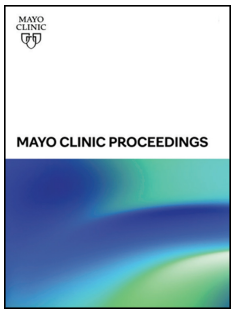
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Effects of Sauna Bathing on NMR-Based Metabolomic Profiles

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# Sauna bathing improves cardiometabolic profile via metabolomic remodeling

**Metabolomics study design**

Acute sauna exposure (n=63)
-30 min (2×15 min)
-PRE → POST heat exposure

RCT setting (n=47)
-8 weeks exercise and heat intervention
-Control
-Exercise
-Exercise + Sauna

**Mechanisms**

Acute sauna
↓ TG & VLDL
↓ Amino acids
↑ Ketones
→ Enhanced lipid utilization
→ Fasting-like state

Exercise + sauna
↓ LDL & VLDL
↑ HDL size

**Clinical impact**

Exercise-mimetic effect

Improved lipid metabolism

Enhanced metabolic flexibility

→ Cardiovascular prevention

Heat induces cardiometabolic benefits and augments exercise effects



**Exercise → Sauna → Cardiometabolic effects**

**Exercise-like metabolic response**



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**Effects of Sauna Bathing on NMR-Based Metabolomic Profiles**

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Short title: Heat and metabolomics

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**Abstract**

**Background:** Frequent sauna bathing is associated with reduced risk of adverse cardiovascular outcomes. However, the biochemical pathways through which sauna bathing may exert its cardiovascular health effects remain unclear. We therefore investigated the effects of Finnish sauna bathing on various blood-based cardiometabolic biomarkers. Specifically, this study investigated how a single 30-minute Finnish sauna session (AS) and an 8-week exercise-plus-sauna intervention (ESS) influence circulating metabolomic biomarkers related to lipid and amino acid metabolism.

**Methods:** The study included two complementary populations: (1) an acute sauna exposure study including 63 habitual sauna users with at least one cardiovascular risk factor, and (2) an 8-week randomized controlled trial (RCT) including 47 sedentary non-regular sauna users randomized to exercise, exercise plus sauna, and control arms. The exercise intervention consisted of concurrent training three times per week, with the sauna group additionally completing 15 min of post-exercise sauna bathing. Circulating metabolites were quantified using high-throughput 1H-NMR spectroscopy at multiple time points in the acute study and at baseline and post-intervention in the RCT.

**Results:** AS produced consistent metabolic shifts, including significant reductions in concentrations of plasma triglycerides and VLDL particles, decreases in branched-chain and aromatic amino acids, and increases in ketone bodies, suggesting a metabolic pattern compatible with enhanced lipid utilization and a transient metabolic stress response. ESS resulted in additional improvements beyond exercise alone, including reductions in LDL particle number and concentration, greater decreases in VLDL subclasses, and increases in HDL particle size, suggesting additional metabolic effects when heat exposure is added to exercise training.

**Conclusions:** Sauna bathing, as an example of heat exposure, induces favorable alterations in lipid and amino acid metabolism and when combined with regular exercise, augments longer-term improvements in lipoprotein profiles.

**Key words** Sauna bathing, Heat exposure, Intervention study, Randomized study, Cardiovascular disease, Metabolomics

**Abbreviations**

AS, acute sauna study; BCAA, branched-chain amino acids; BMI, body mass index; CHD, coronary heart disease; CON, control; CVD, cardiovascular disease; ECG, electrocardiogram; ESS, exercise and sauna study; EXE, exercise; EXS, exercise plus sauna; GlycA, glycoprotein acetyls; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; NMR, nuclear magnetic resonance; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial; SD, standard deviation; SFA, saturated fatty acids; VLDL, very low-density lipoprotein.

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## Introduction

There is a growing body of research evidence linking passive heat therapy with cardiometabolic health benefits.[1,2] Sauna bathing, a form of passive heat therapy, is a traditional activity in Finland that is becoming increasingly popular in many other cultures, beyond its use for leisure and relaxation purposes.[3] Regular sauna bathing has been linked to improved cardiovascular function as well as several other health benefits.[4] Many observational studies suggest that regular or frequent sauna bathing reduces the risk of vascular diseases, such as hypertension, cardiovascular disease (CVD) mortality, sudden cardiac death, and cerebrovascular stroke.[5-12] The protective effects of sauna bathing on cardiometabolic events have been linked to its beneficial impact on circulatory and cardiovascular function.[13] A single session of sauna has been shown to have favorable effects on the cardiovascular system by improving endothelial function, arterial stiffness, blood pressure, markers of oxidative stress, and brain natriuretic peptides; as well as increasing parasympathetic and decreasing sympathetic nervous activity.[13-18] However, there may be some other cardio-metabolic changes due to regular sauna bathing, which remain to be thoroughly investigated.

