Study protocol: Cardiometabolic health, mental Health, and lifestyle factors in the Meuse-Rhine Region and the impact of a physical activity intervention: the Interreg Meuse-Rhine Blue Zone project.

Background

Cardiovascular diseases (CVD) are the leading cause of death worldwide, with significant geographic variations not only between countries but also between neighbouring regions[1]. To address such disparities, European policies promote interregional cooperation to foster greater social and health equity. According to the World Health Organization (WHO), over 75% of CVD-related deaths could be prevented through adequate lifestyle modifications[2]. Understanding interregional differences in health and lifestyle is therefore essential for developing effective prevention strategies.

The European Interregion Meuse-Rhine (IMR) region presents a unique case for studying these differences. Although the IMR regions—Netherlands-Limburg, Belgian-Limburg, Liège, and Aachen—are geographically close and share a common history, they exhibit substantial disparities in life expectancy, both among each other and compared to national averages[3]. While sociodemographic factors such as gender, age, education, unemployment rates, and income have been suggested as possible explanations[3], these structural factors are difficult to modify through interventions. In contrast, lifestyle-based approaches offer a more feasible and effective means of improving health outcomes. Despite strong evidence supporting the role of lifestyle in preventing CVD[2], there is limited interregional data on cardiometabolic health and lifestyle behaviours in the IMR[3]. The present study seeks to fill this gap by providing objective health measures and assessing key lifestyle behaviours contributing to health disparities in the region.

The first objective of this study is to compare cardiometabolic and mental health across the four IMR regions. Existing evidence primarily relies on static self-reported questionnaires[3], which are prone to recall and social desirability biases[4, 5]. To address this, we will include objective health measures such as blood biomarkers to estimate 10-year CVD risk and fat distribution[6-8]. Additionally, mental health—often overlooked in health-related research—will be assessed both statically using validated questionnaires and dynamically via ecological momentary assessments.

The second objective is to compare six key lifestyle pillars, as defined by the American College of Lifestyle Medicine: physical activity, diet, stress management, sleep quality, social connection, and substance use[9]. Physical activity will be objectively and continuously monitored using a wearable device, while the other five lifestyle factors will be assessed through validated questionnaires at pre- and postintervention.

Finally, we will evaluate the effects of a physical activity intervention on cardiometabolic health, mental health, and the six lifestyle pillars. A recent OECD & WHO report highlights physical activity as one of the most impactful factors for improving both physical and mental health[10]. Since affordability is a critical factor in promoting sustainable physical activity[11], the intervention will be focussed on increasing daily step counts using a wearable device. Research by Vetrovsky *et al.*[12] suggests that self-monitoring is a key driver of physical activity interventions, and goal-setting can further enhance its effectiveness. To test this, we will implement an automated goal-setting system, designed to be a scalable and long-term intervention strategy.

By addressing these objectives, this study aims to generate valuable insights to inform policymakers and support region-specific interventions for improving health and lifestyle across the IMR.

Methods

Study design

This multicentric interventional study will be conducted at four sites: Hasselt University, Liège University, Maastricht University, and Aachen University. The study includes a pre- and post-intervention visit, with a three-month intervention period followed by a three-month follow-up (Figure 1. Study design).

Participants will be recruited via a subscription link, where they will provide demographic information after giving informed consent (*see 'screening questionnaire'*). Based on the inclusion criteria (*see below*), 1000 participants will be included in total (250 participants per site).

Eligible participants will be invited for the first study visit, during which they will receive a wearable device. They will then follow a three-month intervention, after which they will return for a second study visit. This will be followed by a three-month follow-up period, during which there will be no direct contact with the research team. At the end of this period, participants will receive questionnaires via email.

To ensure participants have not had an infection before their scheduled testing day, an automated email will be sent via Castor EDC two weeks in advance. This email will remind them of their study visit and ask whether they have experienced a viral or bacterial infection in the past week. If so, they will be instructed to contact the research team to reschedule their appointment.

