JYU DISSERTATIONS 638

Earric Lee

Alterations to Cardiovascular Function from Sauna Bathing, and Exercise and Sauna in Populations with Cardiovascular Risk Factors

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF SPORT AND
HEALTH SCIENCES

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Esitetään Jyväskylän yliopiston liikuntatieteellisen tiedekunnan suostumuksella
julkisesti tarkastettavaksi Agoran luentosalissa B221.1 Delta
toukokuun 12. päivänä 2023 kello 12.

Academic dissertation to be publicly discussed, by permission of
the Faculty of Sport and Health Sciences of the University of Jyväskylä,
in building Agora, lecture hall B221.1 Delta, on May 12, 2023, at 12 o'clock.

JYVÄSKYLÄN YLIOPISTO
UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2023

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ISBN 978-951-39-9555-3 (PDF)
URN:ISBN:978-951-39-9555-3
ISSN 2489-9003

Permanent link to the online version of this publication: http://urn.fi/URN:ISBN:978-951-39-9555-3

Jyväskylä University Printing House, Jyväskylä 2023

Many are called, but because few chose to be chosen, few are chosen.

- Aldous Huxley -

ABSTRACT

Lee, Earric
Alterations to Cardiovascular Function from Sauna Bathing, and Exercise and Sauna in Populations with Cardiovascular Risk Factors
Jyväskylä: University of Jyväskylä, 2023, 117 p. + original papers
(JYU Dissertations
ISSN 2489-9003; 638)
ISBN 978-951-39-9555-3 (PDF)

A large population of the world leads relatively sedentary lifestyles, and is not physically active enough to achieve the health benefits of exercise. Although exercise has been well-established as a modulator of cardiovascular health, comparatively less is known about the effects of heat therapies such as Finnish sauna bathing on cardiovascular function. Moreover, in spite of the purported benefits of sauna bathing for post-exercise recovery, long-term adaptations to regular post-exercise sauna bathing have yet to be fully elucidated. The aim of the thesis was thus to examine both the acute and long-term effects of sauna bathing on cardiovascular function in populations with cardiovascular risk. In particular, the cardiovascular adaptations from a combination of regular exercise and sauna bathing. The present dissertation consisted of four studies. (I) Acute hemodynamic responses from 30 minutes of sauna bathing were assessed using a non-randomized trial (n = 102). (II) Similar hemodynamic markers were examined before and after a single 30-minute session (n = 77) of exercise followed by sauna bathing (EXS). (III) The effects of sauna bathing and EXS on markers of cardiovascular function were compared using a crossover trial (n = 72) where the participants underwent sauna bathing and EXS on separate days. (IV) Finally, the cardiovascular adaptations to EXS were compared to regular exercise (EXE) using an 8-week multi-arm randomized controlled trial (n = 47). (I) 30 minutes of sauna bathing led to improved arterial compliance and blood pressures acutely. (II) Similar effects in blood pressures were found in EXS, although there were no significant changes to arterial compliance. (III) Sauna bathing alone led to greater acute responses in hemodynamic markers compared to EXS. However, the effects from EXS were still present after 30-minutes of recovery. (IV) Systolic blood pressure, cardiorespiratory fitness, and total cholesterol levels were significantly improved after 8 weeks of EXS compared to EXE. The findings of the present dissertation study suggests that the addition of regular 15-minute sauna bathing post-exercise augments the beneficial cardiovascular adaptations elicited via regular exercise, in populations with cardiovascular risk factors. This is indicative of the complementary effects of regular sauna bathing to exercise and highlights the synergistic potential that ought to be explored further. This dissertation demonstrates that sauna bathing is able to effectively improve key health markers both acutely, and in the long-term when used regularly with exercise.
Keywords: sauna bathing, exercise, cardiovascular function, cardiovascular risk

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Lee, Earric
Liikunnan ja saunomisen aiheuttamat muutokset sydän- ja verisuonitautien riskitekijöihin
Jyväskylä: Jyväskylän yliopisto, 2023, 117 s. + alkuperäiset julkaisut
(JYU Dissertations
ISSN 2489-9003; 638)
ISBN 978-951-39-9555-3 (PDF)

Passiivinen elämäntapa on yleistynyt maailmassa. Suuri osa ihmisistä ei ole riittävän aktiivisia saavuttaakseen liikunnan terveyshyötyjä. Liikunta on vakiinnuttanut asemansa sydän- ja verisuoniterveyden edistäjänä, mutta koko kehon lämpöhoitojen, kuten tyypillisen suomalaisen saunan, vaikutuksista tiedetään hyvin vähän. Aiemmissa tutkimuksissa saunomisen on todettu vaikuttavan positiivisesti fyysisestä rasituksesta palautumiseen, mutta pitkäaikaisen säännöllisen harjoittelun jälkeisen saunomisen vaikutusta terveyteen ei ole riittävästi tutkittu. Väitöskirja koostuu neljästä osatutkimuksesta, joiden tavoitteena oli selvittää saunomisen välittömät ja pitkäaikaiset vaikutukset toimintoihin, keskittyen erityisesti säännöllisen liikunnan ja saunomisen yhdistelmän aiheuttamiin vaikutuksiin sydän- ja verenkiertoelimistöön. (I) Akuutit hemodynaamiset vasteet 30 minuutin saunomisen jälkeen arvioitiin käyttämällä ei-satunnaistettua koetta (n=102). (II) Tutkimuksessa selvitettiin samanlaisia hemodynaamisia markkereita, sekä ennen että 30 minuutin pituisen saunomisen jälkeen, sekä yhdistettynä harjoittelusta palautuminen saunomiseen (EXS) (n=77). (III) Saunan ja EXS:n vaikutuksia harjoitukseen verrattiin cross-over asetelmassa (n=72), jossa osallistujat saunoivat ja EXS eri päivinä. (IV). Lopuksi kardiovaskulaarisia muutoksia EXS:ään verrattiin säännölliseen harjoitteluun (EXE) käyttämällä 8 viikon monihaaraista satunnaistettua ja kontrolloitua tutkimusta (n=47). (I) 30 minuutin saunominen paransi valtimoiden toimintaa sekä verenpainetta akuutisti. (II) Samanlaisia vaikutuksia verenpaineessa havaittiin EXS:ssä, vaikka valtimoiden joustavuudessa ei tapahtunut merkittäviä muutoksia. (III) Pelkkä saunominen johti suurempiin akuutteihin vasteisiin hemodynaamisissa markkereissa verrattuna EXS:ään. EXS:n vaikutukset olivat kuitenkin edelleen olemassa 30 minuutin palautumisen jälkeen. (IV) Systolinen verenpaine, kardiorespiratorinen kunto ja kolesteroliarvot paranivat merkittävästi 8 viikon EXS:n jälkeen verrattuna EXE:hen. Tämän väitöstutkimuksen tulokset viittaavat siihen, että säännöllisen 15 minuutin saunomisen lisääminen harjoituksen jälkeen lisää säännöllisen liikunnan hyödyllisiä kardiovaskulaarisia sopeutumisia henkilöillä, joilla on kardiovaskulaarisia riskitekijöitä . Tämä on osoitus säännöllisen saunomisen ja harjoittelun täydentävistä vaikutuksista ja korostaa niiden yhteistä vaikutusta, mitä pitäisi tutkia edelleen.
Avainsanat: saunominen, liikunta, sydän- ja verisuonitoiminta, sydän- ja verisuonisairauksien riski

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ACKNOWLEDGEMENTS

I wish to thank my supervisor Professor Jari A. Laukkanen for his respect, understanding and for believing in me, in addition to providing an opportunity to work and conduct research independently. I would also like to thank Associate Professor Juha Ahtiainen for his continued support throughout my PhD studies. I was also very fortunate to have received a personal grant from the Finnish Cultural Foundation (SKR), which alleviated a great amount of pressure.

This work was only made possible because of a list of people who I sincerely wish to give credit to, and show appreciation for. Dean Sarianna Sipilä who assisted, and approved my doctoral student application. Tanjaniina Laukkanen, for her help in all stages of this work. Susanna Pasanen, who advised, helped, and forgave me for the times I made mistakes. Eeva-Maija Palonen, for her incredible flexibility and tolerance. All the laboratory staff, namely Risto Puurtinen, Mervi Matero, Jukka Hintikka and Hanne Tähti for their patience and skilled laboratory support throughout every project. Joel Kostensalo for all his hard work and tremendous cooperation in performing the statistical analyses objectively. Eero Haapala and Sira Karvinen for inspiring me to do greater things. All of the participants, who did not give me a hard time despite my poor Finnish language skills at the time, and perhaps still.

I was fortunate to have two leading experts in the field review my thesis. Associate Professor Daniel Gagnon (University of Montreal, Canada) and Professor Tiina Ikäheimo (The Arctic University of Norway, Norway). I sincerely thank them for their invaluable time, and enlightening feedback, which have greatly improved the final version of my thesis. I am also most honored to have Professor Hans Hägglund (Uppsala University, Sweden) as my opponent.

The next person deserves special mention. One of the most important people, whom I will always be grateful for, is Iiris Kolunsarka. Her unbelievable work ethic as a research team member was one of the key ingredients that contributed to the success of the randomized controlled trial, which was the final study. Things would have been very different indeed, without her efforts. To all the connections I am extremely privileged to have, those who would consider themselves my friend, particularly those who stuck around through all the volatility. Although you may think that you had no direct input in my research or writing; the conversations, discussions, and support you provided are the vibrations that allowed me to *be* and explore this potential.

Lastly, to both my parents, and their parents before them. For my existence is a culmination of their efforts and love. I sincerely hope that I have made them, and everyone who has worked with me proud.

This book is specially dedicated to my late Father Lee Yong Peng (李侖憑), his mother, Chen Xing Mei (陳襯梅) and those who continue to live on through me.

Jyväskylä 13.04.2023
Earric Lee

ORIGINAL PUBLICATIONS AND AUTHOR CONTRIBUTION

This dissertation is based on the following four original publications, which are referred to in the text by their Roman numerals.

I **Lee, E.**, Laukkanen, T., Kunutsor, S.K., Khan, H., Willeit, P., Zaccardi, F. and Laukkanen, J.A., 2018. Sauna exposure leads to improved arterial compliance: Findings from a non-randomised experimental study. *European Journal of Preventive Cardiology*, 25(2), pp.130-138. https://doi.org/10.1177/2047487317737629

II **Lee, E.**, Willeit, P., Laukkanen, T., Kunutsor, S.K., Zaccardi, F., Khan, H. and Laukkanen, J.A., 2020. Acute effects of exercise and sauna as a single intervention on arterial compliance. *European Journal of Preventive Cardiology*, 27(10), pp.1104-1107. https://doi.org/10.1177/2047487319855454

III **Lee, E.**, Kostensalo, J., Willeit, P., Kunutsor, S.K., Laukkanen, T., Zaccardi, F., Khan, H. and Laukkanen, J.A., 2021. Standalone sauna vs exercise followed by sauna on cardiovascular function in non-naïve sauna users: A comparison of acute effects. *Health Science Reports,* 4(4), e393. https://doi.org/10.1002/hsr2.393

IV **Lee, E.**, Kolunsarka, I., Kostensalo, J., Ahtiainen, J.P, Haapala, E.A, Willeit, P., Kunutsor, S.K., and Laukkanen, J.A., 2022. Effects of regular sauna bathing in conjunction with exercise on cardiovascular function: A multi-arm, randomized controlled trial. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology*, 323(3), pp. R289–R299. https://doi.org/10.1152/ajpregu.00076.2022

The first publication (I) was designed by Jari Laukkanen and myself, while I designed and selected the statistical approaches for publications II and III. These first three studies were conducted at a lab built by Harvia Finland Oy in Muurame. I selected the research methodology for study IV with the assistance of Jari Laukkanen and Juha Ahtiainen. The intervention (IV) was conducted in the University of Jyväskylä with the help of Iiris Kolunsarka. I personally collected the data for all four studies (I–IV) for the publications as well as prepared most of the figures (I–IV). I performed the statistical analyses for I and II, while Joel Kostensalo performed them for III and IV. I had the main responsibility of the writing process in all the manuscripts.

FIGURES

TABLES

ABBREVIATIONS

AIx	Augmentation index
ANOVA	Analysis of variance
AP	Augmented pressure
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
cSBP	Central systolic blood pressure
CON	Control group
CRF	Cardiorespiratory fitness
CT	Circuit training
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DT	Diastolic time
EXE	Exercise only intervention
EXS	Exercise and sauna intervention
EX+SAUNA	Aerobic exercise plus sauna
HR	Heart rate
HR_{MAX}	Heart rate maximum
LVET	Left ventricular ejection time
MAP	Mean arterial pressure
PP	Pulse pressure
PWV	Pulse wave velocity
RCT	Randomized controlled trial
RPM	Revolutions per minute
SAUNA	Sauna bathing alone
SBP	Systolic blood pressure
SD	Standard deviation
TC	Total cholesterol
VO_2	Oxygen uptake
VO_{2MAX}	Maximal oxygen uptake
WHO	World Health Organization

CONTENTS

1 INTRODUCTION

The existence and use of the sauna first appeared in writing in the year 1112 (Rajala, 2000), although other sources have claimed an even earlier existence dating back to the 1st century BC (Barfield & Hodder, 1987). In spite of what is clearly a storied and lengthy history, the study of sauna bathing as a form of therapy remains somewhat underexplored. There is still a shortage of systematic research evidence to back its prescriptive usage, despite its popularity and potential as a lifestyle intervention akin to physical activity.

In a comparatively similar amount of time, physical activity has undergone a tremendous amount of research and development (Berryman, 2010; Hale 2008). Through the concerted efforts of the scientific community, we have learnt how to distinguish between aerobic and resistance exercise based on both their acute effects and long-term adaptations. More importantly, we have a much better understanding on how to manipulate variables such as volume, load, repetitions and frequency to ensure that the physiological overload would result in disturbances to homeostasis, which over time leads to adaptations (Adolph, 1955, 1964). Consequently, healthcare providers are better able to prescribe exercise to clinical and non-clinical population groups, as research in exercise medicine provides us with up-to-date knowledge on how to address specific diseases and health conditions.

The field of heat therapy as a whole shows promise (Brunt & Minson, 2021), and is gradually catching up to exercise training in that regard. Historically, the study of sauna bathing has been documented since the mid-40s (Hoske, 1945). However, majority of these studies were somewhat obscure, and often in languages other than English. This began to change in the 80s, as research on the sauna became more accessible from the 70s to 80s (Britton et al., 1974; Kauppinen & Vuori, 1986; Leppäluoto, 1988; Luurila, 1980; Röcker et al., 1982; Sohar et al., 1976; Taggart et al., 1972). In the early 90s, this accumulated knowledge was successfully applied to patient groups in the Japanese population (Tei et al., 1995), and were subsequently extended to those with cardiovascular disease (CVD) risk factors (Imamura et al., 2001). Nevertheless, it is important to note that these studies were performed using the infrared sauna either in animal models (Ikeda

et al., 2001; Ikeda et al., 2002), or in clinical populations (Kihara et al., 2002), and may not be directly comparable to the Finnish sauna.

In spite of the present progress, there is still a limited amount of information on the dose-response relationship and cardiovascular adaptations to Finnish sauna bathing, particularly in non-patient groups (Pizzey et al., 2021; Tsonis 2017). Moreover, we have yet to develop a clear understanding of how to manipulate fundamental variables such as exposure time, frequency of use, and temperature to gain a better comprehension of the adaptation threshold (Cullen et al., 2021). Interestingly however, heat exposure has been repeatedly shown to be a valid heat acclimation strategy for athletes (Liecht et al., 2018; Scoon et al., 2007; Stanley et al., 2015), via the mitigation of strain faced by the cardiovascular system in heat (Chalmers et al., 2014; Lorenzo et al., 2010).

With the promising results that were found in sauna studies for patient groups and heat acclimation protocols for athletes, the study of sauna bathing as a form of therapy further expanded. Together with the progress and support from molecular physiology research (Kim, Monroe, et al., 2020), the field has become more prominent, and numerous sauna-related studies have been published since (Brunt & Minson, 2021). However, robust experimental data on the long-term cardiovascular adaptations to Finnish sauna bathing is still lacking. Moreover, regular usage of the Finnish sauna and its compatibility with exercise remains somewhat understudied. Research has shown that the beneficial effects of physical exercise such as increases in mitochondrial enzyme activity and respiratory chain protein content are augmented by heat in vitro (Tamura et al., 2014), and the efficacy of exercise and sauna in combination for patient groups have been reasonably established (Haseba et al., 2016; Ohori et al., 2012). However, this has yet to be shown in a cohort more representative of the general population.

Data collected from different regions of the world shows that 90% of adults in both Australia (Australian Bureau of Statistics, 2015) and Canada (Heart and Stroke Foundation, 2022) have at least 1 risk factor for CVD, while nearly half (47%) of all adult Americans (Fryar et al., 2012) have at least 1 of 3 key risk factors for heart disease. Furthermore, majority of adult population in Europe (Gikas et al., 2016; Timmis et al., 2017) and Asia (Nguyen et al., 2013) have at least one CVD risk factor. This highlights the need for more preventative strategies in coping with the increasing prevalence of CVD risk in the general population. Thus, any plausible lifestyle intervention, especially one that could easily complement exercise such as sauna bathing, is worth exploring.

Therefore, the purpose of the present dissertation was to investigate in populations with at least one cardiovascular risk factor, the acute cardiovascular effects from (1) standalone sauna bathing, and (2) the combination of exercise followed by sauna bathing. A further objective was to (3) compare the difference in responses between sauna bathing, and exercise followed by sauna bathing. Beyond acute responses, the dissertation aimed to (4) determine if the addition of regular sauna bathing to regular exercise would confer increased beneficial adaptations over regular exercise alone, with a randomized controlled trial (RCT).

2 LITERATURE REVIEW

2.1 Cardiovascular disease risk factors

CVD is a leading cause of morbidity and mortality in western countries today (Bahls et al., 2020), and it has been estimated that more than 23.3 million people will die annually from CVDs by 2030 (Mather & Loncar, 2006). A substantial portion of the world population have at least one CVD risk factor, based on the latest data from the World Health Organization (WHO CVD Risk Chart Working Group, 2019). This is represented by a majority of the population in Australia (Collins et al., 2011), Canada (Public Health Agency of Canada, 2013), Europe (Timmis et al., 2017), United States (Fryar et al., 2012), and China (Li et al., 2020), which underlines the problems of public health in our modern society. It is thus vital to develop preventative strategies that target these groups, as it could alleviate the financial burden faced by public healthcare systems worldwide. Furthermore, individuals with CVD risk factors stand to benefit the most from interventions based on lifestyle modification (Eckel et al., 2014).

The five conventional CVD risk factors include: 1) Family history of coronary heart disease (CHD), 2) tobacco use, 3) high blood pressure (BP), 4) obesity, and 5) abnormal blood lipids (Vilahur et al., 2014; Yusuf et al., 2004). Among these, family history of CHD is non-modifiable, whilst the use of tobacco can be altered via cessation. However, the remaining three risk factors of high BP, obesity, and abnormal blood lipid levels are modifiable and could be potential targets of non-pharmacological interventions. Obesity in particular, is a direct contributor to high BP and hyperlipidemia, and is known to lead to the development of CVD independent of other risk factors (Powell-Wiley et al., 2021). In addition, elevated systolic BP (SBP), and total cholesterol (TC) have been shown to have strong associations with CVD event risks (Arsenault et al., 2009; Sesso et al., 2000).

2.1.1 High blood pressure

High BP level is the leading contributor to premature death according to the WHO, and is the risk factor most attributed for death worldwide in 2015 (Williams et al., 2019). High BP has been associated with a four-fold risk of developing heart failure or stroke, and a two-fold risk of CHD (deGoma et al., 2012). High BP directly mediates adverse cardiovascular outcomes through a variety of pathways including cardiac hypertrophy and endothelial injury (Brunner et al., 2005; Chobanian & Alexander, 1996). Furthermore, BP shares a continuous relationship with risk of cardiovascular events across all ages and ethnic groups (Lawes et al., 2003; Vishram et al., 2012), from high BP levels to relatively low values.

Specifically, the European Society of Cardiology, and Hypertension (ESC and ESH, respectively) defines hypertension as "the level of BP at which the benefits of treatment, either with lifestyle interventions or drugs unequivocally outweigh the risks of treatment, as documented by clinical trials", in addition to office SBP values ≥ 140 mmHg and/or diastolic BP (DBP) values ≥ 90 mmHg (Williams et al., 2019). Detailed classification is displayed in Table 1.

TABLE 1 Classification of office blood pressure (BP) and definitions of hypertension grade. BP category is defined by the highest level of BP, whether systolic (SBP) or diastolic (DBP). Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated. The same classification is used for all ages from 16 years (Adapted from Williams et al. 2019).

Category	**SBP (mmHg)**		**DBP (mmHg)**
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

2.1.2 Abnormal blood lipid levels (elevated blood cholesterol)

Abnormal blood lipids, specifically elevated blood cholesterol, is one of the main causal risk factors responsible for the development of atherosclerotic CVD (Benjamin et al., 2020). Longitudinal data from the renowned Framingham study (Gordon et al., 1977; Wilson et al., 1988), as well as others (Miller & Miller, 1975) have found a persistent positive relationship between CVD risk and TC that is statistically robust. Indeed, even exposure to moderately elevated cholesterol levels over the long term can lead to the development of CHD in the later years (Navar-Boggan et al., 2015). Furthermore, it has been estimated that elevated TC accounts for 88.7 million disability-adjusted life years, based on analyses from the Global Burden of Disease (GBD) study (GBD 2015 Risk Factors Collaborators, 2016). In adults over 20 years of age, TC levels of ≥ 240 mg/dL are considered high, while levels between 200 to 239 mg/dL are considered borderline high.

Elevated TC was most prevalent in the WHO European Region (54% for both sexes), followed by the WHO Region of the Americas (48% for both sexes) (Figure 1). As such, untreated TC levels <200 mg/dL has been defined by the American Heart Association as an important component of ideal cardiovascular health (Lloyd-Jones et al., 2010). Although this can be achieved via drug therapy, a wealth of research has shown that non-pharmacological interventions such as increasing ones' levels of physical activity (Piercy et al., 2018) may accomplish that as well. Moreover, lifestyle modifications such as regular exercise also helps mitigate other risk factors like high BP and obesity, and reduces the overall likelihood of CVDs like stroke and type 2 diabetes amongst many others.

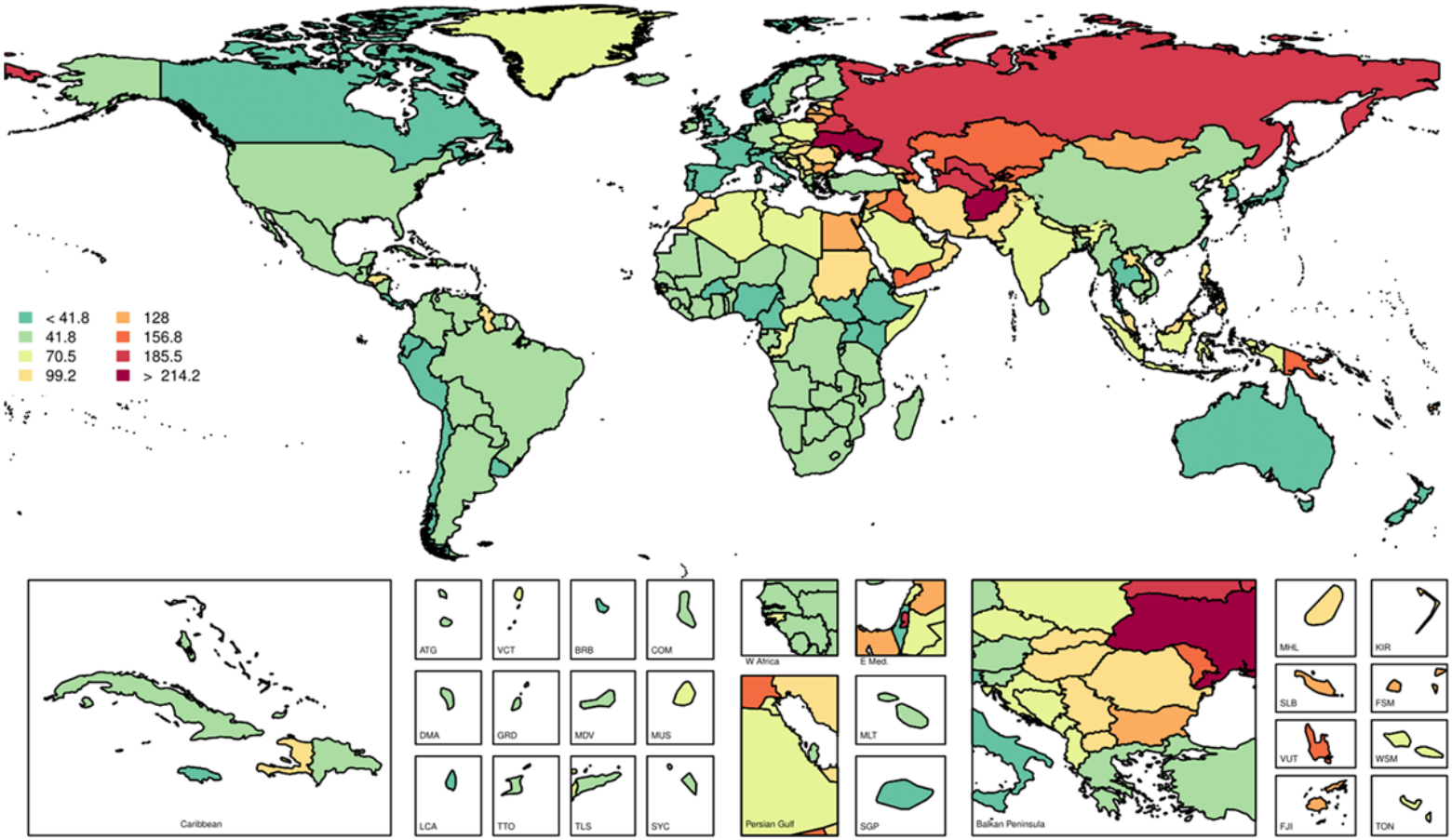

FIGURE 1 Age-standardized global mortality rates attributable to high total cholesterol (TC) per 100 000, both sexes, 2016. Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Micronesia, Federated States of; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa (Adapted from Benjamin et al. 2020).

2.1.3 Obesity

The WHO and several other prominent bodies use body mass index (BMI) to classify overweightness and obesity (Powell-Wiley et al., 2021). Obesity is defined as having a BMI ≥30 kg/m^2, and is a complex, multifactorial problem that has been linked to several CVDs such as pulmonary hypertension and stroke (Rahmani et al., 2020). According to the WHO, the global prevalence of obesity has nearly tripled from 1975 to 2016, and an estimated 13% of the world's adult population (11% of men and 15% of women) were obese (Table 2). Furthermore, people with obesity tend to have a shorter overall lifespan, and often develop and live with some form of CVD for a large proportion of their lives (Khan et al., 2018).

However, appropriate strategies to increase energy expenditure such as physical activity and exercise is one of the tools that could potentially mitigate the weight gain that often leads to obesity and consequently, the rates of obesity (Hill et al., 2012). Indeed, prevention of obesity has been postulated to be easier than its reversal from an energy balance point of view (Stone et al., 2021), as our physiological system appears to respond more favorably to the preservation of pre-existing bodyweight than to defend against positive energy balance and subsequent weight gain (Dullo & Jacquet, 1998; Jebb et al., 1996). Nevertheless, increased physical activity and exercise still confers many benefits to cardiovascular function and overall health, particularly for the obese.

TABLE 2 A comparison of the estimated age-standardized prevalence of obesity (BMI ≥30 kg/m2) among adults between 1975 and 2016. Data are presented as percentages (%) with 95% CI. [Data extracted from https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-obesity-among-adults-bmi-=-30-(age-standardized-estimate)-(-)]

Location	**1975**			**2016**		
	Both sexes	Male	Female	Both sexes	Male	Female
(WHO) Global	4.7 (4 – 5.4)	2.9 (2.2 – 3.7)	6.3 (5.1 – 7.5)	13.1 (12.4 – 13.9)	11.1 (10.2 – 12.2)	15.1 (14 – 16.2)
Africa	2 (1.4 – 2.8)	0.6 (0.3 – 1.1)	3.3 (2.2 – 4.8)	10.6 (9.6 – 11.7)	5.6 (4.5 – 6.8)	15.3 (13.6 – 17.1)
Americas	9.5 (7.8 – 11.4)	7.4 (5.3 – 9.9)	11.5 (8.9 – 14.5)	28.6 (26.6 – 30.5)	25.9 (23.2 – 28.8)	31 (28.2 – 33.7)
Eastern Mediterranean	5.7 (4 – 7.7)	0.2 (0.1 – 0.4)	9 (5.8 – 12.8)	20.8 (19.1 – 22.6)	15.7 (13.5 – 18.1)	26 (23.4 – 28.7)
Europe	9.9 (8.2 – 11.9)	6.4 (4.7 – 8.4)	12.8 (9.9 – 16.1)	23.3 (21.7 – 24.9)	21.9 (19.8 – 24.1)	24.5 (22.2 – 26.7)
South-East Asia	0.4 (0.2 – 0.7)	2.6 (1.5 – 4.3)	0.6 (0.3 – 1.1)	4.7 (3.9 – 5.6)	3.3 (2.4 – 4.3)	6.1 (4.9 – 7.6)
Western Pacific	0.8 (0.6 – 1.1)	0.5 (0.3 – 0.7)	1.1 (0.7 – 1.7)	6.4 (5.2 – 7.7)	6 (4.4 – 8)	6.7 (5.1 – 8.7)

BMI, body mass index; CI, confidence interval; WHO, World Health Organization.

2.2 Cardiovascular function

The primary organ of the cardiovascular system is the heart, which serves as a pump for the transportation of blood supply via the blood vessels. One of the key functions of this system is to shuttle blood to and from the entire human organism. The blood vessels subsequently direct blood flow to specific parts of the body based on the requirements in any particular given moment. As such, the amount of blood and its velocity in the vessels can vary accordingly to the various stimuli present (Klabunde, 2021). The function of the system is achieved through the two main loops of pulmonary and systemic circulation. Pulmonary circulation allows for the blood to be oxygenated, whilst systemic circulation is the means by which nutrients and oxygenated blood are carried to the rest of the body.

The blood vessels can be broadly categorized as arteries, capillaries and veins, with each one serving an intricate and specific purpose in the complex operation. The arteries serve to carry blood away from the heart and can be further distinguished as small and large arteries. With more smooth muscle, the small arteries such as the arterioles regulates blood flow by contracting or relaxing. The large arteries in contrast, are more elastic and thicker to accommodate the high amounts of pressure received from the blood, which is pumped directly from the heart left ventricle to the large arteries (Chaudhry et al., 2022). Nevertheless, BP decreases from the arteries to the veins as a result of the increase in resistance occurring at the arterioles (Figure 2).

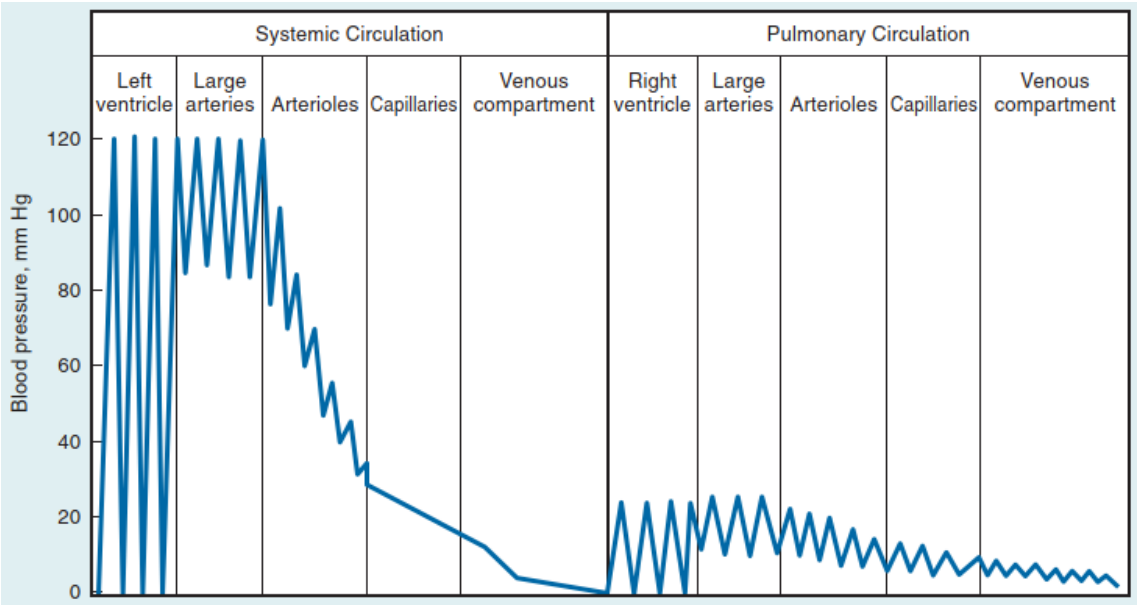

FIGURE 2 The progressive blood pressure changes from the ventricles of the heart to the arteries and the rest of the downstream components of the vasculature (Adapted from Crystal et al., 2019).

Arterioles, with its relatively higher amounts of smooth muscle, is capable of greater change in resistance. Dilation of arterioles leads to a decrease in resistance, thereby increasing blood flow to the rest of the vasculature and a small decrease in BP. Conversely, its constriction increases resistance, which causes a decrease in blood flow to downstream capillaries and consequently leads to relatively larger decreases in BP (Klabunde, 2021). Nevertheless, the loss of pressure at any given point of the vasculature is proportionate to the change in resistance at that point (Crystal et al., 2019). This is based upon Ohm's Law, a fundamental law of physics which states that current flow is equal to the voltage difference divided by resistance. This can be understood by the formula below:

$$Current\ flow\ (I) = \frac{Voltage\ difference\ (\Delta V)}{Resistance\ (R)}$$

From a physiological perspective as it pertains to fluid flow, voltage difference can be taken as the pressure difference, or otherwise known as perfusion pressure. Likewise, resistance may be viewed as the resistance to flow based on vessel compliance and its interaction with the flow of blood (Klabunde, 2021; Pollock et al., 2023). Based on these principles, the equation below is often referred to when considering the governance of blood flow:

$$Blood\ flow\ (Q) = \frac{Pressure\ difference\ (\Delta P)}{Vascular\ resistance\ (R)}$$

The reciprocal nature between blood flow and vascular resistance means that an increase in resistance decreases blood flow at any given perfusion pressure. Blood flow is primarily regulated by changes in vascular resistance as the human organism maintain arterial and venous blood pressures within a tight homeostatic range. However, changes in perfusion pressure could affect flow as well. This highlights the importance of the hemodynamic relationship between pressure differences and vascular compliance that generates blood flow (Klabunde, 2021).

2.2.1 Arterial distensibility and stiffness

Large blood vessels such as the arteries are typically characterized by their elasticity, which consists of a high percentage of elastic fibers. In the natural course of aging and/or presence of pathophysiological conditions such as atherosclerosis, the distensibility of the arteries is diminished (Belz, 1995; Sethi et al., 2014). This can be attributed to blood flow alterations in the vasa vasorum, and in particular, structural changes in the aortic wall. Changes in extracellular matrix protein composition on the vessel wall, increased oxidative stress, and vascular calcification are some of the main contributors to the weakening of the *Windkessel* effect – which facilitates pulsatile blood flow by providing biomechanical dampening of pressure during systole and maintaining arterial pressure during diastole (Lyle & Raaz, 2017).

As such, the distensibility of the arteries play a major role in the optimum function of the vasculature, and consequently arterial blood pressure (Kasliwal et al., 2015). In the past, arterial distensibility was measured either invasively or estimated from models of circulation. However, advances in technology have enabled clinicians and researchers to determine regional or local arterial stiffness non-invasively through several reproducible approaches (Laurent et al., 2006). Principally, arterial stiffness is based on the analysis of the pressure wave or the measurement of pulse wave velocity (PWV). PWV is the velocity at which the pressure pulse wave travels along the entire arterial system. Higher PWV is indicative of increased arterial stiffness, as the pulse wave would travel at lower speeds in more distensible arteries (O'Rourke, 2003).

PWV is typically determined using pulse waveforms from two different points in the vascular system (Figure 3), with the time difference between the 'foot' of each pulse waveform being recorded. The distance between these two points (D) divided by the time difference (Δt) provides the PWV within that particular region or segment (Kasliwal et al., 2015). Carotid-femoral PWV is the most widely accepted propagative model used for this foot-to-foot approach, and is supported by a number of well-documented studies (Izzo Jr, 2014; Sueta et al., 2015; Williams et al., 2018). Moreover, it is a measure that is closely associated with future CVD risk, and offers the closest proximation to the aorta, reflecting the aortic stiffness most accurately.

Regardless of the segment of interest, the precise measurement of D is imperative, as small inaccuracies may lead to large errors in the absolute value of PWV (Chiu et al., 1991). More specifically, shorter distances between the two recordings sites can lead to greater absolute errors in the determination of transit time (Reference Values for Arterial Stiffness' Collaboration, 2010). To mitigate this potential issue, a standardized formula of using 80% of the direct carotid to femoral distance [(common carotid artery - common femoral artery) x 0.8] measured from the right side of the body has been adopted, as it appears to be the most accurate; overestimating the real traveled distance by only 0.4% (Van Bortel et al., 2012).

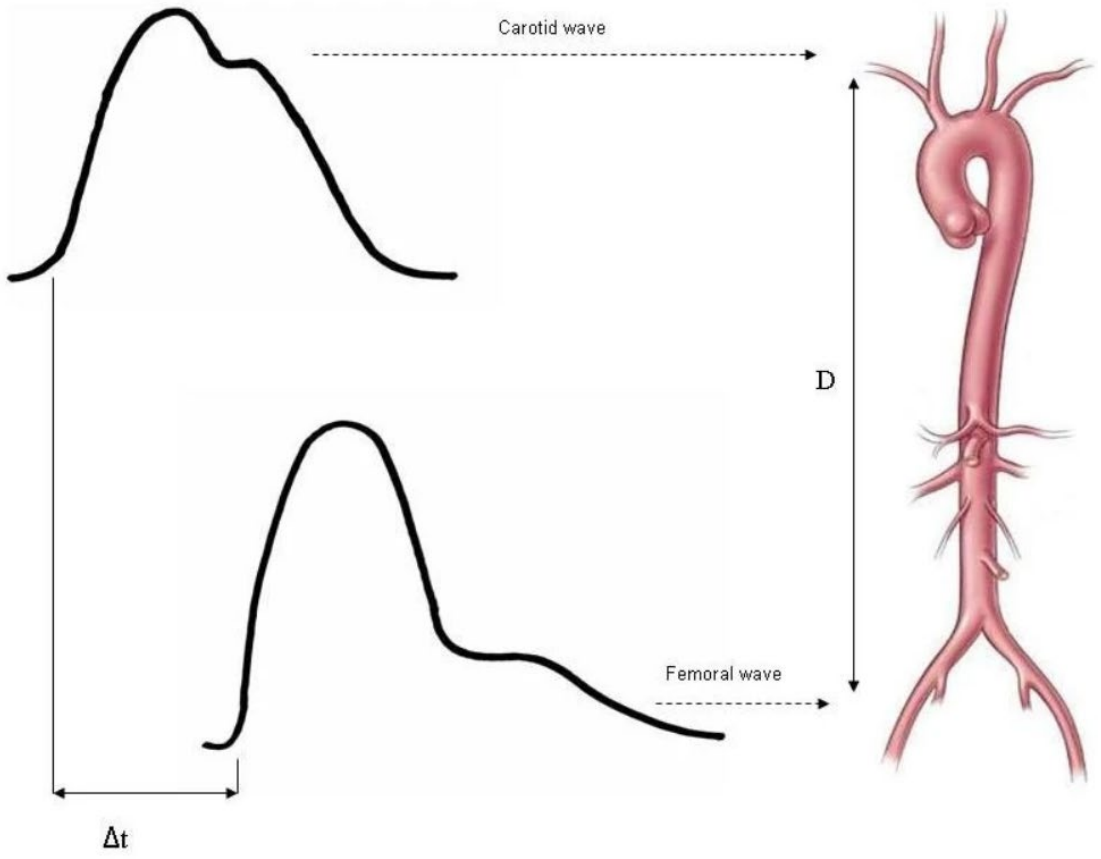

FIGURE 3 The determination of pulse wave velocity (PWV) via the foot-to-foot method. The beginning of the steep rise of the waveform, which corresponds to the end of diastole, is defined as the 'foot' of the pressure pulse wave. The time difference (Δt) is the time the foot of the wave takes to travel over a known distance (D). Current guidelines recommend the distance to be measured on the right side of the body, using 80% of the distance for the calculation [(D x 0.8)/ Δt] (Adapted from Calabia et al., 2011).

