

PREDIFALL - Polymodal Evaluation of Predictors of Falls in Healthy Older Adults: A Prospective Study Protocol

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Study protocol

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Abstract

Background

Falls are a major public health concern among older adults and result from multiple interacting factors. Current approaches to fall assessment often rely on isolated measures and may not fully capture the complex mechanisms underlying falls. The Polymodal Evaluation of Predictors of Falls (PREDIFALL) study aims to investigate multimodal predictors associated with falls by integrating clinical, functional, sensory, imaging, and blood-based assessments using machine learning approaches.

Methods

PREDIFALL is a prospective observational cohort study including 100 healthy older adults aged ≥ 65 years. At baseline, participants will be classified as fallers and non-fallers based on their fall history over the previous 12 months. Participants will undergo comprehensive baseline assessments, including questionnaires, physical activity and sleep monitoring, cognitive testing, mobility and gait evaluation, muscle strength testing, posturography, vestibular and auditory assessment, brain and muscle imaging (magnetic resonance imaging, proton magnetic resonance spectroscopy, ultrasound, and functional near-infrared spectroscopy), and blood-based biomarker and multi-omics analyses. Falls will subsequently be monitored during the 12-month follow-up using a smartphone-based application completed weekly. Machine learning approaches will be used to integrate multimodal data and identify profiles associated with retrospective and prospective falls.

Discussion

By combining multimodal baseline assessments with retrospective fall history and prospective fall monitoring, the study may improve understanding of the mechanisms associated with falls in healthy older adults. In addition, the smartphone-based follow-up will help evaluate the feasibility of longitudinal fall monitoring in community-dwelling older adults. Findings from this study will inform future fall prevention strategies in our aging society.

Background

The increase in life expectancy observed over the past century represents a major societal achievement driven by advances in medicine, public health, and living conditions. However, gains in healthy life expectancy have not progressed at the same rate, resulting in a growing proportion of older adults living with chronic functional decline and vulnerability [1]. A notable health concern associated with aging is the increased number of falls, defined as an event in which an individual comes to rest accidentally on the floor or lower level independent of any significant intrinsic event (e.g., stroke) or overwhelming hazard [2]. Epidemiological data indicate that approximately 30–40% of adults over the age of 65 fall at

least once a year, and this risk increases to 50% among those over 80 [3]. Among these individuals, 20–30% experience moderate to severe injuries, including traumatic hip fractures and brain injuries, leading to a loss of independence, an increase in hospitalization, and an elevated risk of mortality [2]. Furthermore, falls represent a major public health burden, accounting for approximately €2 billion in healthcare costs in France and more than 684,000 preventable deaths worldwide each year [4]. Given the major clinical and societal burden of falls, considerable efforts have been directed toward identifying the risk factors and improving prevention strategies. The leading causes of falls are multifactorial and include behavioral, socioeconomic, environmental, clinical, sensory, neuromuscular, cognitive, and functional factors [5–10]. Increased fall risk may result from individual factors, including age-related changes in mobility, sensory integration, and cognition, as well as medication use and polypharmacy [11], in addition to environmental hazards such as uneven or slippery surfaces and poor lighting. Given the multifactorial nature of falls, various strategies have been suggested, including physical exercise, medication optimization, vitamin D supplementation, nutritional support, environmental modifications, and vision-improving surgery for prevention [12]. Nevertheless, despite decades of research on the development of multiple prevention strategies to reduce falls, the incidence among older adults has remained constant, with no clear decline observed over the years [13]. One likely explanation is that fall risk does not arise from a single deficit, but from the interaction of multiple factors that evolve differently across individuals and aging trajectories. Current screening approaches, which often rely on self-reports, questionnaires, or isolated functional tests, provide only a partial assessment of fall risk and primarily identify older adults who already exhibit important functional decline. This limitation is particularly important because falls also occur in community-dwelling older adults who remain healthy, independent, and high-functioning, suggesting that current assessment tools may be insufficiently sensitive to detect subtle or early fall vulnerability. Consequently, identifying multimodal profiles capable of distinguishing fallers from non-fallers and predicting future falls has become an important challenge. Together, these observations highlight the need for a framework that incorporates a broad range of assessments to capture the multifactorial nature of falls and identify the underlying mechanisms contributing to fall vulnerability in healthy older adults.

Among these, blood-based molecular approaches may help identify biological signatures associated with fall vulnerability. Proteomic techniques can detect subtle alterations in protein expression related to complex physiological and pathological processes and have already contributed to biomarker discovery in several neurological and age-related disorders [14]. In parallel, although still limited in number, recent genetic studies indicate that falls represent a highly heterogeneous polygenic trait involving neurological, psychological, and musculoskeletal pathways [15, 16]. In addition, accelerated biological aging may represent another mechanism potentially contributing to falls. Biological age measures have been associated with frailty, physical decline, and reduced physiological reserve in older adults [17, 18], although their relationship with falls remains unexplored. Incorporating blood-based aging clocks may therefore provide additional insight into the multisystem processes potentially contributing to falls. However, how these molecular and biological aging mechanisms interact with clinical and functional factors associated with falls remains underexplored. One other promising mechanism involves the

sensory and neuromuscular systems. Although sensory and vestibular alterations are prevalent among older adults who fall [19,20], their contribution to multidimensional prediction frameworks remains insufficiently characterized. Further, neuroimaging studies suggest that fall vulnerability may be associated with structural and functional changes in brain networks involved in gait control, sensory integration, and executive functioning [21–23]. Beyond these structural and functional findings, neurochemical and metabolic alterations associated with fall vulnerability remain insufficiently characterized. In this context, proton magnetic resonance spectroscopy (^1H -MRS), an imaging technique that assesses in vivo brain metabolite profiles, may provide additional knowledge for the metabolic mechanisms underlying fall vulnerability. Similarly, muscle imaging studies have primarily focused on structural changes in muscle related to falls [9,24,25], whereas muscle metabolic alterations remain largely unexplored. Therefore, fall prediction approaches that integrate these less explored domains alongside conventional clinical and functional assessments may provide a more comprehensive way to characterize fall vulnerability.

In recent years, predictive modeling using machine learning (ML) has become increasingly common in the fall literature [26–28]. This evolution partly reflects the limitations of conventional fall risk assessments, which often rely on isolated clinical or functional measures and may insufficiently account for the multifactorial nature of falls [27, 29]. In parallel, advances in wearable sensors, posturography, gait analysis, imaging, and biological profiling have produced increasingly high-dimensional data that are difficult to integrate using conventional statistical approaches alone [28, 29]. ML approaches may therefore support the integration of heterogeneous multimodal data, identify nonlinear interactions between features, and help isolate a reduced feature subset that most effectively captures fall vulnerability. However, many existing ML studies have primarily focused on clinical, mobility, posturographic, or wearable-sensor-derived data, often combining only a limited number of modalities [26, 29, 30]. There is still a need for broader multimodal frameworks that integrate biological, sensory, neuromuscular, and imaging markers to better identify profiles associated with prior falls and predict future fall risk in older adults.

To address these gaps, the Polymodal Fall Prediction (PREDIFALL) project will investigate fall vulnerability in healthy older adults whose fall risk is not primarily explained by a specific underlying pathology, using a holistic, multimodal approach. The study combines clinical, functional, imaging, and blood-based assessments, including multi-omics analyses such as proteomics, genetics, and transcriptomics, to better distinguish fall vulnerability. Fall history during the preceding 12 months will be collected at baseline, and participants will subsequently be monitored prospectively for falls over an additional 12-month period using a smartphone-based application completed weekly. This participatory longitudinal follow-up approach aims to improve the accuracy and ecological validity of fall monitoring while reducing recall bias associated with retrospective fall assessments [31].

