol (mg/dL)	1.7 ± 12.1	29.3 ± 14.7	4.9 ± 11.5	0.332

an overall favorable effect of the training intervention on cardiometabolic risk. Training regimens (HIIT/MICT) did not differ significantly in improving the aforementioned parameters.

$\dot{V}O_{2peak}$, a surrogate for cardiorespiratory fitness, is a strong prognostic marker for cardiovascular morbidity and mortality across different BMI groups. It is therefore increasingly recognized as an independent treatment target.[5] In our population, $\dot{V}O_{2peak}$ significantly improved from baseline to study completion in the whole study population by a clinically meaningful amount (from 22.7 ± 6.1 mL/min/kg to 25.4 ± 7.0 mL/min/kg; $P < 0.001$), with no significant differences between the groups. Adherence of overall 82.3% to the intervention was very good, with the highest adherence rate in 1HIIT. Given the observation that lack of time is one common factor reducing long-term adherence to exercise training, exercise regimens that include short bouts of exercise—such as the 1HIIT approach in our study—might hold promise in counteracting this common obstacle to long-term exercise adherence. However, our findings of low- and high-volume HIIT need to be confirmed in larger cohorts.

In line with previous investigations, we did not observe significant differences between 1HIIT, 4HIIT, and MICT in $\dot{V}O_2$peak and markers of atherogenic dyslipidemia.[23]

Central adiposity, for which elevated WC is a reasonable surrogate, has a strong positive association with ASCVD risk.[13] Anthropometric indices that extend WC by other metabolic or anthropometric variables such as TAG (*i.e.*, HTW phenotype)[21,22,24] or height (*i.e.*, waist-to-height-ratio)[18–20] have been shown to refine phenotypic screening and thus have the potential to improve risk stratification. In our study, we included only patients exhibiting elevated WC (obligatory) accompanied by at least two other criteria of MetS according to IDF criteria.[4] Waist-to-height ratio decreased significantly across the study population. Given the suggested general cutoff of 0.5 for metabolic health (waist-to-height ratio[18]), we report that the training intervention in our study population almost normalized this metric (significant decrease from 0.62 ± 0.06 to 0.53 ± 0.06).

Given the association of waist-to-height ratio with MetS/insulin resistance[24] and its predictive superiority for cardiovascular endpoints compared to BMI or WC,[18,20] our findings are in line with previous data showing a favorable impact on cardiovascular risk. Interestingly, HIIT showed similar results to MICT, adding novelty to the literature. However, these findings, due to our small sample size, should be viewed as exploratory in nature, should be interpreted with caution, and have to be replicated in larger cohorts.

Concerning HTW, we found that one-fourth of the population reduced the expression of this phenotype and one-third of the patients reversed their MetS phenotype.[4] Given that the ExMET substudy by Ramos et al. ($n = 81$ patients with MetS, 16 weeks intervention, ExMET study site: Brisbane, Australia) showed overall MetS severity reduction (z-scores) in the whole study population, but not between groups (1HIIT, 4HIIT, and MICT), our result are consistent with previous results.[23] Ramos et al. additionally found 1HIIT to be as effective as MICT to reduce MetS severity, which contributes to the time-efficient 1HIIT approach to reduce MetS phenotype and risk factor managing.[23]

We did not observe any significant changes in lipoprotein metabolism. There was no change in fasting insulin, HOMA-IR, TAG, HDL-C, TAG/HDL-C, Total cholesterol, and LDL-C, which has to be interpreted with caution due to small sample size. Similar patterns have been observed in prior lifestyle intervention studies. Notably, in 262 patients living with type 2 diabetes, a dietary intervention, including sustained carbohydrate restriction over 1 year significantly reduced the expression of atherogenic dyslipidemia (*i.e.*, triglyceride/HDL-C ratio by ~30%), but resulted in a ~10% elevation in LDL-C after 1 year.[25] In this study, lipoprotein markers that depict cardiovascular risk more accurately than LDL-C (*i.e.*, LDL particle count and subfractions) were measured and showed a favorable impact of the intervention on overall CVD risk. LDL-C, as opposed to apolipoprotein B (apoB) (or LDL particle number) less accurately aligns with CVD risk,[26] in particular, in patients with prediabetes, diabetes, MetS, and other metabolic conditions, where LDL particles become cholesterol-depleted or enriched.[7] We observed no significant change of atherogenic dyslipidemia in our patients. Future training studies should address the question of lipoprotein responses to a HIIT protocol, by direct measurements of apoB or LDL-P and by quantification of qualitative changes in lipoprotein metabolism by subparticle analyses.

Reduced capacity for free fatty acid oxidation during rest and exercise, as assessed by RER, has previously been shown to be associated with both atherogenic dyslipidemia and increased adiposity in individuals with an atherogenic lipoprotein phenotype.[27] Exercise potentially impacts on energy substrate partitioning due to increased capacity of free fatty acid oxidation and fatty acid flux in liver and muscle tissue, which result in lower intrahepatic and muscular triglyceride pools, increased insulin sensitivity, and decreased hepatic triglyceride synthesis.[28] In our study, RER at warm-up significantly decreased in all groups. We

neither observed any significant differences attributable to intensity (MICT vs. HIIT) or volume (1HIIT vs. 4HIIT) nor any significant association with atherogenic dyslipidemia. Collectively, significantly lower RER at warm-up might be indicative of increased free fatty acid oxidation capacity after 16 weeks of exercise training. However, this observation has to be interpreted with caution. As a surrogate for the respiratory quotient (RQ), RER is, among others, not only affected by diet but also influenced by ventilation with hyperventilation leading to higher and hypoventilation leading to lower values of RER compared to RQ.

Overall, regarding improvements in CRF and metabolic health, our observations are suggestive of equal benefit of a short compared to a long HIIT protocol and of a more time-consuming MICT protocol, the latter of which aligns with previous findings.[29,30] These findings thus provide further support on potentially effective and less time-consuming exercise protocols.