We have previously reported on the potential beneficial effects of acute sauna exposure on arterial stiffness and compliance, blood pressure, hematological variables, as well as renal markers.[10,13-15,19,20] Although existing evidence suggests that short-term heat therapy may produce widespread beneficial effects on vascular function, there is limited evidence on the effects of sauna exposure on circulating cardiometabolic biomarkers, amino acid metabolism and inflammation. Previous studies have examined this topic by exposing relatively young participants (20-30 years old) to mild temperatures (~30 °C) for prolonged periods (2 or 6 hours),[21,22] or by applying shorter heat exposure (30 min) at relatively low temperatures (50 °C).[23] In addition, few studies have investigated the acute effects of combined heat exposure

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and physical activity on metabolomic profiles,[24,25] but, to our knowledge, no studies have examined the longer-term effects of combined heat and exercise intervention.

In this study, we hypothesized that short-term acute heat exposure through Finnish sauna bathing would induce changes in circulating cardiometabolic biomarkers in middle-aged men and women, as assessed using circulating metabolomic profiles. We also hypothesized that incorporating heat exposure, such as sauna bathing, into an exercise intervention could provide additional benefits for metabolic health. Accordingly, the aim of this study was to evaluate the acute effects of a single sauna exposure and the longer-term effects of an exercise-plus-sauna intervention on circulating metabolomic biomarkers related to cardiometabolic health.

## Materials and methods

This study is based on two sauna studies: an acute sauna exposure study[26] (AS) and a randomized controlled trial (RCT) with three study arms - exercise, exercise plus sauna bathing, and control[15] (ESS). The study designs and protocols were approved by the institutional review board of the Central Finland Hospital District ethical committee, Jyväskylä, Finland (Acute Sauna Study: Dnro 5U/2016, Exercise and Sauna RCT: Dnro 3 U/2019). All study participants provided written informed consent prior to participation. Baseline assessments and sauna measurements for AS were conducted during the month of June and November of 2016. Data for ESS was collected during the last two weeks of September and first two weeks of December 2019.

### *Acute sauna study (AS)*

AS included 102 participants without diagnosed CVD recruited from the city of Jyväskylä, Central Finland region through a local out-of-hospital community health care center.[26] Study

participants were asymptomatic but had at least one cardiovascular risk factor, such as a history of smoking, dyslipidemia, hypertension, obesity, diabetes, or a family history of coronary heart disease (CHD). Individuals with any form of acute or pre-existing CVD were excluded from the study (n=8). For the present study, 63 participants with available laboratory samples for metabolomics measurements were included. Prior to study entry, participants were provided with information about the research purposes and measurement procedures and were screened by a cardiac specialist for a physical examination, medical history assessment, and a resting electrocardiogram (ECG). The clinical evaluation was conducted on separate days prior to the acute sauna exposure experiment. Assessment of demographics, lifestyle factors (e.g., smoking, physical activity, sauna bathing habits), prevalent diseases, and regular use of medication were based on a detailed self-reported questionnaire, which was checked by a cardiologist during screening. Physical activity and sauna bathing habits over the past year were also assessed.

***Sauna exposure protocol of AS***

The traditional Finnish sauna with dry air and relatively high temperature was used.[7] Each session consisted of two 15-minute bouts, resulting in a total sauna exposure duration of 30 minutes. The two bouts were interspersed with a shower in-between. Sauna exposure sessions took place between 09:00 - 15:00 on the specified study days. Sauna rooms were sex-specific, and all participants wore swimsuits during the sauna sessions. Each participant performed one sauna session and only one participant was allowed in the hot and dry sauna bath at a time. Sauna temperature was set at 80˚C and this was controlled and monitored by internal temperature sensors designed by Harvia Oy, Finland. Temperature assessment was continuously recorded with the use of a 2-channel thermometer located in the sauna room. The temperature sensor also monitored the humidity of the sauna room. Based on overall data

collected, the mean ± standard deviation (SD) temperature was 73 ± 2 °C with a relative humidity of 10-20 %.

Study participants were monitored and supervised by a physician and were given the option to leave the sauna at any time they felt any discomfort. All participants completed the recommended sauna protocol with no adverse events or incidents. Participants were asked to drink a 500 mL of still water at room temperature during the entire sauna session and throughout the post-sauna recovery period. The recovery period was 30 minutes, involving resting in a designated relaxing waiting lounge (mean temperature 21 °C).

***Exercise and sauna study (ESS)***

The ESS (NCT04540718) setting has been described in detail elsewhere.[15] Briefly, the study was designed as a multi-arm, RCT investigating the effects of exercise training (EXE) alone and exercise training combined with sauna bathing (EXS) on cardiovascular outcomes, with a sedentary control (CON) group serving as a comparator group. Female and male participants between 30 and 64 years were recruited.[15] Before enrolment in the trial, participants reported that they were not frequent sauna users, defined as using the sauna no more than once per week. The inclusion criteria required study participants to have a sedentary lifestyle and at least one traditional CVD risk factor. Sedentary lifestyle was identified as having a desk-bound job and less than 30min of total physical activity per week. Forty-eight enrolled participants were randomized 1:1:1 into three groups for the 8-week intervention by a researcher with no clinical involvement, with stratification by sex: (1) EXE underwent supervised aerobic and resistance exercise training three times per week, (2) EXS received the identical exercise protocol as the EXE group, followed by a 15-minute post-exercise sauna session three times per week, and (3) CON received standard lifestyle advice.