Using machine learning approaches, PREDIFALL will first investigate combinations of multimodal markers associated with a retrospective fall history to distinguish fallers from non-fallers at baseline. The study will then examine whether these baseline multimodal profiles can predict incident falls during

the 12-month follow-up period, thereby supporting a more holistic characterization of fall vulnerability in older adults.

Methods

Study design and setting

PREDIFALL is an observational, multimodal study conducted in community-dwelling older adults with and without a history of falls. The study will combine comprehensive cross-sectional baseline assessments with prospective fall monitoring over 12 months. It aims to identify clinical, functional, imaging, and blood-based biomarkers associated with previous falls and to predict prospective falls.

The study will be conducted at two centers in Normandy, France, the INSERM U1075 COMETE laboratory and the CYCERON research platform. No therapeutic intervention or random allocation will be performed.

Participants and eligibility criteria

A total of 100 community-dwelling older adults will be recruited, including 50 participants with a history of falls (fallers) and 50 participants without a history of falls (non-fallers). Inclusion criteria include being aged ≥ 65 years, having independent ambulation, having an Mini Mental State Examination (MMSE) score ≥ 24 , having normal or corrected vision, being fluent in French, being affiliated with the national social security system, and providing written informed consent. Fallers are defined as having ≥ 1 fall in the previous 12 months, and non-fallers as having no falls during the same period. Exclusion criteria include having neurological or psychiatric disorders affecting motor or cognitive function (e.g., Parkinson's disease, stroke sequelae, major depression) or other severe comorbidities that could affect participant safety and study outcomes, having undergone recent lower-limb surgery (< 12 months), having polypharmacy (use of more than four medications) or using fall-risk increasing drugs, having significant sensory impairments limiting assessment, having immune-related conditions or recent infections, having contraindications to MRI, having been hospitalized within the past 30 days, participating in another clinical study, or being unable or unwilling to provide informed consent. These exclusion criteria were selected to minimize major pathological contributors to falls and to focus on fall vulnerability in healthy older adults.

Sample size calculation

The planned sample size is 100 participants (50 fallers and 50 non-fallers), determined based on feasibility considerations and study design constraints. A formal a priori sample size calculation based on diagnostic accuracy metrics (e.g., sensitivity and specificity) was not considered appropriate, as the primary aim of the study is the development of exploratory multimodal prediction models rather than

validation of a predefined diagnostic test. Sample size planning for machine learning-based prediction models remains challenging, particularly in high-dimensional settings, and depends on numerous factors, including the number and structure of predictors, outcome prevalence, model complexity, and nonlinear relationships [32, 33]. The optimal sample size varies substantially across datasets and modeling contexts.

Therefore, the present study is designed as an exploratory, hypothesis-generating investigation aiming to identify candidate multimodal biomarkers and develop preliminary predictive models. Internal validation strategies (e.g., cross-validation) will be applied to mitigate overfitting. Findings will require confirmation in larger independent cohorts.

Recruitment procedures

Participants will be recruited through multiple channels to ensure adequate inclusion of community-dwelling older adults. Primary recruitment will be conducted in collaboration with the Saint-Laurent Health Center in Caen, a multidisciplinary university health center accredited by the Normandy Regional Health Agency. This center includes a network of primary care professionals and serves approximately 10,000 long-term patients, with around 500 medical consultations performed daily. Potentially eligible participants will be identified during routine clinical practice and referred to the research team. Additional participants will be recruited through community-based advertising. Flyers will be distributed in public locations, including libraries and shopping centers in Caen, to reach a broader population of independently living older adults. Eligibility will be assessed by a medical doctor during the screening visit (V0) at COMETE Laboratory. Individuals meeting the inclusion criteria will receive detailed information about the study and will provide written informed consent prior to participation.

Study procedures

Once eligibility is confirmed by a medical doctor, baseline characteristics will be collected through standardized questionnaires covering demographics, psychological status, physical activity, sleep, diet, and fear of falling. Participants will be instructed to complete these questionnaires at home prior to the first study visit.

At V0, participants will also undergo initial physical assessments, including anthropometric measurements and handgrip strength evaluation. In addition, participants will be provided with a triaxial accelerometer and instructed to wear it for seven consecutive days to record physical activity and sleep behavior.

Participants will subsequently undergo a comprehensive multimodal assessment across three visits. V0 and the first two study visits (V1, V2) will be conducted at the COMETE Laboratory, whereas the third visit (V3) will take place at the CYCERON research platform. V1 will include cognitive testing, lower-limb muscle strength and power assessment, and functional mobility evaluation. V2 will focus on postural

control, dual-task gait analysis combined with functional Near-Infrared Spectroscopy (fNIRS), and vestibular and auditory function. V3 will include blood sampling and imaging assessments.

To minimize the potential influence of acute exercise on study outcomes, participants will be instructed to refrain from intense physical activity for at least 72 hours before each study visit. All visits will be conducted with a minimum 72 hours and a maximum 6 weeks between sessions. An overview of the study procedure is presented in Fig. 1.

Baseline multimodal assessment

A comprehensive set of validated instruments will be used to collect multimodal data across clinical, cognitive, motor, imaging, and biological domains. All measures, together with their assessment time points throughout the study, are presented in Fig. 2.

cVEMP, Cervical Vestibular Evoked Myogenic Potentials; fNIRS, Functional Near-Infrared Spectroscopy; MRI, Magnetic resonance Imaging; MRS, Magnetic Resonance Spectroscopy, oVEMP, Ocular Vestibular Evoked Myogenic Potentials

Questionnaires

Standardized and validated questionnaires will be used to assess demographic characteristics, functional status, psychological well-being, physical activity, sleep quality, diet, fear of falling, quality of life, as well as behavioral and technology-related factors. The questionnaire battery will include the Fall Efficacy Scale (FES), Short Form-36 (SF-36), Instrumental Activities of Daily Living (IADL), Geriatric Anxiety Inventory (GAI), Geriatric Depression Scale (GDS), International Physical Activity Questionnaire (IPAQ), Pittsburgh Sleep Quality Index (PSQI), a food frequency questionnaire (FFQ), the Edinburgh Handedness Inventory, the Acceptability E-Scale, and the Mobile Device Proficiency Questionnaire (MDPQ-16) [34–44].

All questionnaires will be completed at home prior to the first study visit (V0), in paper format, except for technology-related questionnaires, which will be completed during the follow-up period.

Physical activity and sleep monitoring

Physical activity and sleep behavior will be assessed over a 7-day period using a triaxial accelerometer (DynaPort MoveMonitor, McRoberts BV, The Hague, The Netherlands). Participants will be instructed to wear the device continuously (24 hours/day), except during water-based activities. The device will be positioned on the lower back at the lumbar level using an adjustable elastic belt and will record movement data at 100 Hz.

Daytime physical activity outcomes will include daily step count, physical activity intensity during movement (e.g., walking, stair climbing, cycling), and sedentary time. Nighttime parameters will include total and relative sleep duration, as well as the number of nocturnal awakenings. Data will be processed by validated manufacturer algorithms.

Real-life mobility patterns will be assessed using a GNSS data logger (Columbus P-1 Mark II, Columbus Co. Ltd, Berlin, Germany), worn during waking hours over the same 7-day period. Geolocation data (1 Hz) will be used to derive indicators such as total distance traveled, time spent outdoors, and exposure to different environments (e.g., green spaces, commercial areas).

