STUDY PROTOCOL

# Title:

Nature-based therapy for Metabolic Syndrome - Salzburg

***Title in original language (German):***

*Naturbasierte Therapie von Metabolischem Syndrom - Salzburg*

# Short title:

NATURE-MET-S

# Study protocol

Version 4 | 27.05.2024

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## Content

# 1 Study information

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|---|---|
| **German title:** | **Naturbasierte Therapien von Metabolischen Syndrom – Salzburg** |
| **English title:** | Nature-based therapy for Metabolic Syndrome – Salzburg |
| **Acronym:** | NATURE-MET-S |
| **Study Registry** | Planned registration after positive vote in the ISRCTN registry (https://www.isrctn.com/) |
| **Protocol version:** | Version 4 from 27.05.2024 |
| **Funding:** | HORIZON EUROPE<br>HORIZON-CL6-2022-COMMUNITIES-02-two-stage<br>Project number: 101081420 RESONATE |

### Roles and Responsibilities:

| Name | Affiliation | Rolle |
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| a.o. Univ. Prof. Dr. Arnulf Hartl | Paracelsus Medical University, Institute of Ecomedicine | Principal Investigator, Study management, study design, data interpretation, report and publication |
| Univ. Prof. Dr. Elmar Aigner | University Clinic for Internal Medicine I, University Hospital Salzburg; Paracelsus Medical University | Study design, data interpretation, recruitment, publication |
| Christina Pichler, BA MSc. | Paracelsus Medical University, Institute of Ecomedicine | Operational study management, study design, recruitment, study execution, data analysis and interpretation, report and publication |
| Dr. med. Martin Offenbächer | Paracelsus Medical University, Institute of Ecomedicine, Medical Director Gastein Healing Gallery | Data analysis and interpretation, study execution (study physician), publication |
| Dr. med. Rainer Zembacher | Paracelsus Medical University, Institute of Ecomedicine & University Clinic for Pneumology/ Pulmonary Medicine, Salzburg University Hospital | Data analysis and interpretation, study execution (study physician), publication |
| Vanessa Frey, PhD | University Clinic for Neurology, Neurological Intensive Care Medicine and Neurorehabilitation,<br>University Hospital Salzburg, | Recruitment, data interpretation, publication |

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| | Operational management Paracelsus 10,000 study | |
| Mag.a Sabine Weyringer | Clinical psychologist and health psychologist, psychotherapist in training under supervision | Study design, study implementation |
| Yara Meilinger, BSc. cand. | Paracelsus Medical University, Institute of Ecomedicine | Study design, study implementation, data interpretation |
| Nathalie Gerner, MSc. | Paracelsus Medical University, Institute of Ecomedicine | Statistics, data interpretation |
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# 2 Introduction and rationale

## 2.1 Metabolic Syndrome

The term "metabolic syndrome" (MetS) first appeared in German-speaking countries in 1980 and is also known as the "deadly quartet". It describes a combination of elevated blood sugar levels, high blood pressure, a disturbed fat and cholesterol balance and obesity with abdominal fat distribution (Pott, 2007).

Metabolic syndrome (MetS) is an important driver of the current global cardiovascular crisis. It significantly increases the risk of type 2 diabetes, cardiovascular disease (CVD), and premature death. Genetic polymorphisms, inflammation, endocrinopathies, and unhealthy lifestyle contribute to the association between metabolic syndrome and a number of psychiatric disorders (Ho et al., 2014).

MetS is a combination of clinical signs and laboratory findings that includes five key features: obesity, elevated blood pressure, reduced levels of serum high-density cholesterol (HDL-c), increased levels of serum triglycerides, and high serum levels of fasting glucose. (Noubiap et al., 2022). Metabolic syndrome is generally diagnosed when a patient presents with at least three of its defining components (Grundy, 2008; NCEP, 2001).

Metabolic syndrome is a major public health problem that has been recognized to be a global epidemic by the World Health Organization (WHO) (Saklayen, 2018).

According to the Austrian Social Insurance, 30 to 40 percent of the population have a high health risk of civilization diseases such as MetS or COPD (Hartl, 2020). Around 25% of the Austrian population is affected by MetS, which is caused by sedentary lifestyles, stress, smoking, alcohol consumption, a diet high in fat and cholesterol, increased salt intake, and obesity (Codazzi et al., 2023; Hartl, 2020).

### 2.1.1 Definition of MetS for the inclusion in the study NATURE-MET-S

The NATURE-MET-S study will use the ATP III criteria (Adult Treatment Panel III of the National Cholesterol Education Program) to select study participants in collaboration with the University Clinic for Internal Medicine I and the Paracelsus 10,000 Study.

According to the NCEP ATP III definition, metabolic syndrome is present if three or more of the following five criteria are met: (NCEP, 2001):

- waist circumference > 102 cm (men) or > 88 cm (women)
- fasting triglyceride (TG) level over 150 mg/dl or Rx

- fasting high-density lipoprotein (HDL) cholesterol level less than 50 mg/dl (women) or 40 mg/dl (men) or Rx
- blood pressure over 130/85 mmHg or Rx
- fasting blood sugar ove110 mg/dl or Rx

see also (Huang, 2009).

### 2.1.2 Prevalence and Public Health

The prevalence of MetS in the global general population ranges from 12.5% to 31.4%, and in Europe, it ranges from 22.3% to 31.5%, depending on the definition used. Additionally, the prevalence of MetS increases with a country's level of income (Noubiap et al., 2022).

Prevalence in Europe (EUR, WHO region), general population:

- AHA/NHLBI: 27,9 %
- ATPIII: 25,3 %
- IDF: 31,5 %
- JIS: 26,8&
- WHO: 22,3 %
- Germany: 25,7 % according to AOKN-Population 2019 (Schütte et al., 2023))

The high prevalence of this civilization disease calls for contextualized public health interventions to tackle these conditions (Noubiap et al., 2022).

## 2.2 Nature-based therapies & nature-based biopsychosocial resilience

Academic and policy interest in the potential benefits of exposure to nature for human health and well-being has grown exponentially (World Health Organization (WHO), 2020; J. Zhang et al., 2020). Research indicates that exposure to nature in various forms has positive effects on a range of health and well-being outcomes (c.f. a.o. Frumkin et al., 2017; Hartig et al., 2014; Twohig-Bennett & Jones, 2018).

Beneficial outcomes include reduced mortality (Rojas-Rueda et al., 2019) and a lower risk of developing chronic illnesses such as cardiovascular diseases, diabetes and depression (van den Bosch & Meyer-Lindenberg, 2019). In addition, studies have shown that exposure to nature can improve short-term mood and concentration (Collado et al.,

2017). Notably, during the COVID-19 pandemic, individuals with access to nature coped better during periods of lockdown than those without (Pouso et al., 2021).

Contact with nature can act as “vaccine” (Hartig et al., 1991), “immunization” (Parsons et al., 1998) or "buffer" (Cartwright et al., 2018; Høj et al., 2021; Van Den Berg et al., 2010; Wells, 2021) against stress. It has been found to have a positive impact on stress levels and coping mechanisms in both acute and chronic situations (Korpilo et al., 2018; Roe et al., 2017; Takayama et al., 2019; Wells, 2021).

Nature contact can help individuals build and maintain resilience, which refers to the availability of adaptive resources through three types of resources (White et al., 2023): (1) biological resilience (e.g. improved immune functioning), (2) psychological resilience (e.g. better emotion regulation capacities), and (3) social resilience (e.g. improved social relations). These three types of adaptive resources are referred to as **biopsychosocial resilience** (Davydov et al., 2010; White et al., 2023).