A major limitation is the small sample size of our study, which limits the generalizability of our findings. Furthermore, we did neither control for diet nor offer specific advice on dietary regimens that have shown to improve markers indicative of cardiometabolic risk. In this regard, it is worth noting that evidence from randomized controlled trials[10] and epidemiology[31] indicate that combined approaches that comprise exercise and dietary interventions hold promise in achieving larger cumulative benefit with respect to improvements in markers indicative of metabolic health and/or cardiovascular disease risk. For example, in the CENTRAL-MRI randomized controlled trial, a Mediterranean low-carbohydrate dietary pattern has been shown to be superior to a low-fat dietary pattern in mobilizing atherogenic and diabetogenic fat depots in liver, pancreas, and pericardium in dyslipidemic individuals with central adiposity. Interestingly, exercise had an independent contribution to visceral adipose tissue loss, and the greatest improvements in cardiometabolic risk profile was shown in the intervention group following a Mediterranean low-carbohydrate dietary pattern combined with an exercise intervention, the least benefit was evident in the low-fat-diet group without an exercise intervention.[10] This effect was independent of BMI *per se*. It should thus be noted that some of the benefits of physical activity and/or certain dietary interventions (*e.g.*, anti-inflammatory effects and improvements in metabolic parameters) occur even in the absence of weight loss. One mechanism underlying this observation might be changes in body composition (*e.g.*, loss of ectopic adipose tissue[10]) and in particular, increases in skeletal muscle, and its endocrine function, which comprises the secretion of hormone-like substances called myokines.[32,33]

Overall, it seems plausible to combine exercise and dietary interventions for improving cardiometabolic risk in patients with MetS. Regarding the dietary protocol of choice in this subgroup of patients it should be noted that insulin resistance, the hallmark of MetS, alters metabolic responses to dietary cues and clinically manifests as an intolerance to dietary carbohydrate; that is, glycogen synthesis is impaired and dietary carbohydrate is diverted at increasing rates into hepatic *de novo* lipogenesis.[34] This conceptual framework offers some biological plausibility for the growing body of scientific literature showing superiority of low-carbohydrate dietary patterns for glycemic and weight control in T2DM[5] and for the observation that dietary carbohydrate restriction (in particular if combined with physical activity) has been shown to be superior to dietary fat restriction in the dyslipidemic phenotype with truncal adiposity.[10] This has resulted in the endorsement of low-carbohydrate diets (<26% of total energy) as one strategy to manage hyperglycemia and hyperinsulinemia in T2DM.[35] Besides dietary carbohydrate restriction, weight loss and physical activity, intermittent dietary restriction is an emerging strategy that holds promise in lowering hepatic triglyceride pool and improving markers indicative of metabolic health.[36–38] Based on these considerations, not controlling for diet is a clear limitation of our study, might have attenuated the results and has to be taken into consideration when interpreting the results.

To quantify insulin resistance, we calculated HOMA-IR based on a single fasting insulin measurement instead of taking the arithmetic mean of three consecutive evaluations as recommended.[39] This might limit our ability to reliably evaluate insulin resistance in this analysis. The 17- and 38-min HIIT protocols might be difficult to translate into clinical practice. We think that feasibility would likely justify a modification of these timeframes to a 20- and 40-min regime 3×weekly.

A major strength of this study is the well-controlled study design. The MICT-group was trained according to current recommendations and was considered the "usual care" control group. The 16-week training intervention was fully supervised and each training was conducted by trained staff. Participants showed very good adherence (participants attended to 82.3% of scheduled training sessions). $\dot{V}O_{2peak}$ significantly improved from baseline to study completion in all regimens, which speaks to very good adherence to the training protocol during intervention. The training protocol was tailored to the needs of each patient by exercise scientists, following functional evaluation. Exercise testing before starting the training program was conducted according to current recommendations.[40] This ensures that the appropriate exercise training stimulus is applied to each individual, and is considered the gold-standard for exercise intensity assessment and prescription.[41] We also used percentage HRR instead of maximal heart rate to determine exercise intensity to account for patients with chronotropic incompetence (*i.e.*, due to medication with beta-blockers or left ventricular diastolic dysfunction).

Conclusion

In conclusion, in patients with MetS, HIIT and MICT showed no significant differences in improving exercise capacity or metabolic health. Interestingly, the HIIT protocol lasting 17 min showed similar results compared to the more time-consuming 38-min protocol. Given the observation that time constraints often limit long-term adherence to an exercise intervention, these findings might guide exercise prescriptions, if confirmed in larger cohorts.

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Authors' Contributions

All authors contributed substantially to this article. P.v.K. and K.L. both contributed to the literature search and to the article draft. K.L. supervised the writing process. P.v.K. did the exercise intervention, exercise testing, and both contributed to statistical analysis and data interpretation. S.K., S.M., S.D., N.K., A.D., J.S., A.E.T., U.W., and M.H. critically revised, interpreted data, and edited the article. B.H. assisted with statistical analysis. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Author Disclosure Statement

No conflicting financial interests exist.

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Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes (the LeIKD study): study protocol of a prospective, multicentre, randomised, controlled trial

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ABSTRACT

Introduction Guidelines recommend lifestyle intervention in chronic ischaemic heart disease (CIHD) and type 2 diabetes mellitus (T2DM). However, evidence from randomised controlled trials is scarce in patients with combined entities.

Methods and analysis The Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes (LeIKD) trial is a prospective, multicentre study that will randomise (1:1) patients with CIHD (ICD-10: I20-I25) and T2DM (ICD-10: E11) from one health insurance company into a lifestyle intervention (LS) or usual care (UC). Active LS consists of an individual combined exercise programme of strength and endurance training and nutritional counselling with regular feedback for 6 months. Intervention is supported by telemedicine. Follow-up without individualised feedback will continue for 6 months. The study aims to investigate whether an individualised telemedical supported LS intervention is superior to UC in improving cardiovascular risk factors, physical activity, quality of life, health literacy, major cardiovascular events and health economics in patients with both CIHD and T2DM. Primary endpoint is the change in HbA_{1c} from baseline to 6 months.

Ethics and dissemination The study has been approved by the ethics committee of the Technical University of Munich (registration number: 144/18-S) and at each study site. The study will be conducted according to the World Medical Association Declaration of Helsinki, and results will be published in articles and reports. It is funded by the Federal Joint Committee (www.innovationsfonds.g-ba.de), reference number 01NVF17015, which has no impact on data collection, analysis or interpretation. Dissemination is independent of the funding source.

Trial registration number Clinical trials.gov identifier: NCT03835923. German registry for clinical studies (DRKS): DRKS00015140.

Strengths and limitations of this study

- The LeIKD (Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes) study is one of the largest randomised controlled trials investigating a telemedically supported lifestyle intervention in patients suffering from both chronic ischaemic heart disease and type 2 diabetes mellitus.
- This study evaluates an approach for both patients and healthcare providers with regard to a telemedically supported lifestyle intervention integrating exercise and nutrition in a multimorbid elderly population.
- This study combines health economic data from one health insurance company with telemedical data from individualised exercise and nutrition.
- This study is limited to patients willing to use smartphones.
- This study is limited to insurants from one health insurance company, which may limit generalisation.