Increased stiffness of the central vasculature alters arterial pressure and flow dynamics, and can negatively impact cardiac performance and coronary perfusion (Zieman et al., 2005). The widening of pulsatile pressure and increased shear may potentially aggravate pre-existing endothelial dysfunction and vascular disease (Moore Jr et al., 1994). Stiffening of the vasculature increases the load placed on the heart as well, as it has to produce a higher end-systolic pressure in order to overcome the increased stiffness in the system for the same net stroke volume.

Furthermore, long-term ejection into a stiffer vasculature has also been found to induce cardiac hypertrophy (Lartaud-Idjouadiene et al., 1999). Arterial stiffness has also been shown to be inversely associated with cardiorespiratory fitness (CRF), and directly associated with BMI, SBP, and TC (Tanaka et al., 1998) (Figure 4). These are some of the main reasons why compliance or stiffness of the arteries has been closely linked to the development of CVDs, diastolic dysfunction, and left ventricular hypertrophy (Laurent et al., 2006). As such, PWV is an outcome that warrants more attention.

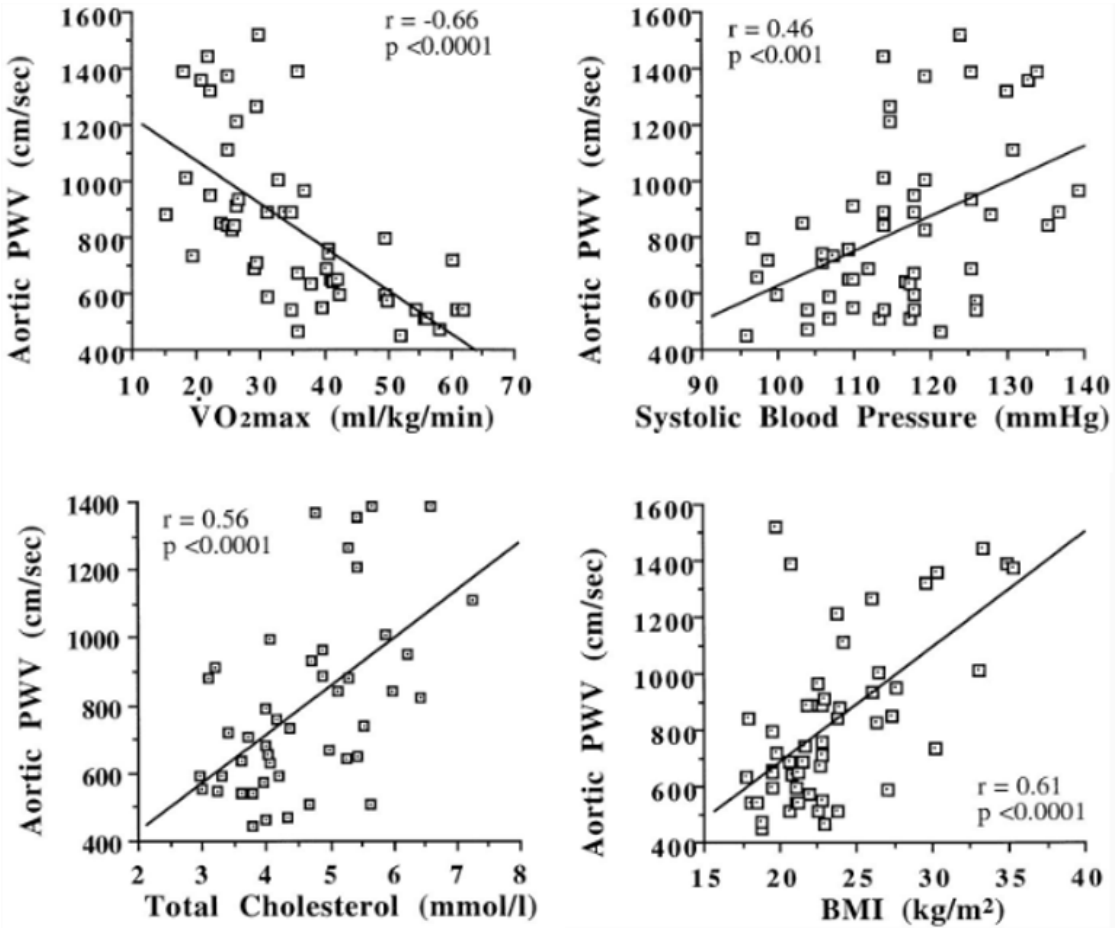

FIGURE 4 Relationship between pulse wave velocity (PWV) with the health determinants of body mass index (BMI), cardiorespiratory fitness (VO_{2MAX}), systolic blood pressure, and total cholesterol. All outcomes show a direct linear relationship, with the exception of VO_{2MAX}, which is inverse. Correlation coefficients are shown inset (Adapted and modified from Tanaka et al., 1998).

2.2.2 Blood pressures

The pressure of blood at any point in the vasculature can be described based on different components of the aortic pulse waveform, which is a composite of the forward pressure wave, and the reflected pressure wave (Pauca et al., 2001). The BP wave that emanates from the interaction between the mechanical properties of the large arteries and left ventricular ejection is the forward wave, while the wave returning from the periphery is the reflected wave (Kasliwal et al., 2015). The typically depicted aortic pressure curve is the amalgamation of these two waves (Figure 5).

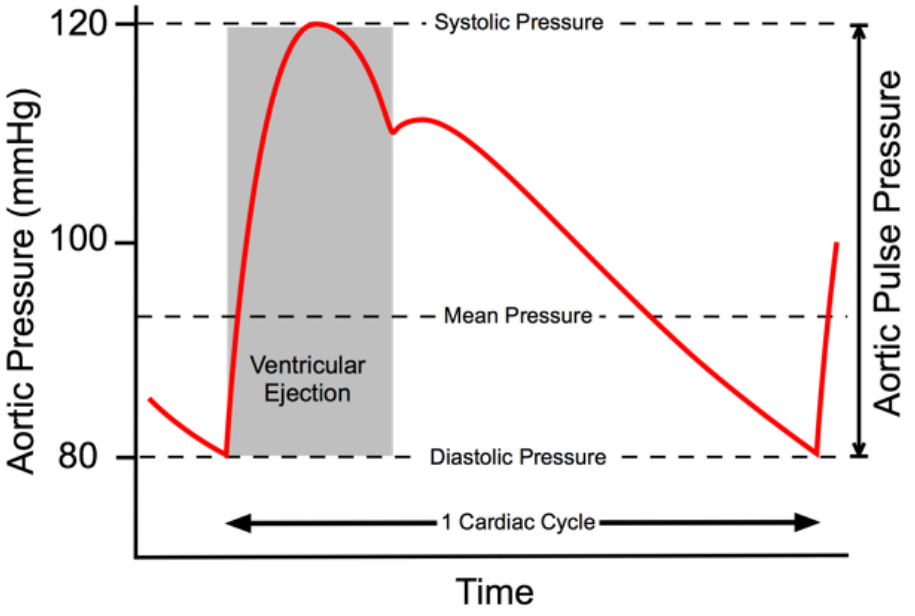

FIGURE 5 A graphical illustration of the aortic pressure curve during a single cardiac cycle under resting conditions assuming optimum systolic/diastolic blood pressure of 120/80 (Adapted from Klabunde, 2021).

Large arteries like the aorta are relatively elastic, which means that they can stretch and store the energy caused by contraction of the ventricles. The lowest pressure in an artery at the beginning of the cardiac cycle, during which the ventricles are relaxing and filling, is the DBP. The energy that was stored in the artery is then released by the recoil of the artery wall. This leads to a rise in pressure during ventricle contraction at the end of the cardiac cycle. The peak pressure in an artery at this phase is the SBP (Klabunde, 2021).

SBP is thus governed by the two principal factors of stroke volume and arterial compliance. The relationship that SBP has with stroke volume is direct; increases in stroke volume typically increases SBP, while its relationship with arterial compliance is inverse (Chaudhry et al., 2022). The difference between SBP and DBP is known as the pulse pressure (PP), and because of this intricate link, PP is also proportional to stroke volume and inversely proportional to arterial compliance, where an increase in elasticity decreases both PP and SBP. Practically therefore, the stiffer the artery, the larger PP will be.

Although DBP and SBP values do bear clinical significance, the primary pressure that sustains blood flow in the organs is the mean arterial pressure (MAP), which is the average pressure in the arteries over the duration of one cardiac cycle. However, due to the shape of the aortic pressure curve, the geometric value of MAP is less than the arithmetic average of SBP and DBP, and is closer to DBP. MAP is derived via the following equation: DBP + 1/3 (PP), and provides for a more complete assessment of vascular function.

Although there is no single value that can be ascribed for normal MAP, the maintenance of a minimum level of 60mmHg is vital for blood perfusion, and dropping below this level for a prolonged period of time can lead to serious

consequences (DeMers & Wachs, 2022). In addition, DBP, MAP and SBP have been shown to be inversely correlated with BMI in both men and women (Figure 6). Therefore, BP determination serves an important purpose of providing a valuable insight into the status of the vasculature in both acute, and chronic conditions.

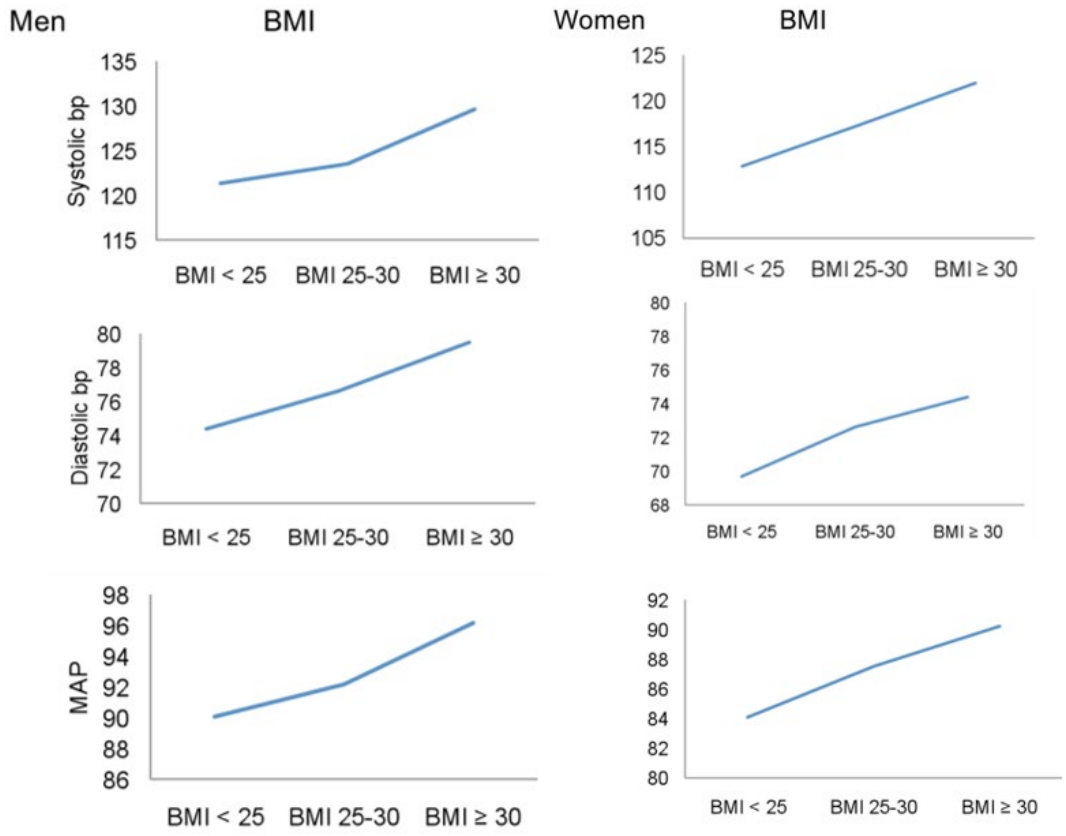

FIGURE 6 Associations of blood pressure (BP) and mean arterial pressure (MAP) to body mass index (BMI) categories for both men and women (Adapted and modified from Emaus et al., 2011).

2.2.3 Cardiorespiratory fitness

CRF is arguably one of the most important measures of functional capacity and overall health (Blair et al., 1989), and has been postulated to be a more robust predictor of mortality than other established CVD risk factors (Myers et al., 2002). Indeed, low CRF has been well documented as an independent risk factor of CVD morbidity and mortality (Gupta et al., 2011; Kodama et al., 2009; Laukkanen et al., 2022), and is supported by findings from animal models, which have shown that more physically active rodents with higher aerobic capacity have 28%–42% increases in life span compared to those with low aerobic capacity (Koch et al., 2011). A recent meta-analysis also showed that unfit individuals had twice the risk of mortality regardless of BMI (Barry et al., 2014), which highlights the importance of improving and maintaining CRF.

CRF or aerobic capacity, is commonly quantified by the measure of oxygen uptake (VO_2) and consequently, maximal oxygen uptake (VO_{2MAX}). VO_{2MAX} is a representation of the maximum aggregated capacity of 1) the pulmonary system for oxygen uptake, 2) the cardiovascular system for the transportation of oxygen, and 3) the muscular system to utilize the oxygen, in sequence (Poole et al., 2008). The concept of oxygen supply and utilization during exercise, and VO_{2MAX} were first established by A.V Hill and colleagues from a series of seminal work published in the 1920s, and largely stemmed from his interest in the study of endurance performance (Hill et al., 1924). These landmark studies have paved the way for researchers to expand and build upon to form the comprehensive framework that constitute our current understanding (Bassett Jr, 2002).

VO_{2MAX} can be determined reliably both directly or indirectly, depending on factors such as the application, research interest, or the population in question (Smirmaul et al., 2013). Direct methods are typically maximal incremental exercise tests on the treadmill or cycle ergometer, whilst indirect methods commonly involve the use of one of the well-established and validated submaximal testing protocols (Buttar et al., 2019) and subsequent mathematical estimations associated with it (Lee & Zhang, 2021). Regardless of the method in which it is derived, VO_{2MAX} remains a significant prognostic marker of CVD mortality (Celis-Morales et al., 2017), and has been shown to have an inverse relationship with PWV (Figure 4) and BP (Figure 7).

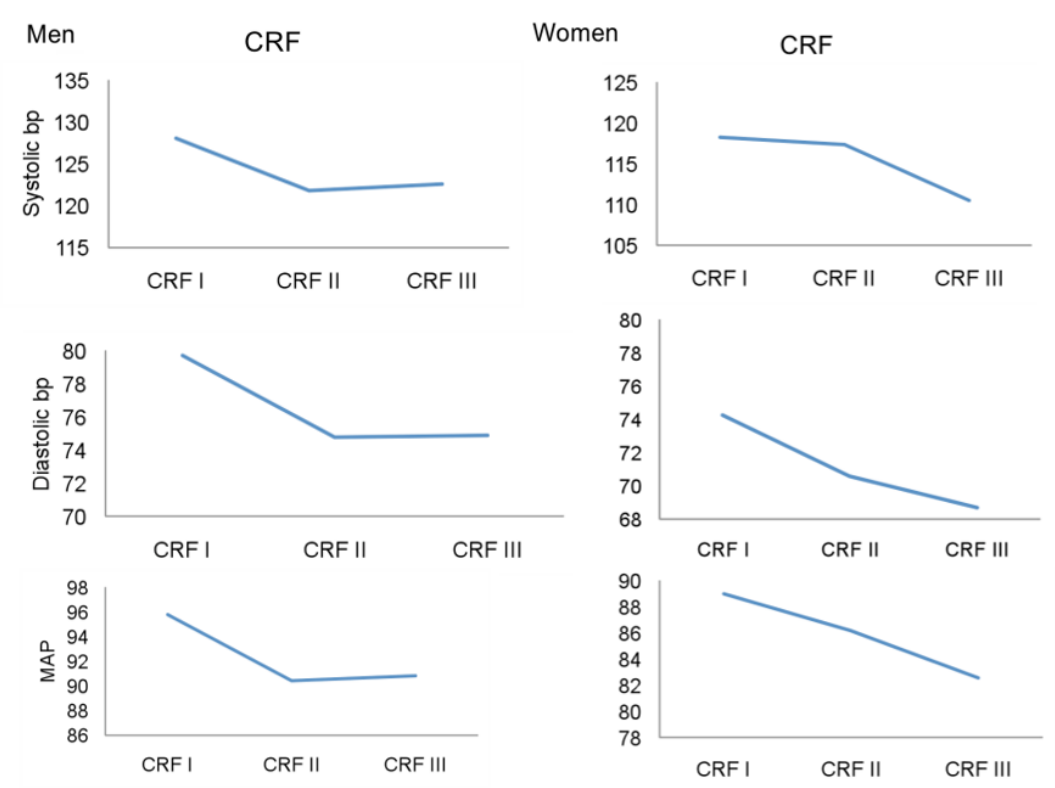

FIGURE 7 The relationship between blood pressures (BP) to cardiorespiratory fitness (CRF) based on categories of fitness level (low fitness, CRF I, VO_{2MAX} <32.4

ml/kg/min for women and < 39.6 ml/kg/min for men; medium fitness, CRF II, VO_{2MAX} = 32.4 - 37.5 ml/kg/min for women and 39.6 - 46.5 ml/kg/min for men; high fitness, CRF III, VO_{2MAX} >37.5 ml/kg/min for women and >46.5 ml/kg/min for men) (Adapted and modified from Emaus et al., 2011). MAP, mean arterial pressure.

2.3 Modulation of cardiovascular function

Physical activity is a well-established modulator of cardiovascular function (Ruegsegger & Booth, 2018). According to the most updated physical activity recommendations, physical activity accumulated in bouts of at least 10 minutes duration may mitigate CVD risk factors and improve a wide range of cardiovascular-related outcomes (Piepoli et al., 2016; Piercy et al., 2018). Additionally, the guidelines suggest a weekly dose of 150 – 300 min of moderate intensity physical activity, 75 – 150 min of vigorous intensity physical activity, or an equivalent combination of moderate intensity and vigorous intensity physical activity.

The terms physical activity and exercise are often used interchangeably. However, it is essential to distinguish between the two when a more nuanced discussion is involved. Physical activity can be defined as any bodily movement produced by the skeletal muscles that require energy expenditure, while exercise is a subcategory of physical activity that involves planning, structure and repetition that is purposefully focused on the improvement or maintenance of one or more aspects of physical fitness and/or performance (Dasso, 2019). In addition to improvements to physical health and function, exercise has also been well documented as a treatment for various chronic diseases (Pedersen & Saltin, 2015).

2.3.1 Physical exercise and arterial stiffness

Exercise has been well-documented to lower PWV acutely (Saz-Lara et al., 2021), particularly in continuous exercise modes which are pre-dominantly aerobic in nature (Kobayashi et al., 2017). Although these acute effects may be functional and transient in nature, exercise training has the potential to decrease the age-related increase in arterial stiffness, thereby improving the prognosis in individuals with increased cardiovascular risk (Ferreira et al., 2006). The application of repeated physiological stress from exercise can drive structural adaptations in the cardiovascular system, even if over a relatively short amount of time (Hellsten & Nyberg, 2015).

Similar to the acute effects, the adaptations of arterial stiffness to long-term exercise training are dependent on the modalities, and intensities of exercise (Ashor et al., 2014). Indeed, a review found that vigorous resistance training increased PWV, while aerobic or combined training had a beneficial lowering effect (Li et al., 2015) in both normotensive and hypertensive populations.

However, this was not seen for patients with isolated systolic hypertension, and underlines the importance of initiating exercise training sooner rather than later, as a preventive measure.

PWV is known to share a close relationship with BP levels (Laurent et al., 2006), as arterial wall stiffness has been shown to be intrinsically pressure dependent, with greater prominence in older individuals (Spronck et al., 2015). Exercise training results in vascular adaptations, which are largely driven by the complex interaction between hemodynamic forces, shear stress and local metabolic factors (Laughlin et al., 2017). Interventional studies have also shown concomitant reductions in PWV when BP is reduced (Collier et al., 2008, Figueroa et al., 2011).

2.3.2 **Exercise and blood pressure**

Single exercise sessions elicit acute and transient cardiovascular responses. However, the frequent repetition of these individual sessions produces more permanent adaptations, many of which are potentially favorable for CVD risk factors such as BP and blood lipids (Thompson et al., 2001). Exercise has been found to lower BP acutely, especially aerobic exercise (de Brito et al., 2019). This is due to the historically well-documented phenomena known as post-exercise hypotension (Kaul et al., 1966; Kenney & Seals, 1993). During the recovery period immediately after the cessation of exercise, there is a decrease in signal transduction from sympathetic nerve activation into vasoconstriction. Together with centrally mediated reductions in sympathetic nerve activity and local vasodilator mechanisms, they result in the hypotension typically seen after exercise (Halliwill et al., 2013).

One of the two recognized vasodilatory phenomenon is the immediate postexercise hyperemia, which can last between several seconds up to 20 min, whereas the second phenomenon is sustained postexercise vasodilatation, which typically lasts in excess of 2 h following moderate-intensity aerobic exercise (Laughlin et al., 2012). The magnitude and duration of immediate postexercise hyperemia is dependent on the length, intensity, and type of exercise (Halliwill et al., 2013). Studies have also shown that the magnitude of postexercise hypotension correlates highly with long-term blood pressure reductions produced by aerobic exercise training in prehypertensive patients (Heckesteden et al., 2012; Liu et al., 2012), and suggests that the magnitude of postexercise hypotension may be able to predict the long-term benefits of exercise training on BP.

Indeed, experimental exercise training studies have shown adaptative BP reductions with twelve weeks (Meredith et al., 1990), and as little as four weeks (Jennings et al., 1991) of aerobic exercise three times per week at moderate intensities. Resistance exercise has also been found to have a positive lowering effect on BP, particularly in older adults over 40 years of age (Ashton et al., 2020). However, it is important to note that some of these changes may have been confounded by higher pre-intervention BP levels, as it has been well-documented that greater reductions are seen in populations with larger initial resting values

(Muntner et al., 2019; Williams et al., 2019). Regardless, untrained individuals with low levels of CRF may not be able to sustain the requisite levels of exercise intensity to affect BP (Thompson et al., 2001), which highlights the interdependence of CRF and exercise training on both the acute responses, and adaptations to exercise.

2.3.3 **Exercise and cardiorespiratory fitness**

Exercise has been recognized to improve CRF (American College of Sports Medicine [ACSM], 2013; Piercy et al., 2018), which is one of the key determinants for endurance sporting performance in athletes and mortality in the general population (Harber et al., 2017; Pedersen & Saltin, 2015). Low CRF has an indirect effect on CVD risk and is partially mediated by risk factors such as elevated BP, hypercholesterolemia, and obesity amongst others (Erez et al., 2015). Numerous physiological factors that influence CRF such as oxygen transport capacity (e.g., cardiac output), diffusion of oxygen to working muscles (e.g., capillary density), and adenosine triphosphate generation (e.g., mitochondrial density) have been postulated to improve via exercise (Hellsten & Nyberg, 2015; Lundby et al., 2017).

Resistance training. Resistance exercise is often anaerobic in nature, and as the name suggests, relies mainly on anaerobic metabolism. The energy required to fuel resistance exercise is drawn from a combination of the body's creatine phosphate stores and glycolysis, and usually involves fast twitch muscles, whereas aerobic exercise relies on aerobic metabolism and the use of oxygen (Patel et al., 2017). In spite of the differences between the energy generation source, adaptations to resistance training do still confer positive effects on a number of markers related to cardiovascular health, such as VO_{2MAX}.

Contrary to the inconclusive findings for arterial stiffness, favorable adaptations to both resting BP and VO_{2MAX} have been found with resistance training, although it has not been a modality typically prescribed to improve CRF like aerobic exercise. Findings from a recent systematic review (Ashton et al., 2020) suggests that resistance exercise may be able to contribute to cardiovascular morbidity and mortality risk reduction, particularly in older adults. Nevertheless, it remains somewhat uncertain whether improvements in VO_{2MAX} from resistance training are more attributable to improved oxygen transport (via increased cardiac stroke volume) or metabolic adaptations resulting in improved use of oxygen at the level of skeletal muscle (Hellsten & Nyberg, 2015).

Circuit training. One effective and commonly used form of resistance training for the development of VO_{2MAX} is circuit-based resistance training or circuit training (CT), which generally comprises of single sets of several different exercises completed in succession, with little rest between sets and exercises. They are often performed with either a high number of repetitions (12 – 15), or more commonly using a pre-defined duration (e.g., 30 s) with a very short rest period between exercises, such as a 1:1 work to rest ratio (Ramos-Campo et al., 2021). The purported advantages of this type of training are that it produced improvements in aerobic conditioning, muscular endurance, and strength, all in just a single workout (Gettman & Pollock, 1981). Furthermore, CT has been

shown to produce a relatively high oxygen demand (45% of individual VO_{2MAX}), and consequently greater excess post-exercise oxygen consumption during recovery compared with a treadmill running when matched for aerobic energy expenditure (Braun et al., 2005).

Even though improvements to VO_{2MAX} via CT have been shown to be independent of participant characteristics, appropriate manipulation of the variables that determine the overall training load could augment the adaptations (Muñoz-Martínez et al., 2017). For instance, significantly larger effect sizes were found for training protocols at 1) an intensity of more than 60% of 1 repetition maximum, 2) for intervention durations lasting 6 to 12 weeks with between 14 – 30 total exercise sessions, and 3) with sessions that take 30 minutes or less (~20 – 30 min). In spite of the benefits in CRF that CT can elicit however, some studies have found the aerobic effects to be much less pronounced in those who are already relatively fit (Kraemer et al., 1995; Wilmore et al., 1978), and as such, recommend this form of training in populations with lower basal levels of CRF or as an introduction to longer term exercise training.

Aerobic training. Aerobic exercise training has been identified as one of the main and most effective way to improve CRF, and can be characterized as any exercise that uses large muscle groups which can be sustained continuously, and is rhythmic in nature (ACSM, 2013; Patel et al., 2017; Piercy et al., 2018). Some examples of aerobic exercise are cycling, dancing, long distance running or jogging and swimming. Aerobic exercise not only improves CRF, but several other markers of cardiovascular health as well (Patel et al., 2017). However, as with any other form of physical exercise, these benefits are often a direct consequence of long-term adaptations, and can only be reaped when they are performed regularly and maintained over an appropriate length of time (Hellsten & Nyberg, 2015).

Indeed, it has been suggested that longer training durations at lower intensities are required to see relatively larger changes in maximal cardiac output and consequently VO_{2MAX}, whereas very short periods of high-intensity aerobic exercise may be needed to reach a threshold for peripheral metabolic adaptations, (Lundby et al., 2017; Ruegsegger & Booth, 2018). This is indicative of the different exercise intensities and durations which are needed for different systems in the body, and underlines the biological implications for a dose–response relationship that has been extensively studied since 1965 (Bacon et al., 2013).

The intensity levels used for aerobic exercise are often expressed relative to VO_2 in the research laboratory. However, the assessment of VO_2 may not always be feasible or practical. Therefore, heart rate (HR) is often used as a practical and objective substitute measure of exercise work rates (Warburton et al., 2006a). Determination of an individual's maximum HR provides a convenient means of estimating the training HR range in most cases, which is why exercise prescription according to a percentage of individual HR maximum (HR_{MAX}) remains the primary technique used by health and fitness professionals (ACSM, 2013).

2.3.4 Sauna bathing

A large population of adults, adolescents and children lead relatively sedentary lifestyles and are not physically active enough (WHO, 2020) to achieve the health benefits of exercise, in spite of its well-documented benefits (Fried, 2016; Warburton et al., 2006b). In addition, untrained sedentary individuals and populations with low exercise capacities may not have the motivation, tolerance, and/or levels of CRF required for exercise (National Center for Health Statistics, US, 2016), which underlines the urgent need for possible alternatives, both as an adjunct to exercise, as well as a potential gateway to better cardiovascular health and lifestyle modification.

One viable intervention that has shown promise thus far is heat therapy, in the form of sauna bathing. The use of sauna bathing for potentially beneficial adaptations was first documented more than two decades ago by Japanese researchers (Tei et al., 1995; Tei & Tanaka, 1996; Tei, 2001). However, the acute effects of sauna bathing have been studied by the Germans (Burckhardt & Vollmar, 1946; Hoske, 1945; Ott, 1947) and Finnish (Eisalo, 1956; Hasan et al., 1966; Pekkarinen & Kinnunen, 1951) much earlier; even though many of these texts remain somewhat obscure, as they were not published in English and have yet to be translated for the public domain.

In fact, the results seen from much of the early research on the acute effects of sauna bathing gave rise to concerns over the well-being of those with cardiovascular risks (Ernst et al., 1986; Taggart et al., 1972), and even the average sauna bather (Sohar et al., 1976). However, as is the case in many other fields of science, there were conflicting reports from subsequent studies (Eisalo & Luurila, 1988; Vuori, 1988). Indeed, many of the acute responses to sauna bathing actually resemble that of acute physical exercise; hormonal alterations, loss of bodily fluids and electrolytes, increases in HR and vasodilatation which results in lower BP (Kukkonen-Harjula & Kauppinen, 1988; Kukkonen-Harjula et al., 1989).

The basic Finnish sauna is a wood paneled room with a rock-filled heater and wooden benches placed well above the floor level where bathers sit on. The air humidity can be slightly modified by tossing water on the heater rocks from time to time. The three key identifiers of a typical sauna in its various adaptations, forms, and sizes are: (1) high temperatures, optimally 80 to 100°C, at the face level of the bathers; (2) air humidity fluctuating between 15 and 30% relative humidity and (3) sufficient ventilation (Hannuksela & Ellahham, 2001; Kauppinen, 1997). The duration of a sauna exposure often varies on an individual basis, but usually lasts between five and 20 minutes (Heinonen & Laukkanen, 2018; Kauppinen, 1989).

The strain that sauna exposure puts on the cardiovascular system is based on a combination of the heat, humidity and length of exposure in the sauna room (Kauppinen, 1997). There is a redistribution of blood induced by an acceleration of the cutaneous skin blood flow; with a simultaneous reduction of blood flow to the kidneys and viscera. It has been suggested that the increase in cardiac output, driven primarily by the elevation in HR, is responsible for these changes (Cheng & MacDonald, 2019; Rowell, 1974), which allows BP to be maintained in spite of

the considerable decrease in peripheral vascular resistance encountered during sauna bathing. However, unlike physical exercise training, comparatively less is known about the acute responses to sauna bathing in cardiovascular health outcomes such as arterial stiffness and CRF. Moreover, research on the possible adaptations to sauna bathing is still somewhat lacking, particularly in the general population.

Early German researchers speculated that the sauna bathing could induce beneficial activity in a number of cardiovascular functions, enhancing overall health and thereby strengthening the defense systems (Ernst, 1989). However, many of these claims were unsubstantiated at the time, even though early research on heat acclimation reported improved cardiovascular stability, orthostatic tolerance and changes in protein pattern which reflect long-term stimulation of the immune defense system (Ernst et al., 1986). Nevertheless, regular sauna bathing has been shown to have promising therapeutic benefits such as lowering of BP, increasing of left ventricular ejection fraction, and improving lung function in hypertensive, chronic heart failure and obstructive pulmonary disease patients respectively (Hannuksela & Ellahham, 2001).

One of the first studies to investigate the effects of repeated sauna exposure (every day for seven days, 2 hours per exposure) in healthy individuals found a greater utilization of carbohydrates as reflected by significant decreases in respiratory quotient values with a concurrent and proportionate increase in VO_2 (Leppäluoto et al., 1986). The authors also concluded that there were no adverse cardiovascular reactions for participants of the experiment, which was similar to the findings made by Ernst and associates (1986), where eight weeks of sauna bathing twice per week showed no long-term deleterious effects. This was followed by a clinical trial that showed that regular sauna bathing (>3 months, twice per week) led to a significant reduction in colds. Specifically, the incidence of colds in the sauna bathing group was half that of the control group (Ernst et al., 1990).

Expanding upon their findings from an earlier acute study (Tei et al., 1995), Imamura and colleagues (2001) found that two weeks of sauna exposure once per day improved endothelial function and reduced bodyweight in individuals with traditional CVD risk factors such as hypercholesterolemia, hypertension, and obesity. These results were supported by a subsequent study on a similar population by the same group (Masuda et al., 2004), which showed lowered BP and oxidative stress marker levels. However, several methodological differences from the aforementioned series of studies need to be duly noted. These studies were conducted using a method known as Waon therapy, which is based on infrared sauna exposure with a temperature of 60°C for 15 minutes, followed by bed rest with blanket cover for 30 minutes. As such, the results may not be directly comparable to the Finnish sauna because of the differences in the room environment and overall stimuli presented.

Some other critical limitations to these studies have been pointed out as well (Beever, 2009). For instance, these studies failed to state the length of time between the last sauna session and the post-treatment measurements, which

could have had a bearing on the results seen. Moreover, they were all hindered by small sample sizes and relatively short intervention durations. More notably, all of the experiments were conducted on a hospitalized population by the same core group of researchers. This highlights the shortage of, and the need for higher quality studies in the area of sauna bathing, particularly for the traditional Finnish sauna.

More recently however, sauna bathing was shown to be associated with lower risk for sudden cardiac death and fatal CVD events, and that the frequency of sauna exposure was inversely associated with cardiovascular and all-cause mortality in a dose-dependent manner (Laukkanen et al., 2015). Specifically, the risk of CVD mortality was 27% lower in men who reported using the sauna 2 - 3 times per week compared to those who reported using it once a week. In addition, all-cause mortality was 40% higher in infrequent sauna users relative to frequent users. Moreover, a longer exposure time was found to be associated with lower risk for sudden cardiac death and fatal CVD events as well. Although more robust experimental studies with larger sample sizes are still needed to verify these findings, many of them do indeed appear to be theoretically plausible based on the prevailing literature on the mechanisms of heat therapy and its similarities to exercise (Kim et al., 2020; McGorm et al., 2018). Indeed, the cardiovascular burden induced by a bout of Finnish sauna bathing has been found to be comparable to moderate aerobic exercise (Ketelhut & Ketelhut, 2019), and when taken together, are suggestive of a possible synergy that may exist between the combination of exercise and sauna bathing.

2.3.5 Exercise in combination with sauna bathing

In 1987, Dr Clifford Hawkins stated that, "The sauna has no proved benefit in promoting fitness or preventing illness, but aches or pains are relieved and stiff joints loosened." He added that, "A sauna is not advisable in those who have recently taken strenuous exercise," (Hawkins, 1987). Concurrently however, another group of researchers in Australia (Ridge & Pyke, 1986) found that post-exercise sauna augmented the acute physiological responses seen from sauna bathing without exercise. Biro and coworkers (2003) later postulated that sauna bathing could potentially be utilized in combination with exercise, and since then, a growing number of studies have found positive modulations in other indices of cardiovascular function via post-exercise sauna bathing in both the acute (Gayda, Bosquet, et al., 2012; Gayda, Paillard, et al., 2012; Rissanen, Häkkinen, Laukkanen & Häkkinen, 2020; Rissanen, Häkkinen, Laukkanen, Kraemer, et al., 2020; Sutkowy et al. 2014) and short-term setting (Kirby, Lucas, Armstrong et al., 2021; Leicht et al., 2018; Scoon et al., 2007; Stanley et al., 2015).

Scoon and colleagues (2007) were one of the first to study a combination of exercise followed immediately by Finnish sauna bathing; on the hypothetical basis that adaptations to sauna bathing may enhance endurance performance. The study found that sauna bathing post-exercise produced a notable ergogenic effect in running performance, which was likely via blood volume increases. However, the study was conducted on a relatively small group of competitive

endurance athletes over a short time frame of three weeks. Furthermore, the sauna duration was for a continuous period of 30 minutes. Although it may have been manageable for this specific group of individuals, it may not be as well-tolerated by the general population. Moreover, it is not a common practice for typical sauna bathing. Nevertheless, the results were promising.

Two acute studies were conducted subsequently by Gayda and associates (2012). The experimental design used in both these studies were the same, with an element of external validity. Crossover comparisons were made between a control condition, a sauna only condition (2 x 8 minutes exposure), and an aerobic exercise followed by sauna condition. The first study (Gayda, Bosquet, et al., 2012) found that whether preceded by aerobic exercise or not, sauna bathing was able to induce a considerable increase in sympathetic drive, and a decrease in parasympathetic drive, in adult patients with untreated hypertension. The subsequent study (Gayda, Paillard, et al., 2012) found a decrease in daytime and 24-hour SBP for the exercise and sauna condition in a similar population. However, longer term studies were still needed to validate these findings.

Approaching it from a somewhat different perspective, Sutkowy and coworkers (2014) sought to determine the effect of sauna bathing on the balance between the oxidation and reduction reactions post aerobic exercise. The study showed that Finnish sauna bathing (3 x 10 minutes) was able to assist in the retention of oxidant-antioxidant balance after aerobic exercise in a relatively large group (43) of young adult men. Taking a similar approach, a group of Finnish researchers (Rissanen, Häkkinen, Laukkanen & Häkkinen, 2020; Rissanen, Häkkinen, Laukkanen, Kraemer, et al., 2020) explored the neuromuscular and hemodynamic effects of post-exercise sauna bathing in combination with several different exercise conditions. The researchers found that when matched for duration, resistance exercise followed by sauna bathing was more fatiguing from a neuromuscular performance standpoint. In addition, aerobic exercise followed by sauna bathing led to greater decreases in SBP. Interestingly, this reduction was sustained for 24 hours after, with a concomitant increase in plasma volume. Although the results of all three of these studies were able to shed some light on the acute effects of exercise and sauna bathing in combination, they lack generalizability as they were conducted on healthy young men. In addition, participants in these studies were regular sauna users.

Using a small sample of well-trained male cyclists (n = 7), a group of researchers (Leicht et al., 2018; Stanley et al., 2015) found that 30 minutes of uninterrupted sauna bathing immediately after daily training induced moderate-to-large plasma volume expansion following six exposures, reaching a peak after just four visits. However, this effect was not sustained as plasma volume levels gravitated towards pre-sauna values. This may be indicative of an adaptation to the thermal impulse that could be characterized as constant (Taylor, 2014). They also showed a significant reduction in parasympathetic and/or enhanced sympathetic modulations after a combination of a single training session followed by sauna bathing. However, repeated exposures over a continuous period of ten days did not result in any obvious effects on cardiac autonomic

control. This may have been due to several reasons. Ten days is a relatively short period of time for cardiovascular adaptations to occur. In addition, well-trained endurance athletes may already possess optimized cardiovascular function, which is likely to be more capable of handling the added stress.

Up to this point, all of the studies that were mentioned did not use CRF as an outcome parameter. This was investigated in a more recent study (Kirby, Lucas, Armstrong et al., 2021), where VO_{2MAX} was assessed in a group of young trained middle-long distance runners. A significant improvement in CRF (~8%) was found in the training plus sauna group compared to the training only group after three weeks. Although the study employed a similar sauna duration (continuous 30 minutes) and number of exposures (9 ± 1), the frequency was dispersed; participants in this study used the sauna three times per week over a course of three weeks. Exercise performance markers such as time to exhaustion and running speed at clamped lactate levels were also improved. These results did not differ between sexes as well (Kirby, Lucas, Cable et al., 2021). However, in spite of the encouraging results, CRF was unfortunately not re-evaluated at the end of the study at the 7-week mark.

As has been highlighted in the preceding chapters, a common intervention for the treatment of chronic conditions and diseases is exercise training. Even though the long-term adaptations are often what is advocated and sought, there are positive effects from a single bout of exercise as well. Increases in insulin sensitivity (Braun et al., 1995; Holloszy, 2005), and decreases in blood lipid (Crouse et al., 1997; Grandjean et al., 2000) and BP levels (Halliwill et al., 2013) have been found after a single session of dynamic exercise, making the post-exercise period an optimum "window of opportunity" for adjunctive interventions, especially in individuals with these CVD risk factors (Luttrell & Halliwill, 2015). It might thus be the ideal time when non-pharmacological interventions such as sauna bathing may act synergistically with enhanced insulin sensitivity and blunted blood lipid levels.