The temperature of the sauna intervention increased 5 °C every fortnight; starting from the beginning 65°C to 80°C at the end of eight weeks. A total of 47 participants completed the

RCT protocol and provided blood samples for the metabolomics profiling conducted in the current study. One participant from the EXS group dropped out due to personal reasons.

**Blood pressure and body mass index assessments**

In both studies, resting blood pressure was estimated as the means of two measurements obtained while the participant was in the supine position, based on a standardized measurement protocol. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. BMI was measured at the study baseline.

**Clinical blood biomarker assessments**

In AS, non-fasting resting blood samples were taken about 60 minutes prior to the sauna session (PRE), immediately after the session (POST), and 30 minutes after the session (POST 30 min).[18] Participants were instructed to abstain from strenuous physical activity 24h before the blood samples were taken. In ESS, blood samples were collected in the fasting state at rest seven days prior to commencement of the intervention and within seven days of intervention completion (PRE and POST samples, respectively). Participants were instructed to abstain from food, drinks (water drinking was allowed), alcohol, and nicotine for 12 h and to refrain from heavy physical activity for 48 h before the measurements. In both studies, PRE samples were used for the determination of the clinical biomarkers,[18] such as total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and plasma glucose concentrations. All samples were collected by a qualified laboratory technician from the antecubital vein into plasma or serum tubes (BD Vacutainer, Plymouth. UK). Whole blood samples were centrifuged 10 minutes at 3500 rpm (Megafuge, Heraeus, Germany), and aliquoted plasma and serum samples were stored at -80°C until spectrophotometry analyzes (Konelab 20XTi, Thermo Fisher Scientific, Vantaa, Finland).

**Analyses of the circulating metabolites**

Circulating metabolites were quantified from PRE, POST and POST 30 min plasma samples of AS and PRE and POST intervention serum samples of ESS using the same high-throughput proton nuclear magnetic resonance ($^1$H-NMR) spectroscopy platform (Nightingale Health Ltd, Helsinki, Finland, biomarker quantification version 2020) Technical details of the platform have been reported previously.[27] A total of 250 metabolomic measures were quantified. However, as is common with plasma samples, glycerol could not be reliably quantified in AS. Consequently, 179-180 measures were included as outcomes in the present analyses. These included lipoprotein numbers in different types and size-based subclasses, their lipid concentrations, fatty acid concentrations and their ratios to total fatty acids, glycolysis-related metabolites, amino acids, ketone bodies, and the composite inflammation marker GlycA. We excluded the lipoprotein lipid ratio measures from the analysis, as they provided partly redundant information. In AS, three values were missing for glutamine, glucose, pyruvate, and 3-hydroxybutyrate, whereas the ESS dataset had no missing values.

Metabolomics analyses are vulnerable to changes in plasma volume. In AS, the mean percentage change in plasma volume compared with pre-measurement was -3.9% (SD 5.1%, range -18.8 to 6.6%) after sauna exposure and -0.4% (SD 3.9%, range -9.6 to 8.3%) 30 min after its cessation. We, therefore, corrected the AS values using the Dill & Costill equation (1):

$$\frac{\frac{HB_{pre}}{HB_{post}} \times 1 - \frac{HCT_{post}}{100}}{\frac{1 - HCT_{pre}}{100}} \times 100 - 100$$

HB refers to hemoglobin and HCT to hematocrit. Hemoglobin (g/l) and hematocrit (%) were measured from the whole blood using Konelab 20 analyzer (Thermo Scientific, Vantaa,

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Finland). In ESS, correction was not required because post-intervention samples were collected at least 48 hours after the end of the intervention, thereby reflecting the overall intervention effect rather than the acute effects of exercise or sauna.

**Statistical analysis**

We performed data analysis using RStudio version 2023.9.1.494 and R version 4.3.2. Metabolite measures typically exhibit non-normal distribution, resulting in skewed residuals in regression-based testing. Consequently, we initially applied Box-Cox transformation (*MASS* package) to the measures, aiming to achieve a distribution as close to normal as possible. We determined lambda parameters for transformation based on baseline data. To ensure comparability across metabolite measures with varying concentrations and units, we scaled them using the baseline mean and standard deviation. Finally, we estimated changes in outcomes through linear mixed-effects models with random intercepts per participant, using the *nlme* package.

We observed baseline differences between groups in ESS. To address potential regression-to-the-mean effects, we incorporated metabolite baseline levels as a covariate in the models. We also conducted sensitivity analyses. In AS, four participants exhibited pre-sauna plasma triglyceride levels > 3 mmol/l, likely due to consuming a fat-containing meal close to the measurements or underlying hypertriglyceridemia. In ESS, one participant in the EXE group had a notable rise in serum triglyceride levels during the study. In sensitivity analyses, we excluded these participants due to their potential to markedly influence the results.
Our statistical approach involved multiple testing. We applied False Discovery Rate (FDR) correction to the results, but our focus remained on interpreting overall trends rather than singular *P*-values. This approach allowed us to examine potential patterns and associations in the data, recognizing the inherent limitations of the exploratory nature of the analyses.