From a public health perspective, it is important to develop low-threshold nature-based therapy interventions that are grounded in a strong theoretical foundation and a robust body of evidence. The NATURE—MET-S study aims to make a contribution towards this goal.

## 2.3 Nature-based Therapies und MetS

The Austrian Moderate Altitude Studies (AMAS) were the first nature-based interventions to address metabolic syndrome. AMAS I (2000) focused on the indicators of metabolic syndrome, which include overweight, disturbed blood sugar and blood fat metabolism, as well as elevated blood pressure. These factors pose significant cardiovascular risks. AMAS II (2006) focused on individuals with high stress levels. The studies have demonstrated that an active connection with nature, which involves a combination of hiking and active or passive regeneration, at moderate altitudes in the Alps (between 1,500 and 2,500 meters) under the guidance of professional coaches, has positive effects on individuals with metabolic syndrome, as well as on clients suffering from stress. These effects include a reduction in blood pressure and heart rate, an increase in the circulation of endothelial stem cells, and a reduction in body weight without the need for specific dietary measures. Additionally, there are positive psychological effects such as improved sleep quality, wellbeing, and social and physical recuperation (Gunga et al., 2003; Neumayr et al., 2014; Schobersberger et al., 2003, 2005, 2010).

Therefore, it can be inferred that nature-based interventions are a safe and effective method for reducing symptoms of metabolic syndrome and improving human health and well-being. However, it should be noted that the studies mentioned above were

conducted in a holiday setting. The proposed study, NATURE-MET-S, will concentrate on integrating nature-based therapies into daily life. This is a novel but promising approach to the secondary prevention of metabolic syndrome.

NATURE-MET-S aims to provide reliable evidence for indication-specific nature-based therapies. In the context of the HORIZON EUROPE project RESONATE[1],, it also aims to provide guidelines for the development and implementation of regionally based, resilience-promoting nature-based therapies in health care.

## 2.4 Nature-based therapies, MetS and Health-related Quality of Life (Primary Outcome 1)

Metabolic syndrome has physiological consequences, including an increased risk of cardiovascular and cerebrovascular disease, diabetes II, chronic kidney disease, and increased mortality risk (Arenillas et al., 2007). Additionally, MetS is associated with reduced health-related quality of life (HRQOL) in the majority of studies (Saboya et al., 2016). The association exists in both directions: This association exists in both directions. An improvement in MetS is correlated with an improvement in HRQOL, as shown in a recent prospective cohort study (Y.-H. Lin et al., 2021).

Health-related quality of life (HRQOL) is a multidimensional construct that encompasses physiological, psychological, and social dimensions. It includes more than just statements about an individual's state of health (Ellert & Kurth, 2013). The concept is comprehensive and multidimensional, reflecting an individual's perception of their own health and well-being. It is suitable for evaluating the impact of nature-based therapies in general (Prossegger et al., 2019) and specifically on Metabolic Syndrome (Strauss-Blasche et al., 2006).

MetS, a complex and multi-faceted disease, can cause psychological, psychological, and psychosocial problems (Y.-H. Lin et al., 2021). Therefore, we will assess the possible change in HRQOL using a generic QOL measure - the SF-12 - to evaluate the quality of life of the MetS study population in the context of nature-based therapy in a controlled and longitudinal manner (Weinhardt & Richter, 2013).

## 2.5 Nature-based therapies, MetS and Allostatic Load (Primary Outcome 2)

Allostatic load is a widely used metric of health risk that can effectively measure the potential health impacts of nature-based therapy on individuals with metabolic syndrome.

[1] Resonate (resonate-horizon.eu)

This is based on the hypothesis that repeated exposure to environmental demands, such as stress, leads to a gradual dysregulation of multiple physiological systems. Stress hormones, a shift in sympathovagal balance, or the production of inflammatory cytokines are prominent indicators of response to environmental challenges. These primary allostatic mediators are followed by secondary mediators, which reflect biological alterations that accumulate over time and increase the risk of clinical disease. The factors that define the metabolic syndrome include HbA1C, HDL/LDL, triglycerides, BMI, and waist-to-hip ratio (McEwen et al., 2016; Osei et al., 2022).

According to allostatic theory, biological adaptations are centrally mediated in response to environmental factors. The Allostatic Load Index (ALI) is a simple aggregate of primary and secondary mediators (McCrory et al., 2023). This index is a valid tool and metric for the assessment of health risks: both in cross-sectional studies as well as in intervention studies (Adams-Campbell et al., 2021; Rosemberg et al., 2020; Suvarna et al., 2020).

Although diet and physical activity are commonly considered the two main factors in preventing and treating obesity and MetS, it is important to note that epidemiological research suggests that these factors do not fully explain the variance (Holmes et al., 2010). Therefore, it is necessary to explore other potential factors that may contribute to the development of these conditions. The use of the ALI as a primary outcome parameter in the present study and in the RESONATE project provides insights into other factors influencing MetS secondary prevention via the triadic interaction of 1) physical activity/green exercise - 2) biopsychosocial resilience/stress and 3) metabolic syndrome.

# 3 Rationale and Research questions

## 3.1 Research rationale

This study examines the effects of a multimodal nature-based therapy program for individuals with metabolic syndrome on their **biopsychosocial resilience**. The program consists of easy hikes on the Salzburg city mountains (Green Exercise) and nature-based mindfulness training[2].

As outlined by White et al. (2023) the concept of **biopsychosocial resilience** encompasses biological, psychological, and social elements:

[2] A detailed description of the intervention is provided in chapter 4.3 Intervention

**Biological resilience** pertains to biological mechanisms that facilitate an individual's capacity to respond to stressors and recuperate. Illustrative examples include diminished inflammatory responses or enhanced blood lipid levels.

**Psychological resilience** is defined as the capacity to cope with stressors at the psychological level. This encompasses the effective regulation of emotions, a conscious perception of oneself and one's environment, and a high level of self-efficacy.

**Social resilience** is the quality of interpersonal relationships, social support, and access to resources in the environment. Social resources, such as a strong social network and group activities, can promote social resilience.

The intervention to be tested is designed to enhance the biopsychosocial resilience of individuals with metabolic syndrome through a **combination of nature-based physical activity and mindfulness training**.

**Exercise therapy** represents an efficacious approach for the prevention and alleviation of the consequences of metabolic syndrome (Myers et al., 2019). Physical activity exerts regulatory effects on fat and glucose metabolism, enhances insulin action, lowers blood pressure, and improves blood pressure control (Golbidi et al., 2012). Moreover, it has been demonstrated that exercise improves sleep quality, which serves as an important protective factor in relation to MetS (Chaudhry et al., 2023; Koren et al., 2016). Additionally, a correlation has been established between exercise and a more positive mood and a higher quality of life (Mahindru et al., 2023). In comparison to indoor exercise, outdoor exercise, also known as "green exercise," has been demonstrated to elicit additional psychophysiological effects, including improved mood and higher emotional well-being (Niedermeier et al., 2017; Pasanen et al., 2014). These benefits may be particularly relevant for individuals with metabolic syndrome.