Sauna bathing immediately following a physical exercise session may augment the thermoregulatory-adaptive response, as core temperature, a key contributor to heat acclimation induced adaptations (Horowitz, 2002) was shown to rise to a greater extent compared with sauna bathing alone (Ridge & Pyke, 1986). The postexercise recovery period, when angiogenic factors are elevated (Richardson et al., 1999), may also be an ideal time in which additional interventions such as sauna bathing could prove more potent. It may be possible that altering blood flow or oxygen delivery post-exercise can have an additive or synergistic effect on angiogenic signaling induced by exercise alone, although this has yet to be experimentally established in humans. Nevertheless, adjunct interventions that are able to take advantage of this mechanism may be a viable option in individuals who are low responders, or resistant to exercise training alone.

Thus far however, only two long-term studies have been conducted to investigate the combination of physical exercise and sauna (Haseba et al., 2016; Matsumoto et al., 2011). Matsumoto and associates (2011) studied female patients

with fibromyalgia syndrome using a 12-week program that combined sauna therapy and underwater exercise. Outcomes for the investigation were pain, symptoms and quality of life scores based on questionnaires. The research showed notable decreases (31 – 77%) in pain and symptoms, as well as improvements in quality of life. However, there was no comparator group, and no objective physiological biomarkers or parameters were measured. Moreover, there was no mention of whether sauna therapy occurred on the same day as the exercise sessions, although it was reported that exercise and sauna therapy were performed two, and three times a week respectively.

Subsequently, Haseba and coworkers (2016) compared the effects of sauna therapy to combined exercise and sauna therapy in patients of both sexes with chronic heart failure. Sauna therapy and exercise trainings were both performed for five days a week, with sauna therapy occurring in the morning, while the exercise sessions that lasted between 40 – 60 minutes were conducted in the afternoons. The research showed similar improvements in cardiac function, exercise tolerance, and decreased cardiac size on chest radiography for both interventions. However, the combined exercise and sauna group produced a statistically higher level of significance to changes in functional classification, ambulation capacity and activities of daily living when compared to the sauna only group.

Although positive results were found in both experiments, it must be noted that both studies were performed on patient groups, and once again, may not be representative of the population at large. Furthermore, these studies were performed using the Waon therapy method, which has been described in the preceding section and is rather different to a typical Finnish sauna bathing session. Crucially, they also did not take advantage of the post-exercise window of opportunity, as sauna bathing was not performed immediately after exercise. Therefore, despite the immense progress we have made to further our understanding on sauna bathing, and exercise in combination with sauna bathing, several gaps in the literature remain.

Presently, we do not have a complete understanding of the acute effects of the Finnish sauna on vascular function markers such as arterial stiffness, in a group of individuals that represents the general population. In addition, it remains somewhat unclear what the cardiovascular responses of these individuals are, to a bout of exercise followed by sauna bathing. Lastly, robust experimental trials investigating the longer-term adaptations to a combination of exercise followed by sauna bathing are still lacking. Having this information will not only help us gain a better understanding of the complementary potential that sauna bathing has with exercise, but also allow us to prescribe it more effectively in conjunction. As such, research into these much-needed aspects is warranted.

3 PURPOSE OF THE DISSERTATION

The purpose of the present dissertation was to systematically examine the acute cardiovascular responses to sauna bathing, and exercise and sauna bathing as a single intervention in populations with CVD risk factors. By utilizing matched durations, these cardiovascular responses were subsequently compared between sauna bathing and the combination of exercise and sauna bathing in the same population group. Finally, the adaptations of cardiovascular function from regular exercise and sauna were compared to regular exercise alone in a similar population group of non-frequent sauna users.

The first study examined the acute hemodynamic responses of typical Finnish sauna bathing, while the second and third study focused on sauna bathing as an adjunct to exercise in a population with CVD risk factors. The main objectives were to:

1. Investigate the acute responses and their recovery profiles after a single session of 30-minute sauna bathing. (I)

2. Explore the acute effects of a short bout of aerobic exercise followed by sauna bathing. (II)

3. Compare the acute responses between a single session of sauna bathing, and a combination of exercise followed by sauna bathing using matched durations. (III)

The final study examined the long-term adaptations to regular exercise and sauna bathing in markers of cardiovascular function in non-frequent sauna users with CVD risk factors. The main objective was to:

4. Determine if regular sauna bathing complements regular exercise, by comparing the adaptations from regular exercise, to regular exercise plus regular sauna. (IV)

The primary hypothesis was that sauna bathing would lead to a beneficial acute response in hemodynamic markers of cardiovascular function. Similar effects were anticipated from a bout of combined aerobic exercise and sauna bathing, based on their comparability. However, the combination of exercise and sauna bathing was expected to elicit a greater response compared to sauna bathing alone. Finally, it was hypothesized that regular exercise and sauna bathing would exert a greater stress and thus lead to more favorable adaptations in cardiovascular function compared to just regular exercise.

4 RESEARCH METHODS

4.1 Participants and ethics

Participants from all four studies had at least one common CVD risk factor, such as elevated blood pressure, obesity, elevated cholesterol, family history of CHD and/or a history of smoking. The same CVD risk factor criteria outlined below was employed. Pre-study resting SBP >139 mmHg and/or DBP >89 mmHg was considered elevated (Williams et al., 2019). Obesity was defined as BMI >30 kg/m^2, and total cholesterol level >239 mg/dl was considered elevated. Family history of CHD was positive if father (<55 years) or mother (<65 years) had premature CHD. History of smoking was positive if the participant was still a smoker at the time of the experiment or if they had quit within the past decade. Prior to participation, all participants were informed about the research purposes and measurement procedures before providing informed written consent. Blood lipid levels, medical history and resting ECGs of every participant was carefully assessed and screened by a cardiologist prior to any exercise testing or training. All participants were free of acute and chronic diseases, illnesses, and injury. A total of 102 participants between the ages of 30 – 64 from both sexes, with at least one CVD risk factor participated in the first three studies comprising papers I – III, while 47 participants took part in the RCT which formed study IV.

In addition to having at least one CVD risk factor, study IV also had the following inclusion and exclusion criteria. Participants were required to have a sedentary lifestyle; identified as having a deskbound job and less than 30 minutes of total physical activity per week and not commuting to work via activities such as running or cycling. Participants also had to be non-frequent sauna users, defined as using the sauna for once a week or less within the past six months. Because there was no intention to treat, Participants were also excluded if they had resting SBP <100 mmHg or >159 mmHg, BMI over 40kg/m^2, or if they were on any CVD medication. The baseline characteristics of the participants used in

all the studies are presented in Table 3. The experimental designs and research protocols for all the studies were approved by the institutional review board of the Central Finland Hospital District ethical committee, Jyväskylä, Finland (Studies I – III: Dnro 5U/2016; Study IV: Dnro 3U/2019).

TABLE 3 Baseline characteristics of participants from all included studies.

Study no. / Parameter	Study I	Study II	Study III	Study IV
Sample size (*n*)	102	77	72	47
Age (years)	52 ± 9	53 ± 10	54 ± 9	49 ± 9
Body mass (kg)	82.7 ± 16.0	83.2 ± 14.8	83.2 ± 15.0	89.0 ± 14.3
Systolic BP (mmHg)	136 ± 16	137 ± 16	143 ± 18	133 ± 12
Diastolic BP (mmHg)	82 ± 10	83 ± 10	86 ± 10	79 ± 10
CVD risk factors				
Obesity	20 (20%)	22 (29%)	22 (31%)	25 (54%)
Elevated BP	14 (14%)	15 (20%)	15 (21%)	16 (35%)
Elevated cholesterol	63 (63%)	51 (67%)	51 (71%)	10 (22%)
Family history of CHD	33 (34%)	31 (41%)	31 (43%)	18 (38%)
Smoking	10 (10%)	12 (16%)	12 (17%)	6 (13%)

BP, blood pressure; CHD, coronary heart disease.

4.2 Experimental approach

To understand the effects of sauna bathing, its therapeutic potential, and the synergy it might have with exercise, three studies examining the acute cardiovascular responses were conducted. The fourth and final study was aimed at investigating the long-term adaptations to a combination of regular exercise and sauna bathing.

4.2.1 Acute effects of sauna bathing (I) and exercise + sauna bathing (II)

The aim of the first study was to determine the acute effects of a single 30-minute session of sauna bathing (SAUNA), on cardiovascular function and hemodynamics. Arterial stiffness and BP were assessed at baseline, immediately after the sauna bathing, and after 30 minutes of rest. The entire duration was split into two 15-minute halves, in which participants were permitted to take a quick 60 second shower. Using a similar approach, the second study examined the effects of a short 15-min aerobic exercise bout, followed by 15 minutes of sauna bathing (EX+SAUNA) as a single intervention. This approach was selected based on the comparability of the acute and ambulatory BP lowering effects between 15- and 30-minute bouts of aerobic exercise (Guidry et al., 2006).

4.2.2 Comparison of sauna bathing and exercise + sauna bathing (III)

This study was conducted to compare the differences in responses between standalone sauna bathing and a combination of aerobic exercise followed by sauna bathing based on the results seen from Study I and II. Utilizing a balanced crossover design, the study compared the acute cardiovascular responses between sauna bathing alone (SAUNA), and exercise followed by sauna (EX+SAUNA). The study design is shown in Figure 8.

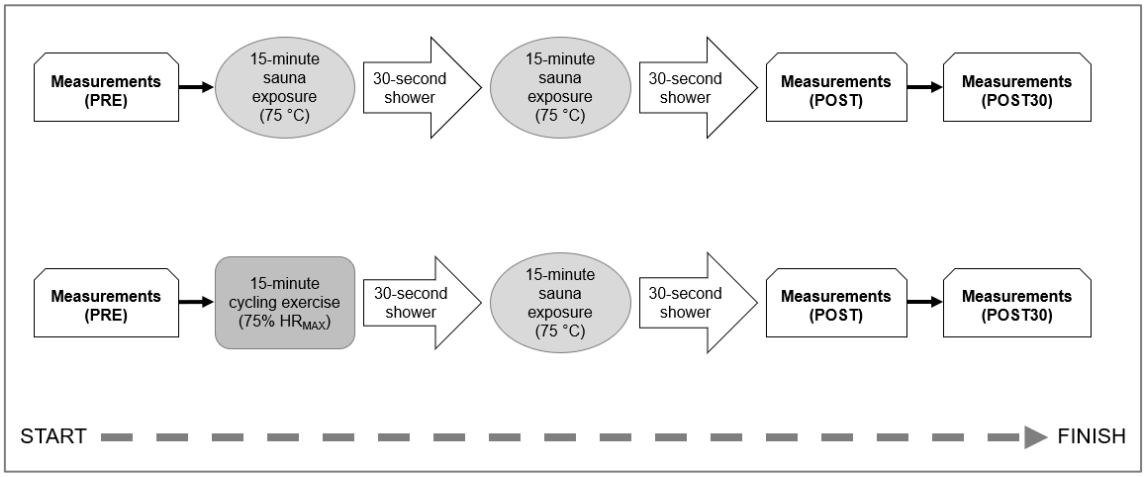

FIGURE 8 Experimental design and flow of Study III. PRE, pre-intervention; POST, post-intervention; POST30, 30 minutes post-intervention; HR_{MAX}, individual heart rate maximum.

4.2.3 Multi-arm randomized controlled trial (IV)

Participants were recruited through medium-to-large organizations (City council of Jyväskylä, Jyväskylä Energy, Central Finland Hospital District) via email invitations. Before the trial began, 60 participants attended an information session where they were briefed about the research purposes, measurement procedures, and intervention period. Five people dropped out. Subsequently, a prescreening session was conducted to collect baseline information (anthropometric data, resting electrocardiogram, and brachial BP) and to ensure that they met the study eligibility based on the inclusion and exclusion criteria. Seven participants who did not meet the criteria were excluded, leading to a final sample size of 48 participants.

Following successful completion of prescreening procedures, the 48 participants were stratified by sex and randomized into the regular exercise and sauna bathing (EXS), regular exercise alone (EXE), or the control (CON) group. One participant dropped out during the first week due to personal reasons, leading to a final sample size of 47. Figure 9 is an overview of the experimental design based on CONSORT guidelines (Boutron et al., 2017).

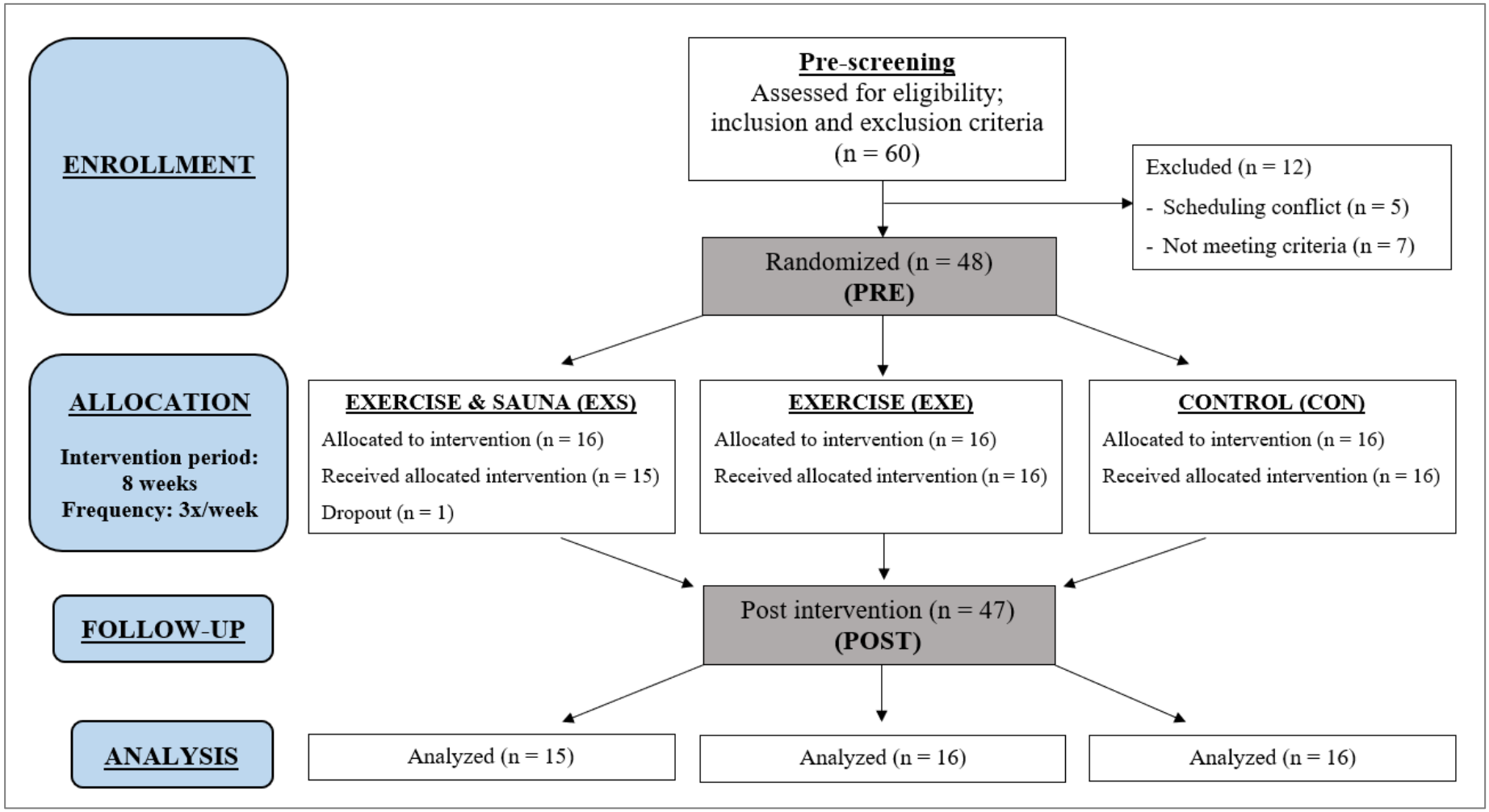

FIGURE 9 Experimental design and process of study IV (Adapted and modified according to CONSORT guidelines)

4.3 Interventions

Typical Finnish sauna was used for all the studies, and is characterized by air with a relative humidity of 10 – 20% and high temperatures (Heinonen & Laukkanen, 2018). There were separate rooms for men and women, and participants wore their own swimsuits for every sauna session. Participants were informed beforehand that they could leave the sauna at any time they felt uncomfortable, but every participant from all the four studies successfully completed the prescribed sauna exposure duration without having to leave the sauna room. Fluid was allowed to be consumed *ad libitum*. Studies I – III utilized a pre-post design with a follow-up measurement 30-minute post to track the recovery of outcome parameters. Study IV was an RCT that consisted of two different interventions.

Study I. A single session of 30-minute sauna bathing that was split into two 15-minute halves. After the first 15-minute interval, participants were permitted to take a short shower before continuing for another 15 minutes. The average temperature achieved over the entire course of the experiment was 73 ± 2 °C, and was recorded continuously as 10-second averages using a two-channel internal temperature sensor designed by Harvia Finland Oy, Finland.

Study II and III. A combination of 15 minutes of cycling exercise at 75% HR_{MAX} followed by 15 minutes of sauna exposure was used. The cycling cadence and its indicator lights were in full view of the participant for the entire 15-minute duration and flashed red when the cadence fell below 65 or surpassed 70 revolutions per minute (rpm). The cycling load in watts was monitored and adjusted throughout the duration of the exercise to ensure that the HR for each participant was kept at 75% HR_{MAX}. The transit time from the end of exercise to entering the sauna was kept to <120s so that the combination of exercise and sauna may be considered as one single intervention. The sauna intervention used in Study III was similar to the one in Study I.

Study IV. Two 8-week long exercise-based interventions with and without regular sauna bathing (EXS and EXE respectively) were used for the study (Figure 10). Both intervention groups exercised three times a week (Monday, Wednesday, and Friday) in the evenings, between 1600 – 2100. Makeup sessions were performed on Saturday if a Friday session was to be missed, and on Sunday, if the Monday session was to be missed. The intervention schedule was rigorously coordinated to ensure that no one missed the session on Wednesdays, and no more than one session out of a possible 24 would be missed by any participant. Training sessions were carried out in groups of 1 - 5 participants with two qualified instructors. The supervised exercise intervention consisted of both resistance and aerobic exercise training and was based on the Finnish national exercise guidelines (UKK-instituutti, 2019), which are adapted from the guidelines of the ACSM.

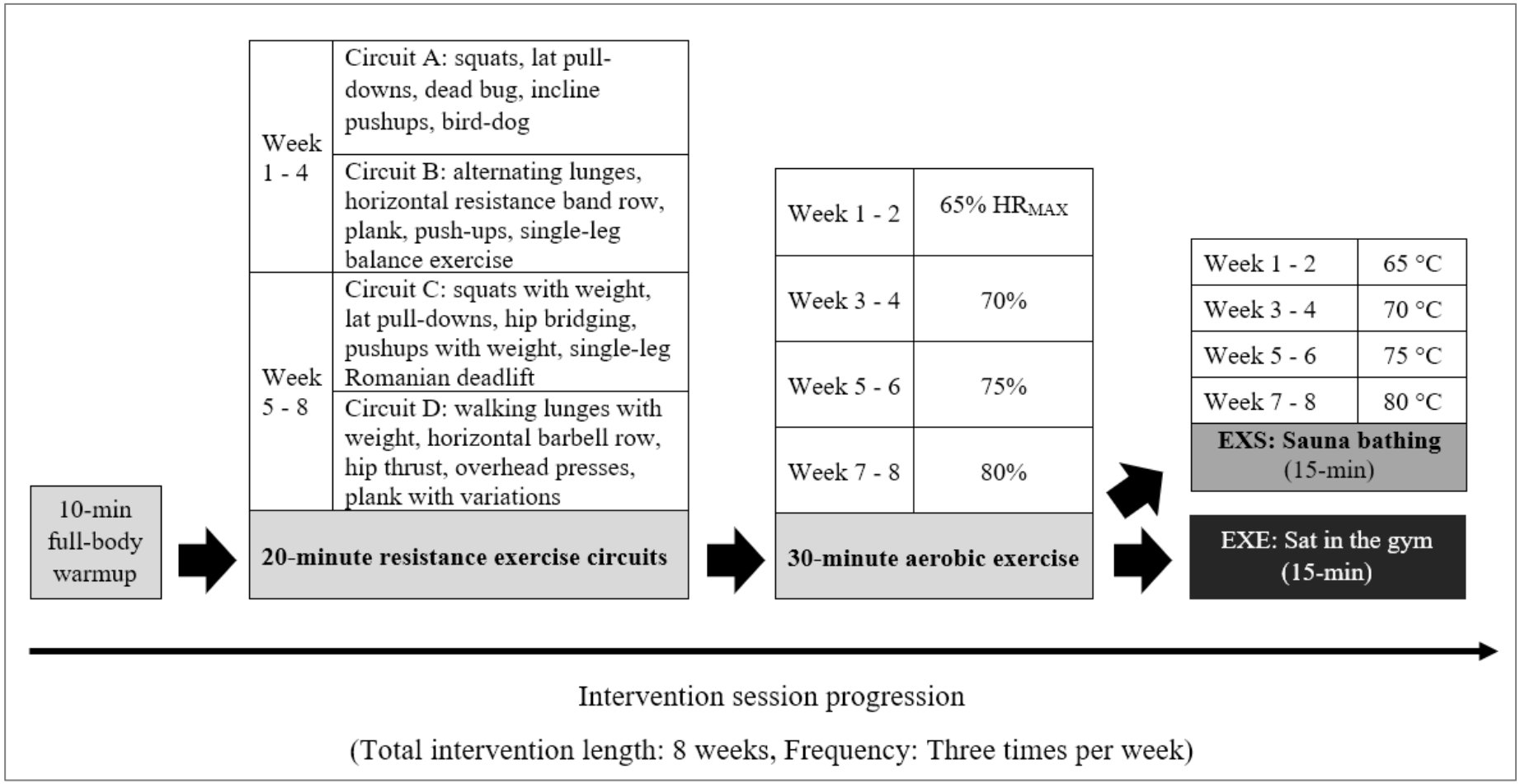

FIGURE 10 Details of the intervention. Loads were increased for resistance exercises when participants were able to complete the movement comfortably with good form. More challenging variations for the bodyweight exercises were introduced when the participant completed the basic movement with no noticeable difficulties. For example, resistance bands were used for dead bugs, bird-dog were executed with eyes closed, etc. EXE, regular exercise group; EXS, regular exercise and sauna group; HR_{MAX}, individual heart rate maximum.

Resistance exercise comprised of both bodyweight, and basic resistance training exercises. These exercises were aimed at providing a full-body workout, and were performed in circuit fashion. There were five movements per circuit, and each movement was performed for 45 seconds with a 15-second break in-between. Completion of an entire circuit took five minutes, and was followed by a one-minute break. The circuits were completed three times per session. Harder variations of bodyweight movements and greater resistance exercises loads for each individual were introduced as performance improved, based on the assessment of the exercise instructors.

Aerobic exercise was performed after resistance exercise using cycle ergometers (Monark 828 E, Varberg, Sweden). Individual HR_{MAX} were first calculated (Nes et al., 2013), then used to prescribe individual aerobic exercise intensity. 65% of individual HR_{MAX} was the starting intensity used for weeks 1 – 2, with a fortnightly increase of 5%. HR was closely monitored and verified every five minutes. Participants maintained a constant pedaling frequency of 65 - 70 rpm, while the magnetic resistance of the bike ergometer was adjusted to achieve the required exercise intensity.

Following aerobic exercise, participants in the EXS group proceeded to the sauna bathing room, while those in the EXE group waited in the gym until the participants in the EXS group completed 15 minutes of sauna exposure before the session was officially over. The temperature of the sauna bathing room started at 65 °C for weeks 1 – 2 and was increased by 5 °C fortnightly. This was monitored and recorded every minute via a commercially available wireless thermometer unit (Wireless thermometer 7410; Suomen Lämpömittari Oy, Helsinki, Finland).

4.4 Data collection

4.4.1 Arterial stiffness

The established guidelines (Tomlinson, 2012) for the measurement of arterial stiffness were closely followed for all the studies (I – IV). Measurements were performed using the PulsePen device (DiaTecne s.r.l., Milan, Italy; www.pulsepen.com) which is composed of one tonometer and an integrated ECG unit. The PulsePen is an acquisition device that serves to non-invasively detect the pressure waveform by means of applanation tonometry. It is the size and shape of a ballpoint pen, with a built-in pressure probe. The unit is connected to the computer by means of an optical fiber that ensures electromagnetic isolation for the participant undergoing the test.

Data analysis is performed by specially designed software at a sample rate of 500 Hz. The device software does not validate measurements if the difference between BP or HR values taken at the time of carotid and peripheral artery recordings was >10%. The same transit distances measured during baseline were used throughout the experiment for consistency and reliability. Transit distances were assessed by body surface measurements using a tape measure from the

suprasternal notch to each pulse recording site (carotid and femoral). Direct carotid to femoral measurement was adjusted to 80% (common carotid artery–common femoral artery x 0.8) for the calculation of PWV as recommended by the guidelines (Van Bortel et al., 2012).

PWV is measured by recording carotid and peripheral (femoral) waveforms in rapid succession at a sample rate of 1 kHz, and defined as the transit distance between the measuring sites divided by the time delay between the distal pulse and proximal pulse wave, using the ECG trace as reference. The pressure values recorded by tonometry are calibrated to the BP values obtained at the brachial artery; where they are assigned to the appropriate pixels and the values for all other pressure-related parameters are re-established. The software applies the well-established concept that MAP remains unchanged from the aorta to the peripheral arteries. MAP was calculated by the software as DBP + 1/3(SBP–DBP) (Salvi et al., 2004).

Left ventricular ejection time (LVET), diastolic time (DT) and augmentation index (AIx) were obtained from the carotid pressure waveform analysis. LVET is defined as the period between the first rise in the pressure waveform to the dicrotic notch, which corresponds to the beginning of DT (Salvi et al., 2013). AIx is a parameter which provides an indication of the contribution of reflected waves to total PP and defined as the difference between the first and second systolic peak on the waveform and was expressed as a percentage of PP (AIx = Augmented pressure/PP x 100) (Munir et al., 2008). The estimations made by the PulsePen software as described are reflected in Figure 11. Intraclass correlation coefficient (ICC) estimates and their 95% confidence interval (CI) were calculated based on a mean-rating (k = 2), absolute-agreement, 2-way mixed-effects model (ICC 2.1: 0.81 with 95% CI = 0.77 – 0.85, SEM = 0.4).

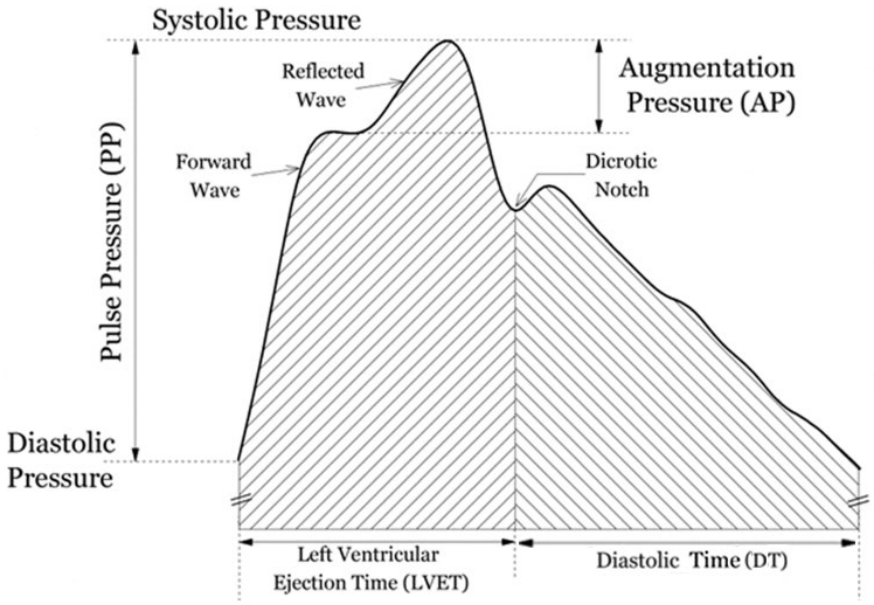

FIGURE 11 Software-derived estimations of augmented pressure, pulse pressure and left ventricular ejection time based on carotid pressure waveform analyses (Adapted and modified from Padma et al., 2018).

4.4.2 Blood pressure

Resting BP measurements were taken on the right upper arm using standard automated oscillometric devices and in accordance with the recommended guidelines (Muntner et al., 2019; Williams et al., 2019). First, the brachial artery was identified from the antecubital fossa, and the center of the bladder length of the cuff (marked on the cuff) was placed over the pulsation of the bare arm. The cuff was placed at the level of each individuals' right atrium and pulled taut, with equal tightness at the top and bottom edges of the cuff.

Participants were informed beforehand to empty their bladders before every visit and were not allowed to talk or move during the entire measurement period. Two sequential readings were taken, and the mean values were used. If the difference in SBP between the two measurements was larger than 10 mmHg, another measurement was taken after a 5-minute rest. The two measured values that differed the least were averaged and used for applanation tonometry analysis. All measurements in every study were taken in a quiet room with a stable temperature of 21°C from the supine position. For study IV, resting BP was taken at the same time of day (0630 – 0930).

4.4.3 Cardiorespiratory fitness (Study IV)

In the RCT (IV), CRF was assessed by a submaximal graded protocol (Andersen et al., 1971, pp. 54-56; Golding et al., 1989, pp. 91-104) on a cycle ergometer (Monark 828 E, Varberg, Sweden). The concept and procedures of the test was explained carefully to every participant before commencement of the test. Thereafter, the seat height was adjusted so that when the pedal is at its lowest point with the ball of the foot on the pedal, the knee was slightly bent. The seat position was noted for every participant and used for retesting. Cadence was kept between 55 - 60 rpm throughout the test. The test consisted of four stages and began with a warmup stage at a workload of 50 watts. The workload was increased by 50 watts for every subsequent stage.

HR was monitored and recorded during the last 30 seconds of every stage, and if the value was not stable, the stage was extended for 60 seconds in order to attain a stable value. After the test was completed, a regression line was plotted using the four points corresponding to each stage and extrapolated to the maximum HR. Maximum HR was calculated (Nes et al., 2013) for each individual prior the test. Based on the regression equation, a perpendicular line was subsequently formed down to the x-axis from maximum HR and absolute oxygen uptake was read off from the graph (Figure 12). Relative VO_{2MAX} was then calculated by first converting from liters (L) to milliliters (ml), then dividing the subsequent value by individual body mass in kilograms (kg).

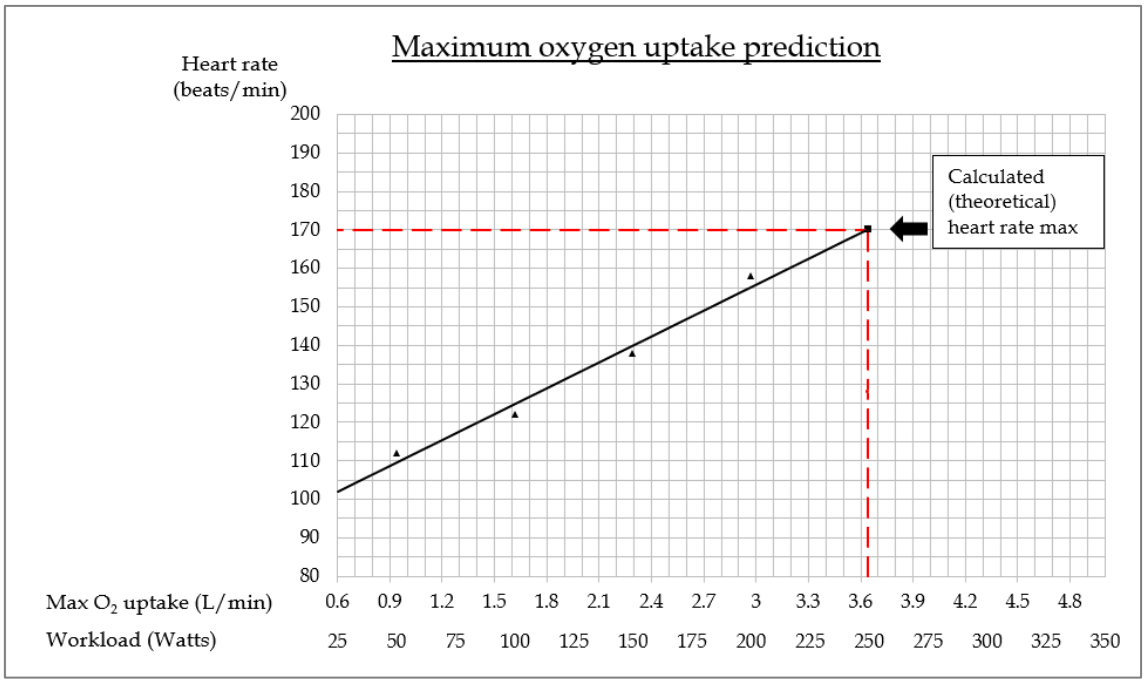

FIGURE 12 Plotted regression line using the heart rates attained from the four test stages (50, 100, 150 and 200 respectively) and the calculated (theoretical) individual maximum heart rate that was used to predict maximum oxygen uptake. O_2, oxygen.

4.4.4 Body composition and blood samples (Study IV)

Body composition measurements and blood samples were collected in the morning (0630 - 0930) in fasted conditions. Participants were instructed to abstain from food, drinks, alcohol and nicotine for 12 hours, and to refrain from heavy physical activity for 48 hours prior to sample collection. Body composition was determined using dual X-ray absorptiometry (Lunar Prodigy Advance, GE Medical Systems, Madison, USA). Total fat mass and total body mass were automatically analyzed (Encore-software, version 14.10.022). Blood was drawn from the antecubital vein into Vacuette SST 6 ml tubes using sterile needles. The sample was centrifuged for 10 minutes at 2000 rpm (Megafuge 1.0 R, Heraeus, Germany) after which serum was removed and stored at -80 °C until chemical analyses.

4.5 Statistical methods and analysis

Categorical variables are presented as frequencies or number (%) while continuous variables are presented as mean ± standard deviation (SD). 95% CIs are presented where appropriate. The level of significance was set at $P < 0.05$ for all studies. The data were tested for normality (Shapiro-Wilk test) and equality of variances (Levene's test) as needed. Family-wise error rates were controlled

for using Bonferroni corrections unless otherwise stated. Statistical analyses for Study I and II were performed using IBM SPSS Statistics, version 25 for Windows (SPSS, Chicago, IL, USA). For Study III and IV, statistical software R version 3.6.3 was implemented.

Study I and II: Data were analyzed for within-group (time) changes with a repeated measure analysis of variance (ANOVA). Within-group differences between before (PRE) vs immediately after (POST), PRE vs 30 min recovery (POST30) and POST vs POST30 were analyzed using pairwise *t*-tests.

Study III: The differences between PRE, POST and POST30 measurements did not follow a normal distribution. As such, a non-parametric approach, the Neyman-Rubin causal model (Neyman 1923; Rubin 1974) was selected. In this model, for the variable Y, the causal effect of treatment T with respect to control C for the individual u is defined as:

$$Y_T(u) - Y_C(u)$$

The effects of the two different interventions (EX+SAUNA and SAUNA) for the same individual cannot be simultaneously measured, which is known as the ***fundamental problem of causal inference*** in the Neyman-Rubin model. We solve the fundamental problem using a combination of scientific and statistical solutions (Holland, 1986). First, by assuming temporal stability; that the responses of the individuals would be the same if the treatments would have been done in the opposite order. The average effect of EX+SAUNA relative to SAUNA was then calculated. The temporal stability assumption was investigated by performing a sign test on the PRE measurements. No statistically significant differences were found in the PRE measurements between EX+SAUNA and SAUNA.

Stable unit treatment value was also assumed, that is, the outcome of one individual does not depend on the interventions done on the other individuals, which is contextually natural. The CI and *p*-values were estimated using non-parametric bootstrap (Efron & Tibshirani, 1994). Because there was no reason to be certain about the ***direction of the difference*** for any of the response variables, a two-tailed alternative hypothesis was used. In this non-parametric bootstrap method, we resampled the empirical distribution of responses by taking random samples equal in size to the original sample (N = 72) with replacement. The resulting distribution asymptotically approaches the true sampling distribution. The analysis consisted of multiple tests for differences between interventions, so we use adjusted *p*-values for inference, where the adjusting has been done using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995)

Study IV: Between group differences PRE and POST intervention were analyzed using independent *t*-tests. The comparisons were done between CON and EXE groups, and between EXE and EXS groups. The comparison of interest is between EXE and EXS, while the comparison between the EXE and CON groups served as a positive control to validate that the exercise intervention was intensive enough to have statistically significant effects with this sample size.

5 RESULTS

5.1 The acute hemodynamic and vascular responses to sauna bathing (I)

5.1.1 Vascular and heart rate responses

AIx, DT, LVET and PWV, decreased significantly from PRE to POST sauna ($P < 0.001$). However, LVET reductions remained after a 30-minute recovery period from sauna bathing (POST30) while PWV, AIx and DT recovered to baseline values. HR increased from PRE to POST ($P < 0.001$), but returned to baseline levels after the 30-minute recovery period. Mean and *p*-values of vascular-related outcomes are shown in Table 4.

5.1.2 Hemodynamic responses

MAP decreased significantly PRE to POST ($P < 0.001$), but returned to baseline values at POST30. PP showed a delayed response; with significant differences PRE-POST30 and POST-POST30, but not PRE-POST. 30 minutes of sauna bathing had a lowering effect on brachial SBP. Statistically significant differences were found PRE-POST and PRE-POST30 ($P < 0.001$, both timepoints). There were no significant changes for other central hemodynamic parameters.

TABLE 4 The acute responses of hemodynamic and vascular parameters to 30 minute of sauna bathing. A repeated measures ANOVA was used to determine within-group (time) changes. Subsequently, paired t-tests were used to determine where these differences were. Sample size (n) was 102, of which 56 were males and 46 were females. AP and PPa are omitted from the table due to not reaching statistical significance based on ANOVA. Significance level was set at 0.002 after using Bonferroni correction for multiple testing (Armstrong, 2014; Streiner & Norman, 2011)

Parameters	Mean ± SD			*p*-values			
	PRE	POST	POST30	ANOVA	Pairwise (PRE-POST)	Pairwise (PRE-POST30)	Pairwise (POST-POST30)
LVET (m/s)	307.4 ± 26.4	277.9 ± 37.8	299.0 ± 34.1	<0.001	<0.001	<0.001	<0.001
PWV (m/s)	9.8 ± 2.4	8.6 ± 1.6	9.0 ± 1.7	<0.001	<0.001	0.366	<0.001
DT (m/s)	635.1 ± 115.1	494.6 ± 113.0	634.3 ± 121.2	<0.001	<0.001	0.923	<0.001
HR (bpm)	65.2 ± 10.4	80.7 ± 15.1	65.9 ± 10.7	<0.001	<0.001	0.245	<0.001
AIx (%)	9.8 ± 16.0	4.1 ± 15.8	7.8 ± 15.7	<0.001	<0.001	0.287	0.072
MAP (mmHg)	99.4 ± 15.0	93.6 ± 10.3	95.9 ± 14.2	<0.001	<0.001	0.032	0.083
PP (mmHg)	42.7 ± 9.2	44.9 ± 9.8	39.3 ± 8.3	<0.001	0.011	<0.001	<0.001
SBP (mmHg)	136.5 ± 16.2	130.3 ± 14.4	129.8 ± 13.8	<0.001	<0.001	<0.001	0.611
DBP (mmHg)	82.1 ± 9.6	75.1 ± 9.3	80.6 ± 9.2	<0.001	<0.001	0.003	<0.001

AIx, augmentation index; ANOVA, analysis of variance; AP, augmented pressure; DBP, diastolic blood pressure; DT, diastolic time; HR, heart rate; LVET, left ventricular ejection time; MAP, mean arterial pressure; PP, pulse pressure; PPa, pulse pressure amplification; PRE, pre-sauna; POST, post-sauna; POST30, post 30 minutes recovery; PWV, pulse wave velocity; SBP, systolic blood pressure.