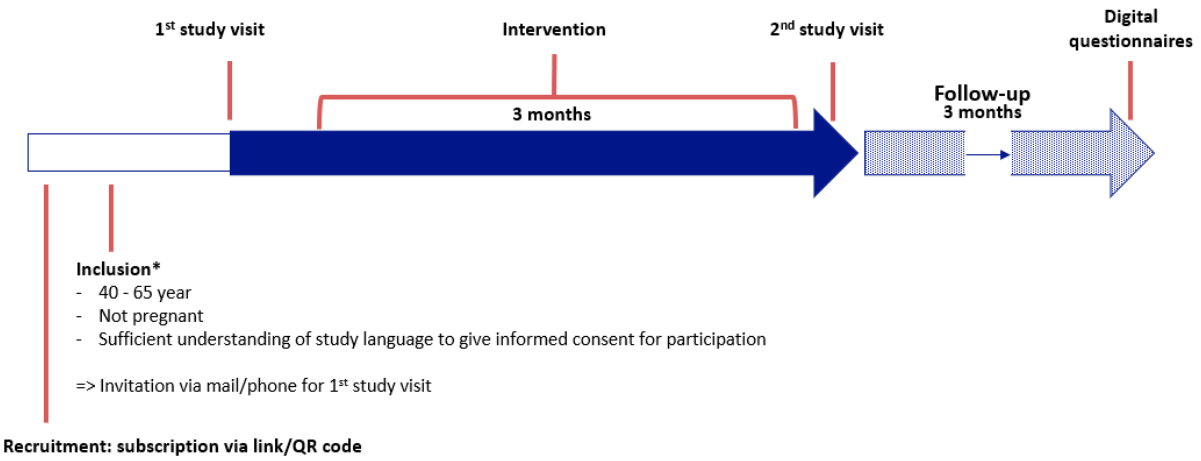

Figure 1. Study design (*Quota: 25% of participants per region with high education [>post-secondary non-tertiary education according to the International Standard Classification of Education; level 4]).

Ethical approval documents for the two sites in Belgium will be submitted simultaneously. Documents for Maastricht University and Aachen University will be submitted afterward, and the ethical approvals will be sent to the Belgian ethical committees.

Participants

A quota for educational level will be implemented, limiting highly educated participants to a maximum of 25% per region to reflect the educational distribution of the IMR population[3]. This ensures a more representative sample, as highly educated individuals are often overrepresented in research.

To minimise seasonal effects on physical activity, participant inclusion will be divided into four groups and spread throughout the year. At each site, approximately 65 participants will start in September 2025, another group in December ‘25/January ‘26, a third group in March/April ‘26, and a final group in June/July ‘26.

Participants will be recruited through online and paper advertisements, including a subscription link to the screening questionnaire. Selected participants will receive detailed study information via phone or email, based on their indicated preference. Data from unselected participants will be deleted after recruitment is completed. Those who agree to participate will be invited for a first study visit, where they will provide written informed consent. Selected participants may withdraw at any time for any reason. In such cases, previously collected research data will be retained, but contact details will be deleted, and their name will be removed from the subject identification list.

Participants will be included if they meet the following eligibility criteria:

- Aged between 40 and 65 years
- Resident of Belgian Limburg, Liège, Netherlands Limburg or Aachen, with the intention to remain there for at least one year
- Able to wear a wrist-worn wearable for at least 10 hours per day during waking hours

- Own a smartphone and have a valid email address
- Adequate proficiency in Dutch or English, defined as the ability to read, understand, and ask questions
- Not pregnant and no plans to become pregnant within the next year

Study visits

During the first study visit, all study procedures and outcome measures will be explained, and participants will provide written informed consent. Next, they will complete questionnaires on their sociodemographic factors (see questionnaire 'sociodemographics'), mental health and lifestyle factors using an iPad or computer. These questionnaires will be accessed via a secured link sent by the EDC Castor system to a fictitious email address created in advance for each participant. A member of the research team will prepare the questionnaires for each participant and verify their correct submission afterward.

Following this, blood pressure and anthropometric measurements will be taken, and a venous blood sample will be drawn by a certified nurse or doctor. Participants will then receive their wearable along with assistance for installation and connection to their smartphone.

Additionally, a subsample of participants (n = 75 per site) will be asked to install M-Path on their smartphone for ecological momentary assessment of mental health. Technical support will be provided as needed.

The same measurements will be repeated during the post-intervention study visit. For sociodemographic factors, participants will be asked if any changes have occurred and, if so, to specify them. In addition, participants will have to answer four questions on intervention adherence and possible barriers they experienced (see questionnaire 'sociodemographics').