## Results

### Baseline characteristics and sauna exposure profiles of the two study cohorts

The baseline characteristics of the study participants are presented in the **Table**. In AS, 46% of the participants were female, whereas in ESS, females constituted the majority (87%). In AS, 16% of participants had hypertension, 46% hypercholesterolaemia, and 31% obesity. The corresponding percentages in ESS were 35%, 22% and 54%, respectively. Study participants were broadly comparable between the two studies, except that AS included regular sauna users, whereas ESS recruited non-regular sauna users. Participants in AS typically were engaged in Finnish sauna bathing approximately three times per week, with individual sessions lasting approximately 20–40 minutes at an average temperature of around 72 °C, reflecting habitual Finnish sauna use. During the 8-week intervention period of ESS, participants completed 15-minute sauna exposure three times per week, with sauna temperature increasing from 65 °C to 80 °C. Compliance in the intervention groups was high, with only two participants per group missing one session.

### Effects of acute sauna bathing exposure on circulating metabolites

In AS, sauna exposure was associated with immediate and consistent changes in circulating metabolite concentrations (**Supplementary Table 1**). The most notable changes in circulating metabolites are presented in **Figure 1**. For many metabolites, we observed notable changes in circulating levels immediately after sauna exposure, with further changes occurring during the 30-minute cooling period. In contrast, some metabolites returned closer to their pre-sauna levels during this recovery phase. Immediately and at 30 minutes post-sauna, plasma triglyceride concentrations decreased significantly, with reductions observed across very low-density lipoprotein (VLDL), LDL, and HDL particle subclass concentrations (**Figure 1, Supplementary Table 1**). VLDL particle number and size also declined, and the

triglyceride-to-phosphoglyceride ratio was reduced. Plasma fatty acid composition shifted toward a more favorable profile, with relative decreases in saturated and monounsaturated fatty acids and a corresponding increase in polyunsaturated fatty acids (**Figure 1**).

Sauna exposure did not affect blood glucose and pyruvate levels, but it did result in a reduction during the cooling period and an acute reduction in citrate levels, which reverted to the pre-sauna level during cooling period (**Figure 1**). Most of the assessed amino acid concentrations decreased during sauna exposure and remained low through the post-sauna cooling period. Glycine was a clear exception, as its level initially increased but was no longer statistically different from the pre-sauna level at the later time point. Alanine, aromatic amino acids (phenylalanine, tyrosine) and branched-chain amino acids (valine, leucine, isoleucine) all declined during sauna exposure and remained low even after the 30-minute cooling period. Concentrations of 3-hydroxybutyrate and acetone, in turn, increased, indicating a transient shift toward ketone body metabolism. These findings were consistent after excluding participants with pre-sauna triglyceride levels >3 mmol/L (**Supplementary Table 1**).

**Effects of sauna bathing combined with exercise training on circulating metabolites**

The key findings from the ESS are presented in **Figure 2**, with the full metabolites results provided in **Supplementary Table 2**. Medium sized VLDL particle concentrations appeared to decrease in the EXS group compared with the CON and EXE groups (**Figure 2A**). When comparing the exercise-plus-sauna group with the exercise-only group, VLDL cholesterol concentration (-0.74, $P = 0.004$, FDR = 0.020) and LDL cholesterol concentration (-0.79, $P = 0.003$, FDR = 0.017) decreased in the EXS group by approximately 0.78 SD (FDR < 0.05) (**Figure 2B and 2C**). In contrast, no significant change was observed in HDL cholesterol (**Figure 2D**). Additionally, HDL size increased in the EXS group compared with the CON (0.34 SD, $P = 0.033$, FDR = 0.30) and EXE groups (0.37 SD, P = 0.020, FDR = 0.054)

(**Supplementary Table 2**). The ratio of monounsaturated fatty acids to total fatty acids (**Figure 2E**), but not the ratio of polyunsaturated fatty acids to total fatty acids (**Figure 2F**), decreased in the EXS intervention group compared with CON (-0.65 SD, P = 0.038, FDR = 0.302) and EXE groups (-0.66 SD, P = 0.033, FDR = 0.076).

From non-lipoprotein-related metabolites, alanine (-0.70, P = 0.007, FDR = 0.027) and glycine concentrations (-0.51, P = 0.007, FDR = 0.027) decreased (**Figure 2G and 2H**). Leaving out the participant from the exercise-only group, who had a noticeable increase in VLDL measures did not meaningfully alter results during sensitivity analysis (**Supplementary Table 2**).

## Discussion

In this study, we investigated the immediate effect of sauna bathing on the levels of circulating metabolites known to be associated with cardiometabolic health. Furthermore, we aimed to determine whether combining exercise training with sauna bathing exposure provides additional benefits for circulating metabolite levels in a longer-term intervention setting. We demonstrated that a single 30-minute sauna bathing session acutely lowers concentrations of circulating triglycerides, relative proportions of saturated and monounsaturated fatty acids, and concentrations of VLDL particles, and branched-chain and aromatic amino acids, while increasing ketone body concentrations. The combination of exercise training and regular sauna exposure produced additional improvements in circulating lipoprotein measures compared with exercise training alone, including reductions in LDL cholesterol concentrations and particle number and increases in HDL size.