INTRODUCTION

Patients with both chronic ischaemic heart disease (CIHD) and type 2 diabetes mellitus (T2DM) have a high morbidity and mortality.[1] Results from the EUROASPIRE-IV survey (n=7998), assessing the implementation of current guidelines in secondary prevention, show that 26.8% of patients with CIHD also suffer from T2DM.[2] Combining the diagnosis of T2DM and CIHD exponentially increases the risk of impaired quality of life (QoL) and mortality.[1 3]

Recommendations for lifestyle intervention are included in current guidelines in CIHD[1] and T2DM.[4] Both have received I A classifications, which is based on evidence from randomised controlled intervention trials. The largest trial (Look AHEAD, n=5145) in T2DM (14% with former cardiovascular event) has revealed that lifestyle intervention

including exercise training in combination with a hypocaloric diet improved glycosylated haemoglobin (HbA_{1c}) over 1 year as compared with usual care.[5] Moreover, results from the ENHANCE trial in patients with T2DM (1:1 randomised, n=296, behavioural intervention, increasing diabetes self-care by monitoring software) have shown a trend towards a mean reduction of HbA_{1c} of 0.4% after 6 months, although this was non-significant due to improvements in both experimental and control groups.[6] Furthermore, results of the DiRECT study (n=306) in an outpatient general practitioner setting have demonstrated a 46% remission of T2DM through weight reduction by meal replacement therapy and exercise counselling after 12-month intervention.[7]

Evidence from a recent study in patients with stable CIHD (n=15 487, physical activity (PA) data by questionnaire, 38.7% T2DM) has revealed that habitual exercise is significantly associated with lower cardiovascular mortality (adjusted HR=0.92).[8] Moreover, in patients with heart failure with reduced ejection fraction (HFrEF), the HF-ACTION study (n=2331, 51.4% ischaemic aetiology of heart failure, prevalence of T2DM 32.1%) has revealed that, after adjusting for prognostic factors, exercise training significantly reduced rehospitalisation rate (HR 0.85, p=0.03).[9]

However, in all of these trials, adherence to intervention has been the key challenge.[5 9] Telemedicine applications, characterised by the WHO as any information and communication technologies that allow remote healthcare services,[10] may support implementation of and adherence to lifestyle measures, as demonstrated by the ENHANCE trial.[6] A recent review by Zhu *et al* (2019) has underlined the effectiveness of telemedical interventions (defined by telephone, vocal support or telemonitoring) in patients with heart failure (10 981 patients with HFrEF, NYHA I-IV, 29 randomised controlled trials) by revealing significant reductions in hospitalisation rate, all-cause mortality and length of hospitalisation in the intervention group.[11] The TIM-HF2 trial investigated the efficacy of a remote patient management (including medical multicomponent telemonitoring system with daily transmission to study centre, monthly phone calls/interviews and option of emergency phone contact) in n=1571 patients with heart failure (New York Heart Association (NYHA) II-III, 1:1 randomisation) on morbidity and mortality (40% ischaemic cause of heart failure, 45% T2DM)[12] and revealed a significant difference in days lost to cardiovascular hospital admissions (4.9% in remote patient management vs 6.6% in UC, p=0.046).

Rationale

Despite this current positive clinical evidence of lifestyle interventions in T2DM and CIHD, the challenge of implementation and adherence to a long-term lifestyle programme remains unresolved. To overcome these major challenges, telemedicine has revealed beneficial effects on adherence and motivation by improving patients' education and awareness[12]; however, this approach is unclear in an elderly and multimorbid patient population.

Therefore, a large, randomised controlled trial assessing the combined effects of exercise and nutrition supported by telemedicine in patients suffering from CIHD and T2DM has yet to be conducted. Data from health economics will be particularly valuable for subsequent implementation into standard care programmes in this population.

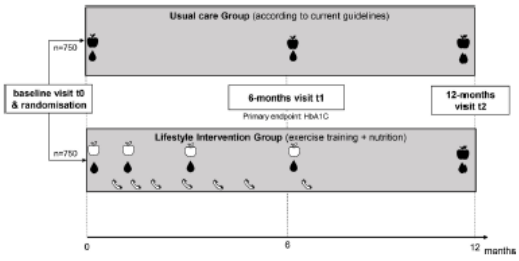

Figure 1 LeIKD (Lifestyle Intervention in Chronic Ischaemic Heart Disease and Type 2 Diabetes) study design. Apple black: food diary without feedback; apple white: food diary with feedback; blood drop: blood glucose profile without feedback; phone: feedback training from core laboratory.

METHODS AND ANALYSIS

Study objectives

We hypothesise that patients with CIHD and T2DM receiving a telemedical lifestyle intervention programme including exercise training and nutritional advice will show significant improvements in cardiovascular risk factors, PA, health literacy, health economic data and clinical events when assessed after 6 and 12 months, as compared with patients assigned to UC.

Study design

The LeIKD study is a prospective, multicentre, randomised, controlled trial. Figure 1 depicts the study flow chart for further details. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing our report.[13] The study will include patients with the diagnosis of both CIHD and T2DM. Patients will be identified by the statutory health insurance fund TK (Techniker Krankenkasse, Hamburg, Germany) according to ICD (International Classification of Diseases) codes for ischaemic heart diseases (ICD-10: I20-I25, ie, history of angina pectoris; acute myocardial infarction; subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction; certain current complication following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction; other acute ischaemic heart diseases; CIHD) and T2DM (ICD-10: E11). A complete list of inclusion and exclusion criteria is shown in table 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Ischaemic heart disease (ICD-10: I20-I25) Diabetes mellitus (ICD-10: E11) and HbA1c≥6.5 or anti-diabetic medication at the time of screening	Mental and behavioural disorders (ICD-10: F00, F01, F02, F11, F12, F13, F14, F15, F16, F18, F20, F21, F22, F23, F24, F25, F28, F29, F44, F72, F73, F17, F84)
≥18 years	Heart failure NYHA IV (ICD-10: I50.14)
Insured at TK health insurance fund	Malignant neoplasm (ICD-10: C25, C34, C56, C72, C73, C78, C79, C97)
Permission to do physical exercises by study investigator	Parkinson's disease (ICD-10: G20)
Written informed consent	Alzheimer disease (ICD-10: G30)
	Infantile cerebral palsy (ICD-10: G80)
	Chronic kidney disease (ICD-10: N18.4 & N18.5)
	Trisomy 21 (ICD-10: Q90)
	Blindness/visual impairment (ICD-10: H54.0, H54.2, H54.3)
	Hearing loss (ICD-10: H90.0, H90.3, H90.5, H90.6, H90.8)
	Care level 1–5
	Insured abroad
	Inability to do physical exercises or conditions that may interfere with exercise intervention
	No optimal cardiac treatment within the last 4 weeks to be assessed and decided on by the local investigator
	Not clinically stable within the last 4 weeks to be assessed and decided on by the local investigator
	Participation in another trial

Care level: needed degree of required assistance in daily life (part of the German health system).
ICD, International Classification of Diseases register; NYHA, New York Heart Association.