To ensure data privacy, raw geolocation data will be used solely to compute aggregated indicators and will be deleted after processing. Only pseudonymized, non-identifiable variables will be retained for analysis in accordance with MR-001 regulations.

Body composition assessment

Body composition will be estimated using the BIA 101 Anniversary Sport device (Akern Srl), which performs multi-frequency segmental bioelectrical impedance analysis (BIA). Using an 8-electrode configuration, the system measures resistance, reactance, and phase angle across eight body segments to estimate muscle mass, fluid distribution, and cellular integrity [45]. The bioimpedance method is based on the principle of passing an electrical current through the human body. This current is of low intensity, imperceptible to the subject. This technique does not pose a risk of electrocution or exposure to ionizing radiation. Participants will lie in a supine position, be isolated from the ground and metal objects, and have their legs abducted to 45°, their shoulders abducted to 30°, and their hands pronated. After skin cleansing with isopropyl alcohol, electrodes will be placed on both hands and both feet using an 8-electrode configuration according to the manufacturer's instructions. The procedure is non-invasive and takes approximately 5–10 minutes.

Foot preference

Participants will be asked to indicate their preferred foot when performing common functional tasks, including kicking a ball, stepping onto a stair, and stamping on the floor. Each task will be scored as left, right, or either, and a composite laterality score will be calculated to determine the dominant lower limb. The identified dominant limb will be used for subsequent unilateral assessments [46].

Cognitive assessment

MMSE will be administered by a medical doctor during V0. [47] The remaining cognitive assessments will be conducted by the experimenter in V1. All cognitive testing will occur in a quiet environment to maintain standardized conditions across participants. The computerized tests will be administered on a 15.6-inch laptop using Inquisit Lab 7 (version 7.1.7, Millisecond Software) [48]. Participants will be seated 70 cm from the screen to ensure optimal viewing conditions and will wear their usual visual

correction, if any, during testing. Each cognitive test will be preceded by a practice session to ensure familiarity. The entire cognitive assessment will last approximately 60 minutes.

Corsi's Block Tapping Test (CBTT)

CBTT is used to assess visuospatial working memory [49]. Cubes will be displayed in random positions on the screen, with each cube highlighted for 500 ms. Participants will be required to observe and reproduce sequences of spatial locations presented by selecting the cubes in the same order. The sequence will start with two cubes and increase progressively up to nine cubes if the participant responds correctly. Each sequence length includes two trials; if at least one is correctly reproduced, the sequence length increases by 1. If both trials are incorrect, the test will stop. The Corsi span will be recorded as the highest sequence length successfully reproduced.

Line Bisection Test (LBT)

LBT is used to assess visuospatial attention and spatial bias [50]. Participants will complete a computerized version of the LBT using a mouse. Fourteen horizontal lines will be presented on the same screen, one under the other, and participants are required to draw a small vertical line through each line, placing it as close to the center as possible. Each line can only be attempted once, and participants must not skip any lines. The score will include the average absolute and percent deviation from the actual center across all trials.

Sustained Attention to Response Task (SART)

SART is used to assess response inhibition [51]. In this task, participants are presented with a continuous stream of digits varying in size and are instructed to press the space key for any digit except '3.' Digits are displayed at approximately one-second intervals, each followed by a mask before the subsequent digit appears. Participants may press the space key during both the digit and mask presentations. The number of errors, defined as responses to the no-go digit, is recorded.

Symbol Search Test (SST)

SST is used to assess selective attention and processing speed via computerized visual search paradigm [52]. During the test, participants are presented with rows of symbols and must determine whether a target symbol is present among a set of search symbols. Responses are made using a mouse to select the matching symbol when present or to indicate the absence of a target symbol. The test duration is 2 minutes, and both the number of correct responses and errors are recorded.

Task-Switching Test (TST): TST assesses cognitive flexibility using a paradigm that involves two categorization tasks [53]. Participants will be required to classify either letters (vowel vs. consonant) or numbers (even vs. odd) using predefined keyboard responses ("E" and "I" keys). In a subsequent mixed block, letters and numbers will be presented within a four-quadrant display. Task rules will depend on stimulus position: stimuli appearing in the upper quadrants will be categorized according to the letter

rule, whereas stimuli in the lower quadrants will be categorized according to the number rule. Participants will be instructed to respond as quickly and accurately as possible. Outcome measures will include response accuracy and reaction time.

Physical and functional assessments

Mobility

Foot Tapping Test (FTT)

FTT is used to assess lower-limb motor function and will be administered via a computerized test [54]. Participants sit on a height-adjustable chair, ensuring a comfortable position with the hip and knee joints flexed to approximately 90°, and place their feet in a natural, relaxed position, heels firmly planted on the floor. They will be instructed to tap a pedal as quickly as possible by moving the forefoot while keeping the heel in contact with the ground for 10 seconds. The test will be performed three times for each foot (right and left), and the average number of taps will be calculated separately for each foot.

One-Leg Stance Test (OLST)

OLST assesses postural steadiness in a static position [55]. Participants stand barefoot with their eyes open, gazing at a white wall 1.5 meters away in front of them. They place their hands on their hips and lift one foot behind them with the knee at an angle of between 45° and 90°, ensuring that the weight-bearing limb always starts with the dominant leg. A stopwatch records the duration until either 60 second elapse or balance is lost. A 30-second rest period follows each trial. Each participant performs a practice trial followed by two test trials per leg, with the best test trial used for analysis. An examiner remains nearby throughout the test to ensure safety and prevent falls due to balance loss.

Sit-to-Stand Test (STST)

STST assesses lower limb strength and functional performance by measuring the time taken to stand up from a chair and sit back down five times as quickly as possible without using hands for support [56]. The subject sits on a padded, armless chair (height 43–48 cm) with their back supported, feet flat on the ground, and arms crossed in front of the chest. They will be instructed to stand fully, extending their knees, and return to a seated position without bouncing or pushing off the chair. After one practice attempt, standardized verbal instructions are provided, and the test begins on the command “Ready, set, go!”. A 6-axis inertial measurement unit (DynaPort 7, McRoberts B.V., The Hague, The Netherlands) records data via the 3-axis accelerometer (± 16 g) and 3-axis gyroscope (± 2000 °/s) at a sampling rate of 100 Hz. It is based on this data that the duration (in seconds) of each cycle and sub-phase of the transition from a sitting to a standing position, and the angular velocities of the trunk (°/s), are determined. The device (106.6 × 58 × 11.5 mm; 55 g) will be worn on the lower back, centred at the lumbar region using an adjustable elastic belt. The test is performed in a stable environment, and deviations such as hand use or incomplete knee extension are noted. Safety is ensured by monitoring for

discomfort or instability, and the outcome is recorded in seconds, with qualitative observations of movement quality if necessary.

Timed Up and Go (TUG)

The TUG test assesses mobility, balance, and functional ability [57]. The participant sits in a standard chair with their back against the backrest and arms on the chair's arms, wearing regular footwear. A 3-meter walkway is marked, and the patient is instructed to stand up on the word "Go," walk the 3-meter line at a comfortable pace, turn around, walk back, and sit down. The DynaPort 7 sensor records the TUG total duration and sub durations (the sit to stand phase, the stand to sit phase, the 2 walking periods and the 2 turns) in seconds.

Six-Minute Walking Test (6MWT)

6MWT measures the distance achieved in a continuous six-minute walking bout and is a global indicator for the submaximal level of functional capacity. We will use a validated modified version of the test with a 10-meter walking path instead of the standard course due to the laboratory conditions [58].