To our knowledge, this is the first study to evaluate the acute effects of a 30-minute sauna exposure on emerging NMR-quantified biomarkers using a traditional hot and dry Finnish sauna. Compared with other forms of passive heat therapy such as Waon therapy or infrared

saunas, traditional Finnish sauna involves higher temperatures and lower humidity, thereby likely leading to distinct hemodynamic and metabolic responses.[2-4,28] Our findings also extend prior observational and interventional studies on sauna bathing and cardiometabolic health.[1,3] These previous studies have shown that acute sauna exposure reduces arterial stiffness, blood pressure, and oxidative stress markers.[13,15,17-19] The present study adds novel metabolomics evidence demonstrating that both acute and repeated sauna exposure may favorably influence lipid metabolism, with acute exposure also affecting amino acid metabolism. These findings are consistent with epidemiological studies linking regular sauna use to reduced risks of cardiovascular and all-cause mortality[6-8] and decreased risk of hypertension,[10] stroke,[11] and venous thromboembolism.[12]. The metabolomic changes observed with sauna exposure may also parallel some of the metabolic effects reported with physical activity.[29]

The observed acute sauna exposure induced reduction in branched-chain amino acids is noteworthy, as these metabolites have been shown to be associated with insulin resistance, type 2 diabetes, and cardiovascular risk.[30] The simultaneous increase in ketone bodies may reflect enhanced lipid oxidation, a process often promoted by exercise training, but also by reduced sitting and increased physical activity.[30,31] Specifically, AS was associated with an increase in circulating 3-hydroxybutyrate and acetone, while acetoacetate remained unchanged and acetate decreased. This pattern suggests enhanced hepatic ketogenesis with preferential reduction of acetoacetate to 3-hydroxybutyrate, consistent with elevated fatty acid oxidation.[32] The concomitant decrease in plasma acetate may reflect increased peripheral utilization of short chain carbon substrates during heat stress. In parallel, concentrations of most amino acids declined, indicating increased tissue uptake or utilization, whereas glycine concentrations increased. Given glycine's established role as a precursor for glutathione synthesis and thereby its involvement in cellular redox balance stress responses,[33-35] this selective increase may reflect a protective metabolic response to heat stress rather than

generalized protein catabolism. Together, these findings suggest that sauna exposure induces a transient, fasting-like metabolic state characterized by enhanced lipid-derived energy metabolism and relative protein sparing.

**Potential mechanisms and clinical implications**

Several physiological mechanisms may underlie the observed effects. First, heat exposure increases heart rate and cardiac output as well as general metabolism,[36,37] mimicking moderate-intensity exercise without muscle contractions, thereby stimulating energy expenditure which likely led to the observed changes in blood metabolites. Second, sauna bathing induces sweating and plasma volume changes, which may contribute to alterations in metabolite concentrations, but plasma volume change in the AS study was modest (4%) and taken into account in statistical modelling, thus, the findings persisted after correction for estimated plasma volume changes. Finally, repeated heat exposure may improve mitochondrial function and enhance fatty acid oxidation, consistent with the observed increase in ketone body concentrations by a single exposure. This suggests a heat-induced metabolic pattern that is compatible with enhanced lipid utilization.

The findings may have potential clinical relevance. The observed acute reductions in concentrations of triglycerides and VLDL particles, also more pronounced following the combined 8-week exercise-plus-sauna intervention compared with exercise alone, suggest that sauna bathing may serve as a complementary lifestyle approach for individuals at increased cardiometabolic risk. The additional effect of sauna and exercise on LDL and HDL metabolism further highlights the potential of combined interventions to maximize cardiovascular protection. The present data provide partial mechanistic explanations for the association between frequent sauna use and lower cardiovascular mortality found in epidemiological studies.[1,7,8]

**Strengths and limitations**

The strengths of our study include the use of a well-characterized population, standardized sauna exposure protocol, and comprehensive metabolomics profiling. The applied sauna exposures in both studies simulated a typical dry and hot Finnish sauna session that lasts for 30 minutes. No adverse events occurred during the entire duration of the AS and ESS studies, suggesting that 30 minutes of sauna bathing using parameters similar to those employed in this study is well tolerated by individuals with a comparable profile. Both acute and RCT study designs were employed, enabling us to investigate immediate and longer-term effects of sauna bathing. Sensitivity analyses were conducted to ensure robustness of findings. Compliance with the 8-week intervention was high, with only two participants missing a single session each, out of 24. Furthermore, the blood samples were collected in a standardized and fasted condition.

However, several limitations should be acknowledged. A key limitation of the AS study is the lack of sauna-naïve participants and the absence of a non-sauna control group.