Eleven centres across Germany have been selected as certified study sites: Aachen (University Hospital, Department for Cardiology), Berlin (Charité, Department for Sports Medicine and Department for Cardiovascular Prevention and Heart Failure), Dresden (University Hospital, Department for Internal Medicine and Cardiology), Freiburg (University Hospital, Department for Cardiology and Angiology), Greifswald (University Hospital, Department for Internal Medicine), Kassel (private practice for Cardiology), Leipzig (University Hospital, Department for Cardiology), Magdeburg (University Hospital, Department for Cardiology and Angiology), Villingen-Schwenningen (private practice for Prevention and Therapy) and the Department for Prevention and Sports Medicine at University Hospital 'Klinikum rechts der Isar' of the Technical University of Munich. Target recruitment rates are derived by the number of insurants at Techniker Krankenkasse with the corresponding ICD diagnoses. Standardised data collection and administration in each site is assured by standard operating procedures (SOPs) and personal training by the trial committee before inclusion of the first patient per site. When living within the area of 50 km from a site, patients will be contacted via phone by the health insurance fund and informed on the background and purpose of the study. In case of consent to participate in the study, the contact details of the potential study participant will be consensually transmitted to the local study site via pin-code safe data room to schedule a screening visit (t0).

Randomisation

All patients will be randomly assigned to either the LS or UC by means of block randomisation, stratified by centre, using a web-based electronic data capture system (secuTrial, interActive Systems GmbH, Berlin, Germany).

Baseline and follow-up investigations

After written informed consent, anamnesis including medical history, medication, physical examination, anthropometry and resting ECG will be performed. Blood samples will be taken and analysed for standard laboratory values (HbA_{1c}, blood count, blood lipids, N-terminal pro-brain natriuretic peptide) in a local laboratory.

Health literacy, eating behaviour, daily PA and QoL will be assessed by the European Health Literacy Questionnaire (HLS-EU-Q16), a German questionnaire on eating behaviour ('Fragebogen zum Essverhalten', FEV), the International Physical Activity Questionnaire (IPAQ) and the Short Form Health Survey (SF-36), respectively. These examinations will be repeated after 6 (t1) and 12 months (t2).

Furthermore, a symptom-limited maximal cardiopulmonary exercise test (CPET) on a stationary cycle ergometer will be performed according to current recommendations at baseline and after 6 months.[14] An exercise stress test (including exercise ECG) will be performed after 12 months. Breath-by-breath CPET data will be transferred to and analysed by the CPET core laboratory at Technical University of Munich (TUM).

To monitor daily PA and blood glucose levels, all patients (both groups) will receive a pedometer (AS80/AS87, Beurer GmbH, Ulm, Germany) and blood glucose metre (GL50evo, Beurer GmbH, Ulm, Germany), which are connected to an app (Beurer Health manager, Beurer GmbH, Ulm, Germany). While the pedometer should be worn throughout the entire duration of the study, patients are asked to measure 3-day blood glucose profiles at three different points in the study: during week 1 (after t0), the week after t1 and the week before t2. Randomised patients are equipped with relevant smartphone applications (apps). If necessary, a smartphone will be provided free of cost for the duration of the study. To ensure data security and privacy, pseudonymised study identification

Box 1 Clinical endpoints

Primary:
- Change in HbA_{1C} (%) after 6 months between groups.

Secondary:
- Change in HbA_{1C} (%) after 12 months between groups.
- Change in health literacy (HLS-EU-Q16, score) between 6 and 12 months between groups.
- Change in daily physical activity (IPAQ, score) after 6 and 12 months between groups.
- Change in average steps per days (7-day average of steps/day measured by pedometers) after 6 and 12 months between groups.
- Change in eating behaviour (FEV, score) after 6 and 12 months between groups.
- Change of quality of life (SF-36, score) after 6 and 12 months between groups.
- Change in healthcare costs (€, health claims data of health insurance fund) after 6 and 12 months between groups.
- Change in weight (kg) after 6 and 12 months.
- Change in waist circumference (cm) after 6 and 12 months.
- Change in LDL-cholesterol concentrations (mg/dL) after 6 and 12 months.
- Change in HDL-cholesterol concentrations (mg/dL) after 6 and 12 months.
- Change in triglyceride concentration (mg/dL) after 6 and 12 months.
- Change in systolic blood pressure (mmHg) after 6 and 12 months.
- Change in diastolic blood pressure (mmHg) after 6 and 12 months.
- Number of the combined endpoint '4-point MACE' after 6 and 12 months.

FEV, questionnaire about eating behaviour; HbA1C, glycosylated haemoglobin; HDL, high density cholesterol; HLS-EU-Q16, Health Literacy Survey Questionnaire; IPAQ, International Physical Activity Questionnaire; LDL, low density cholesterol; MACE, major cardiovascular events defined as cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, hospitalisation due to angina pectoris; SF-36, Short Form-36 Questionnaire.

codes (study IDs) as well as standardised email addresses are used to register in LS apps.

Furthermore, 7-day paper-based food diaries corresponding to these three points in time will be recorded by the study participants and evaluated by nutrition specialists at TUM.

For safety monitoring and analysis, adverse events will be obtained and immediately forwarded to the study site at TUM to be revaluated by a safety committee. All evaluations are performed according to SOPs to ensure objective evaluations and high data quality.

Study endpoints

The primary endpoint is a change in HbA_{1C} levels from baseline to 6 months of LS compared with UC (reduction of HbA_{1C} −0.4% from baseline level).