Participants rest for at least 15 minutes before the test, during which baseline blood pressure and heart rate measurements are recorded. They are instructed to dress comfortably, wear appropriate footwear, and avoid eating for at least one hour before the test. A chair is placed at one end of the walking course for safety. Standardized instructions emphasize walking as far as possible within six minutes, with permission to slow down or rest if needed. Standardized encouragement (e.g., "You are doing well. You have 5 minutes to go") is provided at each minute mark. If the participant stops, they are encouraged to resume walking as soon as they can. The DynaPort7 sensor calculates the total distance covered over six minutes, as well as the number and duration of stops during the test. In addition, post-test heart rate and blood pressure measurements are recorded.

The Recovery From Fall/Stand Test (RFST)

The ability to stand up from a lying position on the back underlies a person's capacity to get out of bed each day. This activity, much like getting up after a fall, requires flexibility, dynamic balance, and muscle strength, skills that may be lacking in individuals with balance disorders and weakness, particularly those with sensorimotor impairments [59]. During the Fall Recovery Test, participants are instructed to lie supine on a mat for two minutes, after a one minute of resting lying. Following an auditory signal, they are required to stand up as quickly as possible and maintain an upright standing position for 3.5 minutes. Trunk movement and postural stability are assessed using inertial measurement units (Xsens® DOT) placed on the trunk and at the level of the fourth lumbar vertebra [60, 61], allowing for the quantification of balance fluctuations. Heart rate is continuously monitored using a chest-worn heart rate sensor (Polar H10®).

All functional mobility assessments will take approximately 30 minutes. An examiner will remain in close proximity to the participant throughout testing to ensure safety and prevent falls.

Muscle strength

Handgrip strength: Grip strength will be assessed with a grip dynamometer (Grip-D, Takei, Japan). Participants sit with shoulders adducted and neutrally rotated, elbows bent to 90°, forearms and wrists neutrally rotated. The arm remains unsupported by the examiner or an armrest, and the dynamometer is held vertically, aligned with the forearm. Participants are instructed to exert maximal force on the dynamometer. The test consists of six repetitions: three trials per hand, each lasting three seconds, with a 60-second rest between trials to minimize fatigue [62].

Lower limb strength and power

Lower limb strength and power will be performed via an isokinetic dynamometer (Cybex, Humac Norm, USA) [63]. Before the assessment, a warm-up consisting of 5 minutes on a stationary bike, followed by 3 unweighted extensions and flexions of each leg whilst seated on the Cybex chair, will be performed. Measurements will only be collected for the dominant limb, identified through a foot preference test. The target muscles are knee extensors and flexors. The range of movement will be set from 90° of flexion to 0° of extension (0° = knee full extension). A familiarization phase will be performed with 12 repetitions at 180°/s. Maximal concentric muscle strength and power will be assessed at 60°/s, 180°/s and 240°/s with 3 repetitions. Finally, maximal eccentric muscle strength and power (when participants resist while the machine moves their limb) will be measured at 30°/s with 3 repetitions. Before each speed is tested (concentric and eccentric), the participant performs 3 submaximal repetitions at the same test speeds. During the maximum strength tests, participants will be verbally encouraged to produce their maximum torque, and a 90-second rest period will be given between sets. The peak torque, the average power of the repetition and the angle recorded at peak torque from the best of the three repetitions will be used for analysis.

The evaluation will take approximately 45 minutes.

Gait

3-D Gait Analysis

The gait analysis is based on general principles of gait testing [64]. A 3D motion capture system (Vicon, Oxford Metrics, Oxford, U.K.) with 10 Bonita 3 cameras and Vicon Nexus 2.15 software will measure the 3D locations of reflective markers to reconstruct the segments of the whole body (except for the head). Once the markers are in place, participants walk in a straight line in a 6-meter-long walkway at the usual self-selected gait speed and then at maximum gait speed. For each walking speed, the participant walks 10 consecutive times in the walkway. Gait speed, stride length, stride duration, step length, step duration, cadence, minimum toe clearance, stance phase and swing phase (including single and double support phases) will be assessed. We will also focus on the vertical velocity of the body's center of mass and the joint kinematics of the lower limbs (hip, knee, and ankle, mainly in the sagittal and frontal planes). The evaluation will take approximately 45 minutes.

Dual-task gait analysis

Cognitive–motor interference during walking will be assessed using a dual-task paradigm performed on a treadmill-based pressure platform (Zebris FDM; Zebris Medical GmbH, Germany). Participants will perform a computerized number-switching task while standing or walking at their self-selected speed [65].

The cognitive task was programmed using PsychoPy (version 2025.2.0) and will be presented on a 43-inch screen (Toshiba, Japan) positioned in front of the treadmill. Participants will view the stimuli while walking and respond verbally, reaction time and accuracy will be recorded. Verbal responses were selected to minimize interference with gait performance associated with manual inputs. The switching task consists of four blocks of 40 trials each: two pure blocks and two mixed blocks. Digits from 1 to 9, excluding 5, are presented either within a square or a circle. In the square condition, participants classify digits as odd or even, whereas in the circle condition, they classify digits as greater or less than five. In pure blocks, only one stimulus type is presented, corresponding to a single rule. In mixed blocks, both stimulus types are presented, and task-switch and task-repeat trials occur in a pseudo-random order. Each stimulus remains on the screen for up to 3 seconds, and responses corrected after an initial incorrect response are scored as errors.

The dual-task gait assessment will consist of four 2-minute walking blocks performed concurrently with the cognitive task. Two blocks will correspond to pure conditions and two to mixed conditions, following the standard structure of task-switching paradigms. In addition, two single-task reference conditions will be performed: (1) a cognitive-only condition conducted while standing on the treadmill, and (2) a walking-only condition without cognitive load.

Spatiotemporal gait parameters will include step length, cadence, stance and swing phase proportions, and center of pressure trajectory. Cognitive performance will be assessed using response accuracy and reaction time. Cognitive switching cost will be calculated by comparing performance between mixed and pure blocks.

Dual-task cost (DTC) will be calculated for both gait and cognitive outcomes as the relative change in performance between single-task and dual-task conditions [66].

Postural, vestibular and sensory function

Postural control

Balance will be assessed using the Synapsys Posturography System (SPS; Synapsys, Marseille, France) with sampling frequency of 100 Hz.

Participants will be asked to stand on the platform, with their arms at their sides and looking straight ahead. They are requested to sit down between each trial. A handrail will be used to prevent a fall. Participants will be equipped with an fNIRS device placed over the dorsolateral prefrontal cortex (dlPFC)

and on the quadriceps muscle. Linear postural parameters (the surface area of foot center of pressure displacement, length, standard deviation, and velocity) and nonlinear postural parameters using Detrended Fluctuation Analysis (DFA) will be measured [67]. DFA will be conducted for static balance tests. The tests are divided into two parts:

Part One: Balance Assessment

During this test, balance assessment conditions will be conducted. The order of trials will be randomized across participants. Static balance will be measured under three conditions: with eyes open while focusing on a cross, with eyes closed, and while viewing an artistic painting. During the painting condition, infrared interference between the head-mounted fNIRS system and the eye tracker prevents their simultaneous use. Therefore, the painting condition will first be performed with eye tracking (Tobii Eye Tracker 5, Tobii AB, Stockholm, Sweden) and without head-mounted fNIRS recording. It will then be immediately repeated with head-mounted fNIRS recording and without eye tracking. The quadriceps fNIRS measurements can be maintained during both trials. Stability limits will be measured by having the participant lean as far as possible in all directions, without lifting their feet, while keeping the torso upright and eyes open.