5.2 Acute effects of exercise and sauna as a single intervention (II)

Significant changes were observed PRE-POST for AIx (P = 0.002), PWV, MAP, LVET and DT (P <0.001). These effects persisted at POST30 for AIx, MAP, LVET (P <0.001) and DT (P = 0.016). An overview of the responses from all the measured outcome parameters is shown in Figure 13. Mean and 95% CI values of the outcome parameters are summarized in Table 5.

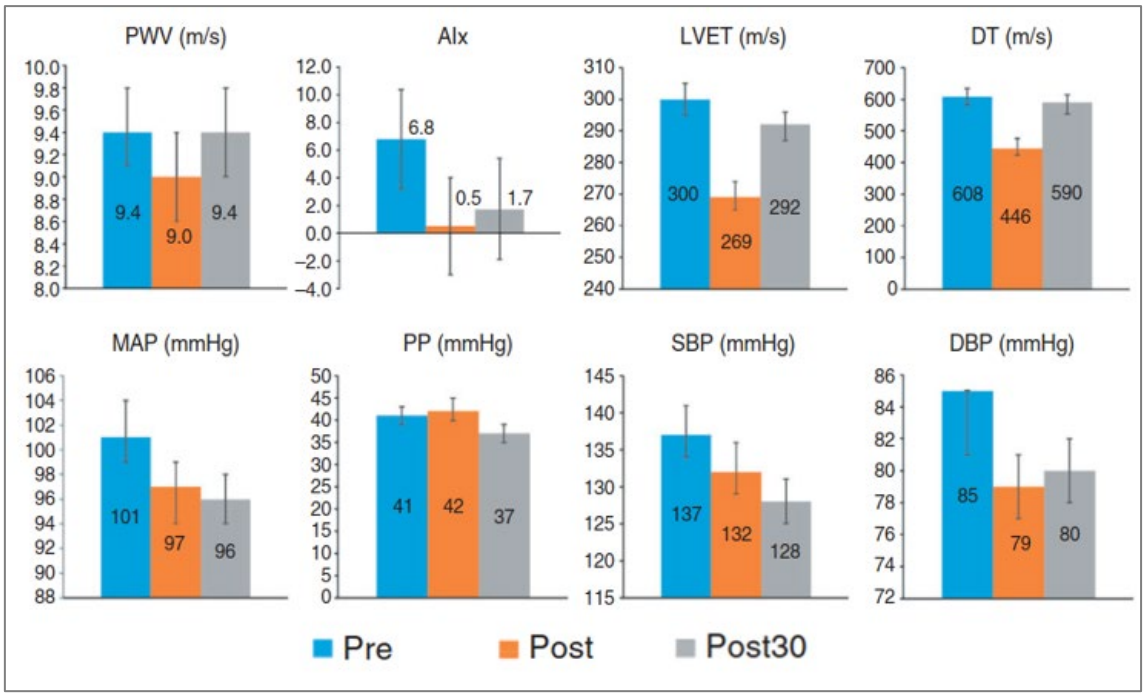

FIGURE 13 An overview of the responses of pulse wave velocity (PWV), augmentation index (AIx), left ventricular ejection time (LVET), diastolic time (DT), mean arterial pressure (MAP), pulse pressure (PP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) to a combination of 15-minute exercise followed by 15 minutes of sauna bathing. Error bars represent 95% confidence intervals. Study sample size was 77 (39 males, and 38 females). PRE, pre-intervention; POST, post-intervention; POST30, post 30 minutes recovery

TABLE 5 Summary of the hemodynamic and vascular responses to a combination of 15-minute exercise followed by 15 minutes of sauna bathing. AP is not presented in the table as it did not reach statistical significance both PRE-POST and PRE-POST30. The data were analyzed for within-group (time) changes with ANOVA. Within-group differences between POST to PRE and POST30 to PRE values were analyzed subsequently using pairwise t-tests.

Parameters	PRE	POST			POST30		
	Mean (95% CI)	Mean (95% CI)	Relative change (vs. PRE)	*p*-value (vs. PRE)	Mean (95% CI)	Relative change (vs. PRE)	*p*-value (vs. PRE)
AIx (%)	6.8 (3.2, 10.4)	0.5 (-3.0, 4.0)	-92.5%	0.002	1.7 (-1.9, 5.4)	-75.2%	<0.01
LVET (m/s)	300 (295, 305)	269 (265, 274)	-10.2%	<0.001	292 (287, 296)	-2.8%	<0.001
DT (m/s)	608 (582, 634)	446 (424, 467)	-26.7%	<0.001	590 (564, 615)	-3%	0.016
PWV (m/s)	9.4 (9.1, 9.8)	9.0 (8.6, 9.4)	-4.7%	<0.001	9.4 (9.0, 9.8)	-0.1%	0.99
MAP (mmHg)	101 (99, 104)	97 (94, 99)	-4.7%	<0.001	96 (94, 98)	-5.2%	<0.001
PP (mmHg)	41 (39, 43)	42 (40, 45)	3.5%	0.37	37 (35, 39)	-9.1%	<0.001
SBP (mmHg)	137 (134, 141)	132 (129, 136)	-3.5%	<0.001	128 (125, 131)	-6.9%	<0.001
DBP (mmHg)	85 (81, 85)	79 (77, 81)	-5.6%	<0.001	80 (78, 82)	-3.8%	<0.001
HR (bpm)	68 (65, 70)	86 (83, 89)	27.1%	<0.001	70 (67, 72)	3.2%	0.04

AIx, augmentation index; ANOVA, analysis of variance; AP, augmented pressure; DBP, diastolic blood pressure; DT, diastolic time; HR, heart rate; LVET, left ventricular ejection time; MAP, mean arterial pressure; PP, pulse pressure; PRE, pre-intervention; POST, post-intervention; POST30, post 30 minutes recovery; PWV, pulse wave velocity; SBP, systolic blood pressure.

5.3 A comparison between sauna bathing and exercise followed by sauna bathing (III)

PRE-POST changes in outcomes measures: The distribution of individual responses in the outcome parameters to the two interventions PRE-POST are displayed in Figure 14. The average Neyman-Rubin causal effect (difference between EX+SAUNA and SAUNA) for each parameter and their respective 95% confidence intervals PRE-POST are shown in Table 6. DBP, and MAP were lower after SAUNA than EX+SAUNA. No statistically significant difference was found for the remaining variables.

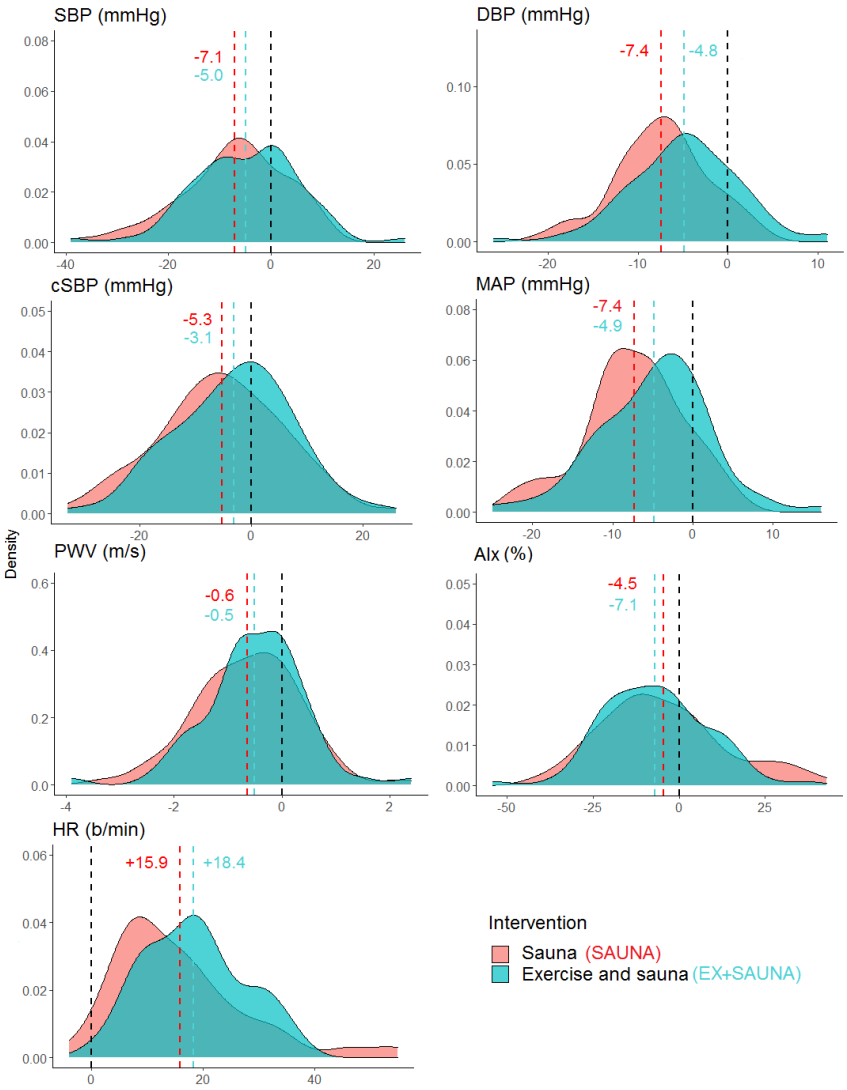

FIGURE 14 The distribution of individual responses to the two interventions between PRE and POST. Significant differences were found for diastolic blood pressure (DBP) and mean arterial pressure (MAP) (P = 0.02 and 0.05 respectively). There were no significant differences for systolic blood pressure (SBP), central systolic blood pressure (cSBP), pulse wave velocity (PWV), augmentation index (AIx) and heart rate (HR).

TABLE 6 Comparison of PRE-POST responses between EX+SAUNA and SAUNA using the Neyman-Rubin causal model. Average CE is the difference between EX+SAUNA and SAUNA. Sample size was 72 (33 females and 39 males).

Parameters	EX+SAUNA		SAUNA		Average CE	95% CI	Raw *p*-value	Adjusted *p*-value
	Mean	95% CI	Mean	95% CI				
PWV (m/s)	-0.5	(-0.7, -0.3)	-0.6	(-0.9, -0.4)	0.1	(-0.2, 0.4)	0.436	0.46
AIx (%)	-7.1	(-10.6, -3.6)	-4.5	(-8.6, -0.2)	-2.6	(-7.7, 2.6)	0.323	0.38
SBP (mmHg)	-5.0	(-7.4, -2.6)	-7.1	(-9.4, -4.8)	2.1	(-0.4, 4.7)	0.103	0.16
DBP (mmHg)	-4.9	(-6.3, -3.4)	-7.4	(-8.6, -6.2)	2.5	(1.0, 4.1)	0.002	0.02
cSBP (mmHg)	-3.1	(-5.5, -0.8)	-5.3	(-7.9, -2.7)	2.2	(-0.6, 4.9)	0.120	0.16
MAP (mmHg)	-4.9	(-6.5, -3.3)	-7.4	(-8.8, -5.9)	2.5	(0.6, 4.3)	0.010	0.05
HR (bpm)	18.4	(16.3, 20.4)	15.9	(13.0, 18.7)	2.5	(-0.5, 5.5)	0.100	0.16

AIx, augmentation index; CE, causal effect; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; EX+SAUNA, aerobic exercise followed by sauna; HR, heart rate; MAP, mean arterial pressure; PWV, pulse wave velocity; SAUNA, sauna only; SBP, systolic blood pressure.

PRE-POST30 changes in outcomes measures: The distribution of individual responses to the two interventions as measured between PRE and POST30 are displayed in Figure 15. PRE-POST30 changes in outcome measures and their average causal effect are shown in Table 7. SBP, DBP, and MAP were lower in EX+SAUNA.

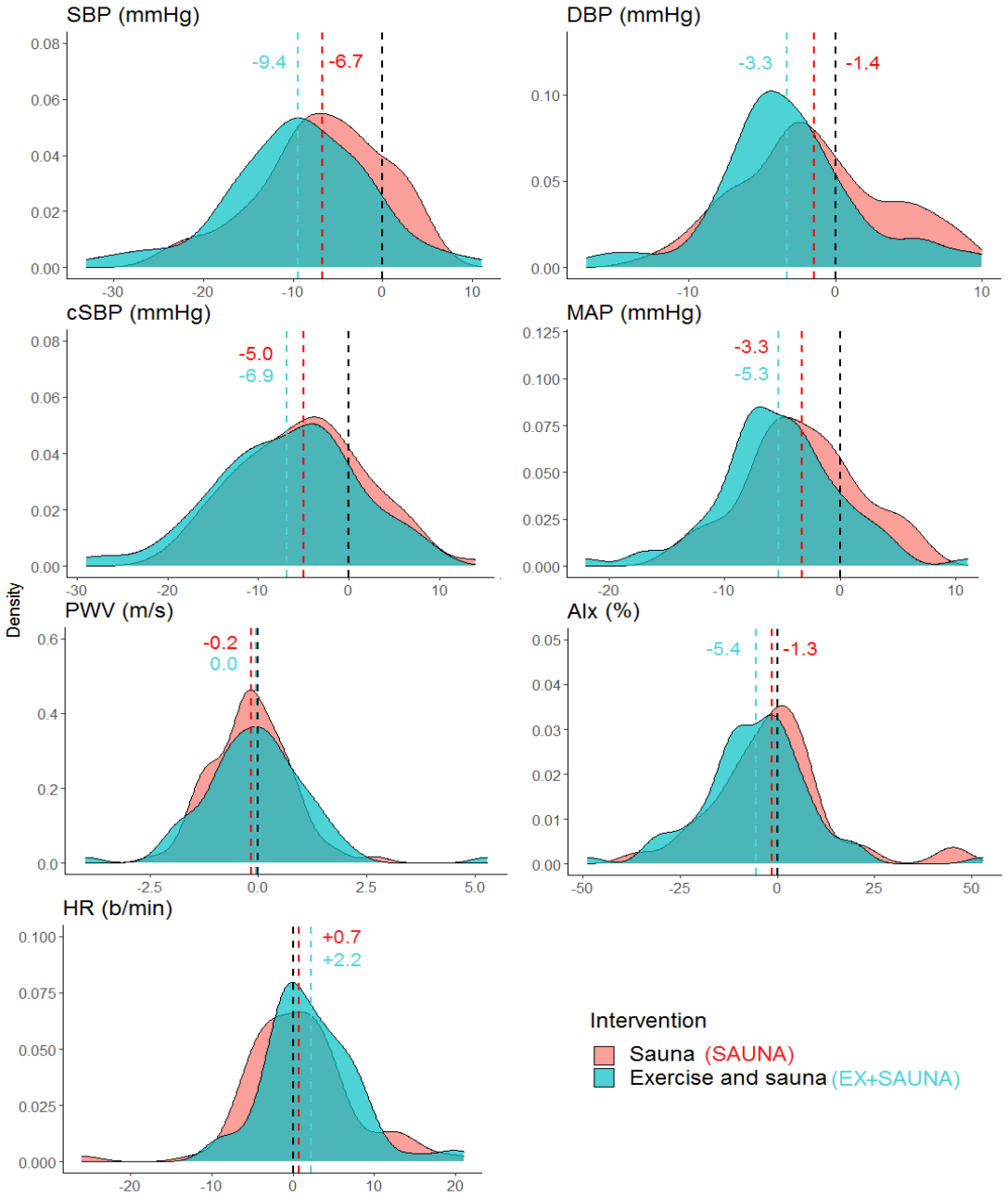

FIGURE 15 The distribution of individual responses to the two interventions as measured between PRE and POST30. Raw *p*-value for augmentation index (AIx) was 0.023, but did not achieve statistical significance after correction (adjusted P = 0.054). AIx, augmentation index; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

TABLE 7 Comparison of responses PRE-POST30 between EX+SAUNA and SAUNA using the Neyman-Rubin causal model. Average CE is the difference between EX+SAUNA and SAUNA. Changes in SBP, DBP and MAP were significantly different between the two interventions.

Parameters	EX+SAUNA		SAUNA		Average CE	95% CI	Raw *p*-value	Adjusted *p*-value
	Mean	95% CI	Mean	95% CI				
PWV (m/s)	-0.0	(-0.3, 0.3)	-0.2	(-0.4, 0.0)	0.1	(-0.2, 0.5)	0.548	0.55
AIx (%)	-5.4	(-8.6, -2.0)	-1.3	(-4.8, 2.2)	-4.0	(-7.6, -0.5)	0.023	0.054
SBP (mmHg)	-9.4	(-11.3, -7.6)	-6.7	(-8.4, -5.2)	-2.7	(-4.9, -0.5)	0.018	0.05
DBP (mmHg)	-3.3	(-4.4, -2.1)	-1.4	(-2.6, -0.3)	-1.8	(-3.3, -0.4)	0.013	0.04
cSBP (mmHg)	-6.9	(-8.7, -5.1)	-5.0	(-6.6, -3.4)	-1.9	(-4.2, 0.4)	0.109	0.16
MAP (mmHg)	-5.3	(-6.6, -4.1)	-3.3	(-4.4, -2.1)	-2.0	(-3.5, -0.5)	0.009	0.04
HR (bpm)	2.2	(0.9, 3.5)	0.7	(-0.8, 2.3)	1.5	(-0.4, 3.4)	0.128	0.16

AIx, augmentation index; CE, causal effect; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; EX+SAUNA, aerobic exercise followed by sauna; HR, heart rate; MAP, mean arterial pressure; PWV, pulse wave velocity; SAUNA, sauna only; SBP, systolic blood pressure.

5.4 Cardiovascular adaptations to regular exercise and sauna bathing (IV)

EXE vs CON: Significant PRE-POST differences were found between the CON and EXE groups for VO_{2MAX}, and fat mass. EXE had greater increases in CRF, and decreases in fat mass. No significant differences were found for BP, arterial stiffness indices and total cholesterol levels (Table 8).

TABLE 8 PRE-POST comparison of means between the EXE and CON group. Both groups had n = 16 participants, with 14 females each. Data were analyzed using independent t-tests.

Parameter	EXE		CON		Mean Difference, 95% CI	*p*-value
	PRE	POST	PRE	POST		
Estimated VO_{2MAX} (ml/kg/min)	29.4 ± 5.7	32.0 ± 6.6	30.1 ± 4.8	26.8 ± 4.6	6.2 (4.1, 8.3)	0.01
SBP (mmHg)	134 ± 14	134 ± 14	130 ± 9	130 ± 10	0.5 (-4.6, 5.6)	0.84
DBP (mmHg)	79 ± 11	80 ± 9	79 ± 5	82 ± 6	-1.9 (-5.5, 1.7)	0.29
Fat mass (kg)	37.8 ± 10.5	36.5 ± 10.1	38.0 ± 12.4	38.0 ± 12.3	-1.3 (-2.3, -0.3)	0.01
TC (mg/dl)	203 ± 34	208 ± 30	215 ± 34	211 ± 29	12 (-8, 27)	0.22
PWV (m/s)	9.2 ± 1.7	9.2 ± 1.4	8.5 ± 1.5	8.7 ± 2.4	-0.2 (-1.2, 0.8)	0.66
AIx (%)	16.1 ± 11.9	17.3 ± 10.0	15.5 ± 11.0	15.4 ± 8.7	1.2 (-6.5, 8.9)	0.76

AIx, augmentation index; CON, control group; DBP, diastolic blood pressure; EXE, regular exercise group; PWV, pulse wave velocity; SBP, systolic blood pressure; TC, total cholesterol; VO_{2MAX}, maximal oxygen consumption.

EXS vs EXE: PRE-POST differences in VO_{2MAX}, SBP and total cholesterol levels were significant between the EXE and EXS groups (Table 9). Specifically, VO_{2MAX} was greater (Figure 16), while SBP (Figure 17) and total cholesterol levels (Figure 18) were lower in the EXS than EXE group after the 8-week intervention period. There were no differences in any other outcome parameters.

TABLE 9 PRE-POST comparison of means between the EXS and EXE group. EXS had n = 15 participants, with 13 females. Data were analyzed using independent t-tests.

Parameter	EXS		EXE		Mean Difference, 95% CI	*p*-value
	PRE	POST	PRE	POST		
Estimated VO_{2MAX} (ml/kg/min)	26.4 ± 6.3	32.0 ± 6.4	29.4 ± 5.7	32.0 ± 6.6	2.7 (0.2, 5.3)	0.03
SBP (mmHg)	134 ± 14	126 ± 11	134 ± 14	134 ± 14	-8.0 (-14.6, -1.4)	0.02
DBP (mmHg)	80 ± 13	80 ± 14	79 ± 11	80 ± 9	-0.6 (-6.0, 4.8)	0.82
Fat mass (kg)	39.6 ± 8.2	37.7 ± 8.5	37.8 ± 10.5	36.5 ± 10.1	-0.6 (-1.9, 0.7)	0.34
TC (mg/dl)	200 ± 32	188 ± 33	203 ± 34	208 ± 30	-19 (-35, 0)	0.04
PWV (m/s)	9.6 ± 1.9	9.2 ± 1.7	9.2 ± 1.7	9.2 ± 1.4	-0.4 (-1.1, 0.3)	0.25
AIx (%)	17.7 ± 10.6	12.6 ± 14.1	16.1 ± 11.9	17.3 ± 10.0	-6.3 (-14.8, 2.2)	0.14

AIx, augmentation index; DBP, diastolic blood pressure; EXE, regular exercise group; EXS, regular exercise followed by sauna group; PWV, pulse wave velocity; SBP, systolic blood pressure; TC, total cholesterol; VO_{2MAX}, maximal oxygen consumption.

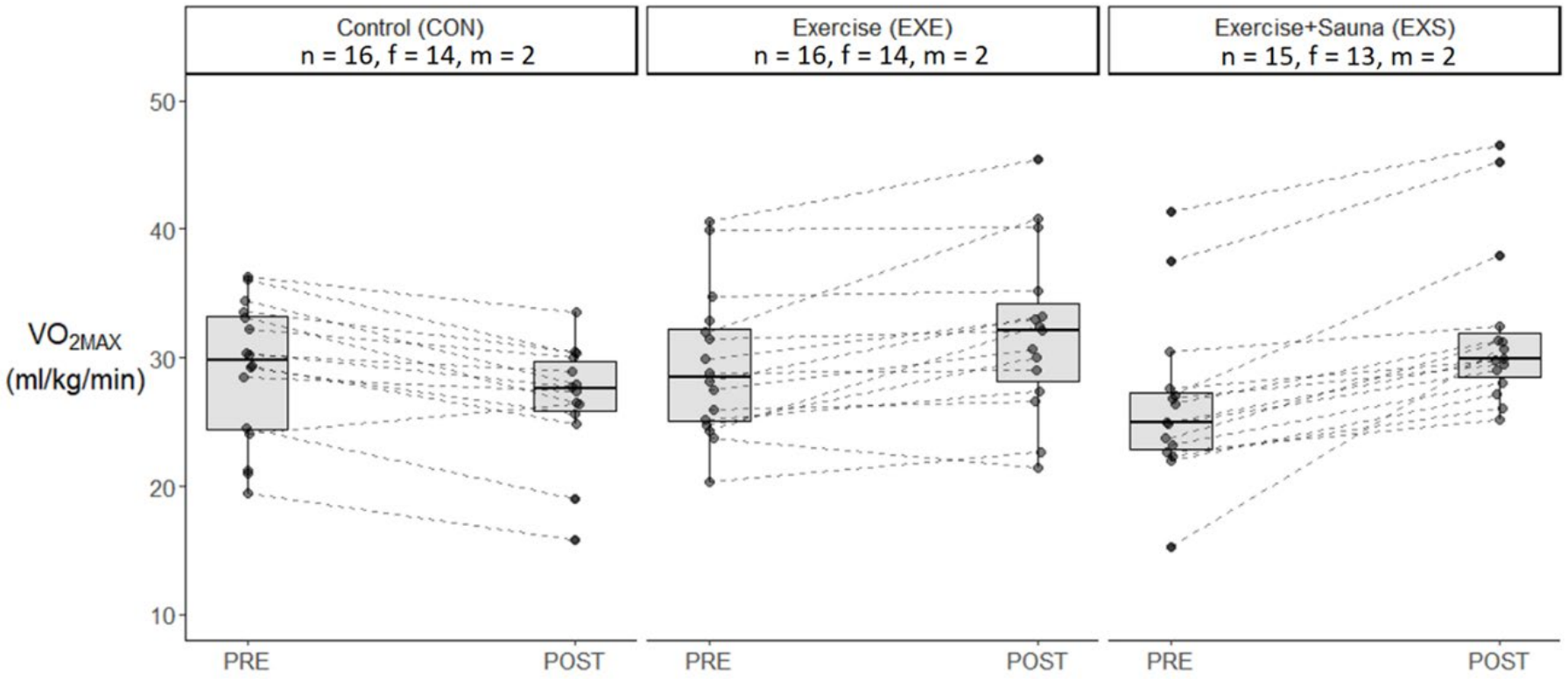

FIGURE 16 Graphical representation of the individual cardiorespiratory fitness (estimated VO_{2MAX}) response in the three groups from PRE to POST. Significant differences were found between CON and EXE (P = 0.01), and between EXE and EXS (P = 0.03). f, female; m, male

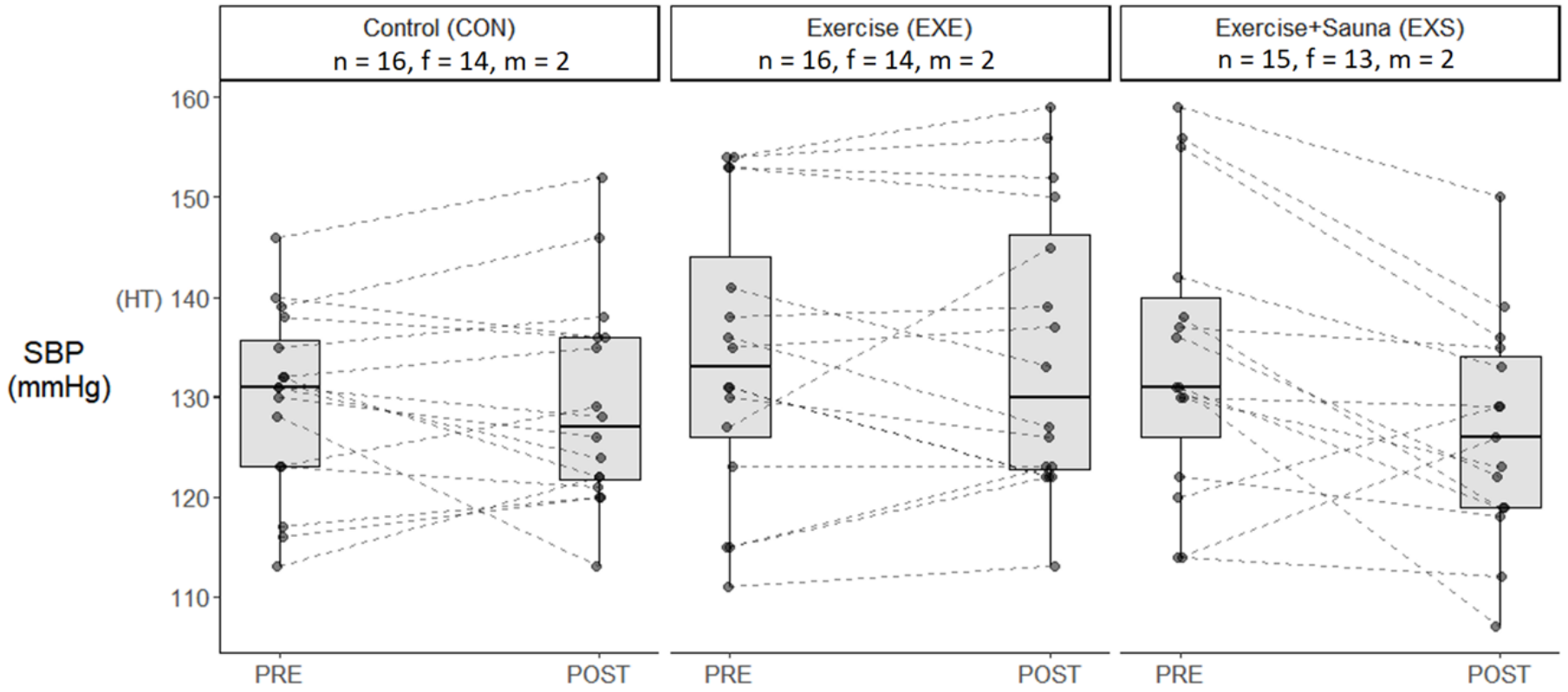

FIGURE 17 Graphical representation of the individual systolic blood pressure (SBP) response in the three groups from PRE to POST. Significant differences were found between EXE and EXS (P = 0.02). Difference in responses between EXE and CON were not statistically significant (P = 0.84). f, female; HT, hypertension classification cutoff point; m, male

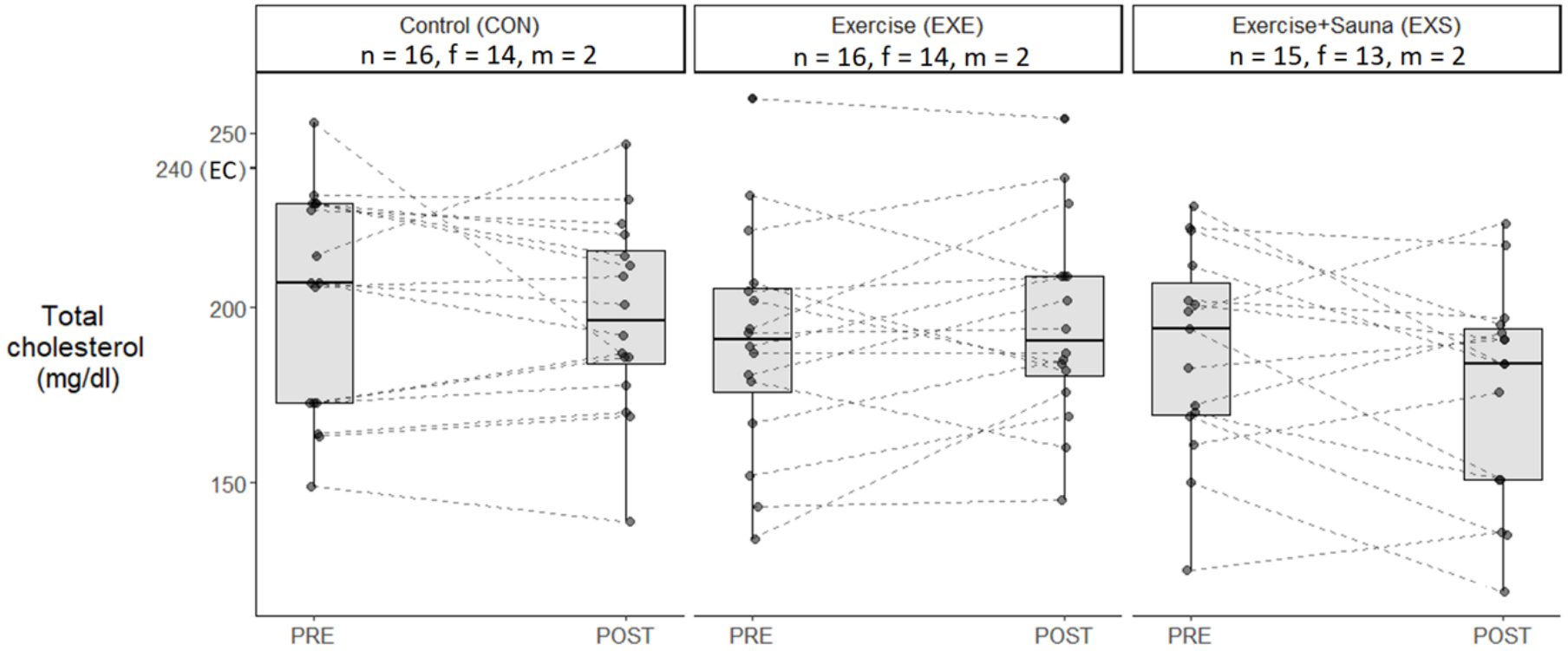

FIGURE 18 Graphical representation of the individual responses in total cholesterol levels within the three groups from PRE to POST. Significant differences were found between EXE and EXS (P = 0.04). Difference in responses between EXE and CON were not statistically significant (P = 0.22). EC, elevated cholesterol levels classification; f, female; m, male

6 DISCUSSION

The purpose of the experiments in this PhD study was to examine the acute cardiovascular and hemodynamic responses to sauna bathing, exercise and sauna bathing as a single intervention, and the long-term adaptations of exercise and sauna bathing in populations with CVD risk factors sequentially. A traditional Finnish sauna was utilized for all the studies, with every bout of sauna bathing lasting 15 minutes in duration. Stationary bike cycling was used as the main form of aerobic exercise (II – IV), while resistance exercise consisted of bodyweight and machine-based exercises performed in a circuit fashion (IV).

The main findings of this PhD study were as follows:

1. 30 minutes of sauna bathing led to an acute reduction in arterial stiffness and other hemodynamic markers. Although many of these outcome measures recovered to baseline levels after a 30-minute recovery period, LVET and SBP changes were still present. (I)

2. A combination of 15 minutes of aerobic exercise followed by 15 minutes of sauna bathing led to similar changes seen from 30 minutes of sauna bathing (I). More importantly, AIx, LVET, MAP, SBP and DBP reductions were sustained after 30 minutes of recovery. (II)

3. When matched for duration, sauna bathing had greater lowering effects on DBP and MAP compared to the combination of aerobic exercise and sauna. However, SBP, DBP and MAP were lower for the combination of exercise and sauna 30 minutes post-intervention. (III)

4. Exercise and sauna bathing showed greater adaptations in CRF, SBP and TC. Specifically, exercise and sauna bathing led to greater CRF, and lower SBP and TC levels compared to regular exercise alone. (IV)

To the best of my knowledge, the series of studies that form the present thesis were the first to investigate the acute effects and recovery from sauna bathing (1), a combination of aerobic exercise and sauna bathing as a single intervention (2), as well as a comparison between these two interventions using matched durations (3), on arterial stiffness and hemodynamic markers. Most importantly however, the final experiment (4) was the first RCT to study Finnish sauna bathing. This unique PhD study series presents novel results on the health benefits of sauna alone and sauna combined with exercise, emphasizing the potential of the Finnish sauna bathing tradition as an additional means to improving cardiovascular health.

6.1 Acute cardiovascular and hemodynamic responses

Heat therapy has many well-documented benefits for the cardiovascular system. The sensory receptors in the skin are stimulated by heat, which decreases the transmission of pain signals to the brain to relieve discomfort (Jezová et al., 1985; Kukkonen-Harjula & Kauppinen, 1988; Vescovi et al., 1990). It also increases the flow of oxygen and nutrients via increased skin blood flow, which helps the repair of muscle tissue via thermoregulatory pathways (Gagnon et al., 2015; Shibasaki et al., 2015). Controlled heat stress has also been shown to augment cardiovascular function (Brunt et al., 2016; Imamura, 2001), although this has yet to be thoroughly explored in the context of Finnish sauna bathing and vascular compliance. However, various animal and cell culture studies have found increases in skeletal muscle capillary density and vascular tube formation enhancement (Hyldahl & Peake, 2020; Kim, Monroe, et al., 2020).

Similarly, though there have been some promising results from studies investigating the conjunctive use of exercise and sauna bathing in different population groups (Gayda, Bosquet, et al., 2012, Gayda, Paillard et al., 2012; Leicht et al., 2018; Scoon et al., 2007), relatively sparse information exists for the general population in spite of the potentially additive effects that post-exercise heating might have on the cardiovascular system (Rosenberg et al., 2017). Nevertheless, this has been shown in a number of *in vitro* (Cheng et al., 2017; Tamura et al., 2014;) studies as well. In support of these studies, the acute responses in vascular and hemodynamic function from sauna bathing (I) and exercise and sauna bathing (II) are thereby outlined below.

6.1.1 Sauna bathing (I)

Sauna bathing led to an acute enhancement of several markers of vascular function. Two 15-minute bouts of Finnish sauna bathing led to decreases in AIx, DT, LVET, MAP, PWV, SBP, and DBP. Additionally, whereas other markers had returned to baseline levels after the recovery period, the changes to LVET and SBP were sustained 30 minutes after the sauna exposure.

To a reasonable extent, the hemodynamic changes were somewhat expected, as previous studies have reported similar acute responses (Hannuksela & Ellahham, 2001; Kukkonen-Harjula & Kauppinen, 1988; Kukkonen-Harjula et al., 1989). However, many of the changes to other parameters, particularly in the vascular-related indices are novel findings. Firstly, the study found a decrease in the vascular stiffness markers of AIx and PWV immediately after sauna bathing, which may have been due to vasodilation. While PWV is directly affected by arterial wall compliance, AIx is more of a surrogate indicator of left ventricular systolic loading that is influenced by both left ventricular contractility and wave reflections (Sharman et al., 2009). The reductions in these parameters together with BP thus suggest an acute functional modulation through sauna bathing.

Secondly, there was also a decrease in heart period reflected by lowered LVET and DT. This was a somewhat unexpected finding, as heart period has been found to be inversely related to PWV (Salvi et al., 2013). When the time taken by the left ventricle to do work is shortened (i.e., decrease in LVET), it results in an increase in BP and velocity of travelling waves and thus PWV. However, the results of the study (I) showed otherwise. One plausible explanation for these findings may be an acute alteration of the left ventricular loading conditions arising from sauna bathing, as changes in the left ventricle's ability to eject blood could directly affect LVET (Boudoulas et al., 1982; Othmane et al., 2007). Additionally, it is likely that cutaneous vasodilation and lowered total peripheral resistance (Charkoudian, 2003) may have also contributed to the lower PWV seen, which would explain the parallel decreases in BP as well. Although data on total peripheral resistance was not collected, the decrease in AIx does lend support to this notion. Accordingly, the retention of reductions to LVET were thus not surprising when AIx and PWV recovered to baseline levels after 30 minutes of recovery.

Nevertheless, the sustained reductions in SBP were not expected, especially when markers of arterial stiffness and HR had returned to pre-intervention levels. These may be due to a few reasons. Firstly, sympathoinhibition has been found to partially mediate the reduction in arterial BP following acute heating (Engelland et al., 2020). Increases in sympathetic nerve activity and HR during whole body heat stress is accommodated by the resetting of the arterial baroreflex, which in-turn could have contributed to the post-heating sympathoinhibitory effect. Secondly, there may have been a reduction in stroke volume, as it shares a direct relationship with LVET (Alhakak et al., 2021; Weissler et al., 1968), which was still lowered 30 minutes post-intervention. However, it has been reasonably established that stroke volume is increased slightly, or maintained during passive whole-body heating in spite of decreases in cardiac filling pressures and central blood volume (Brothers et al., 2009). These findings have also been corroborated using more direct measurements (Gagnon et al., 2016; Wilson et al., 2009).

It has also been reported previously that an increase in core temperature of 0.8°C led to decreases in a number of indices of cardiac systolic function, such as left ventricular ejection time and pre-ejection period, both of which are indicative

of increased cardiac systolic function (Frey & Kenney, 1979). However, these findings and their comparability to Study (I) ought to be contextualized appropriately. Many of the above-mentioned studies used water-perfused garments and suits, and were performed with the participants seated (Frey & Kenney, 1979) or in supine position (Brothers et al., 2009; Gagnon et al., 2016; Wilson et al., 2009) throughout the entire protocol. On the other hand, data collected from participants in Study (I), as well as all the other studies found in this dissertation (II – IV) were from the supine position after 7 – 10 minutes of posture stabilization. Regardless of the differences in methodologies, the similarities in results found between the studies are suggestive of augmented cardiac systolic function as a result of heat stress from sauna bathing.

Sauna-induced fluid loss has been well-documented (Hannuksela & Ellahham, 2001; Heinonen & Laukkanen, 2018; Kauppinen, 1997; Podstawski et al., 2014), and reduction in plasma and interstitial fluid volumes have been found to lead to decreases in cardiac output, preload, and venous pressure (Kyle & Freis, 1980; Mack & Nadel, 2011; Sawka et al., 2005). As such, that would appear to be another likely explanation for the reduced levels in LVET and SBP seen during the recovery period, especially since HR had already returned to resting levels. It is also possible that the sympathetic and/or parasympathetic regulatory response from the heart were altered as a result of sauna bathing, which has been fairly well-established (Gayda, Bosquet, et al., 2012; Lammintausta et al., 1976; Radtke et al., 2016; Sudakov et al., 1988). This is supported by evidence that heat exposure triggers autonomic nervous system activity (Iguchi et al., 2012; Rowell, 1990), and is further substantiated by the HR variability data that was collected from the same study population as the presented thesis studies I - III (Laukkanen et al., 2019).