Heat adapted individuals are known to have different physiological and thermoregulatory responses compared to non-heat adapted persons. Therefore, the acute findings may not be directly generalizable to sauna-naïve populations, although the ESS included non-regular sauna users. Additionally, essential thermoregulatory variables such as core temperature, skin temperature, sweat loss, sweat rate, and oxygen consumption were not measured, which limits the comparability to other similar studies. In the AS study, blood samples were collected in a non-fasting state. Thus, time-dependent, postprandial, hydration-related, or resting effects cannot be completely excluded. However, our primary aim with this design was to characterise acute responses to a single sauna exposure, which was achieved despite participants being habitual sauna users. The shorter-term, before–after design was therefore appropriate. Our study identified potential metabolic players rather than exact causal pathways. To investigate long-term adaptation, we used the ESS setting, which, however, did

not include a sauna-only intervention. As such, we are unable to ascertain the longer-term effects of regular sauna use alone. The analysis performed here can be considered as an exploratory analysis of the original RCT; the primary aim of which was to detect changes in blood pressure and cardiorespiratory fitness.[15] Dietary habits of the participants were not controlled and standardized during the 8-week intervention, which could have influenced the results. Finally, the intervention period of eight weeks could be considered as relatively short, and with a modest sample size, may have limited the ability to detect smaller effects in the context of the present analyses. In the RCT, the majority of participants were women, and there was no sauna-only group. Nevertheless, the data obtained via metabolomics analyses provide valuable new insights in the field of heat therapy. However, the nature of the additional metabolomic analyses in AS and ESS studies necessitates cautious interpretation. Thus, clinical outcome trials are needed to determine whether these metabolomic changes translate into reduced cardiovascular risk.

**Conclusions**

In conclusion, sauna bathing is associated with rapid and favorable changes in lipid and amino acid metabolism, characterized by reductions in concentrations of circulating triglycerides, VLDL particles and amino acids, alongside increases in concentrations of ketone bodies. Regular exercise and sauna bathing further improved lipoprotein profiles beyond those of exercise alone, particularly through reductions in concentrations of VLDL and LDL particles and increases in HDL particle size. These findings provide novel mechanistic insight into the cardiometabolic effects of heat therapy and support its role as a potentially effective adjunct to exercise as a lifestyle-based intervention.

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**Conflict of interests**

Given their role as an Editorial Board member, Dr Laukkanen had no involvement in the peer-review of this article and has no access to information regarding its peer-review. The remaining authors have no conflicts of interest.

**Author contributions**

All authors have planned the study aims and analysis strategies and have contributed to interpretation of the results. Jari A. Laukkanen and Earric Lee conceptualized the original studies. Jari E. Karppinen performed statistical analyses. Jari A. Laukkanen and Eija K. Laakkonen supervised the current sauna and metabolomics study. Jari A. Laukkanen, Ilkka H. A. Heinonen, Setor K. Kunutsor, Jari E. Karppinen, and Eija K. Laakkonen, drafted the manuscript. All authors reviewed, edited and contributed to the final manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All researchers designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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**Data availability statement**

All data supporting the results are presented in the manuscript. Data are available in the repository; it will be provided upon reasonable request.

**Figures/Tables**

**Figure 1. Acute effects of sauna exposure on circulating metabolites.** Forest plots showing standardized changes in circulating metabolites following sauna exposure. Points represent effect estimates derived from linear mixed-effects models, and horizontal lines indicate 95% confidence intervals. Filled symbols denote statistically significant changes ($P < 0.05$), whereas open symbols indicate non-significant changes ($P \geq 0.05$). Abbreviations: BCAA, branched-chain amino acids; BOHB, β-hydroxybutyrate; GlycA, glycoprotein acetyls; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; VLDL, very low-density lipoprotein.

**Figure 2. Effects of exercise and sauna interventions on circulating metabolites.** Changes in circulating metabolites from pre- (PRE) to post-intervention (POST) in Control, Exercise, and Exercise & Sauna groups following the 8-week intervention. Points represent individual participants, and boxplots show the median and interquartile range (whiskers, 1.5× IQR). Values are Box–Cox transformed and standardized (SD units). Brackets indicate within-group changes or between-group differences in change with significance derived from linear mixed-effects models adjusted for baseline metabolite levels. *P < 0.05, **P < 0.01. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; VLDL, very low-density lipoprotein.