Intervention (3 months)

The intervention will be based on the physical literacy model for older adults as described by Jones *et al*.(2018) to promote long-term physical activity participation[13]. This model takes an ecological approach, with a primary focus on the intrapersonal level by enhancing physical competence, motivation, confidence, and knowledge. Additionally, it incorporates interpersonal, organisational, and community factors to create a supportive environment for sustained physical activity.

Participants will receive a wearable (model to be determined based on the public procurement procedure) to track their physical activity levels. Step goals will be provided before the intervention begins and again in weeks 4, 7, and 10 via email. These personalised goals will be based on each participant's actual step count from the previous week (see Table 1. Goal-Setting Algorithm).

The initial goal will encourage participants to increase their baseline step count by 500 steps per day. If they meet this target, their next goal (week 4) will be to increase by 1,000 steps per day from baseline. If they do not meet the first goal, they will again be encouraged to increase by 500 steps per day. Participants who significantly exceed their goal (>500 steps/day above their goal) will be encouraged to maintain their activity level, with reassessment at each goal-setting point. Participants who meet all targets will achieve a total increase of 2,000 steps per day. This is based on the findings of Stens *et al*., which indicate that every additional 1,000 steps per day reduces the risk of incident cardiovascular disease (CVD), regardless of baseline activity levels[14]. Furthermore, an umbrella review by Mair et al. shows that comparable digital interventions typically lead to an average increase of 1,000 to 2,000 steps per day[15].

Table 1. *Goal setting algorithm*

Mail with goal & webinar	Week	Measurement
	Baseline	X (pre-intervention)
Goal 1: Monday	Week 1	
	Week 2	
	Week 3	X

Goal 2: Wednesday	Week 4	
	Week 5	
	Week 6	X
Goal 3: Wednesday	Week 7	
	Week 8	
	Week 9	X
Goal 4: Wednesday	Week 10	
	Week 11	
	Week 12	X (post-intervention)

The mailing system is designed based on the findings of Mair et al., who identified key behaviour change techniques in digital health interventions[15]. These include 'graded goal setting' (progressively increasing goals), 'prompts and cues' (multiple reminder emails), 'feedback on behaviour' (motivating participants based on their previous activity), and personalised content (adapting goals based on prior achievements), all of which are shown to be effective in promoting behavioural change.

In addition, educational videos will be made available via a YouTube channel to enhance knowledge and engage participants at organisational and community levels by highlighting local initiatives at each site, such as organised walks and existing walking routes. Each email will include a link to a new video.

The webinars will focus on increasing daily step count, as this is central to the intervention goals. The following themes will be covered:

- Promotion of walking and its benefits.
- Incorporating non-exercise physical activities into daily life, such as gardening, household chores, parking further from a building entrance, and opting for cycling or walking instead of using a car or public transport.
- Engaging in structured physical activities that can be performed at home, such as walking, running, cycling, and seated gymnastics.
- Practical strategies for increasing step count, incorporating behaviour change techniques such as 'action planning' and 'implementation intentions'.

Follow-up (3 months)

During the follow-up period, participants will no longer receive new step goals via email. However, they are required to continue wearing the wearable and synchronising it weekly. The educational videos will remain accessible on the YouTube channel.

Outcome measures

1. Health

1.1. Cardiometabolic health

1.1.1. 10-year cardiovascular disease (CVD) risk

A venous blood sample will be collected in two tubes: one 9ml lithium-heparin (Li-hep) tube and 6ml ethylenediaminetetraacetic acid (EDTA) tube. These samples will be used to assess the following parameters:

- Cholesterol (total cholesterol [CHOL]; high-density lipoprotein cholesterol [HDL-CHOL], low-density lipoprotein cholesterol [LDL-CHOL]),
- Inflammation (high-sensitivity C-reactive protein ([hs-CRP])

- Kidney function (creatinine to estimate the glomerular filtration rate)
- Glucose metabolism (glycated haemoglobin [HbA1c])

CHOL, HDL-CHOL, LDL-CHOL, hs-CRP and creatinine will be analysed from the Li-hep tube, which will be centrifuged immediately after collection (room temperature, 1,290 × g, 15 minutes, brake setting 9). HbA1c will be analysed from whole blood collected in the EDTA tube. Plasma from the Li-hep tube and whole blood from the EDTA tube will be aliquoted immediately and stored at -80°C until analysis.