During the cooling down period from sauna bathing, HR variability increased which indicates the dominant role of parasympathetic activity and decreased sympathetic activity of cardiac autonomic nervous system after sauna (Laukkanen at al., 2019). Sauna bathing is traditionally used for relaxation and pleasure purposes to release body stress, and it may have a positive modulating effect on parasympathetic activity of the autonomic nervous system. This may be an important contributor to the beneficial effects on cardiovascular function and decreased resting BP. This is supported by updated evidence showing that typical Finnish sauna bathing did not acutely improve peripheral flow-mediated dilation in healthy middle-aged and older adults (Gravel et al., 2019). Conversely however, individuals with possibly compromised endothelial function similar to the present study (I) population could see acute improvements, which has been shown recently (Gravel et al., 2021).

6.1.2 Aerobic exercise and sauna bathing (II)

The results seen from a combination of a short 15-minute bout of aerobic exercise followed by 15 minutes of sauna bathing was remarkably comparable to the results seen from sauna bathing alone (I). Similar to 30 minutes of sauna bathing, EX+SAUNA lowered AIx, DT, LVET, MAP, PWV, SBP and DBP. However, the

reductions in AIx, DT, LVET, MAP, SBP and DBP were retained after 30 minutes of recovery, whereas only decreases in LVET and SBP were retained for sauna bathing (I). In addition, although there were no changes to PP immediately after EX+SAUNA, it showed a decrease after 30 minutes.

It has previously been suggested that an energy expenditure threshold for exercise may need to be reached, either through short periods of vigorous intensity or longer periods of moderate intensity exercise, in order for arterial stiffness improvements to be reflected (Ferreira et al., 2006). The findings from this study (II) thus appears to suggest that 15 minutes of cycling at 75% HR_{MAX} was sufficient both in intensity and duration to induce an acute alteration in arterial compliance. And even though PWV recovered to baseline levels after the 30-minute recovery period, the decreases in AIx remained. This is likely due to the effects of post-exercise hypotension (Halliwill et al., 2013) compounded by the vasodilative effects of sauna bathing. Additionally, the cardiovascular strain from sauna bathing has been shown to be comparable to moderate exercise (Ketelhut & Ketelhut, 2019), thus it is reasonable to assert that post-exercise sauna bathing may have served as a source of physiological stress akin to aerobic exercise on the cardiovascular system.

LVET and DT, which represents the cardiac cycle, was shortened immediately after EX+SAUNA. However, there was a parallel increase in HR which would suggest that cardiac output would have remained fairly constant. And even though their values at 30 minutes post-intervention were lower than at baseline, they were returning to pre-intervention levels. Conversely, BP values of MAP, SBP and DBP were lowered after the protocol of EX+SAUNA, and did not appear to be recovering back to baseline levels 30 minutes post-intervention. MAP is derived from SBP and DBP [(MAP = DBP + 1/3 (SBP - DBP)], with DBP being the major constituent. As such, the lowering of MAP was expected given the reductions seen in both SBP and DBP. Furthermore, these findings are consistent with the prevailing literature, as even short bouts of exercise have been shown to lead to lowered BP levels more than 60 minutes post-exercise (de Brito et al., 2019).

Residual vasodilatation has been found after cycling exercise (Halliwill et al., 2013), and heat therapy has been reported to evoke a shear stress response that leads to greater decreases in blood pressure than 30 minutes of treadmill running (Thomas et al., 2016). Coupled with earlier research which found that increased shear stress promotes histamine formation in larger blood vessels like the aorta (DeForrest & Hollis, 1978), it would appear that the combination of these factors may have been responsible for the decrease in BP values. Recent research (Gayda, Paillard, et al., 2012) showed that aerobic exercise and sauna reduced SBP 15 minutes post-intervention, as well as for 24-hour SBP, 24-hour MBP, and daytime SBP. However, unlike other experiments such as this exercise and sauna study (II), there were no reductions in measures of DBP.

Left ventricular relaxation has previously been shown to be unaffected by heat stress (Brothers et al., 2009), and 30 minutes of sauna bathing alone (I) did not have a prolonged effect on DBP and DT compared to the findings of this

study (II), which suggests that the retention of decreases to DBP and DT may be attributable to the EX+SAUNA protocol, even though Gayda, Paillard and colleagues (2012) showed otherwise. These contradictory findings may have been due to the differences in experimental conditions and study populations, as the present study (II) employed 15 minutes of continuous sauna with no breaks and a lower relative humidity. In addition, the authors (Gayda, Paillard, et al., 2012) did not report fluid intake in their study, which may have had a bearing on the results that were found. However, even though fluid was permitted to be consumed *ad libitum* in all of the studies in the present dissertation (I – IV), it is known that this would still be inadequate to match sweat losses, which would result in incomplete fluid replacement (Lynn et al., 2009), and consequent decreases in cardiac preload.

6.2 Differences in acute responses between sauna bathing alone and exercise and sauna bathing (III)

A major difference between exercise and sauna bathing is that the systemic heat stress response is induced in the absence of skeletal muscle contraction. Extreme heat stress conditions drive the left ventricle without the stretch induced influence of blood venous return (Kimball et al., 2018). Peripheral vasodilation to the skin during heat stress facilitates the diversion of blood to superficial tissues, thereby decreasing central blood volume (Kirsch et al., 1986; Rowell, 1974). This consequently leads to lowered central BP levels, which necessitates an increased heart rate via greater sympathetic drive to sustain cardiac output and maintain cardiovascular function. In comparison, the increases in heart rate during aerobic exercise is primarily driven by the greater oxygen demand and utilization from working muscles (McArdle et al., 2015). In this balanced crossover study, both interventions showed similar responses in cardiovascular and hemodynamic indices. However, while pre and post intervention comparisons revealed that SAUNA had a greater immediate lowering effect on DBP and MAP, pre-intervention and 30 minutes post-intervention comparisons showed that the depressive effects of EX+SAUNA were still retained for SBP, DBP and MAP.

The reductions to BP values immediately after both interventions were clinically relevant (>5mmHg), whilst SAUNA was able to elicit significantly greater responses in DBP and MAP. These findings are contrary to the results reported by one of the first few studies comparing between sauna alone, and exercise followed by sauna (Gayda, Paillard et al., 2012). The authors speculated that one of the reasons for the lack of change in DBP for both interventions may have been due to the insufficient heat stimulus, which appears to be the case when taken into context together with the findings from this study (III). This is supported by a few key differences between the experimental setups of these two studies.

Firstly, participants in the study (Gayda, Paillard, et al., 2012) were exposed to two 8-minute periods of sauna bathing which was separated by a 10-minute rest period, whereas participants in this study (III) had two 15-minute exposures with only a minute of cold shower in-between. Secondly, the post-intervention measurements were not taken immediately after, but 15 minutes later. Although post 15-minute measurements were not taken, pre to post 30-minute SAUNA results showed that DBP had already returned to near pre-intervention levels. Therefore, it is also likely that the process of recovery may have already taken place during the first 15 minutes immediately after the intervention. Thirdly, although both of the studies utilized cycling on a stationary bike as the aerobic exercise modality, the participants in this study (III) proceeded immediately after exercise (<1 minute) to the sauna room. Results from earlier research (Paolone et al., 1980) has also shown that DBP is decreased when a bout of exercise is followed immediately by sauna bathing, although no changes were found in SBP.

The greater retention of reductions to SBP, DBP and MAP after 30 minutes of recovery in the EX+SAUNA intervention can be partially attributed to postexercise hypotension, as it has been well-documented to last up to 60 minutes, and even with comparatively shorter bouts of exercise (de Brito et al., 2019). Another plausible explanation is that sauna bathing may have presented as a source of additive stress to the initial bout of aerobic exercise, which has been reported in competitive athletes (Skorski et al., 2019). Furthermore, sauna bathing postexercise has been successfully employed as a tool for heat acclimation (Taylor, 2014), with various experimental studies reporting its efficacy (Leich et al., 2018; Scoon et al., 2007; Stanley et al., 2015).

Indeed, the acute BP lowering effects of aerobic exercise followed by sauna has also been shown in an apparently healthy group of men by Rissanen Häkkinen, Laukkanen and Häkkinen (2020), despite a different aerobic exercise and sauna protocol. Interestingly, there were no significant changes to DBP post-intervention and 30 minutes post-intervention in that study. However, the reductions to SBP followed a similar trend, which the authors speculate may be due specifically to the combination of aerobic exercise and sauna bathing, as they did not find the same changes with resistance training followed by sauna bathing. It must be highlighted that most of the findings from existing studies on the combination of aerobic exercise and sauna had comparable findings, in spite of the diverse study population characteristics. These results also bear importance for practical applications, as BP recovery and postexercise hypotension after a single bout of exercise has been shown to be predictive of an individual's BP response to long-term exercise training (Hecksteden et al., 2013; Liu et al., 2012). Moreover, acute postexercise responses in indices of vascular function such as shear rate have been shown to be able to predict adaptations to training (Dawson et al., 2018). Thus, it is reasonable to assert that the acute effects seen from EX+SAUNA may be indicative of changes that could follow as a result of longer-term practice.

The cardiovascular stress that can potentially be induced by a combination of exercise and sauna bathing may have broader implications and wider utility

than we presently recognize. Adding sauna bathing postexercise could perhaps enhance the adaptations to cardiovascular function that are already known to occur from long-term exercise training. Therefore, experimental data is needed to corroborate these assertions.

6.3 Adaptations to regular exercise and sauna bathing (IV)

Regular exercise has been reasonably well-established to improve several key markers of cardiovascular health, such as BP and CRF (Bull et al., 2020). Exercise recommendations and its evolution have been guided by such findings over the decades. For improvements in cardiovascular health and function, the present guidelines (Piepoli et al., 2016; Piercy et al., 2018; UKK-instituutti, 2019) suggest a minimum of 150 minutes of moderate-intensity exercise per week with at least two sessions of resistance exercise, which were met by the intervention used in the multi-arm RCT (IV). Accordingly, this study showed that eight weeks of combined exercise training three times a week for 50 minutes each time (30 minutes of aerobic, and 20 minutes of resistance exercise) was able to improve CRF and reduce body fat mass when compared to sedentary controls.

6.3.1 Adaptations to the exercise intervention

The resistance exercise component was in the form of circuit training, which has been shown to increased CRF independent of both the training characteristics and population used in the studies (Ramos-Campo et al., 2021). This systematic review with meta-analysis also found that greater effects were observed in programs with a duration of more than 20 sessions and a frequency of 3 sessions per week, which supports the present findings. Additionally, Ramos-Campo and colleagues (2021) found a substantially large effect of circuit training on body composition and fat mass loss with no change in body mass, which is also consistent with the results seen in this study. However, the influence that the study population may have had cannot be completely ruled out, as it has previously been shown that untrained sedentary individuals such as the ones used in our study have more capacity to improve their body composition, even with relatively short periods of training (Willis et al., 2012). Moreover, exercise has also been documented to induce a larger increase in total energy expenditure for these groups of individuals (Westerterp, 2017).

Programs of circuit resistance training combined with aerobic exercise has been shown to be very effective for improvements in CRF and body composition in earlier works (Gettman et al., 1982). The primary adaptation of the cardiovascular system to circuit training are improvements in maximal stroke volume, and as a consequence greater cardiac output, which leads to an increase in CRF (Haennel et al., 1989). Similar improvements to body composition and CRF have also been reported in other experiments using comparable training interventions (Ho et al., 2012; Khalafi et al., 2022). In particular, eight weeks of

combined aerobic and resistance training has been documented to result in greater improvements in a several mitochondrial-related outcomes such as whole-muscle oxidative capacity (Irving et al., 2015), which likely explains the improvements seen in CRF and body composition based on the exercise intervention that was used in the study (IV).

Despite the salutary adaptations that the exercise intervention was able to confer, there were no significant reductions to BP when comparing between the EXE and CON group. This was expected as combined training has previously been shown to have no effect on SBP, and only a modest decrease in DBP (Cornelissen & Smart, 2013). Furthermore, a more recently published review (Schneider et al., 2021) reported that the level and quality of evidence for combined training to decrease BP in a similar population of middle-aged and older adults is rather low. Finally, although it has been well-established that exercise interventions are more effective at addressing pre-existing elevated levels of BP (Muntner et al., 2019; Williams et al., 2019), the baseline values of the participants were within the normal range, as they were neither pre-hypertensive nor hypertensive.

6.3.2 Adaptations to regular exercise followed by post-exercise sauna bath

CRF. CRF adaptations to regular exercise in combination with repeated passive heat exposure in the form of sauna bathing has yet to be thoroughly investigated mechanistically. However, cardiovascular adaptations to exercise and heat exposure for purposes of heat acclimation have been reasonably well documented (Lorenzo et al., 2010; Taylor, 2000; Taylor, 2014), which provides us with a vital fundamental framework from which to explain the results seen in CRF between the EXE and EXS group. The major determinants that may have contributed to the present findings are detailed accordingly below.

In order for optimal heat adaptation to be induced, a constant physiological strain, known as the adaptation impulse, has to be maintained (Taylor, 2014). This is based on the principle that if the external stimulus remained constant (e.g., no change in temperature of sauna room, frequency of sauna use, or exposure duration), its physiological impact on factors such as vasodilatory responses and shear stress will wane as adaptation ensues. This would ultimately result in the same metabolic and thermal stress over time, which by design, leads to a progressively smaller overload even when repeated (Adolph, 1955, 1964; Taylor, 2000, 2014). As such, the differences seen in CRF between EXE and EXS could thus be partially attributed to the fortnightly increase in temperature (5 degrees Celsius) used in the sauna room, which was similar to the progressive increase in aerobic exercise intensity (5% HR_{MAX} fortnightly) of the intervention. Nevertheless, this remains speculative as these results were not corroborated by measures of core temperature.

Cardiovascular stability may have been augmented by the addition of regular sauna bathing, as exercise training and passive heat stress has been shown to have additive effects that leads to improved myocardial contractility, over exercise training or heat stress alone in animal models (Levy et al., 1997).

The addition of regular post-exercise sauna bathing could have also led to improved myocardial compliance, thereby rendering it more efficient (Horowitz et al., 1986). These postulations remain speculative however, as myocardial efficiency and ventricular compliance was not measured in the present study and would require rather invasive procedures in human studies. Furthermore, results from these early animal studies need to be interpreted carefully and with due caution. Firstly, the animals were at the end of their weaning stage (Baker et al., 2013) at the commencement of these experiments. Secondly, due to the nature of these studies, the rats were exposed to continuous increased temperature exposure which was meant to mimic heat acclimation. Thirdly, and perhaps more crucially, the animals were exposed to these conditions between 30 – 60 days (Levy et al., 1997) and sixty days (Horowitz et al., 1986), at a stage of their lives where 42.4 days is approximately one human year (Quinn, 2005; Sengupta, 2013).

Nevertheless, early evidence did suggest that heat adaptation decreases the heart's sympathetic response (Berlyne et al., 1974), with reductions in HR at fixed work rates (Taylor, 2014) secondary to increases in stroke volume (Taylor, 2000). This is an essential point to highlight, as CRF in the present study (IV) was quantified using a submaximal test via the extrapolation of HR at fixed workloads in stages (Golding et al., 1989), which might have been a reflection of the adaptations outlined above.

Although a sauna bathing duration of 15 minutes by itself, might only produce a small adaptation impulse capable of merely slight to moderate homeostatic disturbance (Taylor, 2014), the usage of post-exercise sauna bathing was able to complement, and to an extent, amplify the salutary adaptations seen in regular exercise. It is well established that after a bout of aerobic exercise, pro-angiogenic factors such as vascular endothelial growth factor is upregulated (Halliwill et al., 2013; Luttrell & Halliwill, 2015). Similarly, heat stress has been demonstrated to elicit similar responses (Kuhlenhoelter et al., 2016), with repeated application further shown to improve muscle capillarity (Kim, Reid, et al., 2020) at a comparatively shorter duration of six weeks (Hesketh et al., 2019). This is also supported by studies based on animal models, which showed that post-exercise whole body heat stress additively enhanced mitochondrial adaptations induced by aerobic training, with no antagonistic or opposing effects (Tamura et al,. 2014). Therefore, the interplay between exercise, particularly aerobic exercise, and post-exercise heat exposure could have a more prominent role in angiogenesis than what is currently known or understood.

In light of both the past and present evidence that has been delineated, it is likely that the differences in CRF between EXE and EXS were driven more by functional rather than morphological adaptations (Taylor, 2014; Zeisberger & Roth, 2010), and is further supported by the lack of change in vascular-related parameters such as PWV and AIx for both intervention groups. Although it must be noted that eight weeks is a relatively modest duration for an intervention, and morphological changes may still occur over a substantially longer period of time (Hellsten & Nyberg, 2015; Taylor, 2014). Nevertheless, it remains plausible that the improvements in CRF might have been a consequence of plasma and red-cell

volume expansion (Scoon et al., 2007; Stanley et al., 2015), mediated by an upregulation of hormones in the renin-angiotensin-aldosterone system (Hannuksela & Ellahham, 2001).

The downstream effect of these enhancements could have increased cardiac output, which has been speculated by a number of authors and led to the suggested use of post-exercise sauna bathing as a possible ergogenic (Kirby, Lucas, Armstrong et al., 2021; Kirby, Lucas, Cable et al., 2021; Scoon et al., 2007; Stanley et al., 2015). Although supporting data on these hormones were not collected, the outcomes were somewhat reflected by the changes in BP seen in EXS.

BP. In order to adapt to heat stress, the human organism makes a cascade of functional cardiovascular adjustments to stabilize BP and blood volume (Taylor, 2014). One such adjustment that characterizes this is the expansion of plasma volume, in order to maintain stroke volume whilst coping with fluid loss (Taylor, 2000). Over time, this consequently leads to a larger stroke volume and lower cardiac frequency at a given workload (Mitchell et al., 1976; Shapiro et al., 1981), a reduction in the vasodilatory threshold (Fox et al., 1963; Rowell, 1974) and an increase in skin blood flow (Cheng & McDonald, 2019; Rowell, 1990; Taylor, 2014). Another vital, albeit lesser-known adaptation response to heat stress is the improvement to arterial endothelial function (Hodges et al., 2018), which was also found in the present study (unpublished findings). Indeed, many of these adaptations have also been documented in studies using other forms of passive heat stress (Brunt & Minson, 2021), which all contribute to a lowering of BP.

Nevertheless, there are some noteworthy exceptions. For instance, eight weeks of single leg heating did not change endothelial or calf microvascular function in a group of young healthy females (McGarity-Shipley et al., 2021). It is worth noting however, that local heating and whole-body heating may not be directly comparable. Improvements in endothelial function for older adults with peripheral artery disease may also be absent (Akerman et al., 2019). Although as Akerman and colleagues (2019) succinctly pointed out, the progression of these types of diseased states may have reached a point where endothelial dysfunction are no longer reversible or mitigatable. This is substantiated by a meta-analysis showing that even exercise did not improve flow-mediated dilations in the same patient population group (Parmenter et al., 2015).

Notwithstanding, it is more likely than not that these beneficial adaptations to SBP from EXS was a consequence of the interaction, and possible synergy between exercise and post-exercise sauna bathing, as several previous studies (Gayda, Paillard, et al., 2012; Paolone et al., 1980; Ridge & Pyke, 1986; Scoon et al., 2007) investigating acute effects have shown. More recently, sauna bathing has also been suggested as an additional source of cardiovascular stress, especially when performed post-exercise (Skorski et al., 2019; Rissanen, Häkkinen, Laukkanen & Häkkinen, 2020; Rissanen, Häkkinen, Laukkanen, Kraemer, et al., 2020). As mentioned in the preceding section, the EXE intervention did not result in any significant or meaningful change to BP when compared to CON. This

suggests that the exercise intervention alone, absent of regular post-exercise sauna bathing was an insufficient stimulus for lowering BP in this group of individuals with CVD risk factors. Likewise, performing regular sauna bathing alone, three times per week for eight weeks is unlikely to lead to SBP changes of the same magnitude.

The remarkable adaptation of SBP to the EXS intervention needs to be considered in the appropriate context for it to be better appreciated. Based on the prevailing guidelines, SBP reductions of 5mmHg has the potential to directly improve individual BP categorization, and possibly reduce the need for pharmacological therapies (Benjmain et al., 2019; Pizzey et al., 2021; Zhou et al., 2018). Indeed, the beneficial linear association between the degree of SBP reduction and the risk of CVD and all-cause mortality has been reported previously in a network meta-analysis (Bundy et al., 2017). Furthermore, a wealth of evidence (Tsao et al., 2022; Whelton et al., 2017; Williams et al., 2018; Zhou et al., 2018) also suggests that higher BP categories are associated with increased incidence of chronic disease. In practice therefore, interventions that can elicit larger decreases in SBP, such as EXS are arguably more effective for risk reductions.

A recent systematic review found that exercise interventions were just as effective as antihypertensive drug therapies in hypertensive adults (Naci et al., 2019), with an increased effectiveness for exercise when higher SBP cut-off points were used. Furthermore, the authors found that there was no dose-response relationship between combined training exercise intensity and SBP reduction. A number of observations can be drawn from this in the context of the present study (IV). Firstly, the degree to which EXS was able to lower SBP over the course of eight weeks is comparable to that of antihypertensive medication (8.0 vs 8.8 mmHg, respectively). Secondly, although higher pre-existing levels of BP might inevitably mean more room for improvement, the present population studied in this dissertation were not predominantly hypertensive, and only had elevated BP levels (e.g., pre-hypertensive) as a CVD risk factor.

Lastly, the present findings highlight the potential of postexercise sauna bathing as an adjunct to regular exercise, particularly when the exercise intervention by itself, is insufficient to induce salutary BP adaptations. The practical relevance of these results should not be underestimated, as regular sauna bathing could indeed have more utility than simply being a recovery modality. It is reasonable to assert that it might also be a complementary tool, given that when used in conjunction with regular exercise, it was also able to lower TC levels.

TC. TC is a useful parameter for initial CVD risk detection and monitoring long-term responses to interventions (Cooper et al., 1992; Halperin et al., 2006). Beyond risk detection and stratification, TC level is a compelling surrogate measure, as cholesterol is a major component of the lipids of all atherosclerotic lesions (Myant, 1981). As such, cholesterol concentration levels may very well be predictive of heart attacks, especially when viewed from a statistical standpoint. Indeed, early studies both epidemiologically (Heiss et al., 1991) and

experimentally (Poli et al., 1988) have reported positive correlations between serum cholesterol levels and intima-media thickness of the carotid artery. This is further supported by more recent evidence, where higher TC levels was strongly associated with greater risk of myocardial infarction (Wilson, 2013) and higher BP categories (Wilson et al., 1998).

In the present study (IV), BP and TC levels were concomitantly decreased in EXS. Comparable findings have been reported in a several other studies that used different forms of heat therapy (Ely et al., 2019; Guo et al., 2014; Rivas et al., 2019) as well. Two crucial aspects may be garnered from these results. Firstly, they are collectively in support of the postulation that BP is influenced by TC (Ferrara et al., 2002). This is somewhat expected, as hypercholesterolemia has been shown to induce endothelial dysfunction (Hayakawa & Raij, 1999; Ohara et al., 1993). Moreover, TC has been shown to be inversely correlated to endothelium-dependent vasodilation (Shimokawa & Vanhoutte, 1989). Secondly and more importantly, it highlights the inherent utility of heat therapy, especially when statistically significant reductions in TC from exercise training are relatively diminutive (~1%) and not frequently observed (Leon & Sanchez, 2001).

Several exercise-training studies (Kraus et al., 2002; Sopko et al., 1985; Thompson et al., 1997) have reported beneficial alterations to lipid profiles absent of body or fat mass changes. Indeed, 24 weeks of supervised endurance exercise consisting of 3 sessions per week (Halverstadt et al., 2007) has been shown to lower TC independent of baseline body, and fat mass in a similar population of middle to older-aged adults at risk for CVD as well. However, the reductions in TC levels observed in the EXS group were significantly greater than those reported in previous exercise training studies (12 mg/dL vs. 2.1 mg/dL, respectively). This may be indicative of an independent effect of EXS on TC, given that these changes occurred in the absence of changes to body composition and mass. At the same time, it lends support to the notion that the amount of exercise performed may have a direct effect on TC (Kraus et al., 2002). Nevertheless, these findings may offer new practical implications as healthcare professionals search for adjunct and supporting life-style therapies that can complement exercise interventions and reduce CVD risks (Ely et al., 2017).

Heat exposure has been reported to have an acute effect on TC that is comparable to exercise, independent of physical characteristics (Yamamoto et al., 2003). It has also been suggested that persistent exposure to a hot environment may have an inhibiting effect on lipid synthesis (Kurakake et al., 1998). The adaptation of lowered TC may have been directly related to cholesterol mobilization from serum into cellular membranes as a result of repeated heat exposure. By increasing cholesterol concentration in the membrane, the cell consequently becomes more thermal resistant (Cress & Gerner, 1980). In addition, the possible effects of hyperthermia-induced lipolysis (Thorne et al., 2020) cannot be ruled out. Elevated temperatures induce a hypermetabolic response that also increases glycogenolysis, which has been shown in heat therapy studies (Lee & Kim, 2015; Rivas et al., 2019). However, it is important to note that these findings

were based on hot water immersion and may not be directly generalizable to other heat therapy modalities such as sauna bathing.

6.4 Strengths and limitations

The present dissertation has several strengths, particularly in terms of experimental design and statistical approaches. All the studies were based on an appropriately large number of participants which provided sufficient statistical power for data analyses. Notably, the data analyses for studies III and IV were performed by an independent statistician who was not involved in the data collection process. Furthermore, all the variables were coded. For study III, a balanced crossover design with a more robust statistical method was employed, which allowed the responses seen to be directly attributed to the respective interventions. Study IV utilized a multi-arm randomized controlled design and was the first registered trial of its kind to investigate the long-term effects of Finnish sauna bathing, and regular exercise and sauna bathing in a more representative population.

The assessment of cardiovascular and hemodynamic parameters was performed using standard protocols according to the most up-to-date guidelines at the time the respective studies conducted. These include measurements taken using the PulsePen tonometer, as well as automated oscillometric devices for BP. Moreover, the devices used have all been well validated, including the dual X-ray absorptiometry for body composition. All sessions were attended by a medical doctor, and training sessions (IV) were supervised by experienced and qualified training instructors. The compliance of all the experiments was also excellent, with a 95% adherence rate. However, there are also some limitations that need to be highlighted. Study I and II had rather diverse sample characteristics, which limits generalizability. These studies also did not have a control condition and/or group, which would have made the results seen more robust. Because the sessions were split into two 15-minute bouts, an additional measurement taken after the first 15-minute would have allowed for a more detailed and nuanced examination of each intervention.

Study III lacked an aerobic exercise only intervention, which would have enabled a comparison between aerobic exercise and EX+SAUNA, and aerobic exercise and SAUNA. This would have perhaps provided a more complete picture on the additive and complementary effects of sauna bathing on exercise. The data interpretation is also somewhat limited with the lack of cardiac output measurements. Studies I – III did not control for menstrual phase, so the degree of influence that the differences in menstrual phases may have had cannot be determined. They were also comprised of mostly frequent sauna users, although that was adequately addressed in the inclusion and exclusion criteria for the sample population of study IV.

In spite of addressing some of the methodological concerns arising from prior experiments, study IV lacked a sauna-only group, which would have given

additional insight as to whether the benefits seen from the study could be attributed solely to sauna bathing. Diet of the participants was not controlled for, and thus may have had a bearing on the results. However, participants did follow the same diet a day before each measurement was taken. Finally, the study sample consisted mostly of women (41 females, 6 males) which meant that stratified randomization had to be used in order to balance the groups. However, this could also be viewed as a strength, as the lack of experimental data among females has been a well-recognized issue in scientific research (Holdcroft, 2007).

6.5 Future directions

When taken into context together with the prevailing literature, the findings from the present dissertation suggest that adding sauna bathing post-exercise confers a beneficial additive effect both acutely, and over the long term. Although these results provide substantial promise for the field of heat therapy, particularly in the long-term usage of sauna bathing, several important points need to be taken into account. Unlike exercise training, we still do not know how to prescribe the use of sauna bathing effectively. Specifically, as several notable authors (Brunt & Minson, 2021; Cullen et al., 2020; Pizzey et al., 2021) have aptly pointed out we do not have a complete understanding of the major determinants of heat stress, such as the optimum frequency, duration and the temperature of exposure. Temperature is a vital consideration as it is perhaps the closest measure of intensity for heat therapy studies.

Although earlier research has shown the positive cardiovascular effects of sauna bathing when used 4 or 5 times a week (Haseba et al., 2016; Ohori et al., 2012), future research ought to investigate if health benefits are still present when the frequency of sauna bathing is reduced to twice, or even once a week. This will enable us to have a better understanding of what the minimum effective dose is, with regards to the optimal frequency of exposure. Along the same lines, the duration of exposure should also be studied further. Findings from the current literature (Brunt & Minson, 2021; Cullen et al., 2020) and experiments (Haseba et al., 2016; Hussain et al., 2019; Ohori et al., 2012; Sobajima et al., 2013), together with the present dissertation seem to indicate that a 15-minute exposure time is sufficient for adaptations. However, we do not know if a shorter exposure time (i.e., ten or even five minutes) when performed regularly, would induce the same adaptations. Especially when episodic increases in shear stress have been reported to elicit significant increases in endothelial function and vascular reactivity (Hodges et al., 2018).

Many of the options to validate exercise intensity, such as the percentage of one repetition maximum or repetitions in reserve for resistance exercise, and percentage HR_{MAX} or $VO2_{MAX}$ for aerobic exercise, have been developed over decades. However, the field of heat therapy has yet to follow suit. Understanding how to manipulate temperature as a surrogate measure of intensity will undoubtedly allow us to better comprehend the dose-response relationship of

passive heat exposure, which includes modalities such as hot water immersion and sauna bathing amongst others. Nevertheless, it is worth noting that the average sauna user often might not possess their own sauna room nor can they freely adjust the temperature in a public sauna, which is why future research will need to focus on the complex and intricate interplay between exposure frequency, duration and temperature for cardiovascular benefits and health optimization.

Another important aspect that ought to be examined closer is the broader application of sauna bathing for disease states, such as heart failure and other physical conditions. As has been noted earlier (Hussain & Cohen, 2018), sauna bathing may be a viable option for populations who are unable to meet the minimum threshold necessary for exercise-induced cardiovascular adaptations. Although sauna bathing has been reported to improve outcomes for patients with heart failure, its effectiveness on other debilitating cardiovascular diseases remains to be explored. Additionally, sauna bathing may also be a promising adjunct strategy for musculoskeletal diseases and injuries, based on the current evidence (Kim, Monroe, et al., 2020; Kim, Reid, et al., 2020). However, adherence to exercise and/or sauna bathing remains a barrier for many, as both activities require effort, resources, and time.

Finally, it is worth mentioning that the energy expenditure of a single sauna bathing session has also yet to be fully elucidated. Given that sauna bathing increases HR and consequently cardiac output, experimental data on oxygen consumption for what is considered a "typical" sauna bathing session will bring considerable value. Not only will it better serve the general public via more refined guidelines and recommendations, healthcare practitioners also stand to benefit from more precise information to direct their prescriptions. The study of heat therapy, especially as it pertains to Finnish sauna bathing, is still very much in its infancy. And as our knowledge in this growing area continues to develop, sauna bathing may perhaps become an essential part of a healthy lifestyle. One that is not only for the affluent or those residing in the Nordic region, but accessible for everyone in the world.

7 MAIN FINDINGS AND CONCLUSION

The main findings, and the conclusions of this dissertation are summarized as follows:

1. 30 minutes of heat exposure using the Finnish sauna leads to positive acute alterations in cardiovascular function. This is represented by improved arterial compliance and systemic BP. Although many of the markers such as DBP and PWV had returned to baseline levels, the changes to LVET and SBP were still present after a 30-minute recovery period. This physiological response is suggestive of the possibility, of beneficial adaptations to long-term sauna bathing in a population with CVD risk factors (I).

2. A combination of 15 minutes of aerobic exercise followed immediately by 15 minutes of sauna, as a single intervention was able to reduce AIx, PWV, LVET, DT, DBP, SBP and MAP acutely, in adults with CVD risk factors. With the exception of PWV, which recovered to baseline levels after 30 minutes, the reductions seen in all the other parameters were retained. This may be indicative of a plausible synergistic potential, when sauna bathing is performed immediately after exercise (II).

3. The acute cardiovascular and hemodynamic responses to sauna bathing alone, and the combination of aerobic exercise followed by sauna bathing were comparable when both interventions were matched for time. However, sauna bathing elicited comparatively lower DBP and MAP levels immediately post-intervention, whilst the combination of exercise followed by sauna bathing had lower SBP, DBP and MAP after 30 minutes of recovery. In populations with lower exercise capacities, sauna bathing alone, and to a larger extent, a combination of exercise followed by sauna bathing could be used to induce similar acute effects as exercise (III).

4. Regular exercise performed according to the recommended guidelines of three times a week, 50 minutes each time, for 8 weeks was able to improve CRF and body composition in a sedentary population with CVD risk factors. The addition of a regular 15-minute sauna bathing session post-exercise augmented the gains in CRF, and reduced SBP and total cholesterol levels substantially. These findings are encouraging, and possess practical utility, as the critical methodological determinants of sauna bathing, such as the frequency, and duration of exposure were well-tolerated and repeatable.

YHTEENVETO (SUMMARY IN FINNISH)

Saunomisen perinne on ollut olemassa useita tuhansia vuosia. Vaikka se sai alkunsa pohjoismaissa, sen suosio on sittemmin kasvanut huimasti. Monet muutkin maanosat, kuten Australia, Kanada ja jopa kuumat lauhkeat alueet, kuten Lähi-itä ja Kaakkois-Aasia, ovat ottaneet saunomisen käyttöön erilaisissa muodoissa. Sen laajasta käytöstä huolimatta monet saunojat, myös säännöllisesti saunaa käyttävät, eivät kuitenkaan ole tietoisia saunomisen mahdollisista terveyshyödyistä.

Vaikka saunomista koskeva tutkimus ulottuu 1940-luvulle asti, monet näistä kirjoituksista ja julkaisuista eivät ole päässeet suuren yleisön tietoisuuteen. Tämä johtui suurelta osin siitä, että tutkimukset tehtiin ja julkaistiin pääosin Saksassa ja vasta myöhemmin myös Suomessa. Vaikka monissa näistä tutkimuksista raportoitiin myönteisiä ja pitkän aikavälin vaikutuksia, ne eivät olleet suuren yleisön saatavilla. Lisäksi monissa näistä aiemmista tutkimuksista ei ollut nykyaikaisen tieteellisen huippuosaamisen tunnusmerkkejä, kuten kokeellista toistettavuutta ja metodologista tarkkuutta.

Tämä vankkojen todisteiden puute ei kuitenkaan estänyt saunojien rutiineja tai kylpylöiden omistajien pyrkimyksiä. Itse asiassa saunominen on koettu niin rentouttavana ja hyvinvointia edistävänä toimintana, ettei sen myyminen alkuaikoina vaatinut tieteellistä näyttöä. Yhteiskuntamme vaurastuessa alkoi kuitenkin ilmaantua toisenlaisia ongelmia ja haasteita. Ihmiset alkoivat käyttää aikaansa tuottavuuteen ja työhön, ja monet alkoivat myös sairastua sairauksiin, jotka johtuivat vähäisemmästä fyysisestä aktiivisuudesta.

Fyysinen aktiivisuus ja säännöllinen liikunta ovat olennaisia terveyden ylläpidolle. Tämä koskee erityisesti niitä, joilla on riski sairastua sydän- ja verisuonitauteihin. Liikunnan määrän ja/tai intensiteetin on kuitenkin oltava riittävällä tasolla, jotta elimistö pystyy sopeutumaan ja selviytymään stressistä. Tästä on tullut suuri haaste nyky-yhteiskunnassamme, minkä vuoksi tarvitaan täydentäviä hoitomuotoja. Se on myös yksi syy siihen, miksi lämpöhoito ja saunominen ovat herättäneet uudelleen tieteellistä kiinnostusta.

Saunomisen on osoitettu aiheuttavan sellaisia muutoksia sydän- ja verenkiertoelimistössä, jotka ovat verrattavissa erityisesti aerobiseen liikuntaan. Saunomisen ja liikunnan välillä on kuitenkin myös merkittäviä eroja. Tärkein ero on supistuvien lihasten käytön puuttuminen. Tärkeää on myös se, että verenkierron jakautuminen muuttuu, mikä johtaa korkeampaan mekaaniseen stressiin valtimoissa saunomisen aikana. Teoriassa tämä voisi olla myös tapa aktivoida ja käyttää sileitä lihaksia. Edellä mainitut seikat ovat tärkeimpiä syitä siihen, miksi liikunta ja saunominen voivat täydentää toisiaan.

Tässä väitöskirjassa havaittiin, että 30 minuutin saunominen pystyi akuutisti parantamaan valtimoiden verenkiertokykyä ja verenpainetta. Nämä vaikutukset olivat suurempia ja kestivät pidempään, kun yhdistelmänä oli aerobinen liikunta ja sen jälkeen saunominen. Vielä merkittävämpi havainto oli, että säännöllinen liikunta yhdistettynä säännölliseen saunomiseen paransi sydän- ja hengityselimistön kuntoa, systolista verenpainetta ja kokonaiskolesterolipitoisuutta.

Tämän väitöskirjan viimeinen koe oli myös ensimmäinen rekisteröity monihaarainen satunnaistettu kontrolloitu tutkimus, jossa tutkittiin saunomisen pitkäaikaisvaikutuksia.

Vaikka tämän väitöskirjan puitteissa kerättiin ja raportoitiin paljon uutta tietoa, on vielä monia haasteita, jotka on ratkaistava, ennen kuin pystymme ymmärtämään paremmin pitkäaikaisen saunomisen vaikutuksia ja sen synergiaa liikunnan kanssa. Tällä on ratkaisevia käytännön vaikutuksia, sillä monet sairaudet estävät niitä sairastavia ihmisiä saavuttamasta terveyden kannalta tarvittavaa liikunnan intensiteettiä ja määrää.

Ensimmäiseksi olisi löydettävä keino standardoida saunomismenetelmät. Tällä hetkellä ei ole yksimielisyyttä altistumisen kestosta, altistumistiheydestä ja käytettävästä lämpötilasta. Jos nämä kolmen muuttujaa yhtenäistettäisiin eri tutkimuksissa, saisimme tuloksista vertailukelpoisempia. Jotta tämä tapahtuisi, tarvitsisimme saunatutkijoiden yhteenliittymän, joka antaisi selkeämmän suunnan tuleville saunatutkimuksille.

Toiseksi tarvittaisiin enemmän perustietoa saunomisesta, kuten hapenkulutuksesta ja energiankulutuksesta saunomisen yhteydessä. Näin saisimme paremman käsityksen siitä, kuinka rasittavaa tyypillinen saunominen on suhteessa saman kestoiseen aerobiseen liikuntaan. Näin myös terveydenhuollon ammattilaisilla olisi käytettävissään tietoa, jota he voisivat hyödyntää saunomisen liittyvässä ohjeistuksessa.

Lopuksi totean, että saunomisen on oltava nykyistä tärkeämpi osa julkisen terveydenhuollon keskustelua. Jos sairaalat ja hoitolaitokset osallistuisivat aktiivisesti tähän keskusteluun, olisi meillä suurempi mahdollisuus monikeskustutkimuksiin ja yhteistyöhön, joissa hyödynnetään suurempia ja monipuolisempia kohortteja. Näin saisimme enemmän tietoa siitä, mitä meidän on muokattava, jotta saunominen voitaisiin optimoida terveyttä edistäväksi toiminnaksi.

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ORIGINAL PAPERS

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SAUNA EXPOSURE LEADS TO IMPROVED ARTERIAL COMPLIANCE: FINDINGS FROM A NON-RANDOMISED EXPERIMENTAL STUDY

by

Lee, E., Laukkanen, T., Kunutsor, S.K., Khan, H., Willeit, P., Zaccardi, F. and Laukkanen, J.A., 2018

European Journal of Preventive Cardiology vol 25(2), 130-138

https://doi.org/10.1177/2047487317737629

Sauna Exposure Leads to Improved Arterial Compliance: Findings from a Non-Randomized Experimental Study

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This study was supported by the Tekes, the Finnish Funding Agency for Technology and Innovation, Helsinki, Finland

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ABSTRACT

Background: Heat therapy has been suggested to improve cardiovascular function. However, the effects of hot sauna exposure on arterial compliance and the dynamics of blood flow and pressure has not been well documented. Thus, we investigated the short-term effects of sauna bathing on arterial stiffness (AS) and hemodynamics.