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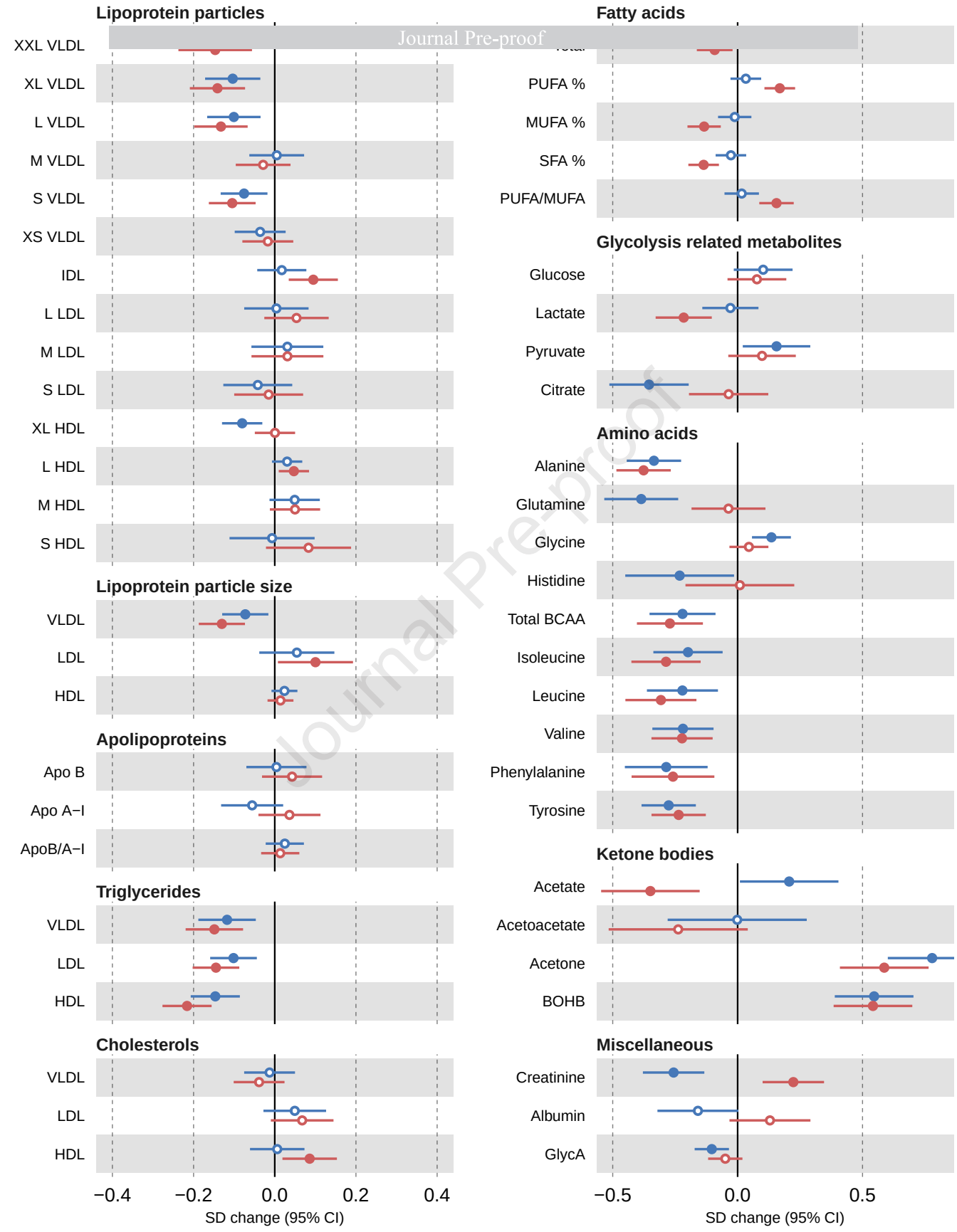
**Table.** Characteristics of participants in the Acute Sauna Study and Exercise and Sauna RCT