**Mindfulness training** has been demonstrated to be an effective intervention for improving a range of biopsychosocial conditions, including depression, anxiety, stress, insomnia, addiction, pain, and prosocial behavior (D. Zhang et al., 2021). With regard to metabolic syndrome, studies have indicated that mindfulness training can positively influence both causal parameters for the development of metabolic syndrome, such as chronic stress, and clinical key parameters of MetS.

Clinical studies have demonstrated, among other findings, an enhanced capacity to cope with stress, including a reduction in depressive symptoms (Momeni et al., 2016; Rosenkranz et al., 2013; van der Zwan et al., 2015), a reduction in blood pressure (Hughes et al., 2013; Momeni et al., 2016), a reduction in inflammatory responses

(Rosenkranz et al., 2013) and a general improvement in the metabolic profile through a reduction in triglycerides, total cholesterol and glucose levels (Xue et al., 2018). A study by Creswell and colleagues (2012) also provides evidence that mindfulness training can reduce feelings of loneliness. This is of particular relevance in the context of metabolic syndrome, as loneliness is both a risk factor for the development of metabolic syndrome (Henriksen et al., 2019) and a concomitant factor of the disease (Whisman, 2010). Moreover, a longitudinal study demonstrated that mindfulness training has a positive socioeconomic impact, for instance, in the form of a reduced utilization of disability pensions (Fjorback, 2012).

In light of the aforementioned background, it can be hypothesized that the implementation of a nature-based therapy program, comprising green exercise and mindfulness training, may enhance the biopsychosocial resilience of individuals diagnosed with metabolic syndrome, when compared to a control group.

## 3.2 Research questions

A two-arm randomized controlled clinical trial (NATURE-MET-S) is to be conducted based on the initial situation described above.

**The primary objective** of the clinical study is to analyze the impact of a multimodal nature-based therapy combining green exercise and mindfulness training on biopsychological resilience in a sedentary population with metabolic syndrome and low nature contact prior to the study.

Primary outcomes to measure biopsychosocial resilience are:

1) Quality of Life and 2) Allostatic Load,

**The secondary objective** is to provide data on environmental, social, and economical aspects of the intervention to contribute to innovation actions and to establish nature-based therapies as secondary prevention measure in health care.

In addition to the NATURE-MET-S study, similar studies on nature-based secondary prevention of MetS are being conducted simultaneously in Padua (Nature-Met-P) and Barcelona (NATURE-MET-B) to compare different types of nature exposure. The three studies are jointly developed and implemented. Although these are not multicenter studies, they are three comparable nature-based intervention studies for people with MetS (Barcelona, Salzburg) or at risk of MetS (Padua). This allows for a comparison of the effects of different types of natural environments: 1) coastal blue in Barcelona, 2) urban green in Padua, and 3) rural mountainous in Salzburg

The following research questions are to be investigated in the NATURE-MET-S study:

1) **What is the effect of a nature-based intervention on biopsychosocial resilience in patients with Metabolic Syndrome compared to a control group (T1 day 1, T2 day 35, T3 day 70)?**
    a. Does health-related quality of life improve? *Primary Outcome*
    b. Does the Allostatic Load Index improve? *Primary Outcome*
    c. Are there changes in vital and lung function parameters and in the complete blood count? *Secondary Outcome*
    d. Are there any changes in psychological and health economic parameters? *Secondary Outcome*

2) **How sustainable are possible effects of the nature-based intervention compared to the control group? (T1 day 1 -T4 day 180)?**
    a. Are there sustainable changes in psychological and health economic parameters up to day 180 (online questionnaire)? *Secondary Outcome*

3) **How is the nature-based intervention evaluated by the study participants? (T1 day 1 -T4 day 180)?**
    a. <u>individual sessions</u> – *Primary Outcome*
        i. What possible positive and negative emotions are induced by exposure to nature?
        ii. How was the natural exposure carried out (alone/group, public transport)?
        iii. iii) Where did the natural exposure take place?
    b. <u>the whole nature-based intervention</u> – *Secondary Outcome*
        i. Quantitative and qualitative via interviews

The parameters listed under point 3.a are collected using MyCap mobile app[3].

[3] https://projectmycap.org/

## 3.3 Study design

| | |
|---|---|
| **Study type:** | Two-armed randomized controlled clinical study |
| **Study arms:** | 2 |
| **Study centers:** | Paracelsus Medical University,<br>Institute of Ecomedicine<br>Department of Internal Medicine I<br>with Gastroenterology - Hepatology, Nephrology, Metabolism and Diabetology<br>University Hospital Salzburg |
| **Sponsor:** | Investigator sponsored and initiated trial / Funding: Horizon Europe RESONATE, Project Nr. 101081420 |
| **Control group:** | Yes (Waiting-List Control Design) |
| **Randomization:** | Yes |
| **Allocation ratio:** | 1:1 |
| **Observation period:** | *180 days* |
| **Analysis:** | Intention-to-treat |

# 4 Methods: Study participants, Intervention and Outcome Parameters

## 4.1 Study setting

The study aims to recruit 140 individuals aged 40-65 years with metabolic syndrome from the outpatient clinics of Internal Medicine I (University Hospital Salzburg) and eligible patients from the Paracelsus 10,000 Study (Frey et al., 2021) over a 6-month period. The participants will be randomly assigned to either the intervention or control group. The intervention arm will be conducted in two consecutive rounds in September 2024 and March 2025. The control group participants will undergo examination simultaneously with the intervention group. They will subsequently have the chance to participate in the nature-based therapy program, which follows a waiting-list-control design. The nature-based intervention comprises green exercise/hiking and nature-based mindfulness training on the Salzburg city mountains (Lymeus et al., 2020; Pichler et al., 2022). The nature-based intervention should have accessible starting and ending points via public transportation.

## 4.2 Inclusion and exclusion criteria

### 4.2.1 Inclusion criteria

Participation is open to individuals who fulfill all of the following inclusion criteria:

1) Individuals aged between 40 and 65 of any gender who meet the internationally recognized criteria for metabolic syndrome according to the NCEP ATP III criteria (NCEP, 2001):
2) Metabolic syndrome is defined by the NCEP ATP III as present if three or more of the following five criteria are met:(NCEP, 2001):
    1. waist circumference > 102 cm (men) or > 88 cm (women)
    2. fasting triglyceride (TG) level over 150 mg/dl or Rx
    3. fasting high-density lipoprotein (HDL) cholesterol level less than 50 mg/dl (women) or 40 mg/dl (men) or Rx
    4. blood pressure over 130/85 mmHg or Rx
    5. fasting blood sugar ove110 mg/dl or Rx

3) Sedentary lifestyle: Category 1 (low physical activity) of the International Physical Activity Questionnaire – Short Form (IPAQ-SF)) (International Physical Activity Questionnaire, 2005)

4) Low nature users:
    1) Category 1, 2 und 3 of the Monitor of Engagement with the Natural Environment Survey (MENE) – question “nature use” (Natural England, 2020)
5) Smartphone users

### 4.2.2 Exclusion criteria:

1) Acute contraindications:
    a. Malignant hypertension
2) Contraindications or differential diagnosis
    a. Severe respiratory or lung disease (COPD according to GOLD Standard 3 and 4, severe asthma, emphysema)
    b. Arteriosclerotic event (e.g. myocardial infarction) < 6 months ago
    c. Uncontrolled metabolic diseases (e.g. uncontrolled diabetes mellitus)
    d. insulin-dependent diabetes mellitus
    e. Diagnosis or treatment of a malignant disease < 3 years in the past
    f. Orthopedic illnesses that do not allow participation in hikes
3) Factors that prevent or hinder participation in the intervention program
    a. Alcohol abuse
    b. Pregnancy
    c. insufficient knowledge of German language (written and spoken)
4) Factors that prevent self-management
    a. Presence or indication of clinical depression (< 13 points WHO-5)
    b. Serious other untreated psychiatric illnesses (e.g. schizophrenia)
5) Certain medication intake
    a. Taking preparations for weight reduction
6) Participation in another interventional study
    a. within the period of the clinical trial (t1-t4) and less than 4 weeks before the start of the trial (t1)
7) Participation in therapeutic weight loss programs
    a. within the period of the clinical study (t1-t4) and less than 8 weeks before the start of the study (t1), e.g. Optifast®52 Program

## 4.3 Intervention

Nature-based therapy (NBT) consists of the components green exercise/hiking and nature-based mindfulness training.