Secondary endpoints (box 1) include changes in health literacy, PA, eating behaviour, QoL, numerous cardiovascular risk factors, the number of major cardiovascular events (cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, hospitalisation for angina pectoris and/or coronary revascularisation) and healthcare costs after 6 and 12 months. The self-reported questionnaires cover the following topics: HLS-EU-Q16 assessing health literacy, including items regarding disease management, prevention and health promotion[15]; IPAQ assessing PA during the last 7 days, including items for time spent on moderate, vigorous or sitting activities[16]; FEV assessing eating behaviour, including items regarding cognitive control of eating habits, restrained eating, disturbance of eating habits and experienced feelings of hunger[17]; and SF-36 assessing QoL, including items regarding physical and mental well-being.[18]

Intervention

The intervention is centrally provided by the study group at TUM, which means that the individual study sites can focus on patient recruitment and follow-up investigations. This also ensures a standardised and objective support of patients enrolled to the trial.

Lifestyle intervention group (LS)

Patients assigned to LS will receive individualised recommendations on nutrition as well as on their individual exercise programme. They will also receive two weekly newsletters on PA, motivation and nutrition by mail.

Exercise and daily activities

The individual exercise training consists of both endurance and strength training and starts 2 weeks after randomisation. It is provided and monitored via the LeIKD app (IDS Diagnostic Systems AG, Ettlingen, Germany). The patients will be allocated to one of four different levels of fitness based on their maximum exercise capacity (percentage of normal peak oxygen consumption (%$\dot{V}O_2$peak)[19] and relative $\dot{V}O_2$peak (mL/min/kg)), as further depicted in table 2, at baseline and 6 months visit.

Despite different templates for each level, the initial aim is to encourage all patients to exercise on a daily basis. Every template consists of four endurance and two strength training sessions per week with an initial duration of 10–15 min and an increase of duration (up to 30–50 min) and intensity over time. The endurance training varies between low, moderate and vigorous intensities, as well as continuous and interval sessions. Intensities are individually calculated according to a threshold-based approach,

Table 2 Thresholds for endurance and strength exercise group allocations based on maximum exercise capacity

Exercise training level	Thresholds for endurance exercise group allocation based on percentage of normal $\dot{V}O_2$ peak (%)	Thresholds for strength exercise group allocation based on relative $\dot{V}O_2$ peak (mL/min/kg)
1	≤75.0	≤16.0
2	75.1–90.0	16.1–22.0
3	90.1–110.0	22.1–30.0
4	>110.0	>30.0

$\dot{V}O_2$peak: peak oxygen uptake.

and incorporate patients' CPET data in order to provide a best-practice individual exercise recommendation.[20 21] All endurance sessions will be monitored by a heart rate sensor (H7 Heart rate sensor, Polar, Kempele, Finland) and recorded in the LeIKD app.

The strength training includes more than 30 different exercises with multiple variations and levels of intensity. All exercises can be performed at home and may incorporate conventional household items such as water bottles. Each session includes several exercises targeting different muscle groups (whole body, lower extremities, upper extremities, trunk muscles) and consists of at least two sets per exercise.

In addition to the LeIKD app, patients will receive a printed booklet with all exercises and access to an online platform, where they have access to instructional videos.

Training adaptation

The core laboratory for exercise training (TUM) will be able to access all exercise data via secured web platform to monitor adherence of the participants. In order to increase adherence and motivation, patients can choose their preferred mode of endurance training (eg, riding a bike or walking). Furthermore, patients are contacted via phone in weeks 3, 5, 9, 13, 17 and 21 (before t1) by exercise physiologists from TUM to review potential problems and, if necessary, individually adapt the type, amount, duration and/or intensity of the exercise sessions. Despite potential changes, the exercise training aims at increasing the duration to at least 150 min per week of moderate PA, or a mixture of moderate-to-vigorous PA with less than 150 min per week to meet general health recommendations.

Beyond structured endurance and strength training, patients are encouraged to increase their daily PA. Therefore, based on the average steps per day in the first 2 weeks, patients are advised to gradually increase their daily PA within 6 months. After 6 months (t1), heart rate zones for the different intensity domains will be adapted according to the results of CPET at 6 months visit. Two weeks later, all LS patients will be contacted by phone to be informed about their progress and the upcoming exercise schedule. The second part of the study primarily aims at maintaining the level of PA and exercise without regular feedback. Therefore, the patients will receive another exercise schedule based on their preferences (eg, less sessions with longer duration) in order to improve long-term motivation and adherence. No further individual contact is planned until the subsequent visit after 12 months (t2). In case of urgent safety-related issues or technical problems, the exercise programme will be individually adapted by study personnel if requested.

Nutrition monitoring

In addition to 7-day food diaries in weeks 1 (after t0), 27 (t1) and 52 (t2), patients in the LS will be asked to complete food diaries in weeks 5 and 14. Based on their food diaries, they will receive individualised nutritional advice based on the principle of energy density[22] by either mail or local postal service centrally coordinated from nutritionists at TUM. This information will primarily contain recommendations about replacing high density (calories per gram) with lower density level.[22] This principle is intended to lead to a reduction in caloric intake.[22] Patients will be engaged to improve food choices based on principles of a balanced and healthy diet according to the German Nutrition Society (DGE). Nutritional advices focus on quality of food, consumption of fruits and vegetables, preferring calorie-free beverages and avoiding alcoholic drinks, preferably consuming rather fish than meat and avoid highly processed foods. This will empower the patient to make healthier, qualitatively better food choices based on their individual meal preferences and thereby support weight maintenance or reduction.

Health literacy

To increase health literacy particularly regarding PA and nutrition, all LS patients will receive two weekly emails with background information on PA, motivation and nutrition along with cooking recipes.

In order to improve health literacy, all patients are advised to measure their own blood glucose concentrations at different times during the day, as well as in different activity contexts, including (but not limited to) before and after one of their strength or endurance training sessions.

Patient and public involvement

Patients have not been involved in the development of the initial study protocol. Patients participate when adapting the individual exercise intervention and change of diet according to the nutritionist's feedback, see the Intervention section. A group of random patients was invited to participate at a *focus group meeting* to discuss and further develop questionnaires.

Usual care

Patients in the UC group are treated according to the ESC guidelines on the management of stable coronary artery disease[4] and all patients will receive detailed standard recommendations on nutrition and PA[23 24] after the baseline examination (t0) by email. These include a recommendation to perform 150 min of moderate or 75 min of higher intensity activities and several other lifestyle-related advices (see online supplemental document) to assure even access of information for every patient. They will not receive a lifestyle intervention or individualised feedback.