Before participants begin completing the questionnaires on an iPad, an electronic sphygmomanometer (Omron®, Omron Healthcare, IL, USA) will be placed on the dominant arm. While they complete the questionnaire in a seated position, the cuff remains in place. After they finish, systolic and diastolic blood pressure as well as resting heart rate will be measured four times and documented as the mean value of the final 3 measurements. Mean arterial pressure (MAP) is calculated as MAP = systolic BP + (2 x diastolic BP) / 3.

The 10-year risk of cardiovascular disease (CVD), including non-fatal stroke, non-fatal myocardial infarction, or death due to CVD, will be calculated using different risk models based on participants' health status. SCORE2 will be used for apparently healthy individuals (without a history of CVD or diabetes mellitus)[6], SMART2 for those with a history of CVD (including coronary artery disease, cerebrovascular disease, peripheral arterial disease, abdominal aneurysms, and polyvascular disease)[16], and SCORE2-Diabetes for individuals with type 2 diabetes[7].

All risk calculations incorporate the blood lipid profile, systolic blood pressure, sex, age, and smoking behaviour, while also accounting for regional risk variations. Additionally, the SMART2 model includes kidney function, diabetes status, body mass index, medication use, and duration of previous CVD. The SCORE2-Diabetes model also includes HbA1c and diabetes duration.

1.1.2. Anthropometrics and body fat distribution

To measure anthropometrics and body fat distribution, participants will be in light clothing. Body height will be measured to the nearest 0.1 cm using a wall-mounted Harpenden stadiometer. Body weight will be measured to the nearest 0.1 kg using a digital, calibrated weighing scale. Body mass index (BMI) will be calculated as weight (kg) divided by height squared (m^2).

Waist and hip circumferences will be measured to the nearest 0.1 cm using a flexible metric measuring tape. Waist circumference will be taken at the midpoint between the lower rib margin and the top of the iliac crest. Hip circumference will be measured at the widest part of the hips at the level of the greater trochanter. The waist-to-hip ratio will be calculated by dividing waist circumference (cm) by hip circumference (cm).

1.2. Mental health

To assess mental health, participants will complete the Hospital Anxiety and Depression Scale (HADS), a widely used tool designed to measure symptoms of anxiety and depression[17]. The questionnaire consists of 14 items, with 7 items assessing anxiety (HADS-A) and 7 items assessing depression (HADS-D). Participants rate each item based on their experiences over the past week on a 4-point scale (ranging from 0 to 3). The total scores for each subscale (anxiety and depression) reflect the severity of symptoms, with higher scores indicating greater severity. The HADS has been translated and validated into all study languages (original language: English; translated into Dutch, French and German).

Ecological Momentary Assessment (EMA) will be used in a subsample of participants to assess daily affect fluctuations[18]. EMA consists of multiple short assessments throughout the day, enabling the monitoring of both the frequency and dynamics of momentary affect in real-life settings over several days[19]. A total of 300 participants (75 per site) will take part in EMA for one week at baseline (week 0, before the start of the intervention) and again in week 13 (one week after completing the intervention). Participants will be randomly selected from the first three starting groups at each site using a random number generator in Excel. However, since EMA may

be burdensome and time-consuming for participants and requires an internet data bundle, they will first be asked if they are willing to participate. If a selected participant declines, the next scheduled participant will be invited.

An M-Path standard premium research account will be used to develop the EMA protocol (https://m-path.io/landing/). Participants will install the M-Path app on their smartphones, which will send auditory notifications eight times per day at random moments within a selected 15-hour time window (see Table 2: Sampling Scheme). Participants will have 15 minutes to respond to the questionnaire; otherwise, the notification will expire or be overridden by the next notification. Questionnaires that are not completed will be considered missing data. Therefore, participants are instructed to complete as many questionnaires as possible each day, as soon as possible after receiving the beep, but to skip questionnaires when completion is impossible (e.g., when driving). The interval between two consecutive notifications will vary randomly, but there will always be at least 15 minutes between them. The questionnaires will be identical for each beep, but the order of questions will be randomised.

Additionally, participants will complete a morning and evening questionnaire at the first and last beeps of the day, respectively. The morning questionnaire will assess sleep quality from the previous night, and the evening questionnaire will include quality of life questions and bowel movement information. The time interval for completing the morning and evening questionnaires will be extended to 2 hours to account for daily differences in participants' wake-up and bedtimes.