The hikes are designed to accommodate individuals with varying levels of fitness. Each hike lasts between 1.5 and 2 hours. Participants will traverse distances between 3 and 6 kilometers and ascend to elevations of up to 300 meters on the Salzburg city mountains. A heart rate monitor (wristwatch) will be provided to each participant, which will be calibrated to their specific gender, age, height, and weight. This monitor will be used throughout the intervention. It is recommended that participants complete the hikes within the range of 60-70% of their maximum heart rate (Steele et al., 2021). Additionally, it is advised that training be conducted at a medium level of exertion on the Borg scale (12-16) (Borg, 1982; Löllgen, 2004). A guided group is limited to a maximum of 15 participants and is accompanied by a hiking guide and a mindfulness trainer.

Mindfulness training is based on concentrative movement therapy (Stolze & Badura-MacLean, 2002), a body psychotherapy method that combines physical movements and concentration to promote awareness and mindfulness of one's own body. The objectives of this form of mindfulness training are threefold: firstly, to enhance body awareness through targeted movement exercises; secondly, to reduce stress and promote general well-being; and thirdly, to cultivate mindfulness by training individuals to focus their attention on the present moment.

**Intervention group (Nature group) :**

*Week 1 (day 0 – day 7): Onboarding*

a. 3 x 1,5-2h Green Exercise (guided hikes on the Salzburg city mountains, 3-6 km each, 100-300 hm, max. 15 people per group)
b. Within these hikes, participants will receive 20 minutes of nature-based mindfulness training under the guidance of a therapist in a pre-selected restorative and safe location. It is important to note that participants will learn mindfulness training during the process so that they can continue to practice it independently.
c. It is required that all participants engage in the guided hikes during the initial week of the program.

*Week 2 – Week 5 (day 8 – day 35): Integration*

a. 3 x 1,5-2h Green Exercise per week (guided or self-guided hikes (participants can choose) on the Salzburg city mountains, 3-6 km each, 100-300 hm)
b. During these hikes, participants will engage in 20 minutes of mindfulness training in a natural and safe environment.
c. In weeks 2-5, participants may elect to embark on the hikes independently or to participate in the guided hikes.

*Week 6 – Week 10 (day 36 – day 70): Self-guided*

a. 3 x 1,5-2h self-guided Green Exercise peer week (Hikes close to home according to prepared tour recommendations 3-6 km, 100-300hm)
b. During these hikes, participants will engage in 20 minutes of mindfulness training in a natural and safe environment.
c. In weeks 6-10, no further guided hikes will be offered; participants will be encouraged to conduct the sessions independently. During this period, participants will receive notifications to conduct the therapy sessions via the MyCap app. They will also be requested to complete the app-based questionnaire three times a week during the therapy sessions.

In weeks 11-26, participants will no longer receive reminders to complete therapy sessions. Similarly, they will no longer receive active requests to complete the app-based questionnaire.

The tour recommendations are located throughout Salzburg city to prevent repetition and promote self-determination.

The tour offers recommendations for hikes of varying difficulty levels. Following the initial guided hike, participants are classified according to their fitness level. This is achieved by measuring their heart rate during the hike using a heart rate monitor and by assessing their perceived exertion using the Borg scale (Löllgen, 2004).

The therapy sessions are documented at the location of the mindfulness training sessions using the smartphone app *MyCap*. MyCap is a free, mobile, REDCap-based application for study participants that can be installed on iOS and Android devices to collect the results reported by participants for a specific study previously created in REDCap. The integration of MyCap into REDCap provides a comprehensive and secure data collection system, which is particularly well-suited to longitudinal studies that require frequent requests for information from participants (Harris et al., 2022). The questionnaire

asks about the current mood (SPANE, PRS), the perceived exertion, whether the therapy session is being conducted in a group or individually, and whether the patient used public transportation to get to the session (see also 4.4 Outcome parameters).

The aim of the intervention is to integrate nature-based physical activity and mindfulness training into everyday life.

**Control group:**

The control group participants will undergo examination simultaneously with the intervention group.

For ethical reasons, the control group participants will also be offered the intervention after the study (outside the clinical trial).

The intervention will be standardized to enable comparison of results with other study sites, namely Barcelona (NATURE-MET-B) and Padua (NATURE-MET-P).

## 4.4 Outcome parameters

### 4.4.1 Primary endpoints

The primary endpoint of the present clinical study is the effect of the intervention on biopsychosocial resilience (White et al., 2023), quantified in relation to MetS by recording following parameters. (see also Figure 1 for definition of time points) :

**I. Primary endpoints t1-t3**

1) Health-related quality of life (SF-12) (Weinhardt & Richter, 2013)

Health-related quality of life is measured by the German version of the Short Form Health Survey SF-12. The SF-12 measures health-related quality of life in two summary scales (physical health (PH) and mental health (MH)) (Weinhardt & Richter, 2013). This means that the SF-12 can map the two summary scales of the SF-36. However, the SF-12 consists of only 12 items and can therefore be completed in less time (Y. Lin et al., 2020; Ware & Gandek, 1998; Wee et al., 2008). The total scale ranges from 0 to 100 points, with higher scores reflecting better quality of life (Ware & Gandek, 1998).

The threshold for a clinically significant change in QoL should always be considered in relation to the change in other parameters (e.g. ALI) (Ware et al., 1995). In general, a change of 2.5-5.0 points on a summary scale is considered clinically relevant (Fan et al., 2004).

In the present study, a change in the SF-12 total score of 2.5 points or more is therefore defined as a clinically relevant change.

2) Allostatic Load
    a. Allostatic Load Index 1 (derived from: (Adams-Campbell et al., 2021; McCrory et al., 2023):
        - Dehydroepiandrosterone sulfate (DHEA-S)
        - Heart rate variability (HRV)
        - Systolic and diastolic blood pressure
        - Resting heart rate
        - Peak Expiratory Flow (PEF)
        - HDL Cholesterol
        - LDL Cholesterol
        - Triglycerides
        - HbA1C
        - Waist-hip ratio
        - C-reactive protein (CRP)
        - Interleukin-6
        - TNF-alpha

    b. Allostatic Load Index 2 (experimental, non-invasive):
        - Dehydroepiandrosterone sulfate (DHEA-S) from saliva
        - Heart rate variability (HRV)
        - Systolic and diastolic blood pressure
        - Resting heart rate
        - Peak Expiratory Flow (PEF)
        - Waist-hip ratio
        - C-reactive protein (CRP) from saliva

A clinically relevant change in the Allostatic Load Index (ALI) is defined as a reduction in the ALI value that reflects a significant improvement in physiological markers associated with chronic stress and metabolic dysfunction. To be considered clinically relevant, a change should indicate a significant improvement in the above biomarkers, leading to improved overall health and reduced risk of metabolic and cardiovascular disease. In clinical trials, a reduction in ALI of approximately 0.5 to 1.0 standard deviations is often used as a threshold for clinical relevance. This range indicates a significant reduction in physiological stress, which can have a significant impact on overall health and the risk profile for complications associated with metabolic syndrome (Osei et al., 2022). In the present study, a reduction in ALI of 0.5 standard deviations or more is therefore defined as a clinically relevant change.