Claims data from statutory health insurance fund

In order to investigate the effect of the intervention on health economics, a cost-effectiveness analysis based on claims data from one statutory health insurance (SHI) fund will be carried out as part of this study's health economic evaluation. Claims data can be obtained and analysed on an individual basis, as these data are directly

transmitted from healthcare providers to SHI funds for billing and reimbursement purposes.

Sample size calculation

Based on the results of the ENHANCE trial[6] (mean difference of 0.4%±1.8%, 80% statistical power, 5% significance level and an estimated dropout rate of 15%), a number of 750 patients have been calculated to detect a statistically significant difference of the primary endpoint between the groups. For an equally distributed comparison between patients living in urban and rural areas, the estimated number has been doubled to 1500.

Data handling

The evaluation is based on three data sources: patient reported data, medical data and SHI claims data.

Patient-reported data include, among others, questionnaires (assessed and documented at study sites), PA data (eg, pedometer by app) and nutrition diaries (centrally coordinated at TUM). Medical data are either assessed and documented by study site. SHI claims data are derived by health insurance. All data sources are pseudonymised in the same way by study IDs. No interim analysis will be conducted.

Patient-reported data and medical data will be extracted from the electronic data capture system secuTrial by the interActive Systems GmbH (Berlin, Germany). secuTrial is compliant with the Directive 2001/20/EC guidelines for Good Clinical Practice. Moreover, the compliance with all legal requirements for the interActive Systems GmbH in the handling of all collected data will be monitored by the evaluating institute within the scope of order data processing. SHI claims data will be provided by the stationary health insurance fund TK. The different sources are linked by study ID and validated for the analyses.

Statistical analysis

The aim of the statistical analysis is to compare changes in outcomes between different points in time (ie, baseline, after 6 months and after 12 months) and study groups (ie, LS and UC). Therefore, outcomes will be measured and analysed at all different points in time in both study groups (see figure 1) following the intention-to-treat principle. Statistical analysis has been described in a study evaluation protocol. Descriptive variables and changes in outcomes will be summarised separately for both study groups. An analysis of covariance will be conducted to evaluate all between-subject effects and to identify interactions of between-subject and within-subject effects, including within-covariate interactions. To consider relevant differences between the study groups regarding the baseline variables, adjustments can be made for possible confounders (eg, comorbidities). Additionally, an analysis of variance will be used to evaluate all within-subject effects between the three points in time. To compare differences between groups, t-tests (for parametric data) or Mann-Whitney U tests (for non-parametric data) will be applied. Additionally, multivariate analyses are performed to identify and investigate factors influencing the study's primary and secondary outcomes. Sensitivity analyses will be conducted to assess the robustness of the results to variation in key parameters. This will comprise per-protocol analyses and, if applicable, as-treated analyses, which will be defined in a statistical analysis plan before the database is locked.

In order to investigate our intervention's effect on health economics, a cost-effectiveness analysis will be carried out as part of the health economic evaluation. In this analysis, a modified societal perspective will be adopted to account for healthcare system costs. This perspective will cover the costs of our intervention, as well as the general costs for medical care (eg, outpatient and inpatient diagnostics and treatment), pharmaceuticals, rehabilitation, remedies and aids, as well as sick leave payments during the study period. Lastly, the incremental cost-effectiveness ratio will be calculated as the change in average costs between the IC and CG divided by the difference in average change on HbA_{1c} levels between the LS and UC. All analyses will be performed with a significance level of α=0.05 and will not be adjusted for multiplicity. Therefore, analyses of secondary endpoints should be interpreted as hypothesis-generating.

ETHICS AND DISSEMINATION

The LeIKD study has been approved by the local ethics committee of the TUM (protocol 27.03.2018, identification code: 144/18-S) as well as each ethics committee responsible for other participating study sites. The study will be conducted according to the World Medical Association Declaration of Helsinki. Protocol modifications must be approved by all legal authorities if necessary and further communicated. Study participation is voluntary and patients are only included after written and verbal informed consent. Patients can withdraw from study participation at any time without personal legal consequences. The results of the study will be published by the study group in presentations, articles and reports, independently of the funding sponsor. The authors were involved in study proposal (MH, VA, BH), are part of the steering committee (SN, VA, BH, MH and SM) and will be involved in study coordination and dissemination (all authors).

Discussion

The LeIKD study will be one of the largest randomised trials investigating a telemedical lifestyle intervention in patients suffering from both CIHD and T2DM. This multimorbid, mostly elderly patient population has a significantly increased morbidity and mortality and poses a substantial and increasing socioeconomic burden.[2]

In the UK Prospective Diabetes Study (UKPDS), a 1% reduction in HbA_{1c} was associated with a significant ($p<0.001$) reduced risk in diabetes-related deaths (−21%), myocardial infarction (−14%) and microvascular

complications (−37%).[25] However, the authors state that they were not able to define a threshold regarding diabetic complications and that any improvement of diabetic control by reduction of HbA_{1C}, independent of baseline HbA_{1C} concentration, reduces the risk of complication.[25] The European Medicines Agency has set their non-inferiority margin for changes in HbA_{1c} to 0.3%,[26] which is slightly less than what we expect as a treatment-related mean difference between the groups (−0.4%) based on the results of the ENHANCE trial.[6]

Currently, it has not been investigated before in a large randomised trial, whether QoL and health economic aspects may significantly be improved by a telemedical lifestyle intervention for patients with cardiovascular disease.[11] Therefore, the LeIKD study will address an important and challenging patient population, will closely evaluate adherence to lifestyle interventions, will include a telemedicine platform and devices, and will include economic data analysis.

The TEMA-HF 1 study including 160 patients with HFrEF showed promising results by telemedical intervention (data of weight, blood pressure and heart rate electronically submitted to hospital, alert if necessary) during 6 months of rehabilitation after acute heart failure.[27] Results for all-cause mortality (17.5% death rate in the control group vs 5% in the intervention group, p=0.012), hospitalisation (0.82±0.93 hospitalisations/subject in the control group vs 0.80±0.97 in the intervention group, p=0.934) and hospitalisation costs (€1458±3420 in the control group vs €902±2277 in the intervention group, p=0.23) are promising, even though the sample size was relatively small.[27]

The long-term implementation of lifestyle intervention is a key challenge in all lifestyle trials. In the HF ACTION study in HFrEF, the authors identified (1) low motivation, (2) limitations due to comorbidities and (3) the disease condition itself as the main contributors towards low adherence rates.[9] The LeIKD study aims at changing the patients' lifestyle in their personal environment, an approach that has succeeded previously.[12] Moreover, as monotonous exercise regimens will most likely lead to a decline in adherence, the LeIKD study will deliberately extend variation of exercise regarding volume, intensity, load of training, individualised training scheme and target to improve exercise capacity.