Part two: Vestibular stimulation

Given the absence of an established consensus regarding the determination of vestibular stimulation thresholds for balance perturbation, the present protocol was designed to identify the lowest stimulation intensity inducing measurable postural instability. Previous studies have used different operational definitions depending on the outcome of interest, including vestibular perceptual thresholds based on the first perception of dizziness, postural instability, or body motion perception [68, 69], whereas other work has specifically focused on balance perturbation thresholds [70].

During the test, participants will stand on a posturography platform. They will be equipped with a Galvanic Vestibular Stimulator device (NeuroCom International Inc., USA). Electrodes will be placed on the mastoid bone to deliver vestibular stimulation. An alternating 25-second, 0.04 Hz stimulation will be applied, which is a low-frequency alternating current passed between the two mastoid electrodes. The balance disruption threshold test will begin at a low stimulation level and gradually increase in small increments up to 1 mA. The safety of the GVS protocol at this intensity has been confirmed in our previous study involving similar populations, without any reported adverse effects [71]. The entire postural assessment will last approximately 30 minutes.

Vestibular & auditory assessment

Fukuda Test

This test is a diagnostic tool used to assess the presence of weakness or asymmetry in the vestibular system. During this test, the participant stands upright with their arms extended forward, perpendicular to the body, and with eyes closed. The participant is asked to take 50 steps in place, with each step at an

angle of approximately 45°. The angle of deviation, the angle of rotation of the participant and distance of deviation from the starting point are measured [72].

Video Head Impulse Test (vHIT)

vHIT quantitatively evaluates the vestibulo-ocular reflex. The participant sits in a chair while the examiner moves their head in various directions to stimulate all semicircular canals. Eye movements are recorded and analyzed using high-speed cameras (ICS® Impulse), and head movements are measured using motion sensors integrated into the vHIT goggles [73].

Ocular (oVEMP) and Cervical (cVEMP) Vestibular Evoked Myogenic Potentials

The VEMP (Vestibular Evoked Myogenic Potential) is used to assess the function of the otolithic organs, the saccule and utricle, which play a central role in the perception of linear movements. This method specifically measures the functional activity of these two otolithic organs [74, 75].

The test is based on a fundamental property of the vestibular structures: the saccule and utricle respond to sound stimulation or bone conduction. We will record these responses using a VEMP system (ELIOS, Echodia - Electronique du Mazet, Le Mazet-Saint-Voy, France) as myogenic potentials [74].

VEMP is divided into two main categories: cVEMP (cervical VEMP), which evaluates saccular function, and oVEMP (ocular VEMP), which evaluates utricular function.

cVEMP (Cervical VEMP)

This test measures the reflex activity of the sternocleidomastoid muscle in response to auditory stimulation. Electrodes are placed on the SCM muscle on the same side as the tested ear. A sound is delivered into the tested ear while the patient, lying on their back, lifts their head to contract the sternocleidomastoid. Muscle relaxation patterns are analyzed to determine the auditory response threshold.

oVEMP (Ocular VEMP)

oVEMP focuses on the utricle and the extraocular muscles contralateral to the tested ear. Electrodes are positioned on the skin near the contralateral eye muscles. A bone-conducted stimulation is used, and contractions of the extraocular muscles are analyzed by the software [75].

Evaluation of Time Constant via Rotational Chair Test

This test provides a quantitative evaluation of the function of the semicircular canals by analyzing vestibulo-ocular reflexes [76]. During the test, the participant is seated and secured in a rotational chair (Gigatorque, Difra®) with the head fixed and centered on the axis of rotation. The participant wears goggles that record eye movements using infrared digital video cameras. Once in darkness, the chair accelerates at 60°/s until it reaches a velocity of 60°/s (clockwise or counterclockwise). After 90

seconds of constant-speed rotation, where around 60 seconds representing the average habituation time of the semicircular canals [77], the chair decelerates at $60^\circ/\text{s}^2$ until it comes to a complete stop. A 90-second post-rotational pause follows. The procedure is then repeated in the opposite direction to the initial rotation. The primary outcome measure will be the vestibulo-ocular reflex time constant, defined as the time required for the slow-phase eye velocity to decay to 37% of its peak value. Directional asymmetry between clockwise and counterclockwise rotations will also be examined [76].

Hearing screening test

Hearing screening will be performed using a tablet-based application comprising a pure-tone test, SoTone, and a speech-in-noise test, SoNoise (SONUP, France), installed on Android tablets (Samsung Galaxy Tab A7, Samsung Electronics Co. Ltd.) [78]. Calibrated circumaural headphones (DD45, RadioEar, Denmark) are connected to the tablets via bluetooth to ensure audio quality. Both tests are tuned to predict a pure-tone average (PTA) exceeding 30 dB HL, the threshold for disabling hearing loss in France. The SoTone test uses only 2 presentation levels (i.e., 25 dB HL and 45 dB HL) at 4 frequencies (i.e., 0.5, 1, 2, and 4 kHz) for both ears to predict a PTA of more than 30 dB HL. If 2 or more tones are not perceived at 25 dB HL, hearing loss is predicted with 96% sensitivity and 84% specificity. The SoNoise test automatically determines the speech reception threshold. The speech material consists of triplets of words (digit-common noun-color) presented at varying signal-to-noise ratios. Speech reception threshold assessment utilizes a forced-choice method in which the signal-to-noise ratio is adjusted adaptively. The SoNoise test predicts a PTA greater than 30 dB HL with 90% sensitivity and 89% specificity. The application automatically records the duration of each test.

The entire vestibular & auditory assessment process will take approximately 45 minutes.

Imaging and spectroscopy

MRI system

All magnetic resonance imaging (MRI) scanning sessions will be conducted at the CYCERON research platform using a 3-T MRI scanner (3T SIGNA PREMIER, GE Healthcare) equipped with a 48 channels head coil and a 30 channels flexible AIR coil to ensure high-quality data acquisition for both brain and muscle acquisitions.

Brain MRI/S: Conventional brain MRI will include morphological and functional sequences. The protocol will include: acquisition of high-resolution whole-brain MRI to enable structural analyses and precise voxel placement for spectroscopy (1mm isotropic MPRAGE T1 weighted and a 1mm isotropic 3D CUBE T2 weighted FLAIR); acquisition of resting-state functional MRI (rs-fMRI) to assess spontaneous brain activity and functional connectivity across large-scale neural networks (2mm isotropic 2D-EPI using an hyperband acceleration of 4 simultaneous slices, TR = 1s); and acquisition of proton magnetic resonance spectroscopy (^1H -MRS, PRESS) spectra in predefined brain regions of interest to assess the relative concentrations of key neurometabolites. Brain regions for ^1H -MRS acquisition were selected based on their involvement in executive functioning, motor control, gait regulation, and age-related neural

alterations potentially associated with falls. The right dorsolateral prefrontal cortex (rDLPFC) was selected because of its role in executive control, attentional allocation, and dual-task processing during gait and balance tasks [79–81]. The posterior cingulate cortex (PCC) was selected because it represents a central hub of the default mode network and is particularly vulnerable to age-related metabolic alterations [81, 82]. The right pre-supplementary motor area (pre-SMA) was selected because of its involvement in motor planning and cognitive-motor integration during locomotion and balance control [83, 84].

Participants will be positioned supine in the MRI scanner and required to remain still throughout the approximately 45-minute acquisition. During the rs-fMRI scan, participants will be instructed to remain awake with their eyes open and to let their thoughts flow without focusing on any specific task. All acquisitions will follow established quality standards for brain imaging and magnetic resonance spectroscopy.

¹H-MRS will be acquired from a 20 × 20 × 20 mm voxel placed in the right dLPFC, posterior cingulate cortex, right pre-supplementary motor area using a PRESS sequence (TR = 3000 ms; TE = 30 ms).