**II. Primary endpoints – Perception of the intervention and short-term effects (t1-t4)**

The evaluation of individual nature-based interventions is conducted using the MyCap mobile app (Harris et al., 2022). Participants are asked to complete the following questionnaires for each session:

1) Nature connection at the nature exposition site
2) Individual or group setting
3) Provide details on the mode of transportation used to reach the intervention site, such as public transport, car, or bicycle.
4) Perceived Exertion during physical activity via Borg Scale (Löllgen, 2004)
5) Surrounding photo (no identifiable persons!)
6) Affective states:
    a. German version of the Scale of Positive and Negative Experience (SPANE) (Diener et al., 2009)
    b. German short version of the Perceived Restorativeness Scale (PRS), (Pasini et al., 2014)
7) Ecologic aspects
    a. Landscape
    b. Environmental attitudes
    c. Crowding
8) Overall satisfaction with NbT session

### 4.4.2 Secondary endpoints

The analysis of the following parameters is defined as secondary endpoints

**III. Secondary endpoints t1-t3**

1) <u>Vital parameter and lung function parameters</u>
    a. height, weight, oxygen saturation
    b. forced expiratory spirometry (PEF, FEV1, FVC, MEF)
2) <u>Laboratory parameters</u>
    a. full blood analysis (blood sampling from the vein)[4]

**IV. Secondary endpoints t1-t4**

1) <u>Resilience</u> (questionnaires)
    a. State-Trait-Assessment of Resilience Scale (STARS), (Lock et al., 2020), German version

[4] A total of 25 ml of blood is taken.

   b. Perceived Stress Scale, German version (Cohen et al., 1983; Schneider et al., 2020)
   c. Brief Sense of coherence scale (SOC-3) (Schumann et al., 2003)

2) Mindfulness (questionnaires)
   a. Five Facet Mindfulness Questionnaire (FFMQ-15) (Baer et al., 2012), German version

3) Physical activity (Questionnaire)
   a. International Physical Activity Questionnaire – Short Form (IPAQ-SF), German version (IPAQ, 2019)

4) Nature contact (questionnaires)
   a. Nature connectedness (Inclusion of Nature in Self Scale (INS), German version, (C. Martin & Czellar, 2016; adapted from P. W. Schultz, 2002) and Nature Connectedness Index (NCI)
   b. Direct nature contact (People and Nature Survey 2023, M1-Q1, (Marshall, 2023)
   c. Indirect nature contact (Gu et al., 2023; adapted from L. Martin et al., 2020)

5) Subjective well-being and quality of life (questionnaires)
   a. Intercultural Quality of Life Comic (Pichler, 2020)
   b. OECD-4 (OECD, 2013)

6) Social aspects (questionnaires)
   a. Loneliness: German short version of the De Jong Gierveld Loneliness Scale (Gierveld & Tilburg, 2006)
   b. Community cohesion: German short version of the Community Cohesion Scale, (Weinstein et al., 2015)

7) Motivation (questionnaires)
   a. Ideal self, based on (Ganesan, 2020)
   b. Self-determined motivation (Astell-Burt et al., 2024)

**V. Integrative evaluation parameters (t1-t4)**

1) Environmental aspects (t1-t4):
   a. (Perception of local nature, PANS-6, People & Nature Survey 2023 (Marshall, 2023))
   b. Environmental concerns adapted from (W. Schultz, 2001)
   c. Pro-Environmental Behavior, Revised Pro-Environmental Behavior Scale (R-PEBS), adapted in consultation with the author (Brick et al., 2017)

2) Health economic aspects (t1-t4)
   a. Quality Adjusted Life Years (QUALY): calculation from SF-12

b. Use of Care Services (cost savings)
c. Willingness to pay via Contingent Valuation Method (CVM)

3) Process evaluation (t1-t4)

The following parameters are collected from the study participants for process evaluation:

a. Satisfaction with the intervention
b. Willingness to repeat
c. Willingness to recommend

In addition, qualitative interviews are conducted with study participants and members of the study team for process evaluation after the intervention. The questions used for the interviews are included in the appendix.

## 4.5 Study timeline

Participation in the clinical study involves four measurement time points over a period of 180 days:

- **T1 (day 1):** Baseline data assessment directly before the intervention for intervention and control group; data assessment at the premises of the Paracelsus Medical University Salzburg
- **T2 (day 35):** data assessment after the onboarding (week 1) and integration phase (week 2-5) for all study participants of the intervention and control group at the premises of the Paracelsus Medical University Salzburg
- **T3 (day 70):** data assessment for all study participants of the intervention and control group after the first follow-up phase (week 6-10) at the premises of the Paracelsus Medical University Salzburg
- **T4 (Tag 180):** data assessment for all study participants of the intervention and control group after the first follow-up phase (week 6-10) via online questionnaire

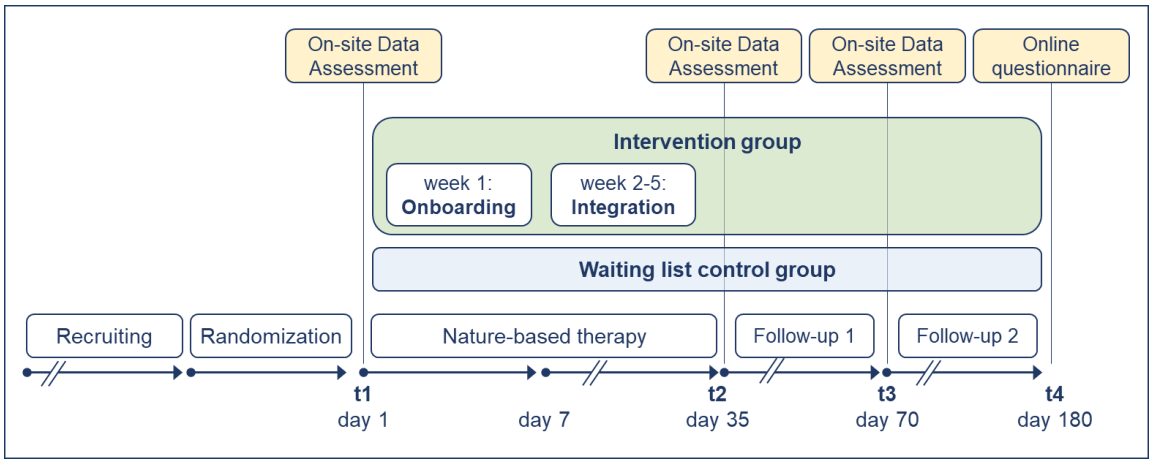


Figure 1: Study timeline

The present clinical study is planned in two rounds:

- **Round 1**: from September 2024: intervention group, waiting list control group
- **Round 2:** ab March 2025: intervention group, waiting list control group

The implementation in two rounds results from the capacities of the study team (hiking guides, therapists).