Next to the individual feedback, we intensively aim at increasing health literacy (by using pedometers, blood glucose monitoring and weekly newsletters). Health literacy and the role of personal guidance are thought to play a major role in patients' long-term adherence. This will be quantified within the LeIKD study by health literacy questionnaires and comparison of episodes with individual feedback for the first 6 months and thereafter without.

In LeIKD, individual nutritional recommendations aim at motivating the patients to change their diet by triggering their intrinsic motivation rather than imposing strict rules from the study personnel. Patients design their own diet supported by general recommendations from newsletters, as well as implementing feedback from nutritional specialists by replacing food of high by low density. Thereby, we will follow an educational approach to support the lifestyle changes and improve health literacy.

SHI claims data from the trial will add valuable information regarding the economic impact of a lifestyle intervention. Furthermore, it will provide an overview of current treatment quality in Germany in light of the observed conditions. Compared with clinical trials, claims data analyses have been shown to reflect real-life healthcare provisions.[28] Other benefits of this data source include cost-efficient data generation and access to a large study population. Linking all data will ideally provide a deeper insight into real-life treatment and patient-relevant assessments, thereby also contributing to improve healthcare research.

The LeIKD study represents one of the largest lifestyle intervention trials in the field of cardiology and diabetology. Furthermore, to our knowledge, no other trial has thus far evaluated the effects of a 12-month telemedical lifestyle intervention in a population with both CIHD and T2DM. The multicentre approach as well as the close link to one of the largest insurance companies in Germany, which identifies patients according to their ICD codes in the area of study centres, will ensure an optimised recruitment strategy and potential for optimal health economic analyses and long-term follow-up. The LeIKD study will thereby contribute towards establishing a standard procedure for a telemedical approach of lifestyle intervention in a population with CIHD and T2DM.

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Dear participant in the LeIKD study,

We are pleased that you have agreed to participate in the LeIKD study. Below you will find your exercise and nutritional recommendations.

Exercise recommendations

Regular physical activity is important for improving or maintaining health and physical and mental well-being. It leads to an increase in mobility and helps to reduce the risk of many diseases and support their treatment.
According to the current guidelines on coronary heart disease and the guideline on type 2 diabetes issued by the European Society of Cardiology (2013) and the World Health Organisation (WHO), the following exercise recommendations for endurance training result:

o At least 150 minutes / week with moderate intensity (e.g. 5x30 minutes / week) or
o At least 75 minutes / week with higher intensity
As a rule of thumb:
At a moderate intensity you can still talk in whole sentences, but you will notice that this is already a little difficult. At high intensity you are no longer / hardly able to formulate whole sentences.
Apart from active sports, physical activity in everyday life also has a positive effect on your health. Use the stairs instead of the lift or go for a short walk during the day. Avoid sitting for too long or interrupt this with a little physical activity (e.g. standing or walking while talking on the phone). This should ideally be supplemented by muscle-strengthening exercises and coordination and balance exercises.

Nutritional recommendations

The patient guidelines of the National Care Guideline for Coronary Heart Disease (2017) and for the treatment of type 2 diabetes (2015) recommend
- If overweight, try to lose weight; if normal weight, avoid weight gain
- Healthy, calorie appropriate and balanced diet
- At least 5 portions of fruit and vegetables a day (1 portion is roughly the size of your own hand)
- Prefer foods with complex carbohydrates and low glycemic index
- Limit as far as possible foods with added sugar (especially ready-made products, sweet drinks and sweets)
- Protein content of the diet about 0.8 grams of protein per kilogram of body weight (10-20% of the daily energy intake); if kidney damage is present, reduce the amount in consultation with the doctor if necessary
- Moderate salt consumption (approx. 6 g salt per day); caution with finished products, as these often contain a large amount of salt
- Sufficient supply of dietary fibre (approx. 30 g per day) from whole grain cereals and pulses
- Fish twice a week if possible, including once high-fat fish (mackerel, herring, salmon) to supply healthy omega-3 fatty acids
- Pay attention to a good fatty acid composition in high-fat foods
- Vegetable fats and oils are preferable (e.g. rapeseed oil, olive oil, seeds and nuts, avocados); a handful (approx. 30 g) of unsalted nuts can be eaten daily to supplement the diet
- High-fat meals with many saturated and trans fatty acids (e.g. fatty meat, fatty finished products, food from the deep fryer, cream, fatty confectionery and bakery products, crisps etc.)) as low as possible
- Drink enough: a minimum of 1.5 litres a day is recommended. Sugar-sweetened drinks (fruit juices and lemonades) should be avoided as far as possible and more use should be made of non-calorie drinks such as water or unsweetened teas
- Alcohol only in small quantities and above all not daily

We thank you for your participation in the study and wish you all the best,
Your LeIKD study team at TU Munich