Muscle MRI/S: Muscle composition and metabolite concentrations will be assessed using MRI and ¹H-MRS, respectively. As aging is associated with increased adipose tissue within skeletal muscle and impaired mobility [85, 86], high-resolution structural images of the bilateral thigh muscles will be acquired using a 3D multi-echo proton-density weighted Dixon sequence (IDEAL, Iterative Decomposition of water and fat with Echo Asymmetry and Least-Squares estimation to quantify muscle fat fraction (FF). Acquisition parameters are: TR/TEs = 8.7/3.8, ms; flip angle = 3°, 72 slices, 5-mm slice thickness, in-plane resolution = 0.9 mm x 0.9 mm. Regions of interest will be defined at the mid-thigh level (centred on the last on the proximal end of the short head of the biceps femoris muscle), and FF will be calculated based on the separation of water and fat signals. Muscle cross-sectional area (CSA) corrected for intramuscular FF will also be determined using these data.

For ¹H-MRS, voxel will be positioned within the vastus lateralis muscle of the dominant limb. Spectra will be acquired using a PRESS sequence with TR = 3000 ms, TE = 35 ms, 128 acquisitions per spectrum, a spectral bandwidth of 5000 Hz, and 4096 spectral points. Water suppression and shimming will be performed using the GE Auto Prescan procedure. Spectra will be processed using Osprey. Absolute carnosine concentration will be determined from the ratio of the integrated C2-H carnosine resonance to the unsuppressed intramuscular water signal, with appropriate relaxation and muscle-water-content corrections [87], and expressed in mmol/kg wet weight. This muscle was selected due to its large volume, its well-documented sensitivity to age-related neuromuscular remodeling, and its potential relevance to gait mechanics and falls [88–90]. Metabolite concentrations will be quantified using dedicated spectroscopy analysis software.

Participants will be positioned supine in the MRI scanner. The total acquisition time for muscle MRI/S will be approximately 45 minutes. To minimize motion artifacts, the lower limbs will be carefully positioned

and stabilized using fixation supports, and participants will be instructed to remain as still as possible throughout the acquisition. All images will undergo visual quality control prior to analysis.

Prior to the main data collection, pilot measurements will be conducted in five participants to assess feasibility, optimize sequence parameters, and ensure participant comfort. Data obtained during this pilot phase will not be included in the final analyses.

Ultrasound

Vastus lateralis pennation angle, as an indicator of muscle quality [91], will be assessed using real-time B-mode ultrasonography (Clarius HD3, Clarius Mobile Health, Vancouver, Canada) with a linear probe (L15HD). Participants will lie supine for 10 minutes prior to imaging to allow fluid redistribution and minimize measurement variability.

The measurement site will be standardized at the mid-thigh level, defined as 50% of the distance between the greater trochanter and the lateral border of the patella [92]. The probe will be positioned longitudinally, parallel to the muscle fascicles, with minimal pressure applied to avoid tissue deformation. Participants will be instructed to remain relaxed throughout the procedure. Images will be acquired to clearly visualize the superficial and deep aponeuroses and the muscle fascicles. A minimum of five images will be recorded for each participant, and the three best-quality images will be selected for analysis. Pennation angle will be measured offline using ImageJ software (National Institutes of Health, Bethesda, MD, USA) as the angle between the deep aponeurosis and the muscle fascicles. Fascicles will be included only if their insertion direction toward the aponeurosis is identifiable and at least ~ 25% of the fascicle length is visible within the field of view. When the full fascicle is not visible, the visible portion will be linearly extrapolated following its orientation. All ultrasound settings will be kept constant across participants (frequency: 20 MHz, gain: 50 dB, dynamic range: 75). Image analysis will be performed independently by two trained assessors to ensure inter-rater reliability. The total duration of the ultrasound assessment will be approximately 15 minutes. Muscle ultrasonography will be performed in line with the current guidelines and recommendations for musculoskeletal ultrasonography by the European Federation of Societies for Ultrasound in Medicine and Biology [93].

Functional Near-Infrared Spectroscopy (fNIRS)

Cortical and muscular hemodynamic responses will be assessed using fNIRS during the dual-task gait analysis. Data will be acquired using a portable continuous-wave fNIRS system (PortaLite MkII, Artinis Medical Systems, Elst, Netherlands) controlled via OxySoft software (version 4.2.0.1).

Two sensors will be used simultaneously: one positioned over the right dlPFC due to its involvement in executive and dual-task processing [94] and one over the dominant side VL muscle. The dlPFC optode will be placed according to the international 10–20 EEG system at the Fp2 location, corresponding to the right prefrontal cortex. The muscle optode will be positioned at the mid-thigh level over VL.

Prior to sensor placement, the skin will be cleaned and, if necessary, shaved to improve signal quality. Optodes will be secured using adhesive patches and covered with a dark band to minimize interference from ambient light. A short stabilization period (~ 2 minutes) will be allowed after signal initiation to ensure optimal signal quality. Data acquisition will include a 1-minute baseline recording in a static standing position, followed by continuous recording during the dual-task gait protocol. Each cognitive condition (task-switching task) will be performed in 2-minute blocks, with a 30-second baseline period recorded prior to each block and an additional 30-second baseline period recorded at the end of the trial.

Changes in oxygenated (HbO) and deoxygenated hemoglobin (HbR) will be recorded. Data will be processed using standard fNIRS analysis pipelines, and motion artifacts will be identified and corrected prior to analysis.

Biological and genetic measures

Blood samples (approximately 30 mL) will be collected in the morning in fasting participants and drawn into multiple tubes (dry, fluoride, heparinized and EDTA) according to support forthcoming analysis.

Phenotypic age will be calculated using the clinical PhenoAge algorithm, based on chronological age and nine clinical blood biomarkers: albumin, creatinine, fasting glucose, CRP/hs-CRP, alkaline phosphatase, white blood cell count, lymphocyte percentage, mean corpuscular volume, and red cell distribution width [95]. This measure will be used to explore whether phenotypic age is more strongly associated with falls than chronological age. In addition, blood biomarkers related to aging processes, cognition, and neuromuscular function will be quantified, including BDNF, IGF-1, GDF-15, NfL, AST, cystatin C, electrolytes, HbA1c, lipid profile, vitamin B12, 25-OH vitamin D, and circulating cytokines such as IL-6, IL-7, IL-8, TNF- α , IL-10, and IL-15 [96, 97].

Proteomic and genomic analysis will be performed when all samples will be collected. Analysis will use plasma samples, obtained from K2-EDTA tubes processed within 15 minutes of collection. Samples will be centrifuged, aliquoted, and stored at -80°C at the CHU Caen Normandie Biological Resource Center (InnovaBIO) until analysis.

Proteins will be extracted, digested, and analyzed using mass spectrometry. Quantified proteins will be normalized and assessed for differential expression, and functional enrichment analyses (e.g., Gene Ontology, Reactome, WikiPathways) will be performed to support biological interpretation.

Genome-wide SNP analysis will be conducted to explore genetic variants potentially associated with fall-related phenotypes. DNA will be extracted and genotyped using high-density SNP arrays. In addition, RNA sequencing (RNA-seq) will be performed on dedicated samples to explore transcriptomic profiles, including expression quantitative trait loci (eQTLs), alternative splicing, and gene expression signatures.