Design: Experimental non-randomized study

Methods: There were 102 asymptomatic participants (mean, 51.9 years) who had at least one cardiovascular risk factor. Participants were exposed to a single sauna session (duration: 30 minutes; temperature: 73°C; humidity: 10-20%). Pulse wave velocity (PWV), augmentation index (AIx), heart rate (HR), blood pressure (BP), mean arterial pressure (MAP), pulse pressure (PP), augmented pressure (AP) and left ventricular ejection time (LVET) were assessed before, immediately after, and 30 minutes after a single sauna session.

Results: Sauna bathing led to reductions in PWV, BP, MAP and LVET. Mean PWV value before sauna was 9.8 m/s and decreased to 8.6 m/s immediately after sauna ($p<0.001$ for difference), and was 9.0 m/s after the 30-minute recovery period ($p<0.001$ for ANOVA). SBP was 137 mmHg before sauna, decreasing to 130 mmHg after sauna ($p<0.001$), which remained sustained during the 30-minute recovery phase ($p<0.001$ for ANOVA). After a single sauna session, diastolic blood pressure (DBP) decreased from 82 to 75 mmHg, MAP from 99.4 to 93.6 mmHg and LVET from 307 to 278 ms^{-1} ($p<0.001$ for all differences). Pulse pressure was 42.7 mmHg before the sauna, 44.9 mmHg immediately after sauna, and reduced to 39.3 mmHg at 30-minutes recovery ($p<0.001$ for ANOVA). Heart rate increased from 65 to 81 bpm^{-1} post-sauna ($p<0.001$); there were no significant changes for AP and pulse pressure amplification (PPa).

Conclusion: This study shows that PWV, SBP, DBP, MAP, LVET and DT decreased immediately after a 30-minute sauna session. Decreases in SBP and LVET were sustained during the 30-minute recovery phase.

Key words: Arterial stiffness, pulse wave velocity, sauna bathing, heat therapy, experimental study

INTRODUCTION

Heat therapy has many benefits for the human physiology. The heat stimulates the sensory receptors in the skin, decreasing transmissions of pain signals to the brain to relieve discomfort, and increases the flow of oxygen and nutrients to the muscles, helping to heal damaged tissue, through thermoregulatory mechanisms and pathways.[1,2] Previous studies have also shown an association between controlled heat stress and augmented cardiovascular function.[3-5]

In line with these findings, it has also been suggested that heat therapy may improve microvascular function.[6] There are different ways to apply heat therapy, such as using dry heat or warm water immersion.[1] However, the use of dry heat via hot sauna exposure has been gaining popularity, especially after it has been shown to alleviate acute and chronic conditions such as asthma, headaches, hypertension, incidence of colds and other related broncho-constructive disorders.[7-9] Indeed, our prospective population-study has also demonstrated that there is a strong association between sauna exposure and a lowered risk for CVD outcomes[10]. In addition, it has been suggested that sauna therapy may improve vascular compliance, which has been previously documented in subjects with coronary heart disease (CHD) risk factors,[11] although the effects of sauna bathing on arterial compliance has not been reported.

Arterial stiffness (AS) has been recognized as a risk factor for atherosclerotic CVDs and mortality.[12,13-15] Although resting blood pressure (BP) levels is considered a close surrogate measure to AS, studies have shown that AS is a more accurate indicator of vessel function.[16] Consistently, some studies have shown that AS is considered to be a stronger risk factor for cardiovascular mortality than brachial BP alone[16,17] and, therefore, increased AS is independently associated with adverse cardiovascular events.[18] However, to our best knowledge, no experimental studies on the acute effects of sauna bathing on AS and hemodynamic parameters have been conducted.

Pulse pressure (PP) and mean arterial pressure (MAP) have been well documented as markers of cardiovascular risk in different clinical settings[19,20] Pulse pressure is a pulsatile

component of the BP curve as opposed to MAP, defined as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), and has been demonstrated to predict cardiovascular mortality in the general population.[21,22]

The current gold standard for assessing AS is through the measurement of pulse wave velocity (PWV). However, a change in PWV could be supplemented via alterations in vascular pressure and/or left ventricular ejection time (LVET). This reflects a natural change in arterial wall properties without hemodynamic shifts, as the pulsatile nature of blood flow in large arteries are mainly regulated by arterial distensibility, ventricular function and arterial pressure. Better understanding of these underlying mechanisms may help in explaining the acute physiological responses of the vascular system in maintaining homeostasis against heat exposure.

Therefore, using a non-randomized experimental study, we aimed to investigate the acute hemodynamic and vascular responses among asymptomatic participants with cardiovascular risk factors and their recovery profiles after 30 minutes of sauna bathing. This study will further clarify if sauna bathing leads to significant alterations in vascular and hemodynamic function, including changes in PWV, MAP, PP and LVET among this population.

METHODS

Participants

A total of 102 (n) participants were recruited from the city of Jyväskylä, Central Finland region, through the local out-of-hospital health care center. The study group consisted of asymptomatic participants (no cardiovascular symptoms) with at least one cardiovascular risk factor, such as a history of smoking, dyslipidemia, hypertension, obesity, diabetes, or family history of CHD. All participants with acute or diagnosed CVD were excluded. Prior to the participation in the study, all participants were informed about the research purposes and measurement procedures, and were screened by a cardiac specialist. The research protocol and study design were approved by the institutional review board of the Central Finland Hospital District ethical committee, Jyväskylä, Finland (Dnro 5U/2016). All study participants provided written informed consent prior to the inclusion in the study. The study was performed as stated by the declaration of Helsinki.

Clinical Examination

A clinical evaluation with baseline data collection was conducted on a separate day prior to the experiment. All baseline and sauna measurements were conducted during June and November 2016. During the screening visit, medical history, physical examination, blood lipid levels and resting ECG were assessed. A maximal exercise test was conducted on a separate day to determine their level of fitness. Resting blood pressure was estimated as the mean of two measurements obtained while the participant was in supine with a standardized measurement protocol. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

Sauna Exposure

Sauna exposure in this experiment was based on a traditional Finnish sauna, which is characterized by air with a relative humidity of 10-20% and high temperature.[10] In our study, relative humidity of the air was 15-20% and the temperature over the entire course of the experiment was 73 ± 2 °C. The sauna temperature in each room was recorded continuously as 10 second averages using a 2-channel internal temperature sensor designed by Harvia Oy, Finland. Sauna exposure was based on typical Finnish sauna bathing sessions; the total duration was 30 minutes, and it was interspersed with a short, two-minute shower at 15-minute intervals. Participants wore their own swim suits during the sauna session and there were separate sauna rooms for women and men; the sauna rooms were similar in the terms of space, humidity, temperature and air conditioning.

Before the sauna experiments, all participants received written and verbal instructions informing them to avoid meal, caffeine and smoking within 3 hours of the measurement, and that speaking and sleeping during the measurement was prohibited. All measurements were taken in a quiet room with a stable temperature (21 °C) on the right side of the body in the supine position. Participants were supervised by a physician and were allowed to leave the sauna at any time they felt uncomfortable. All participants underwent the recommended sauna protocol successfully. They were instructed to rest in a designated waiting lounge at room temperature (temperature 21 °C) for the whole recovery period after the immediate post sauna measurement. Water intake was ad libitum. Study participants were allowed to drink 500 ml still water during sauna and recovery period, according to guidance of the local ethical committee

Outcome definitions

Assessment of Arterial Stiffness Parameters

The measurement of AS during this experiment followed closely established guidelines.[23] Measurements of AS are performed by using The PulsePen device (DiaTecne s.r.l., Milan, Italy; www.pulsepen.com) which is composed of one tonometer and an integrated

electrocardiogram (ECG) unit. The PulsePen is made of a pressure probe the size and shape of a ball point pen with a built-in acquisition device that serves to non-invasively detect the pressure waveform by means of applanation tonometry. The unit is connected to the computer by means of an optical fiber that ensures the electromagnetic isolation for the patient undergoing the test. Data analysis is performed by specially designed software at a sample rate of 500 Hz.[24] The device software does not validate measurements if the difference between BP or heart rate values taken at the time of carotid and peripheral artery recordings was >10%. All measurements before and after the sauna were taken by a single trained operator of the tonometer. The same transit distances measured during baseline clinical evaluation were used throughout the experiment for consistency and reliability.

PWV was measured by recording carotid and peripheral (femoral) waveforms in rapid succession at a sample rate of 1 kHz, and defined as the transit distance between the measuring sites divided by the time delay between the distal pulse and proximal pulse wave, using the ECG trace as reference. Transit distances were assessed by body surface measurements using a tape measure from the suprasternal notch to each pulse recording site (carotid and femoral). Direct carotid to femoral measurement was adjusted to 80% (common carotid artery – common femoral artery x 0.8) for the calculation of PWV as recommended by current guidelines.[25] Transit time was defined as the difference between the delay of the distal pulse wave to the R wave belonging to the ECG qRs complex and the delay of the proximal pulse wave to the R wave belonging to the ECG qRs complex. The pulse wave delay was determined by calculating the time elapsed from the peak of the R wave and the "foot" of the pressure pulse wave.

The pressure values recorded by tonometry were calibrated to the BP values obtained at the brachial artery; where they were assigned to the appropriate pixels and the values for MAP and all other pressure-related parameters were re-established. The values deduced by the software apply the established concept that the MAP remains unchanged in the tract from the aorta to the peripheral arteries. MAP was calculated by the software as DBP + 1/3(SBP - DBP).[24] LVET was determined as the difference between heart period and diastolic time. Assessments of various AS parameters are shown in **Figure 1**.

Left ventricular ejection time (LVET), diastolic time (DT), and augmentation index (AIx) were obtained from the carotid pressure waveform analysis. The point corresponding to the end of LVET and the beginning of DT is identified by the dicrotic notch in the carotid pulse waveform. This point is automatically estimated by the PulsePen software.[26] Augmentation index is a parameter which provides an indication of the contribution of reflected waves to the total PP and was defined as the difference between the second and first systolic peak on arterial pulse waveform and was expressed as a percentage of central pulse pressure ((AIx) = AP/PP x 100).[27]

Assessment of Blood Pressure

Supine brachial systolic and diastolic blood pressures (SBP and DBP respectively) were obtained using Microlife BP A200 (Microlife Corp., Taipei, Taiwan) for better sensitivity and accuracy[28].Two sequential readings were measured and the mean values were used. Participants rested in the supine position for 10 minutes before PWV was measured at baseline. However, due to the nature of the study, AS was measured immediately and 30 minutes after the sauna exposure without having laid supine for 10 minutes.

Statistical Analyses

Data are presented as means ± standard deviations (SDs) and frequencies as appropriate. Normally distributed data were analyzed for within-group (time) changes with a repeated measure analysis of variance (ANOVA). Normality was checked using the Shapiro-Wilk test as well as through observing the Q-Q-plots. Non-normally distributed data was log-transformed to achieve normality and thereafter analyzed. The level for significance was set at $p \leq 0.05$. Within-group differences between before vs. immediately after, before vs. 30 minutes recovery and immediately after vs. 30 minutes recovery from sauna were analyzed using pairwise t-tests, and p-values were corrected for Bonferroni by multiplying all pairwise p-values with the number of comparisons conducted for each variable.

All statistical analyses were carried out with Stata version 14.1 (Stata Corp, College Station, Texas) and IBM SPSS Statistics v.22 software (IBM Corporation, Armonk, New York, USA).

RESULTS

Characteristics of participants

In this study population, there were 56 male and 46 female participants. The characteristics of the participants are shown in **Table 1**. The mean (SD) age and BMI of participants was 51.9 (SD 9.2) and 27.9 (kg/m^2) (4.7) respectively and the most common underlying clinical conditions were dyslipidaemia (63%) and hypertension (14%). Body weight of the participants did not change statistically significantly during the sauna session (pre-sauna: 82.7 (16.0) kg vs post-sauna: 83.0 (15.7) kg).

Changes in arterial stiffness

Table 2 shows changes in measures of AS after 30 minutes of sauna exposure. Mean PWV value before sauna was 9.8 m/s, decreased significantly to 8.6 m/s immediately after sauna, and was 9.0 m/s after a 30 minute recovery period ($p<0.001$ for ANOVA). Values of AIx and LVET decreased statistically significantly immediately after sauna; for LVET, the decrease was still significant after 30 minutes recovery. However, AIX recovered to its initial levels after 30 minutes of recovery (**Table 2**). Diastolic time decreased significantly due to sauna exposure from 635.1(±115.1) to 494.6 (±113.0) m/s, and increased back to the pre-sauna level after 30 minutes recovery.

Changes in arterial pressure, augmented pressure, pulse pressure and pulse pressure amplification

Changes in measures of central hemodynamics are shown in **Table 3**. MAP decreased significantly from 99.4 (± 15.0) mmHg before sauna to 93.6 (± 10.3) mmHg immediately after

sauna, but MAP recovered at 30 minutes after sauna to 95.9 (± 14.2). However, changes from immediately after sauna to 30 minutes recovery in MAP were not statistically significant. Pulse pressure decreased significantly from after the sauna exposure to the recovery period, being 44.9 (± 9.8) mmHg immediately after sauna, and reducing to 39.3 (± 8.3) mmHg at 30-minutes recovery (**Table 3**). There were no statistically significant changes for AP and PPa at all time points during the sauna bathing.

Changes in brachial blood pressure and heart rate

Sauna bathing had significant effects on BP (**Table 4**). SBP was 137 mmHg before sauna, which decreased significantly to 130 mmHg immediately after sauna ($p<0.001$ for difference), and remained at 130 mmHg after the 30 minutes recovery ($p<0.001$ for pre- and post 30-minutes sauna difference). The corresponding values for DBP were 82 mmHg, 75 mmHg, and 81 mmHg, respectively **(Table 4).** Heart rate increased from 65 bpm to 80 bpm as a result of the 30 minutes' sauna exposure but returned to 66 bpm after the 30 minutes' recovery period **(Table 4).**

DISCUSSION

This study showed that heat exposure of sauna has acute effects on AS among participants who have at least one cardiovascular risk factor. The main finding from this study was that sauna bathing has several important effects on vascular and hemodynamic function. We found that sauna bathing leads to lower levels of PWV, AIx and diastolic time, with short-term decreases in both MAP and DBP, which were observed immediately after sauna. On the other hand, levels of SBP and LVET were sustained until the end of 30-minute recovery phase. The indices of AS including PWV, AIx, MAP and LVET changed in the same direction during the sauna bathing. Heart rate and PP yielded a short-term response in the opposite direction; showing an increase immediately after the sauna exposure before returning to resting levels or even below the baseline level, while no notable changes were found for AP and PPa.

PWV was modulated positively after 30 minutes' heat exposure while the reduction in SBP levels remained significant when comparing baseline values to 30 minutes' recovery data. It has been previously shown that PWV is more closely related to left ventricular systolic function than to heart period.[26] The association between PWV and LVET can be attributed to myocardial function, where the two share an inverse relationship. The decrease in LVET in parallel with PWV was therefore an interesting finding.

As postulated by Salvi and coworkers,[26] when there is a decrease in systolic ejection time, the time taken by the left ventricle to do mechanical work is shortened, thus resulting in an increase in BP and velocity of travelling waves, which in turn leads to an increase in PWV. However, the opposite was found as a result of sauna exposure. Nonetheless, the authors concluded that PWV may be a determinant of LVET; this is supported by the results from our study in that the changes in PWV and LVET were similar immediately after sauna and at 30 minutes recovery period.

These findings are further supported by the observation that changes in cardiac afterload did not affect the duration of left ventricular ejection.[29] Secondly, LVET could be the time interval of the cardiac cycle responsible for the relationship between PWV and HR.[30] In this study, LVET decreased from 307 to 278 ms^{-1} after sauna exposure and recovered towards initial

levels after a 30 minute period, which may at least partly indicate a higher HR after sauna. Indeed, results from this experiment showed an acute increase in HR after the sauna exposure. This is consistent with the changes in DT due to sauna bathing, where DT was decreased immediately after sauna and returned to initial levels during the recovery.

The increase in HR seen in our study did not have a significant contribution to PPa, although it has been postulated that changes in HR and LVET would mediate changes in AP and AIx, and thus modifying PPa level.[31] Our results showed that acute sauna exposure increased HR and decreased LVET, which in turn resulted in a significant decrease in AIx, even though AP showed no change. This may be indicative of the contribution of HR to wave reflection and AIx.[32] Augmentation index is commonly accepted as a measure of enhancement of central aortic pressure by a reflected pulse wave and is considered to measure a different aspect of AS.[27] This study showed that AIx decreased significantly after sauna, which may be associated with peripheral vascular changes (vasodilation) after sauna bathing, although it is likely that the increase in PP mediated the decrease in AIx.

Interestingly, the results from our study showed a transient increase in PP with no significant concomitant decrease in PPa. High PP has been shown to be an independent predictor of mortality in patients with heart failure[33] and has been postulated to be a significant predictor of CHD risk.[34,35] In addition, a reduction in PPa has been proposed as a potential mechanical biomarker of global arterial function and cardiovascular risk.[31] The increase in PP and HR through sauna exposure also did not coincide with an increase in PPa as suggested by other studies[32]. However, in this study, the decreases in PP were found after a 30 minutes recovery period, suggesting beneficial cardiovascular effects of a 30 minute sauna exposure.

In our current study setting, sauna bathing was able to acutely reduce BP and MAP. Decreases in BP and MAP, is a clinically important finding from this study showing the effect of sauna on BP parameters. Because hot sauna bathing can produce acute vasodilation which leads to a significant drop in BP,[36] longer term sauna bathing could potentially lead to a reduction in systemic BP, which is supported by our recent findings on regular sauna bathing and a lowered risk of hypertension.[37] In patients with slightly elevated BP, a single sauna session produces positive lowering effects on systemic BP.[38] These findings are comparable

with exercise training and blood pressure-related studies[39,40] investigating the acute effects of BP changes. Decreases in systemic BP with a concomitant increase in HR seen in the current study is likely due to sympathetic and parasympathetic regulations of the heart. Furthermore, passive heating has been shown to reduce PWV.[41] In addition to increased body temperature and its positive effects, sauna bathing may have decreased plasma volume which is further related to changes in hemodynamic parameters such as decreased AS and systemic BP. Therefore, it is possible that heat therapy such as sauna may reduce AS via body dehydration.[42] Therefore, in assessment of PWV during sauna sessions, body fluid balance hydration status should be taken into account which includes ensuring adequate hydration status.

Strengths

Our study was based on a large number of participants, which provided adequate pre-defined power to assess changes in hemodynamic and vascular responses after sauna bathing. The assessment of cardiovascular parameters including BP and AS was performed using standard measurement protocols[24,43]. The measurement of the PWV is a simple and rapid way to assess the compliance of great arteries. An expert operator may assess PWV data in 5-8 minutes (including the insertion of patient's data in the computer). This allowed us to collect data that represented the respective time points more accurately. Arterial tonometry with simultaneous ECG was obtained with the use of a commercially available tonometer that has been well validated previously.[25,44,24] The measurement of the PWV is a simple, non-invasive and rapid way to assess the compliance of great arteries. An expert operator may assess PWV data quickly including the insertion of patient's data in the computer and measurement protocol is convenient for the subjects. In addition, although the assessment of AS has been documented to have reasonable levels of reproducibility, with an intra-observer coefficient of variation (CV) of 4.8% and interobserver CV of 7.3%, our utilization of a single trained operator throughout the whole study adds more reliability to the results. Sauna bathing is a safe activity in populations with cardiovascular risk factors and it has been shown that acute exposure to

Finnish sauna and cold-water immersion causes haemodynamic alterations in chronic heart failure patients without serious adverse events

Limitations

The sauna intervention was short term and we employed a before- and after-design without the use of a control group as this study was designed to explore the effects of a single sauna session. Based on data from the non-randomized study focusing on changes in AS, many vascular system alterations appear to be functional and transient due to a single sauna session. However, structural changes such as alterations in the elastin-collagen fibers and re-organization of the extracellular matrix of the arterial wall cannot be discounted, and may still occur with long-term regular sauna exposure. This is an area that warrants further research as the sauna remains as one of the more accessible, convenient, and safe modes of heat exposure that can provide possible cardiovascular benefits. Further studies utilizing a similar intervention method and longer-term randomized controlled trials are needed in order to gain a better perspective of the effects of sauna (heat stress) on the cardiovascular system and its overall health effects. Although the duration and method used for the sauna exposure mimicked a typical Finnish sauna, we did not measure PWV over the entire duration of recovery to track its time course profile in this population. As a result, we do not have complete information of when PWV and other related AS indices recovered to the baseline level. The diversity of the participants included in the study may have influenced the results, in that the youngest participant was 32 years of age, while the oldest was 75 years. In addition, the body composition of the participants also varied greatly within genders, ranging from 23.8 to 31.0 kg/m^2 for women, and between 25.1 to 30.6 kg/m^2 for men. However, the size of the study population was large enough to show significant hemodynamic and vascular effects of sauna in population with risk factors for CVD, and therefore, the results may be generalized to a similar patient population. Finally, though the target temperature for sauna exposure in our experiment as set by the sauna meter was 84 °C, the mean temperature recorded by the internal temperature sensor was 73 ± 2 °C, which may seem lower for a typical Finnish sauna session. However, this is usually the case for typical sauna sessions; when sauna

temperatures are set between 80-90 °C, the true temperature within the sauna room is usually lower. This was evident because we employed a reliable 2-channel internal temperature sensor which recorded the room temperature continuously as 10 second averages.

Conclusions

This novel study indicated that sauna bathing leads to improvements in cardiovascular function, including improved arterial compliance and decreased systemic BP. The study shows that 30 minutes of heat exposure in the sauna leads to positive changes in PWV and other arterial-related indexes. Further research is needed to show whether sauna bathing combined with physical exercise may produce similar or pronounced effect on AS parameters.

Authorship

EL, TL, SK, HK, PW, FZ and JL contributed to the conception and design of the work. EL, TL, SK, FZ, and JL contributed to the acquisition, analysis, or interpretation of data for the work. EL, TL, SK, FZ and JL drafted the manuscript. EL, TL, SK, HK, PW, FZ and JL critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

This study was supported by the Tekes, the Finnish Funding Agency for Technology and Innovation, Helsinki, Finland.

Conflict of Interest: none declared

Figure legends

Figure 1. Arterial stiffness, hemodynamics and vascular parameters. (Figure is modified from Salvi et al) [26]

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Table 1. Baseline characteristics	
Parameters (n = 100)	**Mean ± SD**
Age (years)	51.9 ± 9.2
Body weight (kg)	82.7 ± 16.0
Body mass index (kg/m^2)	27.9 ± 4.7
Systolic blood pressure (mmHg)	136.5 ± 16.2
Diastolic blood pressure (mmHg)	82.1 ± 9.6
Resting HR (bpm)	65.2 ± 10.4
Total cholesterol ($Chol_{tot}$; mmol/L)	5.4 ± 1.0
Low density lipoprotein (LDL; mmol/L)	3.0 ± 0.8
High density lipoprotein (HDL; mmol/L)	1.4 ± 0.4
Triglycerides (mmol/L)	2.0 ± 1.7

Table 2. Changes in arterial stiffness related outcomes

Parameters	Pre Mean (SD)	Post Mean (SD)	Post 30 min Mean (SD)	p-value (ANOVA)	Pairwise p-value for pre-post difference	Pairwise p-value for pre-post 30 min difference	Pairwise p-value for post-post 30 min difference
PWV (m/s)	9.8 ± 2.4	8.6 ± 1.6	9.0 ± 1.7	<0.001	<0.001	*N.S*	<0.001
AIx	9.8 ± 16.0	4.1 ± 15.8	7.8 ± 15.7	<0.001	<0.001	*N.S*	*N.S*
LVET (m/s)	307.4 ± 26.4	277.9 ± 37.8	299.0 ± 34.1	<0.001	<0.001	<0.001	<0.001
DT (m/s)	635.1 ± 115.1	494.6 ± 113.0	634.3 ± 121.2	<0.001	<0.001	*N.S*	<0.001

Note: PWV, pulse wave velocity; AIx, augmentation index; LVET, left ventricular ejection time; DT, diastolic time; N.S., non-significant

Table 3. Central hemodynamic variables

Parameters	Pre Mean (SD)	Post Mean (SD)	Post 30 min Mean (SD)	p-value for ANOVA	Pairwise p-value for pre-post difference	Pairwise p-value for pre-post 30 min difference	Pairwise p-value for post-post 30 min difference
MAP (mmHg)	99.4 ± 15.0	93.6 ± 10.3	95.9 ± 14.2	<0.001	<0.001	*N.S*	*N.S*
PP (mmHg)	42.7 ± 9.2	44.9 ± 9.8	39.3 ± 8.3	<0.001	*N.S*	<0.001	<0.001
AP (mmHg)	1.5 ± 0.9	1.6 ± 0.8	1.4 ± 0.9	*N.S*	*N.S*	*N.S*	*N.S*
PPa, (%)	28.8 ± 10.1	25.9 ± 13.4	27.5 ± 10.8	*N.S*	*N.S*	*N.S*	*N.S*

Note: MAP, mean arterial pressure; PP, pulse pressure; AP, augmented pressure; PPa, pulse pressure amplification; N.S., non-significant

Table 4. Heart rate and brachial blood pressure response

Parameters	Pre Mean (SD)	Post Mean (SD)	Post 30 min Mean (SD)	p-value for ANOVA	Pairwise p-value for pre-post difference	Pairwise p-value for pre-post 30 min difference	Pairwise p-value for post-post 30 min difference
SBP (mmHg)	136.5 ± 16.2	130.3 ± 14.4	129.8 ± 13.8	<0.001	<0.001	<0.001	*N.S*
DBP (mmHg)	82.1 ± 9.6	75.1 ± 9.3	80.6 ± 9.2	<0.001	<0.001	*N.S*	<0.001
HR (bpm)	65.2 ± 10.4	80.7 ± 15.1	65.9 ± 10.7	<0.001	<0.001	*N.S*	<0.001

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; N.S., non-significant

II

ACUTE EFFECTS OF EXERCISE AND SAUNA AS A SINGLE INTERVENTION ON ARTERIAL COMPLIANCE

by

Lee, E., Willeit, P., Laukkanen, T., Kunutsor, S.K., Zaccardi, F., Khan, H. and Laukkanen, J.A., 2020

European Journal of Preventive Cardiology vol 27(10), 1104-1107

https://doi.org/10.1177/2047487319855454

The acute effects of exercise and sauna as a single intervention on arterial compliance

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This work was supported by Tekes, the Finnish Funding Agency for Technology and Innovation, Helsinki, Finland.

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Word count: 1111

According to the World Health Organization (WHO), 1 in 4 adults are not active enough on a global level,[1] and a substantial percentage of the current world population have at least one cardiovascular risk factor.[2,3] However, physical activity accumulated in bouts of at least 10 minutes in duration may mitigate these factors and improve a wide range of health-related outcomes, according to the latest physical activity advisory.[4,5] Aerobic exercise and sauna bathing have each been shown to provide health-related benefits through plausible pathways which include beneficial changes in arterial stiffness and hemodynamic indices.[6,7] Recent evidence has also shown that aerobic fitness is inversely associated with arterial stiffness,[8] and even repeated exposure to strenuous exercise does not appear to compromise vessel integrity.[9] Although the cardiovascular health benefits of aerobic exercise and sauna exposure seem to be comparable in nature, the effects of using exercise and sauna exposure in a single session has yet to be elucidated. Furthermore, using sauna bathing as an adjunct to a shortened length of aerobic physical activity has the potential to serve as a gateway toward habit change in populations who are inactive. As such, we investigated arterial stiffness and hemodynamic-related alterations associated with using aerobic exercise and sauna bathing as a single intervention, in a population with at least one cardiovascular risk factor.

Participants (n=77) were recruited from the city of Jyväskylä, Central Finland region, through the local out-of-hospital health care center. To be eligible for inclusion, participants had to be free of a prior diagnosis of cardiovascular disease (CVD) and exhibited at least one of the following cardiovascular risk factors: a history of smoking, diabetes, hyperlipidemia, hypertension, obesity, or family history of coronary heart disease. Participants were free from diagnosed and/or symptomatic CVD, musculoskeletal injury or any other physical or mental condition that will prohibit the participation in the experiment. Prior to the participation in the study, all participants were informed about the research purposes and measurement procedures, provided written informed consent, before being screened by a cardiac specialist.

The research protocol and study design were in accordance with the ethical standards approved by the institutional review board of the Central Finland Hospital District ethical committee, Jyväskylä, Finland (Dnro 5U/2016), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The experimental design consisted of 15 minutes of aerobic exercise on a cycle ergometer (Ergoselect 200K, Fysioline Oy, Tampere, Finland), followed immediately by 15 minutes of sauna exposure. Participants were asked to keep the cadence between 65-70 revolutions per minute (rpm) for the entire 15-minutes. Cycling cadence and its indicator lights were in full view of the participant at all times and would flash red when the cadence fell below 65 or surpassed 70 rpm. Cycling load in watts (W) was monitored and adjusted throughout the duration to ensure that the heart rate (HR) for each participant was kept at 75% of their individual maximal exercise HR; pre-calculated using the data obtained from a clinical exercise test that was conducted on a separate day. The transit time from the cessation of exercise to entering the sauna was under 120 seconds. Sauna exposure was based on a typical Finnish sauna characterized by low humidity and relatively high temperatures (73 ± 2 °C).[7] Fluid was consumed *ad libitum* throughout the entire experiment.

Blood pressure (SBP and DBP), mean arterial pressure (MAP), pulse pressure (PP), pulse wave velocity (PWV) as a measure of arterial stiffness, augmentation index (AIx), left ventricular ejection time (LVET), diastolic time (DT) and HR were taken at three different time points in the respective orders; before (PRE), immediately after (POST), and after a 30-minute recovery period (POST30). All measurements at the different time points were measured using the PulsePen device (DiaTecne s.r.l., Milan, Italy; www.pulsepen.com) composing of one tonometer and an integrated ECG unit, by the same assessor to minimize ascertainment biases and adhered closely to published guidelines.[10] Data is presented as means ± SD. Data was analyzed for within-group (time) changes with a repeated measures

analysis of variance (ANOVA). Within-group differences between POST to PRE and POST30 to PRE values were analyzed using pairwise *t*-tests, and *p*-values were corrected for Bonferroni by dividing all pairwise p-values with the number of comparisons conducted for each variable. The level for significance was set at $p \leq 0.05$. All statistical analyses were carried out with IBM SPSS Statistics v.22 software (IBM Corporation, Armonk, New York, USA).

Descriptive characteristics of the population are shown in **Table 1**. **Figure 1** shows the changes in outcome parameters from the experimental protocol of 15 minutes cycling followed by 15 minutes of sauna exposure. Compared to pre-intervention values, significant changes were observed post-intervention for PWV (9.4 vs 8.9 m/s, $p<0.001$), AIx (6.8 vs 0.5, $p=0.002$), MAP (101 vs 97 mmHg, $p<0.001$), LVET (300 vs 269 m/s, $p<0.001$), and DT (608 vs 446 m/s, $p<0.001$). Effects persisted after 30-minutes for MAP (101 vs 96 mmHg, $p<0.001$), AIx (6.8 vs 1.7, $p<0.001$), LVET (300 vs 292 m/s, $p<0.001$) and DT (608 vs 590 m/s, $p=0.016$). In addition, PP was significantly reduced compared to pre-intervention values (41 vs 37 mmHg, $p<0.001$).

The study showed that AIx decreased significantly after a combination of exercise and sauna, and although it may be associated with peripheral vascular changes such as vasodilation from the sauna bathing, this decrease in AIx was not mediated by an increase in PP as seen in sauna exposure alone, after 30 minutes of recovery.[7]

The similar and parallel changes seen in LVET and PWV were not expected, as they have been shown to share an inverse relationship.[11] The decrease seen in LVET is indicative of the shortened time taken by the left ventricle to do mechanical work, which normally leads to an increase in PWV. However, our results showed that PWV was reduced as well; which could be attributed to our study protocol. The current study protocol of aerobic exercise followed by sauna exposure also led to significantly lowered PP during the recovery period. This is

comparable to a recent study,[12] where changes to PP were retained 45 minutes after cessation of an acute bout of aerobic exercise. However, our results showed a reduction in MAP as well, after a 30-minute recovery period.

Our findings indicate that a combination of aerobic exercise and sauna led to positive alterations on MAP, PP and AIx, and these changes were retained after a 30-minute recovery period. Therefore, the benefits of combining aerobic exercise with sauna use should not be discounted, as it may be a gateway to encouraging a more optimum lifestyle. Long-term interventions involving the use of both aerobic exercise and sauna bathing should be investigated, as beneficial cardiovascular adaptations may be a possibility.

Acknowledgments

We sincerely thank Timo Harvia and the staff of Harvia Oy for sauna test facilities of the research, Poikonen Sanna and Pihlajalinna Oy for the recruitment and logistics assistance, and all the participants for dedicating their time to this study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work supported by Tekes, the Finnish Funding Agency for Technology and Innovation, Helsinki, Finland.

Authorship

EL, TL, SKK, PW and JAL contributed to the conception and design of the work. EL, TL, SKK, FZ and JAL contributed to the acquisition, analysis or interpretation of data for the work. EL, PW, SKK, and JAL drafted the manuscript. EL, SKK, HK, PW, FZ and JAL critically

revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1. Participant characteristics (n=77)

Parameters	**Mean ± SD**
Age (years)	53.3 ± 9.8
Body mass (kg)	83.2 ± 14.8
Body mass index (kg/m^2)	27.8 ± 4.2
Resting SBP (mmHg)	137.1 ± 15.5
Resting DBP (mmHg)	83.3 ± 9.6
Resting HR (bpm)	68 ± 10
Maximum exercise HR (bpm)	174 ± 14
Aerobic exercise HR (bpm)[a]	131 ± 11
Sauna habits	**Number (Percentage)**
Less than once a week	15 (19.5%)
Once a week	14 (18.2%)
2 – 3 times per week	30 (38.9%)
4 or more times per week	18 (23.4%)
Cardiovascular risk classification	**Number (Percentage)**
Active Smoker/History of smoking	12 (15.8%)
Diabetes (Type 1 or 2)	3 (4%)
Dyslipidemia[b]	51 (67.1%)
Hypertension[c]	15 (19.7%)
Obesity (BMI >30 kg/m^2)	22 (28.6%)
Respiratory diseases[d]	10 (13.2%)
Family history of coronary heart disease[c]	31 (40.8%)

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index, [a] exercise heart rate HR was defined as 75% of individual maximal exercise HR, [b] based on use of cholesterol drugs or serum low-density lipoprotein (LDL) cholesterol over 3.5 mmol/L, [c] defined as SBP >140 mmHg, DBP >90 mmHg, or use of antihypertensive therapy, [d] Positive family history of CHD if father (< 55 years) or mother (< 65 years) had premature CHD,[d] respiratory diseases includes asthma and chronic obstructive pulmonary diseases

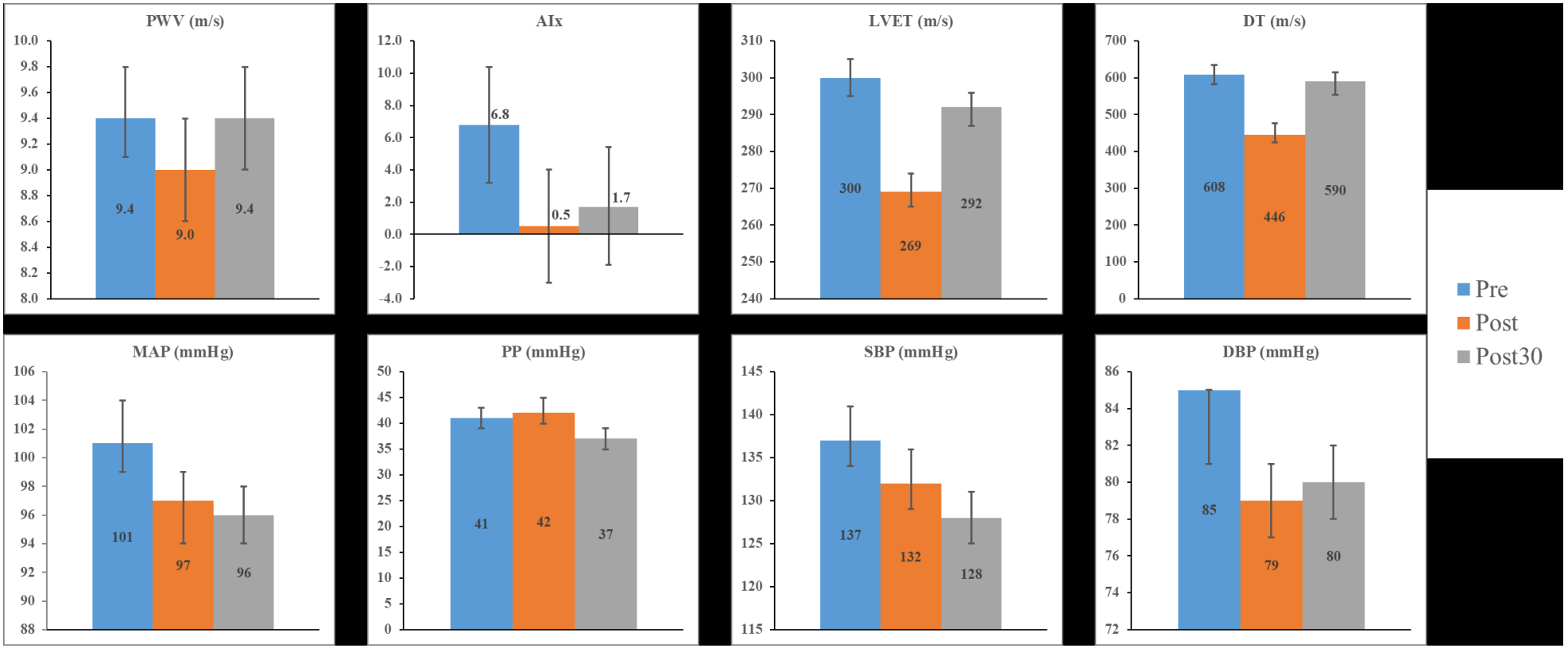

Figure 1. Changes in arterial stiffness and hemodynamic parameters. Error bars represent 95% confidence intervals (CI)

III

STANDALONE SAUNA VERSUS EXERCISE FOLLOWED BY SAUNA ON CARDIOVASCULAR FUNCTION IN NON-NAÏVE SAUNA USERS: A COMPARISON OF ACUTE EFFECTS

by

Lee, E., Kostensalo, J., Willeit, P., Kunutsor, S.K., Laukkanen, T., Zaccardi, F., Khan, H. and Laukkanen, J.A., 2021

Health Science Reports vol 4(4), e393

https://doi.org/10.1002/hsr2.393

Received: 14 July 2021 | Revised: 3 September 2021 | Accepted: 6 September 2021

DOI: 10.1002/hsr2.393

RESEARCH ARTICLE

Health Science Reports Open Access WILEY

Standalone sauna vs exercise followed by sauna on cardiovascular function in non-naïve sauna users: A comparison of acute effects

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Abstract

Background and aims: Sauna bathing and aerobic exercise have each been shown to affect cardiovascular function. However, direct comparisons between standalone sauna bathing and a combination of exercise and sauna on vascular indices remain limited. Therefore, we conducted a cross-over study using matched durations to explore the hemodynamic changes of sauna exposure when compared to a combination of aerobic exercise and sauna exposure.

Methods: Participants (N = 72) with at least one cardiovascular risk factor underwent, on two separate occasions: (a) a 30-minute sauna at 75°C (SAUNA) and (b) the combination of a 15-minute cycling exercise at 75% maximum heart rate followed by 15-minute sauna exposure (EX+SAUNA). Relative changes to arterial stiffness (PWV), augmentation index (AIx), brachial systolic and diastolic blood pressure (SBP and DBP), central SBP (cSBP), mean arterial pressure (MAP), and heart rate (HR) were compared PRE-POST and pre- to 30-minutes post-intervention (PRE-POST30).