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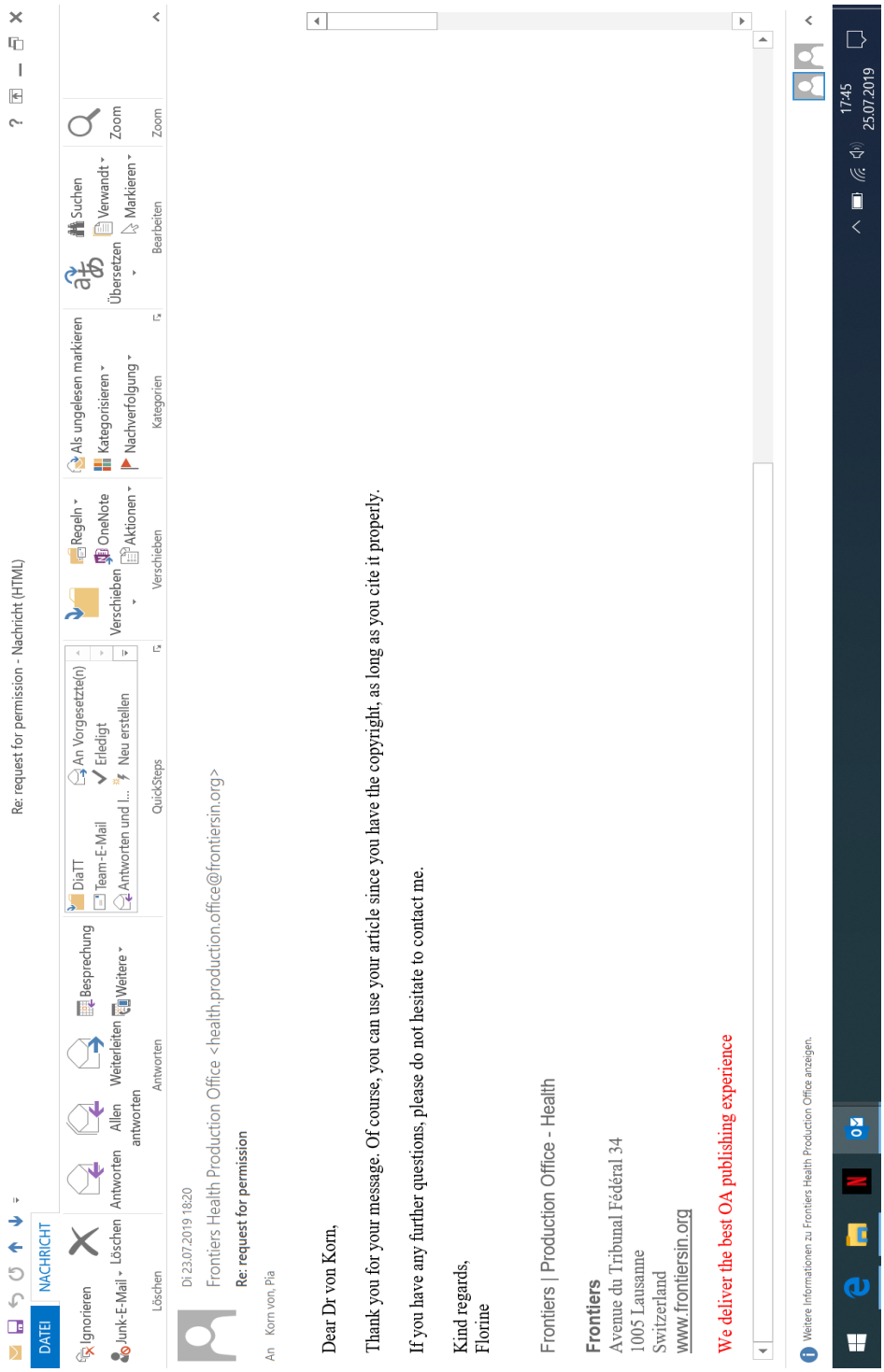

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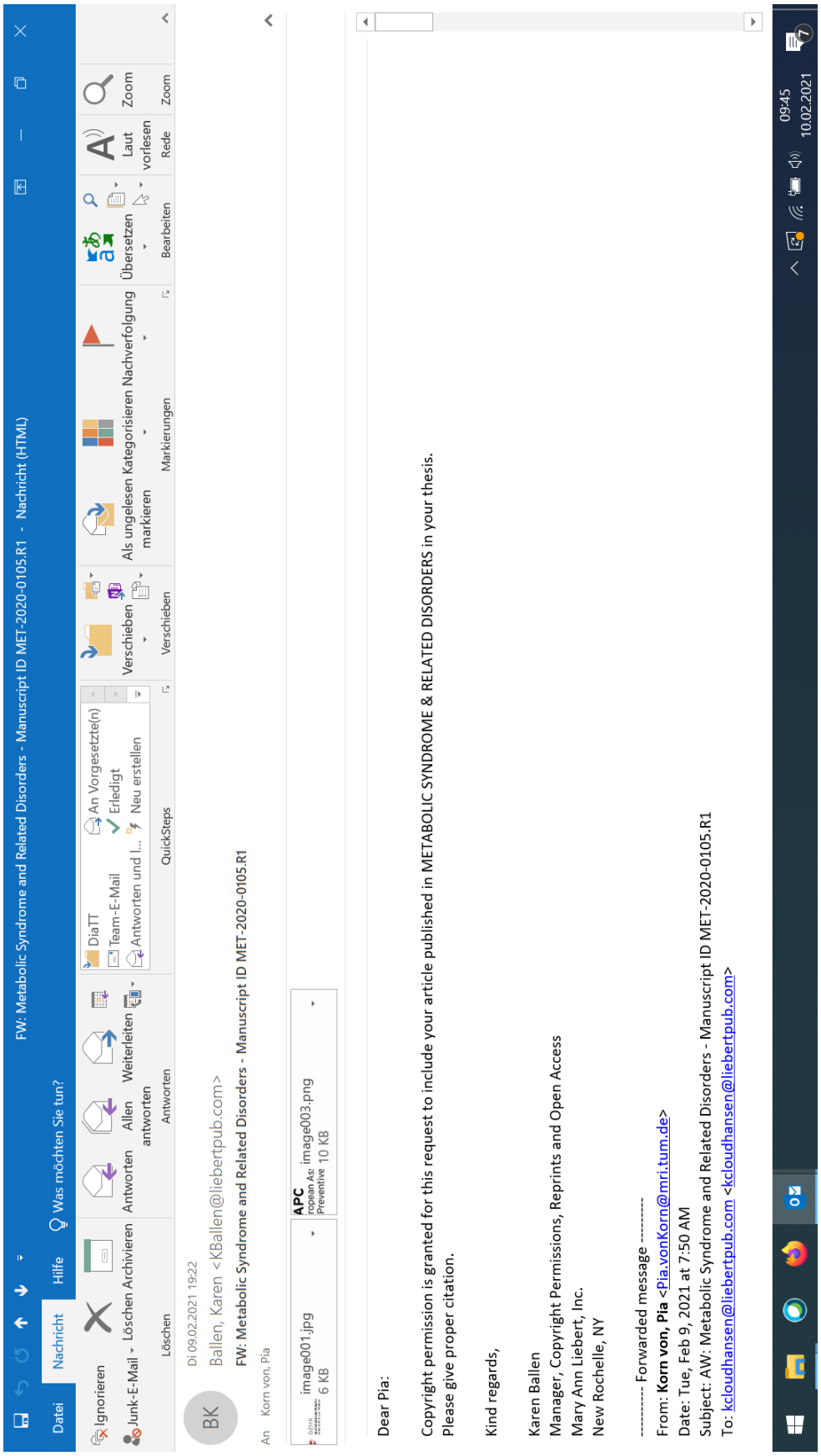

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