Prospective fall monitoring

After completion of the baseline assessment, falls will be monitored prospectively for 12 months using a Progressive Web App (PWA) installed on participants' smartphones or tablets. A fall will be defined as the participant coming to rest on the ground, floor, or a lower level. Every week, participants will receive a push notification inviting them to complete a brief questionnaire about fall occurrence during the week. The questionnaire will ask whether the participant has fallen during this period and will assess fear of falling using a 11-point scale ranging from 0 ("no fear") to 10 ("very intense fear"). As inhibitory control processes are involved in gait adaptation and fall avoidance, repeated cognitive assessments will also be performed during follow-up [98]. Each month, participants will also complete a brief 30-second Go/No-Go task using two visual stimuli associated with predefined responses. Reaction times for correct responses and the number of errors will be recorded to provide repeated measures of inhibitory control during follow-up. If a participant misses two consecutive questionnaires, an additional reminder will be sent through the application. If no response is received after this reminder, the research team will contact the participant by telephone or e-mail. Participants who do not own a compatible mobile device or who are unable to use the application will be contacted directly by the research team each week. The PWA will be accessible only to authorized participants through a personal authentication link. Questionnaire and cognitive-task data will be transmitted via secure encrypted connections and stored on a protected university server. Responses will be linked to a pseudonymized participant code, and no personal data will be retrieved from participants' phones.

Outcome measures

Primary outcome

The primary outcome is the performance of ML models in discriminating fallers from non-fallers at baseline, based on retrospective fall history over the previous 12 months. Model performance will be evaluated using appropriate classification metrics, including AUC-ROC, reflecting the ability of the models to classify participants based on fall history.

Retrospective fall history is used as the primary reference outcome as it represents a well-established and clinically relevant indicator of fall risk in older adults. Using baseline fall status allows the identification of multimodal biomarkers associated with a confirmed fall phenotype.

Secondary outcomes

Secondary analyses will evaluate the ability of baseline multimodal features to predict prospective falls during the 12-month follow-up period using appropriate predictive performance metrics.

Data management

Data will be managed in an electronic database under the responsibility of the study regulatory sponsor (SLB Pharma). Data entry will be performed by investigators or authorized study personnel listed in the task delegation log. All study data, including data collected through the smartphone-based follow-up

application, will be pseudonymized using unique participant identifiers. No directly identifiable personal information will be stored in the study database. A key linking participant identity to study identifiers will be stored separately in a secure location with access restricted to designated personnel. Data will be transmitted via secure encrypted connections and stored on a protected university server (UniCloud) with restricted access limited to authorized members of the research team. Data quality will be ensured through validation checks and monitoring procedures. Data will be retained for the duration of the study and subsequently archived in accordance with applicable regulatory requirements. In addition, anonymized datasets will be made available in open-access repositories (Recherche Data Gouv) for at least 10 years after project completion. Associated metadata and digital object identifiers (DOIs) will remain permanently accessible. Genomic and transcriptomic data will be handled in accordance with relevant data protection regulations, including the General Data Protection Regulation (GDPR). Given the potentially identifiable nature of these data, genomic datasets will not be publicly available in open-access repositories.

Data analysis and machine learning

Descriptive statistics will be used to summarize baseline characteristics and the main variables. Continuous variables will be reported as mean $\pm$ standard deviation or median with interquartile range, and categorical variables will be reported as counts and percentages.

The primary objective of the analysis is to develop machine learning models to classify participants as fallers or non-fallers based on multimodal baseline data. The target variable will be faller status, defined as at least one fall in the previous 12 months versus no fall. Input data will include clinical, functional, imaging, and biological measures, as defined in the protocol.

Given the dataset's multimodal nature, preprocessing will be customized to each data type. For tabular data, preprocessing may include data cleaning, normalization or scaling where appropriate, encoding of categorical variables, and feature selection or dimensionality reduction to reduce redundancy and improve model stability. For imaging data, preprocessing will include standard image preparation steps, and data augmentation may be considered during model training to improve model generalizability. All preprocessing, feature selection, dimensionality reduction, and augmentation procedures will be performed within the validation framework to avoid data leakage.

Supervised machine learning approaches will be used for model development. For structured data, tree-based ensemble methods and regularized regression approaches will be considered, with attention to model complexity and the available sample size. Modality-specific models will first be evaluated for structured and imaging data. Exploratory multimodal models integrating information across modalities will also be developed. The complexity and interpretability of these models will be considered in relation to the available sample size and internal validation performance.

Model development and evaluation will be based on internal validation. Stratified k-fold cross-validation and/or bootstrap resampling will be used to obtain reliable estimates of model performance and limit

overfitting. Hyperparameter tuning, feature selection, and preprocessing will be performed within this framework. Model performance will be primarily assessed using the area under the receiver operating characteristic curve, with 95% confidence intervals. Additional metrics will include accuracy, sensitivity, and specificity. Feature importance will be explored using model-based measures and, where relevant, SHapley Additive exPlanations (SHAP) values to identify the most informative predictors [99].

Secondary analyses will explore the ability of the selected features to predict prospective fall outcomes during the one-year follow-up, with baseline fall status included as a feature.

Missing data will be described separately by modality. For tabular data, missing values will be handled within the preprocessing pipeline using appropriate methods based on the type and pattern of missingness. For imaging data, availability and completeness will be summarized and incorporated into the definition of the corresponding image-based or multimodal analysis datasets. All analyses will be conducted using R and/or Python. All analysis code and machine learning models will be made publicly available via GitHub: <https://github.com/evrimgokce/PrediFALL>.

Discussion

Multimodal and multidisciplinary approach

The PREDIFALL project proposes a holistic multimodal framework integrating clinical, functional, sensory, vestibular, imaging, metabolic, and blood-based molecular assessments to better understand falls in healthy older adults. International experts point out the need for multidimensional approaches to better capture the multifactorial nature of falls rather than relying on isolated clinical or functional assessments [12, 100]. In this context, one of the major strengths of the project is the integration of complementary assessments and expertise from multiple disciplines, including movement sciences, neuroscience, geriatrics, imaging, and data science. Integrating these complementary assessments using machine learning approaches may help identify multidimensional profiles associated with both retrospective and prospective falls.

Blood-based biomarkers and metabolic measures

A major exploratory aspect of the PREDIFALL project is the investigation of blood-based biomarkers, along with brain and muscle metabolic measures, potentially associated with falls in healthy older adults. This exploratory approach carries uncertainty, as the relevance of these markers to falls remains largely unknown. If specific signatures associated with falls can be identified, they may help improve our mechanistic understanding of why some healthy older adults fall while others do not and help refine future multidimensional approaches to fall risk assessment.

Feasibility, limitations, and future perspectives

The multimodal protocol may represent a significant burden for participants, given the large number of evaluations conducted across multiple visits. To improve feasibility and reduce fatigue, assessments will be distributed over three sessions with recovery intervals between them. Pilot imaging sessions will also be conducted before the main study to optimize procedures and participant comfort. Nevertheless, participant burden and long-term retention remain important challenges for the successful completion of the project.

Another limitation is the modest sample size relative to the data's dimensionality. Integrating heterogeneous data across multiple domains requires careful methodological harmonization, robust preprocessing, and appropriate feature selection and validation. Although internal validation and feature selection procedures will be used to reduce overfitting, identified multimodal profiles and predictive models will require replication in larger independent cohorts.

Finally, several assessments included in the project rely on sophisticated equipment and specialized expertise, which may currently limit direct clinical applicability. However, combining these complementary evaluations within the same study may help better understand falls in healthy older adults. A better understanding of the mechanisms underlying falls is an important step toward developing more effective prevention strategies and supporting our aging society to stay active.