Results: Baseline SBP and DBP were 143 (SD 18) mmHg and 86 (SD 10) mmHg, respectively. From PRE-POST, SAUNA had lower DBP (mean difference [95% CI] 2.5 [1.0, 4.1], $P = .002$) and MAP (2.5 [0.6, 4.3], $P = .01$). However, EX+SAUNA had lower SBP (−2.7 [−4.8, −0.5], $P = .02$), DBP (−1.8 [−3.3, −0.4], $P = .01$), and MAP (−2.0 [−3.5, −0.5], $P = .009$) PRE-POST30. There were no statistically significant differences between SAUNA and EX+SAUNA for other measured parameters.

Conclusion: This study demonstrated that when matched for duration, EX+SAUNA and SAUNA elicit comparable acute hemodynamic alterations in middle-aged participants with cardiovascular risk factors. The sauna is a suitable option for acute blood pressure reductions in those who are unable to perform aerobic exercise, and may be a viable lifestyle treatment option to improve blood pressure control.

KEYWORDS
aerobic exercise, arterial compliance, hypertension, lifestyle modification, non-pharmocological therapy

1 | INTRODUCTION

Sauna bathing has been associated with a lower risk for cardiovascular disease (CVD) outcomes,[1] improved vascular endothelial and cardiac function,[2] lower blood pressure,[3] and positive alterations in several hemodynamic markers.[4] Sauna bathing exerts a strain on the cardiovascular system, to maintain blood pressure and sufficient blood flow to other organs and muscles.[5] A recent meta-analysis[6] found sauna use to play a positive role in improving cardiovascular function and functional capacity as well.

Likewise, aerobic exercise has been well documented to provide cardiovascular[7] and disease prevention[8] benefits, especially for older adults[9] and populations with adverse levels of risk.[10] Furthermore, aerobic exercise has also been shown to acutely reduce arterial stiffness,[11] although a recent study[12] suggests that improvements in arterial stiffness are only seen when an impairment is present. Arterial stiffness is a useful marker in the prediction of cardiovascular events and has been shown to be capable of predicting cardiovascular mortality independent of other traditional markers.[13] Nevertheless, several studies have noted the comparable physiological effects of sauna bathing and aerobic exercise.[14,15]

Previous research investigated sauna bathing as a post-exercise intervention with promising results,[16,17] but the mechanisms of action for both modalities were not directly comparable due to methodological differences. Moreover, although some studies have investigated the conjunctive use of exercise and sauna in athletes,[18,19] this information remains somewhat limited in non-athlete populations. However, Rosenberg and colleagues[20] did speculate about the usefulness of adjunctive exercise and heat therapy, which was partially shown by our group,[21] where a combination of 15 minutes of aerobic exercise followed by 15 minutes of sauna bathing showed several notable improvements to hemodynamic function.

Long-term sauna therapy has been shown to effectively improve exercise tolerance,[22] while regular exercise and sauna exposure were able to improve cardiac function and autonomic nervous system activity,[23] albeit in populations with heart-related issues. Therefore, there is reason to believe that the combination of exercise and heat therapy in the form of sauna bathing may indeed complement each other. Both current and previous literature[24,25] are in support of this postulation, demonstrating heat augmented physiological responses. As such, a comparison of the effects between these two interventions using an equal exposure time of 30 minutes will help to further elucidate any therapeutic potential that may exist, given the benefits seen from 30 minutes of acute[26] and regular aerobic exercise.[27]

To the best of our knowledge, changes to arterial stiffness and hemodynamics between sauna bathing, and a combination of aerobic exercise followed by sauna bathing have yet to be investigated. Our group has previously explored the effects of acute sauna exposure,[4] and thus aim to extend our findings and compare the effects of sauna exposure alone against a shortened duration of exercise plus sauna exposure. This may be of considerable benefit for a broader population, including those who have lower exercise capacities.[28] Therefore, the purpose of the study was to explore the hemodynamic changes of a single session of sauna exposure compared to the combination of aerobic exercise and sauna exposure of matched duration, in a population with at least one cardiovascular risk factor.

2 | METHODS

2.1 | Participants

Participants (N = 72; females = 33, males = 39) were recruited from the city of Jyväskylä, Central Finland, through the local out-of-hospital health care center. To be eligible for inclusion, participants had to be free of a prior diagnosis of CVD and exhibited at least one of the following cardiovascular risk factors: a history of smoking, hyperlipidemia, hypertension, clinically diagnosed diabetes, obesity, or family history of coronary heart disease (CHD). Hypercholesterolemia was defined as the use of cholesterol drugs or serum low-density lipoprotein cholesterol over 3.5 mmol/L. Hypertension was defined as having a systolic reading of greater than 140 mm Hg, and/or a diastolic reading of greater than 80 mm Hg on two or more separate resting measurements. Obesity was defined as body mass index >30 kg/m^2. Family history of CHD was considered positive if father (<55 years) or mother (<65 years) had premature CHD. Menstrual status of female participants was not taken into account during recruitment; but none of them were menstruating at the time of the administration of interventions. Among the female participants, 9 were premenopausal, while 24 were postmenopausal. All participants provided written informed consent and were informed about the research purposes and measurement procedures, before being screened by a cardiac specialist. The research protocol and study design were approved by the institutional review board of the Central Finland Hospital District ethical committee, Jyväskylä, Finland (Dnro 5U/2016).

2.2 | Experimental design

Figure 1 is an overview of the study design. In this balanced non-randomized crossover trial, all study participants underwent two interventions, each on a separate occasion (>72 hours apart) between 1000 and 1600. A standalone 30-minute sauna at 75°C (SAUNA), and 15-minutes of cycling on a stationary bike at 75% of individual maximum heart rate, followed by 15-minutes of sauna exposure (EX +SAUNA). A cycling exercise test was conducted on a separate day prior to the experiment to ascertain individual maximal exercise heart rates, which was then used to calculate individual 75% maximum. The exercise test was conducted on an electromagnetically braked cycle ergometer (Monark Exercise AB, Sweden) utilizing a graded exercise test protocol with continuous electrocardiogram recordings (CardioSoft software V.1.84, GE Healthcare, Freiburg, Germany). The symptom-limited exercise test was started with 5-minute warm-up without workload for each participant and continued with 20-W increments applied every 1 minute until volitional exhaustion. All exercise tests were

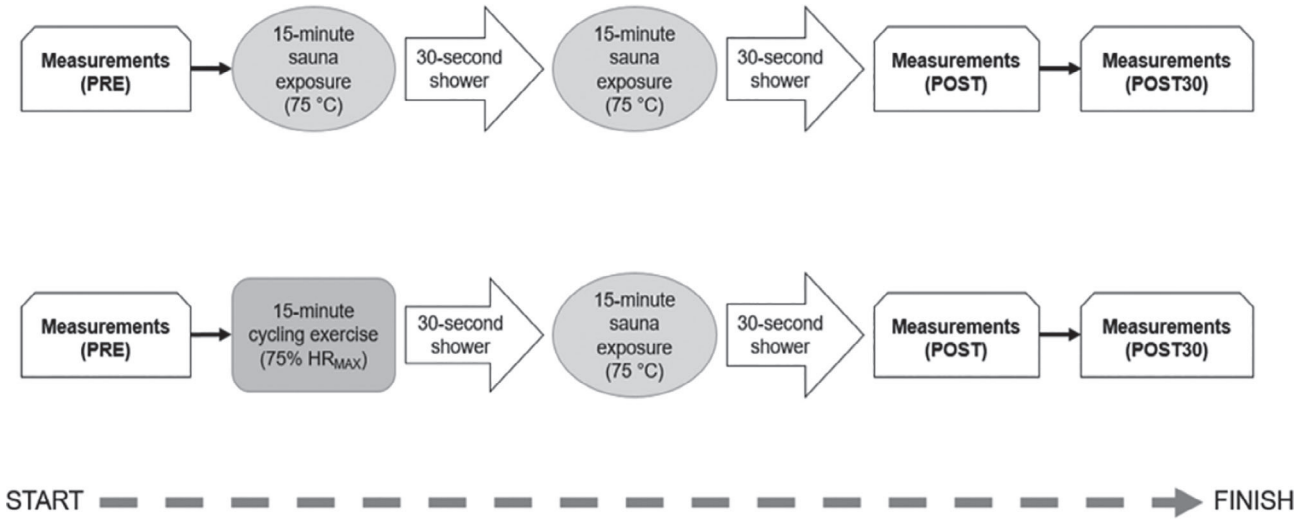

FIGURE 1 Experimental design flow and order

conducted under the supervision of a qualified nurse and physician and the same bike was used for the experiment.

After the first 15-minute period of SAUNA, the participants left the sauna room to have a quick shower (<30 seconds) before going back for the second 15-minute period. Participants were in a seated position during all sauna sessions, and the same sauna room (75°C) was used for all participants. Cycling exercise was conducted within 10 m of the sauna room to minimize transit time during EX+SAUNA. Participants were instructed to keep the cadence between 65 and 70 rpm for the entire 15 minutes. The cycling load in watts was monitored and adjusted throughout the duration of the exercise to ensure that the heart rate for each participant was kept at 75% of their individual maximum exercise heart rate, pre-calculated using data obtained from the exercise test.

The temperature and humidity of the exercise room were 21°C and 25%, respectively. Participants were instructed to abstain from eating 2 hours, caffeine 12 hours, alcohol 24 hours, and exercise and/or sauna 48 hours prior to the measurements. Food intake was not standardized. Fluid was consumed ad libitum. A physician was in attendance at all times and participants were allowed to leave the sauna or stop the experiment at any time if they felt uncomfortable, but all participants underwent the two interventions successfully.

2.3 | Assessment of outcome measures

The measurements of arterial stiffness during this experiment adhered closely to published guidelines.[29] Supine brachial SBP and DBP were obtained using Microlife BP A200 (Microlife Corp., Taipei, Taiwan). Two sequential readings were taken and the mean values were used. All measurements were done on the right side of the body with the participant in the supine position. Transit distances were assessed by body surface measurements using a tape measure. There was a total of three transit distances, carotid artery site to suprasternal notch; carotid artery to femoral artery; and suprasternal notch to femoral artery. Carotid to femoral measurement was adjusted to 80% (common carotid artery − common femoral artery × 0.8) for the calculation of PWV as recommended.[29]

Brachial blood pressures and PWV as a measure of arterial stiffness were taken in their respective order at three different time points; before (PRE), immediately after (POST), and after a 30-minute recovery (POST30). All measurements were taken by a single trained operator of the tonometer to minimize ascertainment biases and to ensure consistency and reliability (ICC 2.1:0.75 with 95% confidence interval [CI] = 0.63-0.83, SEM = 0.4). ICC estimates and their 95% CIs were calculated using two repeated measurements taken 10 days apart (prior to the experiment) from 72 participants via the statistical software R,[30] based on a mean-rating ($k = 2$), absolute-agreement, two-way mixed-effects model. High-quality recordings (defined as an in-device quality index of more than 90% from an average of at least 10 cardiac cycles) were collected using the PulsePen device (DiaTecne s.r.l., Milan, Italy; www.pulsepen.com) using methods that have been documented in previous studies.[4,21] PWV, augmentation index (AIx), central systolic blood pressure (cSBP), and mean arterial pressure (MAP) were subsequently estimated via the software.

Participants were permitted to take a quick shower (<30 seconds) before POST measurements were taken. Water temperature of the shower was not controlled and participants could freely select their desired temperature. Thereafter, they were instructed to rest in a designated waiting lounge (21°C, humidity 25%) in a seated position for a duration of 30 minutes before the final measurement (POST30) was taken. Participants were kept in a supine position for 7 minutes prior to the measurements.

2.4 | Statistical analyses

The individual treatment effects, that is, the differences between pre- and post-intervention and follow-up measurements (PRE, POST, POST30) do not a priori follow a normal distribution. This was

confirmed by 30% of the Shapiro-Wilk normality tests for PRE, POST, and POST30 effects giving *P*-values below .05. Graphical investigations revealed no remarkable differences in the distribution of responses related to age or gender, so controlling for these variables still leaves us with non-Gaussian distributions. As such, the assumptions of the basic parametric approaches, such as Student's *t* test and ANOVA were not satisfied. Therefore, a nonparametric approach was selected. Statistical inference in this work is based on the Neyman-Rubin causal model.[31-33] For the variable *Y*, the causal effect of treatment *T* with respect to control *C* for the individual *u* is defined as

$$Y_T(u) - Y_C(u).$$

The effects of the two different interventions (S and ES) for the same individual cannot be simultaneously measured. This is known as the *fundamental problem of causal inference* in the Neyman-Rubin model. We solve the fundamental problem using a combination of scientific and statistical solutions[31] by assuming temporal stability (the responses of the individuals would be the same if the treatments would have been done in the opposite order) and then calculating the average effect of EX+SAUNA relative to SAUNA. The temporal stability assumption was investigated by performing a sign test on the PRE measurements. No statistically significant differences were found in the PRE measurements between EX+SAUNA and SAUNA.

Stable unit treatment value is also assumed, that is, the outcome of one individual does not depend on the interventions done on the other individuals, which is contextually natural. The CI and *P*-value were estimated using nonparametric bootstrap[34] with 100 000 simulations for each response. A two-tailed alternative hypothesis was assumed as we did not have any reason to be certain about the *direction of the difference* for any of the response variables. In the nonparametric bootstrap method, we resample the empirical distribution of responses by taking random samples equal in size to the original sample (N = 72) with replacement. The resulting distribution asymptotically approaches the true sampling distribution. As N = 72 the bootstrap samples are drawn from a representative approximation for the population sampling distribution. The analysis consisted of multiple tests for differences between interventions, so we use adjusted *P*-values for inference, where the adjusting has been done using the Benjamini-Hochberg method.[35] Unadjusted *P*-values are also reported for the purpose of completeness and meta-analyses.

The reliability of the statistical tests run depends on the validity of the assumption that the participants can be analyzed as a single group. However, it is possible that the responses might be dependent on for example, the age or biological sex of the participant, although this has largely been controlled for with the crossover study design and the inclusion/exclusion criteria. Nonetheless, we ran the analyses in several subgroups to ascertain whether the assumption of homogeneity holds. The analysis was for age, biological sex, initial SBP over 140 or DBP over 80, and menopausal status. Similar responses were observed in each subgroup. Based on these assessments we concluded that controlling for these covariates would not make any noticeable difference in this data set.

The full-sample comparisons were pre-specified, with a priori determined significance level of $P < .05$ to be used for the adjusted *P*-values along with a two-tailed alternative hypothesis. The subgroup analyses and normality tests were exploratory in nature, and were aimed at determining whether parametric tests or models with covariates could be adopted in order to increase the statistical power. Two-tailed alternative hypotheses were assumed here as well. The calculations were implemented with the statistical software R version 3.6.3[30] with the plots done using the ggplot2 package.[36] Continuous data are presented as means ± SD and categorical data as frequencies (percentage of the whole). To ensure that the statistical analyses were nonbiased, variables were coded and analyzed by an independent statistician who was completely blind to the experiment. In addition, the statistician carrying out the analyses was completely uninvolved in the participant recruitment and data collection processes.

3 | RESULTS

3.1 | Characteristics of participants

The characteristics of the participants are presented in Table 1. Mean baseline SBP and DBP were 143 and 86 mm Hg, respectively. The

TABLE 1 Participant characteristics

Normally distributed parameters	**Mean ± SD (N = 72)**
Age (years)	54 ± 9
Body mass (kg)	83.2 ± 15.0
Body mass index (kg/m^2)	27.8 ± 4.3
Non-normally distributed parameters	**Median; IQR**
Resting SBP (mm Hg)	135; 21
Resting DBP (mm Hg)	83; 14
Resting heart rate (b/min)	66; 11
Sauna habits	**Number (%)**
Less than once a week	15 (21)
Once a week	15 (21)
Two to three times per week	25 (35)
Four or more times per week	17 (23)
Aerobic exercise frequency	**Number (%)**
Less than once a week	23 (32)
Once a week	15 (21)
Two to three times per week	19 (26)
Four or more times per week	15 (21)
Categorical parameters	**Number (%)**
Smoker (history of smoking)	12 (17)
Hyperlipidemia	51 (71)
Hypertension	15 (21)
Diabetes[a]	3 (4)
Obesity (body mass index > 30)	22 (31)
Family history of coronary heart disease	31 (43)

Abbreviations: DBP, brachial diastolic blood pressure; SBP, brachial systolic blood pressure.
[a]For diabetes, two were type 2 diabetes and one was type 1 diabetes.

TABLE 2 PRE-POST comparison

	EX+SAUNA		SAUNA					
Parameters	Mean	95% CI	Mean	95% CI	Average CE	95% CI	Raw *P*-value	Adjusted *P*-value
PWV (m/s)	−0.5	(−0.7, −0.3)	−0.6	(−0.9, −0.4)	0.1	(−0.2, 0.4)	.436	.46
AIx (%)	−7.1	(−10.6, −3.6)	−4.5	(−8.6, −0.2)	−2.6	(−7.7, 2.6)	.323	.38
SBP (mm Hg)	−5.0	(−7.4, −2.6)	−7.1	(−9.4, −4.8)	2.1	(−0.4, 4.7)	.103	.16
DBP (mm Hg)	−4.9	(−6.3, −3.4)	−7.4	(−8.6, −6.2)	2.5	(1.0, 4.1)	.002	.02
cSBP (mm Hg)	−3.1	(−5.5, −0.8)	−5.3	(−7.9, −2.7)	2.2	(−0.6, 4.9)	.120	.16
MAP (mm Hg)	−4.9	(−6.5, −3.3)	−7.4	(−8.8, −5.9)	2.5	(0.6, 4.3)	.010	.05
HR (b/min)	18.4	(16.3, 20.4)	15.9	(13.0, 18.7)	2.5	(−0.5, 5.5)	.100	.16

Note: Average causal effect (CE) is the difference between EX+SAUNA and SAUNA.
Abbreviations: AIx, augmentation index; CE, causal effect; CI, confidence interval; cSBP, central systolic blood pressure; DBP, brachial diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PWV, pulse wave velocity; SBP, brachial systolic blood pressure.

three cardiovascular risk factors most commonly present were hyperlipidemia (71%), family history of CHD (43%), and obesity (31%).

3.2 | Changes in outcome measures from PRE to POST

PRE-POST changes in outcome measures within and between interventions, with their corresponding average Neyman-Rubin causal effect (difference between EX+SAUNA and SAUNA) are shown in Table 2. DBP and MAP were significantly lower for SAUNA. However, there was no statistically significant PRE-POST difference between EX+SAUNA and SAUNA for other outcome measures. The distribution of individual responses to the two interventions between PRE and POST is displayed in Figure 2.

3.3 | Changes in outcome measures from PRE to POST30

PRE-POST30 changes in outcome measures and their average causal effect are shown in Table 3. SBP, DBP, and MAP were lower in EX +SAUNA. The distribution of individual responses to the two interventions as measured between PRE and POST30 is displayed in Figure 3.

4 | DISCUSSION

In this study, we compared the effects of sauna bathing alone against a short 15-minute bout of aerobic exercise followed immediately by the sauna, with a matched total duration of 30 minutes for both interventions. Individually, both interventions showed positive alterations PRE-POST as well as PRE-POST30. More specifically, SAUNA had significantly lower DBP and MAP between PRE-POST. However, SBP, DBP, and MAP were lower for EX+SAUNA PRE-POST30.

One of the first studies comparing between EX+SAUNA and SAUNA in a similar population group demonstrated that EX+SAUNA reduced SBP whereas no change was seen in DBP.[16] Additionally, SAUNA had no significant effect on blood pressures. The authors speculated that this might have been due to the insufficient sauna stimulus, which was likely to have been the case; relative to the outcomes seen from our present investigation. We used matched durations for both EX+SAUNA and SAUNA which meant that our sauna exposure time was nearly twice as long compared to the study by Gayda et al.[16] Consequently, this led to a relatively more even comparison as can be seen from our results.

Our results showed that SAUNA induced greater changes PRE-POST compared to EX+SAUNA in both DBP and MAP. Moreover, all pressure-related markers had a clinically relevant reduction of 5 mm Hg or more. This was rather unforeseen, as lower values for EX +SAUNA would have been a more likely outcome due to the prevailing literature on post-exercise hypotension. Nevertheless, the comparability of PRE-POST hemodynamic responses is in support of the findings from a more recent study, which postulated that the cardiovascular stress from exposure to sauna might be similar to that of moderate aerobic exercise.[15] Indeed, the decreases in blood pressures seen in EX+SAUNA from this study were comparable to aerobic exercise of longer durations,[37] despite comprising of only 15 minutes of moderate intensity cycling.

Passive heat exposure has been suggested to improve endothelial function and nitric oxide bioavailability through enhanced dilation of the arterial tree.[38] This is comparable to how exercise increases dilation of arteries supplying skeletal muscle, which has been documented to lead to reduced wave reflection.[39] The efficacy of heat stress from the sauna was inadvertently shown in a more recent study,[40] which sought to utilize the sauna as a post-training recovery tool. Instead of providing a recuperative effect, performance measures were decreased. The authors postulate that this might have been due to the physiological stress from sauna exposure acting like a further stimulus of exhaustion. This is consistent with earlier studies[17,19] that have identified sauna exposure as an additional source of training

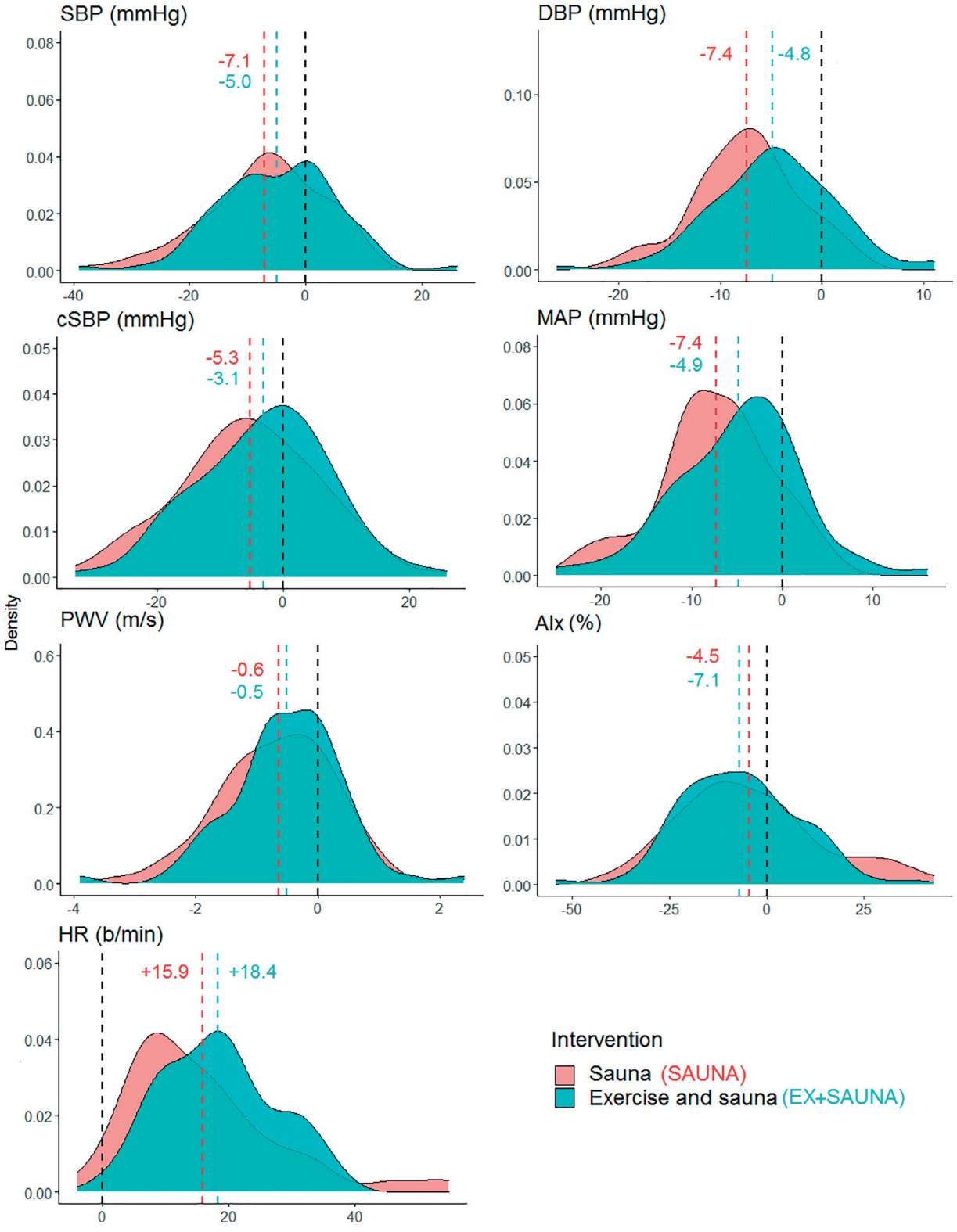

FIGURE 2 The distribution of individual responses to the two interventions as measured between PRE and POST

stimuli for athletic populations. Indeed, a more recent study[41] even considered post-training sauna use as an effective ergogenic aid.

Our findings are also in agreement with results seen by other researchers. Thomas and coworkers[42] showed that 30 minutes of heat therapy induced a shear stress response that led to greater decreases in blood pressure than 30 minutes of aerobic exercise, while our current study found lower pressures PRE-POST from SAUNA compared to EX+SAUNA. One possible explanation for that

TABLE 3 PRE-POST30 comparison

	EX+SAUNA		SAUNA					
Parameters	Mean	95% CI	Mean	95% CI	Average CE	95% CI	Raw *P*-value	Adjusted *P*-value
PWV (m/s)	−0.0	(−0.3, 0.3)	−0.2	(−0.4, 0.0)	0.1	(−0.2, 0.5)	.548	.55
AIx (%)	−5.4	(−8.6, −2.0)	−1.3	(−4.8, 2.2)	−4.0	(−7.6, −0.5)	.023	.05[a]
SBP (mm Hg)	−9.4	(−11.3, −7.6)	−6.7	(−8.4, −5.2)	−2.7	(−4.9, −0.5)	.018	.05
DBP (mm Hg)	−3.3	(−4.4, −2.1)	−1.4	(−2.6, −0.3)	−1.8	(−3.3, −0.4)	.013	.04
cSBP (mm Hg)	−6.9	(−8.7, −5.1)	−5.0	(−6.6, −3.4)	−1.9	(−4.2, 0.4)	.109	.16
MAP (mm Hg)	−5.3	(−6.6, −4.1)	−3.3	(−4.4, −2.1)	−2.0	(−3.5, −0.5)	.009	.04
HR (b/min)	2.2	(0.9, 3.5)	0.7	(−0.8, 2.3)	1.5	(−0.4, 3.4)	.128	.16

Note: Average causal effect (CE) is the difference between EX+SAUNA and SAUNA.
Abbreviations: AIx, augmentation index; CE, causal effect; CI, confidence interval; cSBP, central systolic blood pressure; DBP, brachial diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PWV, pulse wave velocity; SBP, brachial systolic blood pressure.
[a]The actual adjusted value did not reach statistical significance at .054.

may be the increase in skin blood flow during heat exposure, which led to decreased peripheral resistance and consequently lower blood pressures. However, peripheral resistance was not one of our outcome measures and the lack of significant concomitant decreases in PWV as a measure of arterial stiffness partially refutes that supposition. Furthermore, both EX+SAUNA and SAUNA had similar PWV nonsignificant responses throughout the experiment (Tables 2 and 3), despite reductions in majority of the hemodynamic parameters.

The lack of significant changes in PWV for EX+SAUNA is in line with a recent review,[43] which reported no change in PWV after acute aerobic exercise of varying durations. However, this was somewhat of an unexpected finding for SAUNA, as our group had previously shown reductions in PWV.[4] Nonetheless, these results suggest that arterial wall property change was unlikely to have been the cause of the hypotension in this study, and that other mechanisms[44] may have been responsible. Although SAUNA induced greater changes PRE-POST compared to EX+SAUNA, PRE-POST30 comparisons revealed that SBP, DBP, and MAP were lower for EX+SAUNA. This may be indicative of a relatively greater stimulus that EX+SAUNA provided. However, PRE-POST responses do not appear to be in support of this, as SAUNA was superior to EX+SAUNA in lowering both DBP and MAP (Table 2).

Based on the overall evidence from the present study, EX+SAUNA appears to have a relatively longer period of recovery to baseline than SAUNA. It is plausible that the combination of greater fluid loss from the relatively longer duration of heat exposure in SAUNA together with the depressive effects of prior aerobic exercise on blood pressure in EX+SAUNA contributed to this. Sauna-induced fluid loss has been reasonably documented,[45] and the magnitude of dehydration from the sauna has been indirectly shown to be greater than submaximal cycling exercise.[46] This may have been what contributed to the PRE-POST results. Notwithstanding, the effects of post-exercise hypotension have been well established to occur even with relatively shorter bouts of exercise[47] akin to the one used in our current study. It is thus likely that it could have led to the greater PRE-POST30 changes in EX+SAUNA.

While the changes in some markers were still seen after 30 minutes in EX+SAUNA, the hemodynamic responses of both interventions appear to be rather comparable (Figures 2 and 3). These findings may have practical implications, especially if the amount of hemodynamic stress used in our interventions could induce adaptations. Moreover, it should be duly noted that the results seen in this current study were *in spite* of our study population being acclimated habitual sauna users. Therefore, it is plausible that a sauna naïve population may exhibit an even more pronounced cardiovascular response than what was demonstrated. The effects of regular exercise in combination with sauna use need to be investigated using long-term trials in more representative populations, as heat therapy and the sauna may have a broader range of application than we currently recognize.

4.1 | Limitations

In spite of the evidence provided by the current study, several limitations must be noted. From a methodological standpoint, we did not include a standalone exercise intervention. This would have enabled a comparison between EX+SAUNA and an aerobic exercise session of the same duration. However, that was not the purpose of our investigation. The scope of our data interpretation is limited due to the lack of cardiac output measurements and thermal stress (temperature) data, although we did measure heart rate and arterial stiffness.

Menstrual phase was not controlled, and we are unable to determine the degree of influence that the differences in menstrual phases may have had. However, the majority of our female participants were postmenopausal. We did not control for the water temperature of the shower, which may have had an effect on some of the results seen, although we did try to minimize this by limiting the shower time to under 30 seconds. Finally, the majority of our participants were regular sauna users (85%) of at least once a week, which limits the generalizability of our results to a broader population who do not use sauna

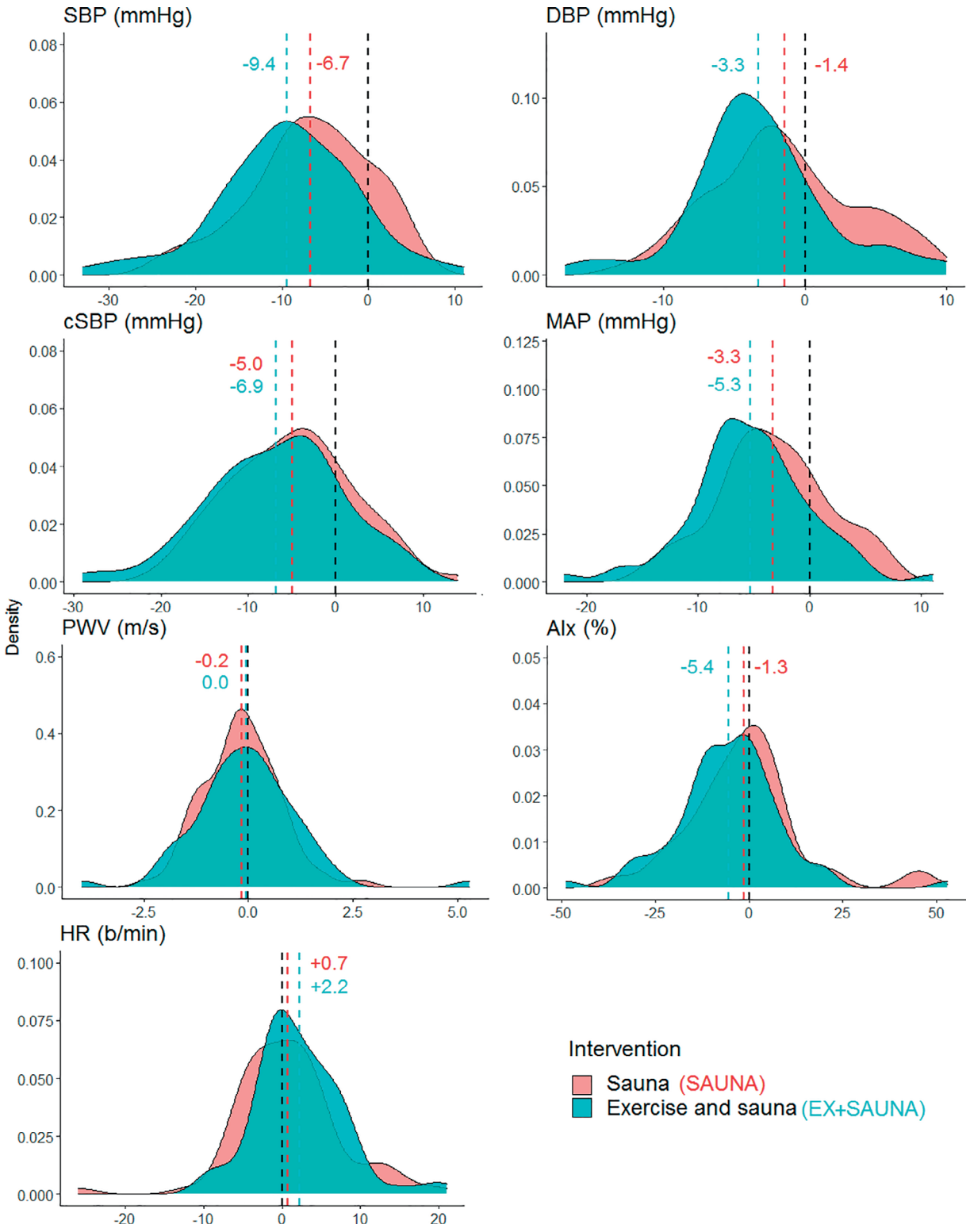

FIGURE 3 The distribution of individual responses to the two interventions as measured between PRE and POST30

regularly. It is thus entirely possible that the current results are specific to the population studied, though the sauna-naïve would presumably demonstrate more pronounced responses as they would be less habituated. Nevertheless, it highlights the need for further investigation in this particular area.

5 | CONCLUSION

The current study shows for the first time the hemodynamic differences between sauna bathing, and a combination of a short bout of aerobic exercise followed by sauna bathing, in a representative

population with cardiovascular risk factors. From an acute standpoint, sauna bathing is able to elicit responses that are comparable to a combination of aerobic exercise followed by the sauna, when matched for duration. For populations who are unable to perform aerobic exercise, sauna exposure may provide some similar benefits acutely.

The long-term adaptations of regular exercise in conjunction with passive heat such as the sauna is an area that needs more attention, and experimental trials are needed to better understand the sauna intricately, as it has shown compatibility with aerobic exercise. In the management of hypertension, emphasis is often given to improving ones' diet, performing regular exercise, or weight control. Sauna use might also be a worthwhile lifestyle treatment option to improve BP control.

ACKNOWLEDGMENTS

We sincerely thank Timo Harvia and the staff of Harvia Finland Oy for providing the sauna facilities in support of this research, Sanna Poikonen and Pihlajalinna Oy for the recruitment and logistics assistance, and all the participants for dedicating their time to this study.

FUNDING

This research received no funding.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

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All authors have read and approved the final version of the manuscript.

The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Lee E, Kostensalo J, Willeit P, et al. Standalone sauna vs exercise followed by sauna on cardiovascular function in non-naïve sauna users: A comparison of acute effects. *Health Sci Rep*. 2021;4:e393. doi: 10.1002/hsr2.393

IV

EFFECTS OF REGULAR SAUNA BATHING IN CONJUNCTION WITH EXERCISE ON CARDIOVASCULAR FUNCTION: A MULTI-ARM RANDOMIZED CONTROLLED TRIAL

by

Lee, E., Kolunsarka, I., Kostensalo, J., Ahtiainen, J.P, Haapala, E.A, Willeit, P., Kunutsor, S.K., and Laukkanen, J.A., 2022

American Journal of Physiology – Regulatory, Integrative and Comparative Physiology vol 323(3), R289–R299.

https://doi.org/ 10.1152/ajpregu.00076.2022

AMERICAN JOURNAL OF PHYSIOLOGY
REGULATORY, INTEGRATIVE AND COMPARATIVE PHYSIOLOGY

Am J Physiol Regul Integr Comp Physiol 323: R289–R299, 2022.
First published July 4, 2022; doi:10.1152/ajpregu.00076.2022

RESEARCH ARTICLE

Don't Deny Your Inner Environmental Physiologist: Investigating Physiology with Environmental Stimuli

Effects of regular sauna bathing in conjunction with exercise on cardiovascular function: a multi-arm, randomized controlled trial

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Abstract

Regular exercise and sauna bathing have each been shown to improve cardiovascular function in clinical populations. However, experimental data on the cardiovascular adaptations to regular exercise in conjunction with sauna bathing in the general population are lacking. Therefore, we compared the effects of exercise and sauna bathing to regular exercise using a multi-arm randomized controlled trial. Participants (n = 47) aged 49 ± 9 with low physical activity levels and at least one traditional cardiovascular disease (CVD) risk factor were randomly assigned (1:1:1) to guideline-based regular exercise and 15-min postexercise sauna (EXS), guideline-based regular exercise (EXE), or control (CON) for 8 wk. The primary outcomes were blood pressure (BP) and cardiorespiratory fitness (CRF). Secondary outcomes included fat mass, total cholesterol levels, and arterial stiffness. EXE had a greater change in CRF (+6.2 mL/kg/min; 95% CI, +4.2 to +8.3 mL/kg/min) and fat mass but no differences in BP when compared with CON. EXS displayed greater change in CRF (+2.7 mL/kg/min; 95% CI, +0.2 to +5.3 mL/kg/min), lower systolic BP (−8.0 mmHg; 95% CI, −14.6 to −1.4 mmHg), and lower total cholesterol levels compared with EXE. Regular exercise improved CRF and body composition in sedentary adults with CVD risk factors. However, when combined with exercise, sauna bathing demonstrated a substantially supplementary effect on CRF, systolic BP, and total cholesterol levels. Sauna bathing is a valuable lifestyle tool that complements exercise for improving CRF and decreasing systolic BP. Future research should focus on the duration and frequency of exposure to ascertain the dose-response relationship.

blood pressure; cardiorespiratory fitness; exercise; heat therapy; sauna bathing

INTRODUCTION

Physical activity and exercise training are well-documented strategies to prevent ailments (1) and various diseases (2). The current health and exercise guidelines (3) recommend 150–300 min of moderate-intensity physical activity spread across three to five sessions per week. In addition, resistance exercise should be performed at least twice a week (3, 4). Evidently, we have come to a firm understanding of exercise and how it can be used to improve cardiovascular health. However, unlike exercise, heat therapy and the health benefits of Finnish sauna bathing are still not well understood, despite its increasing use throughout the world (5), even though observational cohort studies (6–8) have found regular use of the sauna to be positively associated with numerous cardiovascular outcomes.

Indeed, most studies investigating the efficacy of sauna bathing have either been acute (0–30 min after sauna) or short-term (2–4 wk long) (9), and as pointed out by a recent review, long-term experimental evidence in heat therapy (10) based on the Finnish sauna is needed. The efficacy of sauna use on a regular basis when combined with exercise has been shown in both extremes of the population; in well-trained cyclists (11) and runners (12), as well as patients with

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Submitted 13 April 2022 / Revised 27 June 2022 / Accepted 29 June 2022

heart failure (13) and other diseases (14). However, these data are somewhat limited for the general population.

A significant portion of the general population today has at least one cardiovascular disease (CVD) risk factor (obesity, elevated blood pressures, elevated cholesterol, family history of coronary heart disease, and smoking or a history of smoking). This includes the majority of the population in Australia (15), Canada (16), Europe (17), United States (18), and a substantial percentage of people in China (19). This underscores the problems of public health in our modern society. Thus, it is important to develop interventional strategies that target these groups, as they form a larger part of the general population. Furthermore, these groups often stand to benefit most from lifestyle-related interventions (20).