For ethical reasons, the control group is designed according to the principle of a waiting list control group (Elliott & Brown, 2002). This implies that the individuals in the control group will also have the chance to benefit from the nature-based therapy. The offer will be made to the control group after all measurements have been completed (after t4) in spring and fall 2025.

The allocation of groups is random.

## 4.6 Sample size

The calculation of the sample size is based on published study results from the Institute of Ecomedicine. The study investigated the effect of nature-based therapy on individuals with sedentary lifestyles. (Huber et al., 2023; Pichler et al., 2022, ISRCTN43292449 https://doi.org/10.1186/ISRCTN43292449):

- Study type: two-armed randomized controlled clinical trial
- Intervention: nature-based therapy (mindfulness-based forest therapy vs. hiking; Forest vs. Hiking)
- Outcome parameter for sample size calculation: health-related quality of life (SF-12)
- Study population: 50-60 years, sedentary lifestyle, moderate overweight (BMI ≥25–≤30)

The sample size was calculated with a bootstrap simulation (using the software R-GNU, Genal Public License, R Foundation for Computing), applying the F1-LD-F1 model from the nparLD package (Nonparametric Longitudinal Data Analysis) (Noguchi et al., 2012). The initial seed for the variate generator was set at 1 and the re-sampling process was fixed to 1000 repetitions for each sample size. The percentage of significant results was used as an estimator of power.

Regarding clinical studies on lifestyle interventions in overweight individuals, recent literature reports dropout rates ranging from 30% to 50% (Collins et al., 2022; Ruelas et al., 2023).

A drop-out and lost-to-follow-up rate (until T4 = day 180) of 40 % was assumed for the present study, resulting in a sample **size of n=70 per study arm**.

Table 1: Sample size calculation based on Huber et al., 2023

| **Sample size** | **Type** | **FALSE** | **TRUE** | **Power** | **Comparison** |
|---|---|---|---|---|---|
| 10 | nparLD | 698 | 302 | 0,302 | FoHi |
| 20 | nparLD | 485 | 515 | 0,515 | FoHi |
| 30 | nparLD | 316 | 684 | 0,684 | FoHi |
| 40 | nparLD | 183 | 817 | 0,817 | FoHi |
| **50** | **nparLD** | **127** | **873** | **0,873** | **FoHi** |
| 60 | nparLD | 58 | 942 | 0,942 | FoHi |
| 70 | nparLD | 38 | 962 | 0,962 | FoHi |
| 80 | nparLD | 18 | 982 | 0,982 | FoHi |
| 90 | nparLD | 11 | 989 | 0,989 | FoHi |
| 100 | nparLD | 3 | 997 | 0,997 | FoHi |

FoHi = Forest vs. Hiking

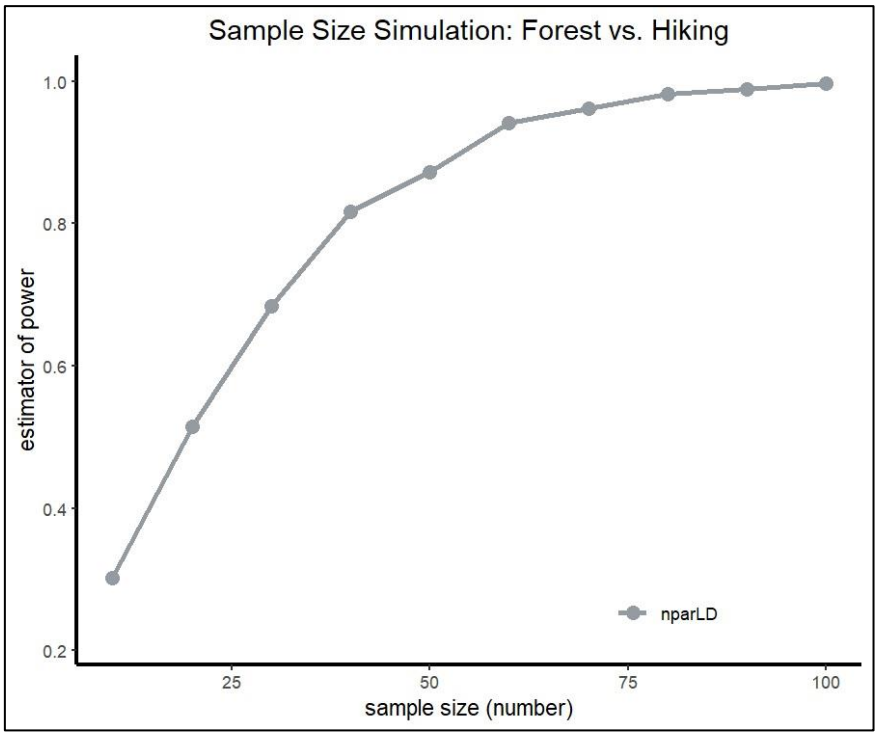


Figure 2: Sample size calculation based on Huber et al., 2023

## 4.7 Recruitment

The clinical study will recruit a total of 140 participants, with 70 in each study arm. The University Clinic for Internal Medicine I of the Salzburg University Hospital (study center 2) will conduct clinical inclusion, while the Institute for Ecomedicine of the Paracelsus Medical University Salzburg (study center 1) will carry out the intervention.

Study participants can register for the study through the Paracelsus Medical University website (primary source, www.pmu.ac.at/ecomedicine).

A total of 140 study participants are recruited through the following channels:

1) Paracelsus 10,000 data base

   People with metabolic syndrome aged between 40 and 65 years will be identified from the database of the Paracelsus 10,000 Study(Frey et al., 2021). A sample of n=500 people, stratified by age and sex, will then be selected from these data and informed by post about the possibility of participating in the study.

2) University clinic for internal medicine I of the Salzburg University Hospital

   In addition, recruitment will take place via the outpatient clinics (metabolic, diabetes, obesity) of the University Clinic for Internal Medicine I of the University

Hospital Salzburg (head physician: Univ. Prof. Dr. Elmar Aigner; active approach of eligible persons, website, distribution of information material).

3) Resident general practitioners and internists

   Information material about the study will be sent to local internists and general practitioners (GPs) in the city of Salzburg and surrounding communities to make eligible patients aware of the opportunity to participate in the study.

The design and content of the digital and analog advertising material are identical.

The communication of the clinical study and the recruitment of study participants will be carried out in compliance with the guidelines for advertising study participation of the Ethics Commission of the Federal State of Salzburg.

An online questionnaire will be used for enrolment and an initial assessment of the inclusion and exclusion criteria. The data collected during registration will be stored on a secure server at the Paracelsus Medical University of Salzburg and will only be used to contact participants and assess their eligibility. The data will be deleted after recruitment is completed.

## 4.8 Informed consent

Participants will be informed in writing (informed consent) and verbally about the study, the required examinations and potential risks before the study begins. To be included in the study, the participant must sign an informed consent form. The inclusion and exclusion criteria and the informed consent will be sent to participants in advance and will be reviewed at the inclusion visit (t1). As part of the informed consent process, participants are also informed that refusing to participate in the trial or withdrawing from the trial at any time will not have any adverse consequences, particularly with regard to their medical care. Participants will also be informed that they may request further information at any time.

Study participants will be informed of the purpose and scope of the collection and use of personal data and, in particular, of the confidentiality obligations of all persons who have access to data that can be used to identify trial subjects as part of the clinical trial. Study participants will also be informed of the data protection measures in accordance with the EU General Data Protection Regulation.