Table 2. Sampling scheme

Beep	Time 1	Time 2	Time 3	Time 4	Questionnaires	Number of items
1	6:00-7:30	7:00-8:30	8:00-9:30	9:00-10:30	Morning questionnaire Block A, B, C, D*	31/32
2-7	7:30- 19:30	8:30- 20:30	9:30- 21:30	10:30- 22:30	Block A, B, C, D*	25/26
	Beeps fire randomly within blocks of 100 minutes					
8	19:30- 21:00	20:30- 22:00	21:30- 23:00	22:30-0:00	Evening Questionnaire Block A, B, C, D*	30/31

*In randomised order. Block A: mood and emotional stress reactivity (11 items), Block B: contextual items (5 items when alone, 6 items when with people), Block C: physical symptoms (8 items), Block D: accuracy check (1 item).

Affect fluctuations consist of two components:

1. Variability – The extent to which affect levels fluctuate, quantified by within-person variance (WPV).
2. Temporal dependency – How affect changes over time, measured using autocorrelation.

To study affect fluctuations, both components of fluctuations should be taken into account. This can be accomplished by investigating 'instability': changes from one moment to the next, thereby capturing both variability and temporal dependency. Instability will be quantified using the root mean square of successive differences (RMSSD) in affect time-series data[20, 21]. Specific formulas for these calculations are provided in the Appendix.

1.3. Health-related quality of life

The EQ-5D questionnaire will be used to assess health-related quality of life in participants[22]. It is a widely used, standardised tool that measures five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3-level scale, ranging from "no problems" to "extreme problems." The questionnaire also includes a visual analogue scale (VAS) where participants rate their overall health on a scale from 0 (worst imaginable health) to 100 (best imaginable health). The EQ-5D questionnaire has been translated and validated into all study languages (original language: English; translated into Dutch, French and German).

2. Lifestyle

A composite score will be calculated to assess participants' overall lifestyle based on six lifestyle pillars, as defined by the American College of Lifestyle Medicine: physical activity, diet, stress management, social connection, sleep, and substance use[9]. Each pillar will be evaluated using validated questionnaires (see below). For each pillar, points will be assigned according to predefined categories, with 0 points assigned to the lowest or worst category, and progressively higher points assigned to better categories. Each pillar will consist of three categories, ensuring a balanced contribution from each pillar to the final score. The scores from all pillars will be summed to create a composite 'lifestyle' score, with higher scores indicating a better lifestyle.

2.1. Physical activity behaviours

Physical activity levels will be continuously monitored throughout the study using an objective wearable device. The device will track steps per day, time spent in sedentary behaviour, light-intensity physical activity, moderate-intensity physical activity, vigorous-intensity physical activity, and sleep duration. In addition, exercise session data (i.e., type of exercise, duration, and heart rate-based intensity) will also be recorded.

Data from weeks 0, 3, 6, 9, 12, 16, 20, and 24 will be included in the analysis. To ensure data validity, only days with a minimum of 10 hours of wear time will be considered. Participants' data will be included in the analysis only if they have at least four valid measurement days, including at least one weekend day.

Before the start of the study, fictitious email accounts will be created by the research team. These accounts will be used for the wearable's app and pre-linked to the DHARMA platform of Hasselt University (Digital Health Research Platform for mHealth Research). When participants synchronise their wearable with the app, their data will be automatically transferred to the DHARMA platform.

Subjective physical activity levels will be assessed using the International Physical Activity Questionnaire Short Form (IPAQ-SF), a tool developed and validated for cross-national monitoring of physical activity and inactivity[23]. The points assigned to calculate the lifestyle composite score are based on the recommendations of the World Health Organization for moderate-to-vigorous intensity physical activity[24]:

- 0 points: Low physical activity (inactive or insufficiently active; i.e., not meeting the guidelines of 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity per week, or an equivalent combination of both).
- 1 point: Moderate physical activity (active; i.e., engaging in 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity physical activity per week, or an equivalent combination of both).
- 2 points: High physical activity (very active, exceeding the recommended MVPA levels; i.e., engaging in more than 300 minutes of moderate-intensity or more than 150 minutes of vigorous-intensity physical activity per week, or an equivalent combination of both).