One traditional CVD risk factor that warrants consideration is elevated blood pressure (BP) level, as increases in BP have been associated with an increase in CVD risk (21). BP has also been well documented to respond favorably to regular physical activity, which plays a pivotal role in the nonpharmacological management of hypertension (22). However, recent evidence suggests that regular heat therapy can lower BP to a comparable, if not larger degree (23). As such, adding regular sauna bathing to exercise could potentially yield even greater benefits than regular exercise alone. In addition to traditional CVD risk factors, cardiorespiratory fitness (CRF) has also been recently highlighted as a strong predictor of health outcomes (24) and is indicative of functional capacity and overall physical health (25). CRF can be measured directly using maximal testing or estimated via submaximal testing and is a significant prognosticator regardless of the method by which it is derived (26).

Our previously published works showed promising results through sauna use (27), as well as via a combination of exercise followed by sauna (28) in acute responses. Our objective for the current experiment was thus to expand these findings and explore the likelihood of cardiovascular adaptations, using BP and CRF as primary outcomes. We seek to provide fundamental and valuable information to the study of heat therapy and sauna use and its potential as a lifestyle intervention that could be prescribed alongside exercise effectively.

As such, we conducted an 8-wk multi-arm randomized controlled trial (RCT) using the current recommended guidelines on physical activity, in a population with CVD risk factors. The primary focus was to compare the cardiovascular adaptations of regular exercise alone (EXE) to regular exercise and sauna bathing (EXS), with a sedentary control (CON) group serving as a comparator against the EXE group to ascertain the efficacy of the 8-wk exercise intervention. To the best of our knowledge, this is the first multi-arm RCT investigating the long-term effects of exercise and sauna use in a nonathletic and nonclinical general population.

MATERIALS AND METHODS

A multi-arm, parallel-group (allocation ratio 1:1:1) RCT (Unique identifier: NCT04540718) was conducted in accordance with Consolidated Standards of Reporting Trials (29) guidelines (Fig. 1). The institutional review board of the Central Finland Hospital District ethical committee, Jyväskylä, Finland, approved this study (Dnro 3 U/2019). All participants provided written informed consent. The data that support the findings of this study are available to researchers upon reasonable request to the corresponding author.

Study Population

Female and male participants between 30 and 64 yr were recruited through medium-to-large organizations (City council of Jyväskylä, Jyväskylä Energy, Central Finland hospital) via email. The inclusion criteria of study participants consisted of a sedentary lifestyle and at least one traditional CVD risk factor. Sedentary lifestyle was identified as having a desk-bound job and less than 30 min of total physical activity per week. The CVD risk factors were elevated cholesterol, family history of coronary heart disease (CHD), hypertension, obesity, and smoking.

Total cholesterol level >239 mg/dL was considered elevated. Family history of CHD was positive if father (<55 yr) or mother (<65 yr) had premature CHD. Prestudy resting systolic BP (SBP) >139 mmHg and/or diastolic (DBP) >89 mmHg was considered elevated (30). Obesity was defined as body mass index (BMI) >30 kg/m^2. Exclusion criteria were *1*) sauna bathing more than once a week within the past 6 mo, *2*) commuting to work via activities such as running or cycling, *3*) previous CHD and/or diabetes, and *4*) any diagnosed and/or symptomatic CVD, musculoskeletal injury, or any other physical or mental condition within 6 mo before the commencement of the study. Participants were also excluded if they had resting SBP <100 mmHg or >159 mmHg, BMI over 40 kg/m^2, or if they were on any CVD medication.

Before the trial commencement, participants (n = 60) attended an information session where they were briefed about the research purposes, measurement procedures, and intervention period. Five participants dropped out. Subsequently, a prescreening session was conducted to collect baseline information (anthropometric data, resting electrocardiogram, and brachial BP) and ensure that the remaining 55 met the study eligibility based on the inclusion and exclusion criteria. Seven participants who did not meet the criteria were excluded, leading to a final sample size of 48 participants.

Randomization and Design

After the successful completion of prescreening procedures, participants were randomized into the EXS, EXE, or the CON group (Fig. 1). The randomization sequence was created using Excel 2016 (Microsoft, Redmond, WA) with a 1:1:1 allocation using simple randomization with stratification by a researcher with no clinical involvement in the trial. Biological sex was used for stratification, as there was a disproportionate number of female to male participants. Forty-eight participants (42 females, 6 males) were enrolled into the trial by the corresponding author. Participants were assigned to their respective interventions (16 per group, 14 females, and 2 males) by a member of the research team who was uninvolved with the data collection and analysis process. To ensure that the statistical analyses were nonbiased, the statistician was blinded to the assignment and completely uninvolved in the participant recruitment and data collection processes.

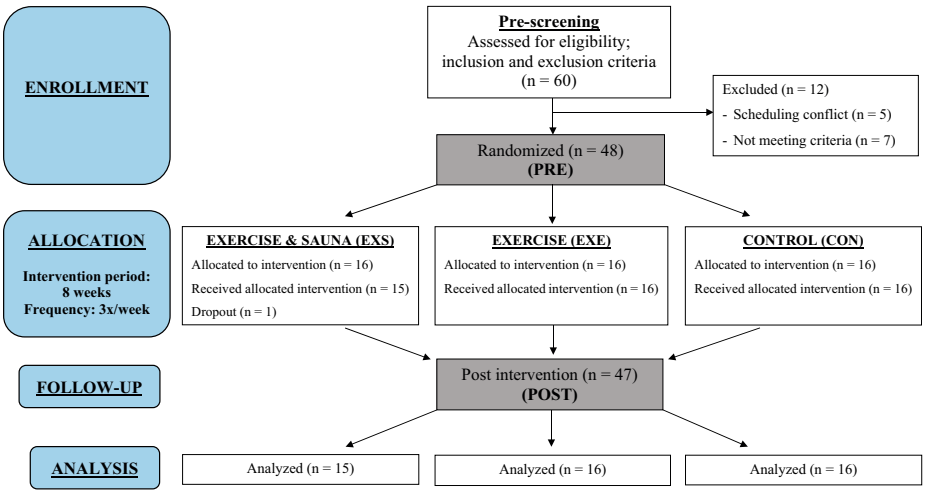

Figure 1. Experimental design (adapted and modified according to CONSORT guidelines template). *n*, number of human volunteers/participants.

Participants in the CON group were informed that a similar 8-wk supervised exercise training program would be offered to them after the trial. This was done to minimize dropout rates and increase adherence to preexisting lifestyle and physical activity habits during the trial period to reduce potential confounding factors. The study consisted of two measurement days completed by all groups and an 8-wk intervention for the EXS and EXE groups. Participants recorded and submitted a food diary the day before their preintervention (PRE) measurement. This was returned to them 48 h before the postintervention (POST) measurement, and they were carefully instructed to follow the same food intake before their measurement days. All participants were reminded regularly to maintain their regular daily activities and diet to minimize the possible influence of external variables on the outcome measures.

The intervention groups exercised three times a week (Monday, Wednesday, and Friday) in the evenings, between 1600 and 2100. Training sessions were carried out in groups of 1–5 participants with two qualified instructors. A predetermined adherence rate of 95% for 24 training sessions was successfully achieved. One participant from the EXS group dropped out during the first week due to undisclosed personal reasons. The exercise intervention was based on the Finnish national exercise guidelines (31), which are adapted from the guidelines of the American College of Sports Medicine (ACSM) and reflect current recommendations (3). Each exercise session lasted 60 min and was performed in the following order: a 10-min full-body warm-up, 20 min of resistance exercise, and 30 min of aerobic exercise. Details of the intervention are shown in Fig. 2.

Resistance training was a mixture of body weight and basic resistance training exercises. Starting loads for each resistance exercise were determined individually on a separate day before the intervention. The exercises were performed in a circuit fashion, with the aim of providing a full-body workout. Each circuit consisted of five movements, and each movement was performed for 45 s with a 15-s break between them. Completion of a circuit took 5 min, followed by a 1-min break. The circuits were completed three times each session. *Circuits A* and *B* were used alternately in each training for the first 4 wk, and *circuits C* and *D* were used in the final 4 wk. Harder variations of body weight movements and greater resistance exercise loads for each individual were introduced as performance improved, based on the assessment of the exercise instructors.

Aerobic exercise was performed using Monark cycle ergometers (Monark 828 E, Varberg, Sweden). Individual maximum heart rates were calculated (32) and used thereafter to prescribe aerobic exercise intensity, starting from 65% of maximum heart rate with a fortnightly increase of 5%. Aerobic exercise heart rate was closely monitored and verified every 5 min. Participants maintained a constant pedaling frequency of 65–70 revolutions per minute (rpm), while the magnetic resistance of the bike ergometer was adjusted to achieve the required exercise intensity. After aerobic exercise, participants in the EXS group proceeded to the sauna room, whereas those in the EXE group waited in the gym until the participants in the EXS group completed 15 min of sauna exposure. The temperature of sauna exposure started from 65°C and was increased by 5°C fortnightly and was monitored and recorded every minute via a commercially available wireless thermometer unit (Wireless thermometer 7410; Suomen Lämpömittari Oy, Helsinki, Finland). Relative humidity of the sauna room was between 10% and 20%. Participants were allowed to leave the sauna at any time if they felt uncomfortable, but all participants in the EXS group completed all 15 min of every postexercise sauna exposure successfully without leaving the sauna room.

Measurement of Outcomes

All measurements (PRE and POST) took place in the exercise and health laboratory, at the Faculty of Sport and Health Sciences, of the University of Jyväskylä. The primary outcomes were estimated relative maximal oxygen uptake ($\dot{V}O_{2max}$) as a measure of CRF and brachial BP. The CRF tests were completed in the evening between 1600 and 2000, and participants were instructed to refrain from heavy physical activity for 48 h and abstain from alcohol and nicotine for 12 h before all CRF tests. A multistage test similar to the YMCA submaximal bicycle test (33) was used. The test consisted of four stages of incremental submaximal workloads lasting 4 min each. Cadence was kept at 50–60 rpm (34), and heart rate was measured via a heart rate monitor (Polar V800;

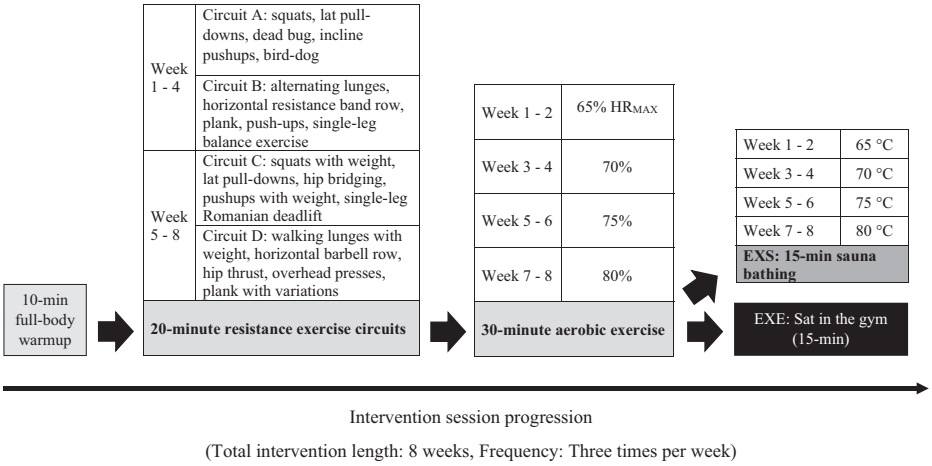

Figure 2. Details of the intervention. Loads were increased for resistance exercises when participants were able to complete the movement comfortably with good form. More challenging variations for the bodyweight exercises were introduced when the participant completed the basic movement with no noticeable difficulties. For example, resistance bands were used for dead bugs, bird-dog were executed with eyes closed, etc.

Polar Electro Oy, Kempele, Finland). After the test was completed, a regression line was plotted using the four points corresponding to each stage and extrapolated to the maximal heart rate. A perpendicular line was subsequently formed down to the *x*-axis and absolute oxygen uptake was read off from the graph (33, 34). From the resulting value, relative $\dot{V}O_{2max}$ was then calculated using individual body mass.

Two separate brachial BP measurements were taken on the right upper arm using automated oscillometric devices. The first measurement was taken with the Omron HEM-7320-LA (Omron Healthcare Co., Ltd, Kyoto, Japan), followed by the Arteriograph (TensioMed, Budapest, Hungary) after a 10-min rest in a supine position, according to the established guidelines (30, 35). If the difference in SBP between the two measurements was larger than 10 mmHg, another measurement was taken after a 5-min rest. The two measured values that differed the least were averaged and used for applanation tonometry analysis. Arterial stiffness indices of pulse-wave velocity (PWV) and augmentation index (AIx) as secondary outcomes were recorded noninvasively with the Pulsepen device (DiaTecne s.r.l., Milan, Italy; www.pulsepen.com) according to published guidelines (36). BP and tonometer measurements were taken by a single trained operator to ensure consistency. Intraclass correlation coefficient (ICC) estimates and their 95% CI were calculated using statistical software R (36), based on a mean-rating (k = 2), absolute-agreement, two-way mixed-effects model (ICC 2.1: 0.81 with 95% CI = 0.77–0.85, SE = 0.4).

Body composition measurements and blood samples were collected in the morning between 0630 and 0930 in fasted conditions. Participants were instructed to abstain from food, drinks, alcohol, and nicotine for 12 h and to refrain from heavy physical activity for 48 h before all measurements. Body composition was determined using dual-energy X-ray absorptiometry, and venous blood samples were collected by a qualified technician from the antecubital vein into Vacuette SST 6-mL tubes using sterile needles. The sample was centrifuged for 10 min at 2,000 rpm after which serum was removed and stored at −80°C until chemical analyses. Serum samples were subsequently analyzed with colorimetric assay, Konelab 20 analyzer (Thermo, Vantaa, Finland) to determine total cholesterol levels. Sensitivities and coefficients of variation (with-in-assay CV % average) were 3.86 mg/dL and 1.00%.

Statistical Analyses

Categorical variables are presented as number (%), whereas continuous variables are presented as means ± SD; 95% CIs are presented where appropriate. Statistical power of 80% with α = 0.05 for a difference of one standard deviation in means can be achieved with n = 15.68 per group when a two-tailed independent samples t test is used. Thus, the final sample size of 15, 16, and 16 (EXS, EXE and CON, respectively, with two males per group) in the three groups was expected to be adequate to detect most clinically significant differences.

Distributions of responses were tested for normality with the Shapiro–Wilk test for each group separately. After the family-wise error rate was controlled by using a Bonferroni correction, the null hypothesis of normality was not rejected for any variable of any group. Between-group differences PRE and POST intervention were analyzed using independent t tests. The comparisons were done between CON and EXE groups and between EXE and EXS groups. The level for statistical significance was set at $P \leq 0.05$. For completeness, we also fitted a mixed linear model for all three groups and each response variable. The details and results of these exploratory analyses are shown in Supplemental Table S1 (see https://doi.org/10.6084/m9.figshare.20160479.v1). The calculations were implemented with the statistical software R (37), with graphics done using the ggplot2 package (38).

RESULTS

Characteristics of Participants

The characteristics of the participants are presented in Table 1. The three most commonly present traditional CVD risk factors were obesity (54%), family history of CHD (37%), and elevated BP (35%). Baseline $\dot{V}O_{2max}$, SBP, and DBP were 28.3 ± 5.6 mL/kg/min, 133 ± 12 mmHg, and 79 ± 10 mmHg, respectively. No sex-based or race/ethnicity-based differences were present.

Exercise versus Control

Significant PRE-POST differences were found between the control (CON) and exercise (EXE) groups for $\dot{V}O_{2max}$ and fat

Table 1. *Baseline participant characteristics*

Characteristics	Total *n* = 47	Control *n* = 16, 14 Females	Exercise Only *n* = 16, 14 Females	Exercise + Sauna *n* = 15, 13 Females
Age, yr	49 ± 9	49 ± 8	51 ± 9	47 ± 8
Body mass, kg	89.0 ± 14.3	86.5 ± 15.6	87.3 ± 13.0	93.5 ± 13.2
Body mass index, kg/m^2	31.3 ± 4.1	31.1 ± 4.7	31.3 ± 4.2	32.2 ± 3.6
Estimated $\dot{V}O_{2max}$, mL/kg/min	28.3 ± 5.6	30.1 ± 4.8	29.4 ± 5.7	26.4 ± 6.3
Systolic BP, mmHg	133 ± 12	129 ± 9	134 ± 14	134 ± 14
Diastolic BP, mmHg	79 ± 10	78 ± 5	79 ± 11	80 ± 13
Risk Factors*	**Number (%)**		**Number/Group Total**	
Obesity (BMI >30 kg/m^2)	25 (54%)	8/16	9/16	8/15
Family history of CHD	18 (38%)	8/16	5/16	5/15
Elevated BP	16 (35%)	7/16	5/16	4/15
Elevated cholesterol (>239 mg/dL)	10 (22%)	4/16	3/16	3/15
Smoker (history of smoking)	6 (13%)	2/16	2/16	2/15

Values are means ± SD. No significant differences were found at baseline between groups for all the parameters. BMI, body mass index; BP, brachial blood pressure; CHD, coronary heart disease; $\dot{V}O_{2max}$, maximal oxygen consumption. *Number of participants with one, two, and three risk factors was 23, 20, and 4, respectively. No participant had more than three risk factors.

mass. Comparatively, EXE had greater increases in $\dot{V}O_{2max}$ and decreases in fat mass. No significant differences were found for BP, arterial stiffness indices, and total cholesterol (Table 2). Female-only data are found in Supplemental Table S2 (see https://doi.org/10.6084/m9.figshare.19575979).

Exercise and Sauna versus Exercise

PRE-POST differences in $\dot{V}O_{2max}$, SBP, and total cholesterol levels were significant between the EXE and exercise and sauna (EXS) groups (Table 3). Specifically, $\dot{V}O_{2max}$ was greater (Fig. 3), whereas SBP (Fig. 4) and total cholesterol levels (Fig. 5) were lower in the EXS than the EXE group after the 8-wk intervention period. There were no differences in any other outcome variables. Female-only data are found in Supplemental Table S3 (see https://doi.org/10.6084/m9.figshare.19576030).

DISCUSSION

In this multi-arm RCT, we compared the effects of an 8-wk exercise and sauna intervention (EXS) to regular exercise without sauna (EXE), using a sedentary population with relatively low physical activity levels and at least one traditional CVD risk factor. A control group (CON) was included to validate the efficacy of the exercise intervention. Our results show improvements in CRF based on the estimated $\dot{V}O_{2max}$ and lower fat mass for the EXE group compared with the CON group. More importantly, the EXS group demonstrated a greater increase in CRF, and greater decreases in SBP and total cholesterol levels, when compared with the EXE group.

To a reasonable extent, the differences seen between the CON and EXE groups were expected. Physical activity guidelines supported by research evidence suggest that 150 min of moderate-intensity exercise per week is sufficient to induce beneficial health adaptations (4). As such, our 8-wk exercise intervention was constructed to adhere as closely as possible to the recommendations (31). Every supervised session included a full-body warm-up, followed by resistance, then aerobic exercise. In addition, exercise intensity was progressively increased throughout the 8 wk, for both resistance and aerobic exercise.

The long-term benefits of exercise training on physical health have been well established (3, 39), and regular aerobic training has been shown to improve both body composition (39) and CRF (40) even at relatively lower intensities, which is consistent with the main findings of the current study. Furthermore, it has been well documented that performing resistance exercise before aerobic exercise leads to higher energy expenditure and fat mass loss (41–43), which was how our training sessions were designed. The results from this experiment are in support of the literature and are

Table 2. *PRE-POST comparison of means between the EXE and CON groups*

Outcome Variable	EXE (*n* = 16, 14 Females) PRE	EXE (*n* = 16, 14 Females) POST	CON (*n* = 16, 14 Females) PRE	CON (*n* = 16, 14 Females) POST	Mean Difference, 95% CI	*P* Value
Estimated $\dot{V}O_{2max}$, mL/kg/min	29.4 ± 5.7	32.0 ± 6.6	30.1 ± 4.8	26.8 ± 4.6	6.2 (4.1, 8.3)	0.00000211
SBP, mmHg	134 ± 14	134 ± 14	130 ± 9	130 ± 10	0.5 (−4.6, 5.6)	0.841
DBP, mmHg	79 ± 11	80 ± 9	79 ± 5	82 ± 6	−1.9 (−5.5, 1.7)	0.295
Fat mass, kg	37.8 ± 10.5	36.5 ± 10.1	38.0 ± 12.4	38.0 ± 12.3	−1.3 (−2.3, -0.3)	0.0125
Total cholesterol, mg/dL	203 ± 34	208 ± 30	215 ± 34	211 ± 29	12 (−8, 27)	0.215
PWV, m/s	9.2 ± 1.7	9.2 ± 1.4	8.5 ± 1.5	8.7 ± 2.4	−0.2 (−1.2, 0.8)	0.662
AIx, %	16.1 ± 11.9	17.3 ± 10.0	15.5 ± 11.0	15.4 ± 8.7	1.2 (−6.5, 8.9)	0.760

Values are means ± SD. Data were analyzed using independent *t* tests. AIx, augmentation index; CI, confidence interval; CON, control; DBP, brachial diastolic blood pressure; EXE, exercise; PRE, preintervention; POST, postintervention; PWV, pulse-wave velocity; SBP, brachial systolic blood pressure; $\dot{V}O_{2max}$, maximal oxygen consumption.

Table 3. *PRE-POST comparison of means between the EXS and EXE groups*

Outcome Variable	EXS (*n* = 15, 13 Females) PRE	EXS (*n* = 15, 13 Females) POST	EXE (*n* = 16, 14 Females) PRE	EXE (*n* = 16, 14 Females) POST	Mean Difference, 95% CI	*P* Value
Estimated $\dot{V}O_{2max}$, mL/kg/min	26.4 ± 6.3	32.0 ± 6.4	29.4 ± 5.7	32.0 ± 6.6	2.7 (0.2, 5.3)	0.0343
SBP, mmHg	134 ± 14	126 ± 11	134 ± 14	134 ± 14	−8.0 (−14.6, −1.4)	0.0198
DBP, mmHg	80 ± 13	80 ± 14	79 ± 11	80 ± 9	−0.6 (−6.0, 4.8)	0.823
Fat mass, kg	39.6 ± 8.2	37.7 ± 8.5	37.8 ± 10.5	36.5 ± 10.1	−0.6 (−1.9, 0.7)	0.339
Total cholesterol, mg/dL	200 ± 32	188 ± 33	203 ± 34	208 ± 30	−19 (−35, 0)	0.0467
PWV, m/s	9.6 ± 1.9	9.2 ± 1.7	9.2 ± 1.7	9.2 ± 1.4	−0.4 (−1.1, 0.3)	0.249
AIx, %	17.7 ± 10.6	12.6 ± 14.1	16.1 ± 11.9	17.3 ± 10.0	−6.3 (−14.8, 2.2)	0.142

Values are means ± SD. Data were analyzed using independent *t* tests. AIx, augmentation index; CI, confidence interval; DBP, brachial diastolic blood pressure; EXE, exercise; EXS, exercise + sauna; PRE, preintervention; POST, postintervention; PWV, pulse wave velocity; SBP, brachial systolic blood pressure; $\dot{V}O_{2max}$, maximal oxygen consumption.

indicative that the 8-wk exercise intervention provided an adequate stimulus for physiological adaptations to both CRF and body composition.

Despite these adaptations, however, there were no differences in changes to BP and other secondary variables such as arterial stiffness between the EXE and CON groups. This may have been partially due to the length of the present intervention, as training interventions are typically longer in duration. Although cardiovascular adaptations such as arterial remodeling and capillary growth have been well documented to occur within the first few weeks of exercise training (44), this did not appear to be the case. The structure of the exercise training likely contributed to this lack of response in the other variables, as the divergent nature of resistance and aerobic exercise has been reasonably established (45). Moreover, combined resistance and aerobic training have been documented to be less effective than aerobic training alone in reducing arterial stiffness (46) and BP (47).

One of the objectives of the current study was to elucidate the synergistic effects of sauna exposure and exercise on the primary variables of BP and CRF, in a sedentary population with traditional CVD risk factors. Specifically, our data suggest that the addition of 15-min sauna exposure, regularly after every exercise session, three times a week for 8 wk was able to improve CRF, SBP, and total cholesterol levels significantly, when compared with performing the same exercise intervention alone. Indeed, previous studies have shown that sauna exposure is an effective additive tool to an exercise program for both clinical (13, 48) and athletic populations (10, 49).

Studies have found positive acute cardiovascular responses from the use of passive heat (50), sauna exposure (27, 51), and sauna exposure with exercise (52, 53). A recent study also showed that postexercise sauna exposure had an augmentative effect, thereby increasing the overall training stress (54). However, to our best knowledge, this is the first multi-arm RCT investigating the cardiovascular and health effects of long-term sauna exposure in the general population with CVD risk factors. The current results suggest that the addition of regular sauna exposure was able to increase CRF and led to a decrease in SBP when comparing the EXS and EXE groups.

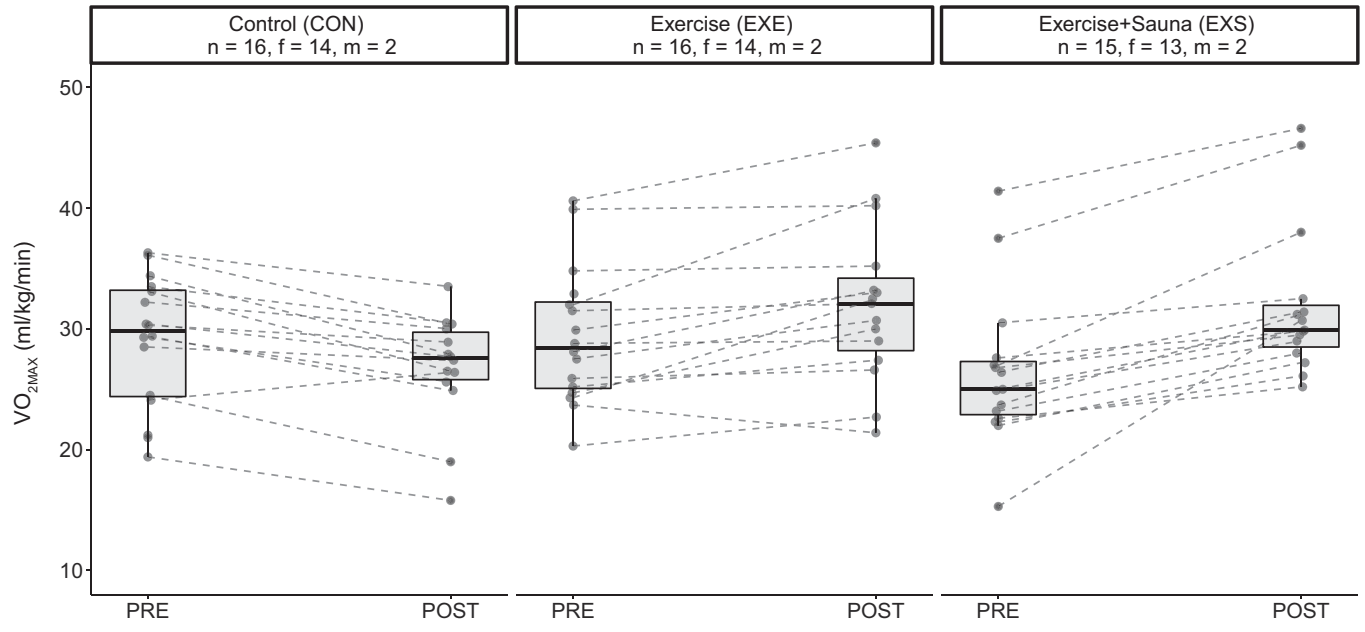

Figure 3. Graphical representation of the PRE-POST changes in CRF (relative $\dot{V}O_{2max}$) of the three groups. CRF, cardiorespiratory fitness; f, female; m, male; PRE, preintervention; POST, postintervention.

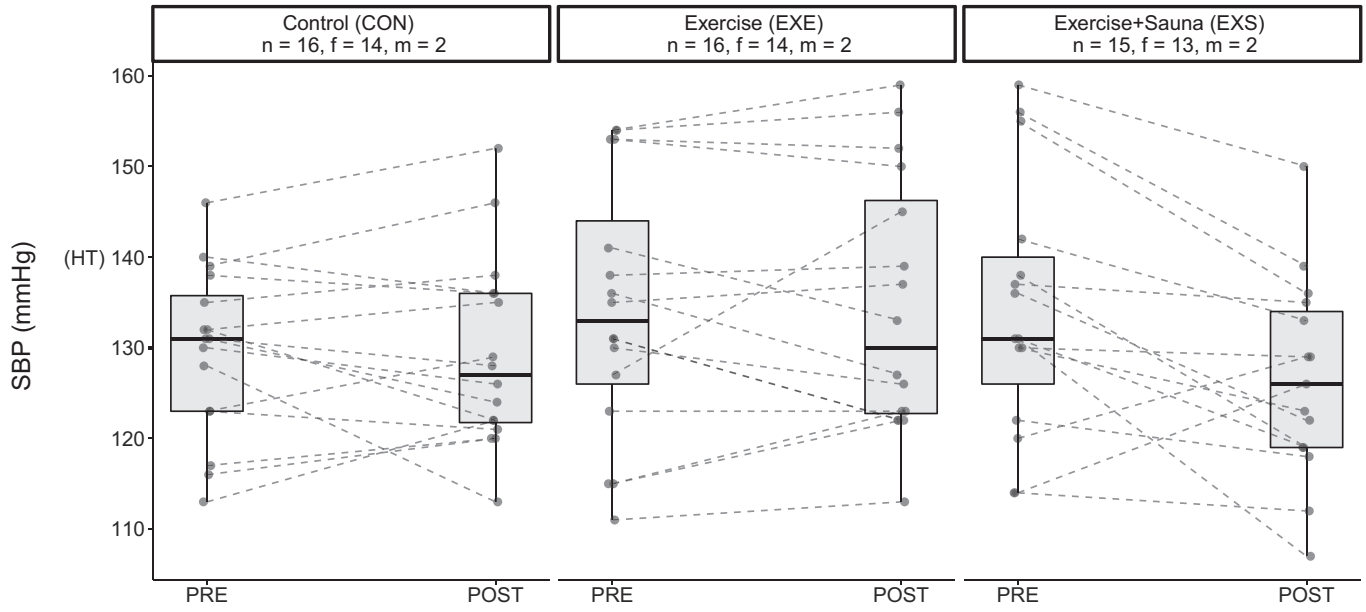

Figure 4. Graphical representation of the PRE-POST changes in SBP of the three groups. HT, Grade 1 hypertension classification; f, female; m, male; PRE, preintervention; POST, postintervention; SBP, systolic blood pressure.

Heat acclimation studies have shown the efficacy of using heat to improve aerobic fitness (55, 56). Moreover, the use of heat has been shown to induce a greater level of acute physiological strain and cellular response at a lower relative workload than hypoxia (57). Therefore, it is more likely that the present cardiovascular adaptations seen in this study may be the result of functional enhancements rather than structural changes in the arteries (58), as there were no significant changes to PWV and AIx as measures of arterial stiffness. Nevertheless, this needs to be further investigated, as heat shock proteins, muscle endothelial nitric oxide synthase content, and capillary density were not measured in the present study.

It is worth noting that CRF adaptations to passive heat exposure in the form of sauna bathing have yet to be thoroughly investigated mechanistically. However, cardiovascular adaptations to heat acclimation have been well documented (59), which provides us with a vital framework that may explain the difference in CRF between the EXE and EXS groups. Exercise training and passive heat have been shown to have additive effects that lead to improved myocardial contractility, over exercise training or heat alone, in animal

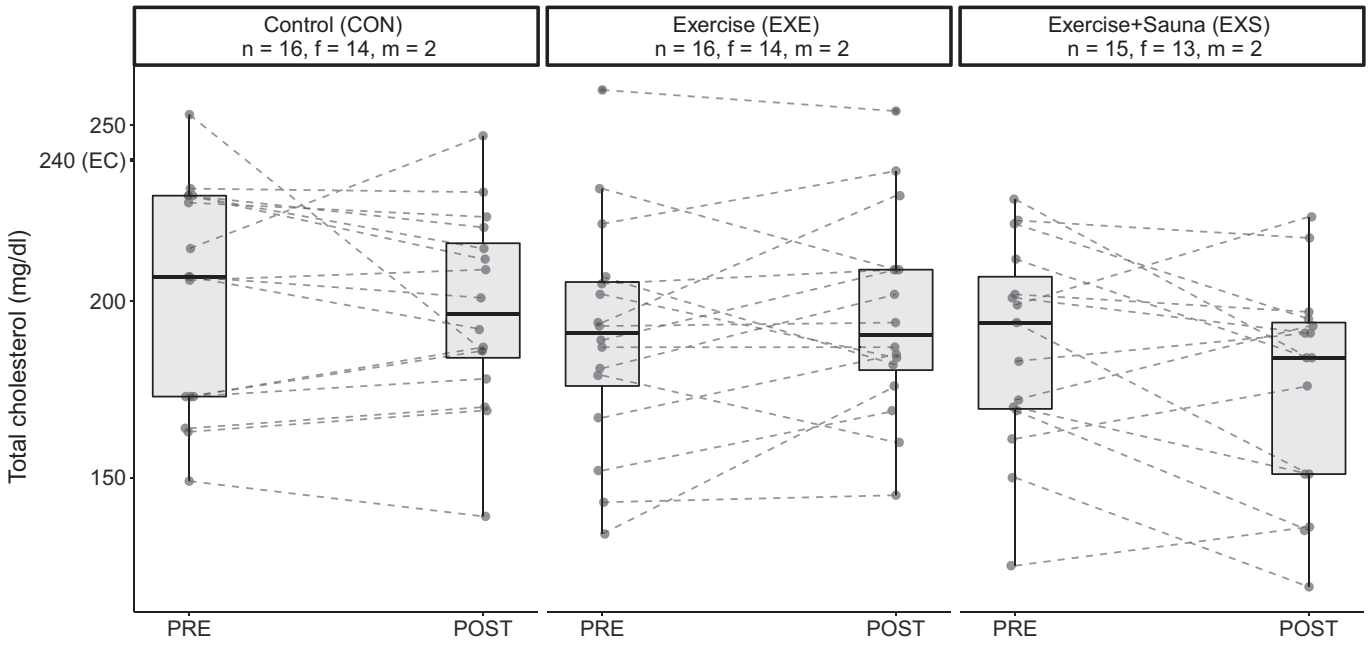

Figure 5. Graphical representation of the PRE-POST changes in total cholesterol levels of the three groups. EC, elevated cholesterol; f, female; m, male; PRE, preintervention; POST, postintervention.

models (60). Eight weeks of heat acclimation has been shown to improve myocardial compliance, rendering it more efficient (60, 61). It is thus plausible that cardiovascular stability may have been augmented by the addition of regular sauna exposure to exercise, and that functional, rather than morphological adaptations were responsible for the differences in CRF between the intervention groups, particularly in the absence of changes to arterial stiffness parameters. Moreover, infrared sauna therapy (13) has also been shown to augment increases in CRF via functional changes, which is consistent with our present findings.

A recent systematic review showed that compared with controls, heat therapy decreased both SBP and DBP by an average of 4 mmHg (23). Based on the latest guidelines on BP (30, 35), it was postulated that a reduction in BP by ~5 mmHg would improve individual BP categorization (23, 62). Although our study did not find differences in DBP between interventions, SBP levels for the EXS group were 8 mmHg lower than in the EXE group postintervention, which is almost an entire BP category. This is a clinically important new finding to highlight, as a recent meta-analysis (63) reported a nearly linear relationship between a 5-mmHg decrease in SBP and a lowered risk of all-cause mortality across all BP categories.

Although higher resting BP before an intervention has been suggested as a potential mitigating factor in the therapeutic effects seen in heat-related studies (23), only 35% of the participants in the current experiment had an elevated resting BP. In addition, there was no difference in the PRE values of SBP and DBP between all three groups. One mechanism that may have contributed to the lower SBP in the EXS group was the concomitant lowering of total cholesterol levels. This agrees with the findings from an earlier study (64), which found that heat therapy was able to improve the blood lipid profile, specifically total cholesterol levels, in a sedentary obese population. In addition, there were improvements to BP but no changes to BMI or body composition, which is remarkably comparable to the findings from our current study. Even though the authors used hot water immersion as opposed to the sauna, there were similarities between our experimental designs worth noting, such as the intervention period and the frequency of exposure. These are crucial factors to consider for future research in the area, as has been pointed out by several others (23, 58).

Some limitations of this study ought to be noted. The trial lacked a sauna-only group, which would have allowed us to determine if the benefits seen could have been solely attributable to the sauna. Diet of the participants was not controlled for during the trial, which could have influenced the results. However, participants followed the same diet a day before each measurement was taken, which improves the consistency and reliability of our data. Maximal oxygen consumption was not measured directly, but the indirect method better suited the study population and added external validity. The study sample had only six male participants. However, we addressed this issue using stratified randomization and included separate tables of results (Supplemental Tables S2 and S3, Supplemental Fig. S1; see https://doi.org/10.6084/m9.figshare.19582801.v1, Supplemental Fig. S2; see https://doi.org/10.6084/m9.figshare.19582813.v1, Supplemental Fig. S3; see https://doi.org/10.6084/m9.figshare.19582822.v1) that excludes the males for a more accurate and complete perspective. Moreover, insufficient female data have been a long-standing problem in scientific research; therefore, this could be viewed as a strength, rather than a limitation of this study.

Indeed, our study does have several strengths. We extended the findings of our earlier research in the acute setting (28, 65), with an 8-wk interventional study using a sedentary population, who were nonfrequent sauna users, to investigate the complementary effects of exercise followed by sauna exposure. Body composition was determined using dual-energy X-ray absorptiometry, while arterial stiffness and BP measurements adhered closely to established guidelines (30, 35, 36). Compliance of the intervention groups was excellent, with only 2 participants each missing a single session out of 24. All other participants completed the 24 sessions successfully with only 1 dropout for the entire study. Moreover, a statistician that was blind to the intervention assignment performed the data analysis using coded variables.

In conclusion, regular exercise using the recommended guidelines three times a week, for 50 min each time, can effectively improve CRF and body composition. The addition of a regular 15-min typical Finnish sauna after exercise supplemented the gains in CRF, reductions in SBP, and lowered total cholesterol levels considerably. Future research should adopt a more systematic approach in the study of heat exposure and seek to understand the optimal exposure durations, frequencies, modalities, and temperatures for various beneficial adaptations.

Perspectives and Significance

The design of this experiment allowed us to ascertain to a reasonable extent the additive effect of regular sauna exposure to exercise on cardiovascular health outcomes such as BP and CRF. These beneficial changes seen are promising, given that the essential methodological parameters of sauna exposure, such as duration and frequency were not only relatively short and tolerable, but practically feasible and replicable as well. Taken into context with mechanistic studies from molecular physiology, this is indicative of the noteworthy potential that passive heat therapy has. In addition, this study opens up opportunities to investigate shorter bouts of regular exercise in conjunction with sauna use and lends support for regular sauna bathing to be a possible therapeutic alternative, particularly for those with compromised exercise capacities, and possibly other rehabilitation settings as well. Sauna bathing is a safe and simple lifestyle modification and steps should be taken to make it more accessible worldwide.

DATA AVAILABILITY

The data that support the findings of this study are available to researchers upon reasonable request to the corresponding author.

SUPPLEMENTAL DATA

Supplemental Table S1; https://doi.org/10.6084/m9.figshare.20160479.v1.

Supplemental Table S2 https://doi.org/10.6084/m9.figshare.19575979.v1.
Supplemental Table S3 https://doi.org/10.6084/m9.figshare.19576030.v1.
Supplemental Fig. S1 https://doi.org/10.6084/m9.figshare.19582801.v1.
Supplemental Fig. S2 https://doi.org/10.6084/m9.figshare.19582813.v1.
Supplemental Fig. S3: https://doi.org/10.6084/m9.figshare.19582822.v1.

GRANTS

The Finnish Cultural Foundation (SKR) partially funded the corresponding author's salary (Grant No.: 00190620 to E. Lee).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

E.L. conceived and designed research; E.L. and I.K. performed experiments; J.K. analyzed data; E.L., J.P.A., E.A.H., and J.A.L. interpreted results of experiments; J.K. prepared figures; E.L. and J.K. drafted manuscript; E.L., J.K., J.P.A., E.A.H., P.W., S.K.K., and J.A.L. edited and revised manuscript; E.L., I.K., J.K., J.P.A., E.A.H., P.W., S.K.K., and J.A.L. approved final version of manuscript.

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