## 4.9 Exclusivity of study participation

The required exclusive participation in the present study during the intervention and observation period will be ensured by verbal and written information at the initial

examination (t1). An appropriate section with a tick box will be added to the informed consent form.

The exclusivity of study participation refers to the exclusion of participation

- in other interventional clinical studies in the period from 4 weeks before the initial examination (t1, day 1) to the time of the last follow-up examination (t4, day 180), and
- participated in therapeutic weight loss programs within the period of the clinical trial (t1-t4) and less than 8 weeks before the entry examination (t1, day 1).

# 5 Methods: Allocation to the intervention groups

## 5.1 Randomization

Randomization is carried out using an open source add-in for Microsoft Excel (Kraus, 2014). Age and gender are to be used as stratification factors. The Kullback-Leibler divergence method is to be used as the allocation method (Endo et al., 2006). Randomization and stratification are performed by a biometrician who is not involved in the recruitment of study participants. The necessary stratification factors are blinded to the staff performing the group allocation.

## 5.2 Blinding

Due to the nature of the planned study (nature-based therapy vs. non-intervention), it is not possible to blind the study participants and investigators to group allocation. However, the group allocation will be blinded to the biometrician conducting the study in order to ensure independent data analysis.

# 6 Methods: Data collection, management and analysis

## 6.1 Data collection

Data collection takes place at four time points: Day 1 (t1), day 35 (t2), day 70 (t3) and day 180 (see also chapter 4.5 Study timeline).

The data collection process at time points t1, t2 and t3 is almost identical. The data collection on day 180 is carried out as an online questionnaire survey. It should be noted that some data is collected only once, e.g: socio-demographics (t1), satisfaction with the intervention (t2).

As part of the initial examination (t1), all study participants will undergo a clinical assessment with the study physician on duty, who will decide whether or not the participant is eligible to participate in the study.

Data will be collected by qualified staff of the Institute of Ecomedicine at the Paracelsus Medical University and the University Clinic for Internal Medicine I at the University Hospital of Salzburg according to the following data collection plan:

- T-1 (as soon as there is a positive vote from the Ethics Committee): recruitment, randomization
- T1 resp. day 1: baseline examination
- T2 resp. day 35: examination after guided intervention
- T3 resp. day 70: follow-up examination 1
- T4 resp. day 180: follow-up examination 2

Digital data entry will be performed in a secure REDCap[5] database system, which will be set up for the NATURE-MET-S study to securely store and process pseudonymized data. REDCap is a secure web application for building and managing online surveys and databases.

In addition, the participants will evaluate the individual therapy sessions using the Mycap mobile app[6]. The following data will be collected:

- Intervention location
- Date, time
- Connectedness to nature
- Individual or group setting
- Details of travel to the intervention location
- Self-assessed physical activity
- Photo of the surroudings (no persons!)
- Affective States (I-PANAS-SF, Perceived Restorativeness Scale (PRS))

**MyCap** is a freely available participant-facing mobile application that can be installed on iOS and Android devices to capture patient-reported outcomes for any REDCap project.

[5] REDCap (project-redcap.org)

[6] https://projectmycap.org/

MyCap's integration with REDCap provides a comprehensive data collection ecosystem and is best suited for longitudinal studies with frequent requests for information from participants (Harris et al., 2022).

All data completed on a participant's device are automatically and immediately synchronized to REDCap. If data are completed while participants are offline, data are synchronized when internet connect is restored and the App is opened.

These are the additional security features of MyCap:

1. Participant data is stored locally on the device in an AES-256+SHA2 encrypted database. Data remains on the device if an internet connection is not available. Applies to both iOS and Android devices.
2. When an internet connection is available, data is transmitted directly to REDCap using an SSL (TLS v1.2) connection. A hash-based message authentication code (HMAC) is used to verify the integrity of the data and to authenticate the sender.
3. Participant entered data (i.e., task responses) are not stored or sent anywhere else. Data exists on the participant's device or on the server.
4. Data is wiped from the device after the Mycap App verifies that data has been successfully transmitted. Note that there is an optional MyCap feature that lets a participant see some of the data s/he has entered for an individual task/instrument/survey. By default, data is wiped.
5. Participants create a 6-digit PIN that is used to open the App. A participant can disable the PIN feature.

## 6.2 Data management

The REDCap database is used for digital data collection. Each study participant will be assigned a six-digit identification number (ID) for anonymization purposes. Personal data will only be stored in ID-encrypted form. The password-protected master list, which contains the assignment of IDs to personal data, ensures that personal data can be deleted when the study is completed. The master list is stored on a secure data server at the Paracelsus Medical University of Salzburg and is only accessible to the researcher responsible for recruitment, eligibility checks and allocation. Data from medical examinations and surveys are stored in spreadsheet files. Only authorized researchers have access to the data. Participants can access their personal data after completion of the study.

Written consent will be obtained from all study participants for the use of their personal data. The consent forms will include a specific clause on the protection of personal data, informing study participants of how their data will be handled and stored, the purpose of the research, the contact details of the data protection officer and their rights.

All personal data will be handled as defined in General Data Protection Regulation (EU 2016/679), and Finnish Data Protection Act 1050/2018.

Each person involved in the conduct of the study (hiking guides, assistants, etc.) will sign a confidentiality agreement before the start of the study, which will be countersigned by the principal investigator of the study. Confidentiality refers to all circumstances that become known through participation in the study, in particular information about study participants, employees and other cooperation partners regarding economic, operational, technical, tax and personal circumstances as well as internal matters of any kind.

The data will be used for scientific purposes and for possible publication in scientific journals and conferences. In addition, the results of the study will be used for the further development and implementation of effective, sustainable and cost-effective nature-based therapies (including health equity, nature conservation and health economics aspects).

Saliva samples from the Padua (NATURE-MET-P) and Barcelona (NATURE-MET-B) studies will be sent to the Paracelsus Medical University for analysis. The probes will only be labelled with an identification number (ID), so the analysis will be completely anonymous and experimenter-blinded.

The blood and saliva samples will be stored in a video-monitored and locked room (Paracelsus Medical University Salzburg, House C, Strubergasse 22) in a freezer at -80°C until analysis. After analysis, the samples will be stored until publication(s). Storage of the samples until publication(s) is necessary in order to fulfil any requests from the journal and to allow for any minor or major revisions.

The NATURE-MET-S study is part of the HORIZON EUROPE project RESONATE[7]. A total of nine studies, including 5 randomized controlled trials, are being carried out within this project. The RESONATE project is structured in such a way that the case studies will not only collect data relevant to their own research question, but also data needed for the tasks of different work packages (WPs) within the project (e.g. health equity

[7] RESONATE: Building individual and community resilience through nature-based therapies, Project Nr. 101081420; Resonate (resonate-horizon.eu)

aspects, nature conservation aspects, process evaluation). As a visual aid, please see Figure 3.