Motivation to be active will be assessed using the Behavioural Regulation in Exercise Questionnaire-2 (BREQ-2), a validated tool based on Self-Determination Theory. The questionnaire comprises 19 items measuring five types of motivational regulation: amotivation, external, introjected, identified, and intrinsic regulation. Higher scores in identified regulation and intrinsic motivation are seen as more desirable, reflecting greater self-determined motivation, while higher scores in amotivation or external regulation suggest lower levels of motivation for exercise[25].

Both the IPAQ-SF and the BREQ-2 have been translated and validated into all study languages (original language: English; translated into Dutch, French and German).

2.2. Diet

To assess diet quality, the Mediterranean Diet Adherence Screener (MEDAS) will be used. This is a validated questionnaire to assess adherence to the Mediterranean diet, which has been linked to improved health outcomes, including cardiovascular and mental health[26, 27]. The MEDAS questionnaire consists of 14

questions that evaluate the frequency of consumption of key foods associated with the Mediterranean diet, such as fruits, vegetables, whole grains, legumes, fish, olive oil, and red meat. Each item is scored on a binary scale (yes/no), with higher scores indicating greater adherence to the diet. The total score ranges from 0 to 14, with higher scores reflecting better adherence to the Mediterranean diet. The points to calculate the composite lifestyle score are assigned as follows:

- 0 points: Lowest adherence to the Mediterranean diet (≤ 7 points)
- 1 point: Higher adherence (8-9 points)
- Highest adherence (≥ 10 points)

The MEDAS (originally in English) has been translated and validated in Dutch but not yet in French. Therefore, the original English version will be translated into French and back-translated by a native speaker to ensure its accuracy.

2.3. Stress management

Stress levels will be assessed using the Perceived Stress Scale (PSS), which has been shown to be a reliable tool for assessing perceived stress in diverse populations and is associated with various health outcomes, including mental and physical well-being[28]. The PSS consists of 10 items that assess the frequency of feelings and thoughts related to stress over the past month, such as feeling overwhelmed, unable to cope, or anxious. Each item is rated on a 5-point Likert scale, ranging from "never" to "very often." Higher scores on the PSS indicate greater perceived stress. The points to calculate the composite lifestyle score are assigned as follows:

- 0 points: high perceived stress (27-40 points)
- 1 point: moderate stress (14-26 points)
- 2 points: low stress (0-13 points)

The PSS has been translated and validated into all study languages (original language: English; translated into Dutch, French and German).

2.4. Social connection

Social connection will be assessed using the Three-Item UCLA Loneliness Scale (UCLA-3), a validated and widely used tool for measuring loneliness and perceived social isolation[29]. The UCLA-3 consists of three questions that evaluate how often individuals feel left out, isolated, or lacking companionship. Each item is rated on a 3-point Likert scale: 1 (hardly ever), 2 (some of the time), and 3 (often). Higher scores indicate greater loneliness and lower perceived social connection. The points assigned for calculating the composite lifestyle score are as follows:

- 0 points: Most lonely (8-9 points)
- 1 point: Moderately lonely (5-7 points)
- 2 points: Least lonely (3-4 points)

The UCLA-3 has not yet been translated into the study languages. Therefore, the original English version will be translated into Dutch, French, and German, and then back-translated by a native speaker to ensure its accuracy.

2.5. Sleep

Sleep quality will be assessed using the Brief Pittsburgh Sleep Quality Index (B-PSQI), a validated and widely used tool for evaluating sleep disturbances and overall sleep quality[30]. The B-PSQI is a shorter version of the original Pittsburgh Sleep Quality Index (PSQI) and consists of four questions that assess key components

of sleep, such as sleep duration, sleep disturbances, sleep latency, and overall sleep quality. Each question is rated on a Likert scale, with higher scores indicating poorer sleep quality. The points assigned for calculating the composite lifestyle score are as follows:

- 0 points: Fairly bad or very bad sleep quality
- 1 point: Fairly good sleep quality
- 2 points: Very good sleep quality

The B-PSQI has been translated and validated into all study languages (original language: English; translated into Dutch, French and German).