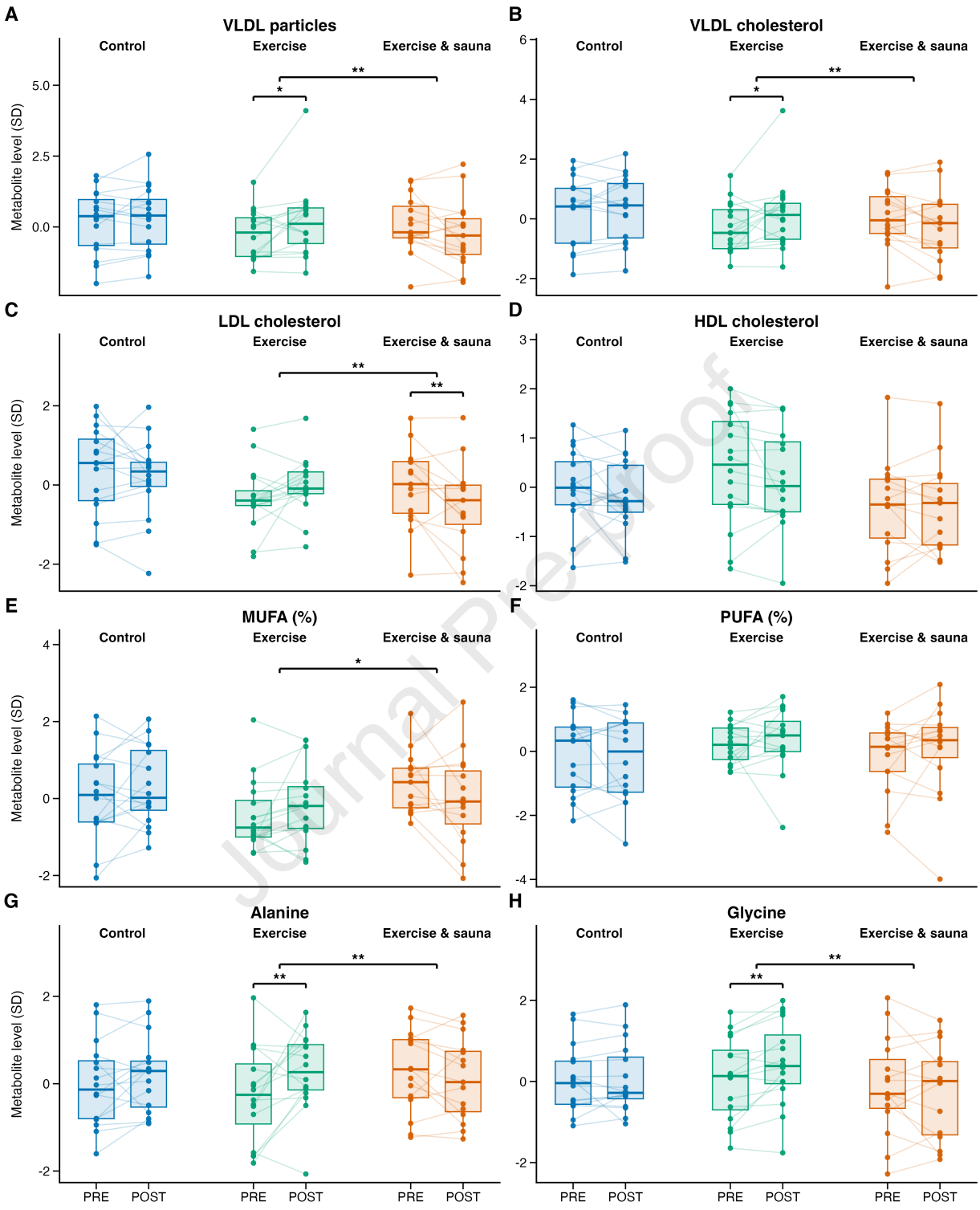
| | **Acute Sauna Study** | | **Exercise and Sauna RCT** | |
|---|---|---|---|---|
| | N (M/F) | Mean or frequency | N (M/F) | Mean or frequency |
| Age (years) | 34/29 | 48 ± 8 | 6/41 | 49 ± 9 |
| Body weight (kg) | 34/27 | 82.7 ± 16.2 | 6/41 | 89.0 ± 14.3 |
| Body mass index (kg/m$^2$) | 34/27 | 27.6 ± 5.0 | 6/41 | 31.3 ± 4.1 |
| Systolic blood pressure (mmHg) | 26/19 | 135 ± 15 | 6/41 | 133 ± 12 |
| Diastolic blood pressure (mmHg) | 26/19 | 83 ± 8 | 6/41 | 79 ± 10 |
| Smokers | 33/29 | 11 (18%) | 6/41 | 6 (13%) |
| **Self-reported health conditions** | | | | |
| Hypertension | 33/29 | 10 (16%) | 6/41 | 16 (35%) |
| Hypercholesteroleamia[#] | 33/28 | 28 (46%) | 6/41 | 10 (22%) |
| Obesity[¤] | 34/27 | 19 (31%) | 6/41 | 25 (54%) |
| Family history of coronary heart disease | 32/29 | 28 (46%) | 6/41 | 18 (38%) |
| ***Fasting clinical blood biomarkers*** | | | | |
| Total Cholesterol (mmol/L) | 33/28 | 5.3 ± 1.1 | 6/41 | 5.3 ± 0.9 |
| Low-density lipoprotein cholesterol (mmol/L) | 33/28 | 2.9 ± 0.8 | 6/41 | 3.4 ± 0.8 |
| High-density lipoprotein cholesterol (mmol/L) | 33/28 | 1.4 ± 0.5 | 6/41 | 1.5 ± 0.4 |
| Triglycerides (mmol/L) | 33/28 | 2.0 ± 2.1 | 6/41 | 1.4 ± 0.6 |
| Glucose (mmol/L) | 33/28 | 5.0 ± 0.9 | 6/41 | 5.7 ± 0.7 |
| ***Self-reported sauna habits*** | | | | |
| Number of sauna sessions per week | 34/29 | | 6/41 | |
| Never | | - | | 6 (13%) |
| Less than once per week | | - | | 22 (47%) |
| Once a week | | 9 (14%) | | 19 (40%) |
| Twice a week | | 10 (16%) | | - |
| Three times per week | | 26 (41%) | | - |
| At least four times per week | | 18 (29%) | | - |
| Mean duration of habitual sauna sessions, (minutes/session) | 33/29 | 30 [21-45]* | | Data not available |
| Average sauna temperature (°C) of habitual sauna sessions | 33/29 | 70 [69-80]* | | Data not available |

Values are reported as mean ± SD or median [interquartile range] for continuous variables and n (%) for categorical variables; [#]defined as total cholesterol > 5.17 mmol/L. [¤]defined as body mass index > 30 kg/m$^2$; M= male, F= female; RCT, randomised controlled trial, *range

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