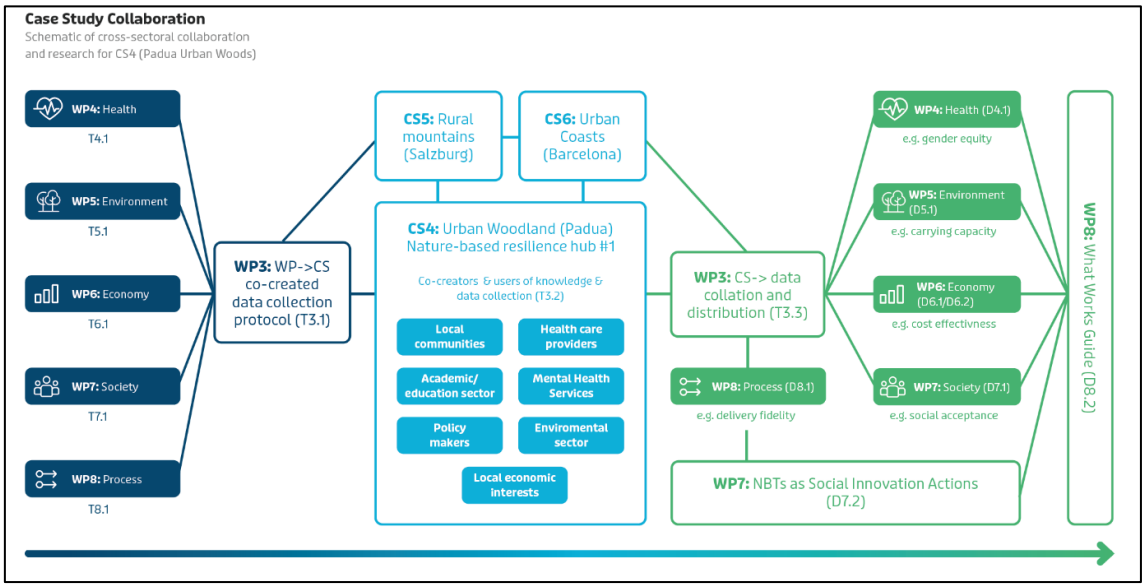


Figure 3: Case study collaboration

The collected data will be transferred via the scientific database system RedCap to a secure server at the University of Vienna (lead partner of the RESONATE project). From there, the data will be distributed to the respective work package leaders via the REDCap database system according to the RESONATE data management plan[8].

Data protection officer at the University of Vienna (RESONATE Lead Partner):

Contact: dsba@univie.ac.at

Requests for information in accordance with Article 15 of the EU General Data Protection Regulation (GDPR): beauskunftung.dsba@univie.ac.at

Data protection hotline: +43 1 4277 110 00

[8] see draft of attached RESONATE data management plan

## 6.3 Statistics

All statistical analyses will be performed using the R-GNU software environment (General Public License, R Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM). Statistical significance will be set at the level of $a < 0.05$ for all tests. Randomly missing values will be replaced using the standard procedure, last outcome carried forward (LOCF). The statistical analysis will be carried out by a biometrician. The data will be blinded again in order to exclude a possible bias with regard to an expected result.

Statistical analyses will be performed in accordance with the intention-to-treat principles and reporting will adhere to the CONSORT-statement, including CONSORT flow chart (Calvert et al., 2013; CONSORT, 2019).

After a positive vote, the study will be preregistered in the ISRCTN registry (https://www.isrctn.com/).

Check for normal distribution

The Shapiro-Wilk test will be applied to check for normal-distribution. Depending on data distribution, parametric or non-parametric tests will be applied.

Analysis of Baseline values

To analyze possible baseline differences between the two groups, a t-test for unconnected samples is performed for normally distributed variables and a Mann-Whitney U-test for non-normally distributed parameters. Nominally scaled variables are analyzed using the chi-square test. If any baseline variables are significantly different between the groups, secondary analysis will be conducted including these variables to adjust for any residual confounding not prevented by the randomization.

Longitudinal Data analysis

Depending on data distribution, parametric or non-parametric tests will be applied. Participant data will be compared in terms of baseline data, including outcome variables as well as demographics (unpaired Student-T-Test or Wilcoxon-test).

For longitudinal data analysis, analyses of variance (ANOVA) or linear mixed models (LMM) are used for normally distributed data.

For non-normally distributed samples, a non-parametric analysis of variance (e.g. f1.LD.f1) is performed using the nparLD package (Noguchi et al., 2012).

Models will include random effects for temporal and spatial correlations and fixed effects for: (1) intervention group; (2) time effects characterizing changes between pre- and post-intervention; and (3) interaction between the intervention group and the pre- and

post-intervention temporal effects, representing the group contrast. This determines whether or not the intervention has an effect. If any baseline variables are significantly different between the groups, secondary analysis will be conducted including these variables to adjust for any residual confounding not prevented by the randomization.

Multiple testing:

We will adjust for multiple testing, e.g., Benjamini-Hochberg or Holm-Bonferroni.

# 7 Methods: Data monitoring

The responsibility for the complete and correct data collection and documentation as well as the safe storage of the data in the context of the clinical study lies with the staff of the Paracelsus Medical University and the University Clinic for Internal Medicine I of the University Hospital Salzburg.

Data will only be shared with the RESONATE Lead Partner in an ID-encrypted form and in accordance with the RESONATE Data Management Plan (see chapter 6.2 Data management).

Data collection and storage is implemented in such a way as to minimize the possibility of inaccurate, erroneous and/or incomplete data entry. Entries and corrections can only be made by authorized persons. All entries and corrections are dated, documented and traceable or recoverable.

Internal audits shall be conducted at least three times: (1) prior to the start of the clinical trial, (2) during the conduct of the clinical trial and (3) after the completion of the clinical trial. The following activities are planned as part of the internal audits:

- Verification that the trial site meets the requirements of the clinical trial, e.g. requirements for the trial population, equipment, storage of trial materials.
- Comparison of source data
- Verification of proper and safe storage of samples

## 7.1 Drop-out

Participants may withdraw from the study at any time without giving a reason. Upon request, all samples collected up to that point will be destroyed and all stored data will be deleted.

## 7.2 Adverse events

Any unexpected or adverse events will be documented and promptly reported to the Ethics Committee.

# 8 Ethics and dissemination

Clinical trial results will be published in peer-reviewed journals and presented at scientific conferences. All publications and dissemination activities will respect the protection of personal data.

Publication rights are held by the parties involved in the study:

| | |
|---|---|
| **Lead partner:** | Institute of Ecomedicine<br>Paracelsus Medical University, Salzburg<br>a.o. Univ. Prof. Dr. Arnulf Josef Hartl and Team |
| **Cooperation partner:** | University Clinic for Internal Medicine I, with Gastroenterology-Hepatology, Nephrology, Metabolism and Diabetology<br>Salzburg University Hospital<br>Prim. Univ. Prof. Dr. Elmar Aigner and Team |
| **RESONATE project partner** | in accordance with the RESONATE Data Management Plan and the RESONATE Authorship Guidelines<br>RESONATE Lead Partner:<br>Department of Cognition, Emotion, and Methods in Psychology<br>University of Vienna<br>Mathew White, BSc MSc PhD and Team |

Following FAIR Guiding Principles for scientific data management and stewardship, RESONATE will ensure that data generated and re-used throughout the project will be findable, accessible, interoperable, and reusable. As the primary repository, we will share and archive data on the Open Science Framework (https://osf.io/), which is a free and accessible platform.

To promote findability and implement our results within the wider nature-based solutions community, we will also share information and links to our results and datasets on OPPLA (https://oppla.eu/), the EU repository for Nature-Based Solutions, to share and archive data. OPPLA is an open platform which can be accessed by people for different purposes, including non-scientific audiences. This will ensure that the results and benefits of the RESONATE project will also reach health care professionals, therapists, and municipalities. The master list, which combines ID and name, is deleted before the study data is published.

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# 10 Tables



# 11 Figures