2.6. Substance use

The Alcohol, Smoking, and Substance Involvement Screening Test-Lite (ASSIST-Lite) will be used to assess participants' use of harmful substances. The ASSIST-Lite is a brief, validated screening tool developed by the World Health Organization (WHO) to evaluate substance use and its associated risks[31]. It includes questions on the frequency of use of various substances, such as alcohol, tobacco, cannabis, stimulants, and opioids. The questionnaire assigns scores based on use patterns, categorizing participants into different risk levels (low, moderate, or high risk). Higher scores indicate a greater likelihood of substance-related harm. The points assigned for calculating the composite lifestyle score are as follows:

- 0 points: No risk (0 points)
- 1 point: Moderate risk (6–12 points)
- 2 points: High risk (12–18 points)

The ASSIST-LITE has not yet been translated into the study languages. Therefore, the original English version will be translated into Dutch, French, and German, and then back-translated by a native speaker to ensure its accuracy.

Statistics

Statistical analysis will be performed using IBM SPSS Statistics (version 28.0.1.1, IBM Corp., Armonk, NY, USA). Data will be expressed as mean ± SD. A Shapiro-Wilk test will assess normality ($p < 0.05$ indicating non-normality). Sociodemographic factors between regions will be compared using chi-square tests for categorical variables. Continuous variables will be compared using independent samples t-tests if normally distributed and Mann-Whitney U tests if non-normally distributed.

Primary outcome measures include the 10-year CVD risk, waist-to-hip ratio, anxiety and depression symptoms (measured using the HADS questionnaire), health-related quality of life, composite lifestyle score, and steps per day. All other measured variables will be considered secondary outcomes. To examine baseline differences between regions, analysis of covariance (ANCOVA) will be performed, adjusting for age, sex, ethnocultural background, educational level, resource perception, employment status, health literacy, and comorbidities. Region will be treated as the independent variable.

To assess intervention effects and regional differences over time, a two-way ANCOVA will be performed, including main effects for time and region, as well as their interaction (time × region). The same covariates as in the baseline ANCOVA will be included.

Additionally, changes in steps per day at weeks 0, 3, 6, 9, 12, 16, 20, and 24 will be analysed using a two-way repeated-measures ANOVA with main effects for time and region, as well as their interaction. If sphericity is violated, the Greenhouse-Geisser correction will be applied. If repeated-measures ANOVA assumptions are not met, a linear mixed-effects model with random intercepts and slopes will be used as an alternative. The same covariates as in ANCOVA will be considered in these models, where applicable.

A p-value of <0.05 will be considered statistically significant for all analyses. Where applicable, corrections for multiple comparisons (e.g., Bonferroni) will be applied.

Data anonymity

Personal data and pseudonymisation keys

Pseudonymisation will be carried out using Castor, ensuring that personal data is protected in accordance with GDPR principles. Participants will register via a secure registration link (sent through Castor), which will automatically assign a unique pseudonymised code in the format 'BZ-Site-incremental 3 digits'. Each questionnaire will be linked to a specific site, with three distinct pseudonymisation keys: one for participants completing the UHasselt/UMaastricht questionnaire, one for those completing the ULiège questionnaire, and one for those completing the UAachen questionnaire. For example, participants from UHasselt will receive codes ranging from BZ-UHa-001 to BZ-UHa-250, those from ULiège will receive codes from BZ-ULi-001 to BZ-ULi-250, and so on for other sites (with abbreviations UMa for Maastricht University and UAa for Aachen University).

The three confidential lists linking participant identities to their assigned pseudonymised codes (the pseudonymisation key) will be stored externally (i.e., not within Castor) and will be encrypted. Local Principal Investigators (PIs) will be responsible for securely storing this subject identification list, as also stipulated in the clinical trial and site agreements. For participants from UHasselt and Maastricht University, the lists will be stored in an encrypted file on Google Drive, which will only be accessible via the username and password of the responsible researcher (Ine Nieste). Access to the pseudonymisation key will be strictly limited to the designated local PIs and investigators, as stipulated in the clinical trial and site agreements:

- Ine Nieste for UHasselt and Maastricht University
- The local PI for ULiège
- The local PI for Aachen University

Ine Nieste will have access to the pseudonymisation keys for all regions, while the local PIs of ULiège and Aachen University will have access only to the key for their respective institution.

Pseudonymised collected study data

All pseudonymised collected data will be securely stored in Case Report Forms (CRFs) at Castor EDC and DHARMA, and only the local PIs will have access to the pseudonymised source data, as also stipulated in the clinical trial and site agreements.

Data collected via the screening questionnaire

Data from screening questionnaires of participants who are not included in the study will be deleted immediately once the required study sample size has been reached.