Abbreviations

¹H-MRS

Proton Magnetic Resonance Spectroscopy

6MWT

Six-Minute Walking Test

ALT

Alanine Aminotransferase

AST

Aspartate Aminotransferase

AUC-ROC

Area Under the Receiver Operating Characteristic Curve

BDNF

Brain-Derived Neurotrophic Factor

BIA

Bioelectrical Impedance Analysis

CBTT

Corsi's Block Tapping Test

cVEMP

Cervical Vestibular Evoked Myogenic Potential

DFA

Detrended Fluctuation Analysis

dIPFC

Dorsolateral Prefrontal Cortex

DNA

Deoxyribonucleic Acid

DTC

Dual-Task Cost

EEG

Electroencephalography

EDTA

Ethylenediaminetetraacetic Acid

eQTL

Expression Quantitative Trait Loci

FES

Fall Efficacy Scale

FFQ

Food Frequency Questionnaire

fNIRS

Functional Near-Infrared Spectroscopy

FTT

Foot Tapping Test

GAI

Geriatric Anxiety Inventory

GDF-15

Growth Differentiation Factor-15

GDS

Geriatric Depression Scale

GDPR

General Data Protection Regulation

GNSS

Global Navigation Satellite System

GVS

Galvanic Vestibular Stimulation

HbA1c

Glycated Hemoglobin

HbO

Oxygenated Hemoglobin

HbR

Deoxygenated Hemoglobin

IADL

Instrumental Activities of Daily Living

IGF-1

Insulin-Like Growth Factor 1

IL

Interleukin

IPAQ

International Physical Activity Questionnaire

LBT

Line Bisection Test

ML

Machine Learning

MMSE

Mini-Mental State Examination

MDPQ-16

Mobile Device Proficiency Questionnaire-16

MRI

Magnetic Resonance Imaging

NfL

Neurofilament Light Chain

oVEMP

Ocular Vestibular Evoked Myogenic Potential

OLST

One-Leg Stance Test

PTA

Pure-Tone Average

PSQI

Pittsburgh Sleep Quality Index

PWA

Progressive Web Application

RFST

Recovery From Fall/Stand Test

RNA

Ribonucleic Acid

RNA-seq

RNA Sequencing

rs-fMRI

Resting-State Functional Magnetic Resonance Imaging

SART

Sustained Attention to Response Task

SF-36

Short Form-36

SHAP

SHapley Additive exPlanations

SNP

Single-Nucleotide Polymorphism

SST

Symbol Search Test

STST

Sit-to-Stand Test

TST

Task-Switching Test

TUG

Timed Up and Go

VL

Vastus Lateralis

vHIT

Video Head Impulse Test

Declarations

Ethics approval and consent to participate

The PREDIFALL study was approved by the Comité de Protection des Personnes Sud-Méditerranée IV (National Reference No: 2026-A00859-42; Dossier No.: 26.01463.000594). All procedures involving human participants will be conducted in accordance with the Declaration of Helsinki and applicable national regulations. Written informed consent will be obtained from all participants prior to study inclusion and baseline assessment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Author Contribution

AL is the principal investigator for this study. EG and CM wrote the first draft of the manuscript. All authors were involved in the preparation and design of the study. All authors read, revised, and approved the final version of the manuscript.

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Availability of data and materials

Data collection for this study is currently ongoing and no datasets have yet been generated or analyzed. Following completion of the study, de-identified non-genetic data will be made available through a publicly accessible data repository in accordance with institutional and ethical regulations. Genetic and genomic data will not be publicly available due to privacy, ethical, and data protection considerations.

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Figures

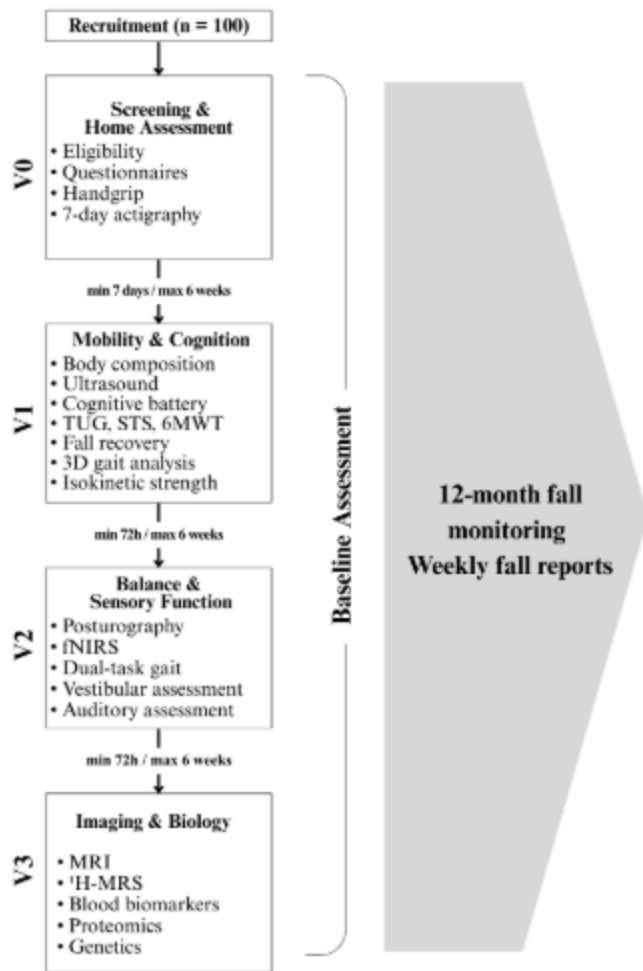


Figure 1

Study procedure

Procedure		V0	V1	V2	V3	Follow-up
Medical Exam & Informed Consent		X				
Actimetry		X				
Progressive Web App (fall monitoring)						X
General health characteristics	Demographics	X				
	Geriatric Depression & Anxiety Inventory	X				
	Instrumental Activities of Daily Living	X				
	Fall Efficacy Scale	X				
	International Physical Activity Questionnaire	X				
	36-Item Short Form Survey	X				
	Pittsburgh Sleep Quality Index	X				
	Food Frequency Questionnaire	X				
	Foot Preference	X				
	Handedness Inventory	X				
	Acceptability E-Scale*					X
	Mobile Device Proficiency Short Form*					X
	Foot Preference	X				
	Body composition measurement		X			
Cognition	Mini-Mental State Examination	X				
	Cognitive Test Battery		X			
Mobility, gait & muscle strength	Foot Tapping		X			
	One-Leg Stance		X			
	Sit-to-Stand		X			
	Timed Up and Go		X			
	Six-Minute Walk		X			
	Gait Analysis		X			
	Dual-Task Gait Analysis			X		
	Handgrip strength	X				
	Lower limb strength and power		X			
	Lower limb proprioception		X			
Postural, vestibular & sensory	Fukuda			X		
	Video Head Impulse Test			X		
	oVEMP & cVEMP			X		
	Posturography			X		
	Fall Recovery Test			X		
	Hearing screening			X		
	Rotational chair			X		
Imaging	Brain MRI & MRS				X	
	Muscle MRI & MRS				X	
	Muscle ultrasound		X			
	fNIRS			X		
Blood	Blood draw				X	

 At least 7-day interval

 Starts immediately after V3

 At least 3-day, at most 6-week interval

* Performed at least 2 months after V3

Figure 2

PrediFall schedule of assessments

cVEMP, Cervical Vestibular Evoked Myogenic Potentials; fNIRS, Functional Near-Infrared Spectroscopy; MRI, Magnetic resonance Imaging; MRS, Magnetic Resonance Spectroscopy, oVEMP, Ocular Vestibular Evoked Myogenic Potentials