Data collected via the wearable

To set up the account for syncing the wearable with participants' smartphones, fictitious email addresses will be used. Each participant will be assigned a unique email address based on their corresponding pseudonymised code (e.g., BZ-UHa-001@one.com). The pseudonymised physical activity data generated by the wearable will be transferred to the Hasselt University DHARMA (Digital Health Research Platform for mHealth Research) platform via the wearable's open API (Application Programming Interface). Only the local PI's will have access to DHARMA via personal credentials (username and password). The DHARMA platform is a secure and GDPR compliant platform that runs on Amazon servers (EU-based) and is hosted by Hasselt University.

Data collected via M-Path

All data collected via the m-Path app (including questionnaire responses) is initially stored locally in a protected folder on the participant's smartphone. This folder is only accessible through the m-Path app and cannot be accessed by other apps on the device. The data collected in the daily diary is automatically deleted if the app is uninstalled. Participants will be informed that to permanently delete their data, they must uninstall the app. While participants may want to retain their emotional trajectory data for personal use (a benefit of the study), they will not be required to uninstall the app. Instead, they will be advised to delete the data from their phone when it is no

longer needed. Participants, as the legal owners of their data, have the right to make the data unavailable to researchers at any time. They can also delete their data from the m-Path database whenever they wish. These actions can be completed directly within the app, and participants will be provided with instructions on how to do so.

To ensure maximum security and prevent data leakage, the m-Path app uses advanced encryption. All data stored on the phone, including questionnaire responses, downloaded questionnaires, personal information (e.g., alias), options, and notes, is encrypted using AES 256-bit encryption with PKCS7 padding. This ensures that the stored data is in an unreadable format without proper decryption. When the participant's phone is connected to a 3G or higher network, data is transferred to secured servers of M-Path located in Leuven and Heverlee (Belgium). In the unlikely event of a security breach, all affected users will be notified. A data transfer agreement between Hasselt University (sponsor) and M-Path will be established to ensure compliance with data protection regulations.

Mailing system

The emails sent to participants as part of the intervention will be directed to their personal email address. This will be managed by the local Principal Investigator (PI) at each site, who have access to the pseudonymisation key as described above.

Data storage and continuity plan

Blood samples will be stored for 10 years at the University Hospital RWTH Aachen, and source data will be archived in Castor EDC after study completion and stored for 25 years to allow for future reuse or validation of results. Future research that involves the reuse of this data will only occur with the subject’s explicit approval on the informed consent form for data reuse. Additionally, any new study proposal must be approved by the relevant ethical committee before any data can be reused for research purposes. After the 25-year retention period, all personal data, including pseudonymised data, of participants from Hasselt and Maastricht University will be securely deleted by Bert Op 't Eijnde to ensure compliance with GDPR and protect participant privacy. The pseudonymisation key and access to Castor will be transferred to Bert Op 't Eijnde upon Ine Nieste's departure from the University, or if she is otherwise no longer able to fulfil her duties as the responsible researcher, ensuring the continued secure management of the data for Maastricht and UHasselt participants. Similar precautions will be taken at ULiège and Aachen University, as also stipulated in the clinical trial agreements.

Appendix

Formulas to calculate affect fluctuations[18]

- Affect instability: RMSSD

The RMSSD is measured as the square root of the average of the squared differences between affect at measurement i and i +1. For N measurements, the RMSSD is described as: $RMSSD = sqrt\Big(\Big(\frac{1}{N-1}\Big) * sum\ from\ i = 1\ to\ (N-1) of\ \big((x_{i+1} - x_i)^2\big)\Big)$

- Within-person variability: WPV

For N measurements, WPV is given by: $\mathrm{WPV} = \frac{1}{N-1}\sum_{i=1}^{N}(x_i - \bar{x})^2$, where the mean affect score is: $\bar{x} = \frac{\sum_{i=1}^{N} x_i}{N}$.

- Temporal dependency: autocorrelation

Autocorrelation measures the temporal dependency between the (i+1)th and the ith measurement in a time series. Assuming measurements have equally spaced time intervals, we define the interval as h. The hth-order autocorrelation is given by: $Autocorrelation(h) = \frac{\sum_{i=1}^{N-h}(x_{i+h}-\bar{x})(x_i-\bar{x})}{\sum_{i=1}^{N}(x_i-\bar{x})^2}$. Autocorrelation thus indicates how well measurements at time point iii correlate with measurements at the previous time point.

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