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REACH

Deliverable D28: Formalized results of final testing and optimization activities: Summarization of testing and evaluation of final testing of continuously improved system in the form of prototypes in real world environments and presentation of optimization measures (associated with tasks T6.5, T6.6, T6.7, T6.8). D28 is an update on D27. Additional associated deliverables are D12, D13, D23, D31, and D44.

Abstract: In order to provide a comprehensive summary of all testing activities, the medical core group (DTU, HUG, SK, TUM) created a mini protocol template (which requested the outline of some methodological aspects of each study such as study designs, the recruitment phase, population under investigation, etc.), and ensured that data were submitted and provided by the trial manager to the core group. In this deliverable we present, structure, and interpret the formalized results of the final testing and optimization activities of all testing activities in REACH. The deliverable includes the summarization of testing and evaluation of final testing of a continuously improved system in the form of prototypes in real world environments and the presentation of optimization measures. The deliverable is an update on deliverable D27 and associated with tasks T6.5, T6.6, T6.7, T6.8. In reaction to the reviewers' comments we initiated additional trials focusing on *practice cases*. Those trials are specifically ladled and included in the updated overview. A review on factors, i.e., falling, frailty, cognitive decline, sarcopenia, social isolation, and malnutrician, was performed to show the most important co-factors. Addressed in this deliverable is also the role of privacy and the hierarchy of needs which are essential components of the acceptance and use of technology.

Lead Partner:	SK
Participants:	SK, DTU, TUM + all partners (contribution to system integration/optimisation and testing/practice cases)
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Date	Activity	Status
01.06.2019	Deliverable strategy ready	completed
31.08.2019	Deliverable structure ready	completed
31.12.2019	Input of participants/partners ready	completed
15.01.2020	Input integrated and formalized	completed
26.01.2020	Draft of report ready	completed
30.01.2020	Review completed	completed
31.01.2020	Submission to EU	completed

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Tasks of the involved partners with respect to the deliverable (and respective tasks) presented in this report:

Partner	Short task description
TUM	• Member of medical task force – discussion and development of strategy with other members • Development strategy and structure for overall system integration, system optimisation, and testing • Overall coordination of system integration, system optimisation, and testing • Strategy and structure for adding practice cases • Major contribution to system integration, system optimisation, and testing activities in Touchpoints 2 • Contribution to system integration, system optimisation, and testing activities in Touchpoints 1, 3, and 4 • Revision of the deliverable
DTU	• Member of the geriatric/medical task force • Contribution to testing activities in Touchpoint 4 • Co-lead of development of strategy and structure of this deliverable • Co-lead in collecting and integrating inputs for this deliverable • Contribution to development and updating of mini-protocols and trial summaries • Analysis and interpretation of overall trial outcomes • Test of smart home technologies
TU/e	• Contribution to system integration, system optimisation, and testing activities in Touchpoints 1 and 3

EPFL	• Contribution to system integration, system optimisation, and testing activities in Touchpoint 3
CU	• Contribution to system integration, system optimisation, and testing activities in Touchpoint 4
FIAIS	• Contribution to system integration, system optimisation, and testing activities in Touchpoint 2
AM	• Contribution to system integration, system optimisation, and testing activities in Touchpoints 1,2, and 4 • Lead of practice cases development
BZN	• Contribution to system integration, system optimisation, and testing activities in Touchpoint 3
SC	• Contribution to system integration, system optimisation, and testing activities in Touchpoint 2
Arjo	• Contribution to system integration, system optimisation, and testing activities in Touchpoint 2
Philips	• Contribution to system integration, system optimisation, and testing activities in Touchpoint 2 • Contribution to system integration, system optimisation, and testing activities in all Touchpoints with regard to the inclusion of behaviour change techniques
DIN	• Contribution to system integration, system optimisation, and testing activities in all Touchpoints from a standardisation perspective • Extraction o items as inputs for standardisation activities
Sturrm	• Coordination with new simplified REACH structure and business and marketing aspects (e.g. in the context of practice cases).
Lyngby	• Contribution to system integration, system optimisation, and testing activities in Touchpoints 4
SK	• Lead of the geriatric/medical task force • Lead of development of strategy and structure of this deliverable • Lead in collecting and integrating inputs for this deliverable • Development and updating of mini-protocols and trial summaries • Analysis and interpretation of overall trial outcomes • Contribution to system integration, system optimisation, and testing activities in Touchpoint 2 • Practice case testing
HUG	• Member of the geriatric/ medical task force • Contribution to system integration, system optimisation, and testing activities in Touchpoint 1 and 3 • Practice case testing

Contents

Key expressions

Abbreviations for partners:

AH: ArjoHuntleigh
AM: Alreh Medical
CU: University of Copenhagen
DTU: Technical University of Denmark
EPFL: École Polytechnique Fédérale de Lausanne
HUG: Hôpitaux Universitaires de Genève
SC: SmartCardia
SK: Schön Klinik
TU/e: Eindhoven University of Technology
TUM: Technical University of Munich
ZZ: ZuidZorg

Activities of Daily Living (ADLs): Activity categories (e.g. dressing, bathing, feeding, etc.) which are necessary to maintain care independent living.

Activity Recognition Chain (ARC): is commonly used to analyse human activity data by means of machine learning methods and aims to detect activity patterns.

D: Deliverable report.

M: Project month within the project duration (e.g. M19 refers to project month 19, namely August 2017)

Personalized Intelligent Interior Units (PI²Us): Smart furniture which is used to integrate the REACH concepts and functionality seamlessly into the different REACH use case settings. In a broader sense, Touchpoints will mainly materialize as “furniture”, i.e., elements that can be placed and moved within a particular environment or setting (e.g., beds, bathroom furniture, mobile walkers/standers, large-scale interfaces, smart flooring tiles, smart tables, etc.). Additionally, the Touchpoints will also appear as ambient sensor add-on modules and wearables.

Physical Activity: Target condition of REACH. The systemized early detection and intervention-based prevention of physical inactivity and sedentary behavior in a variety of care settings such as homes and everyday life, day care centers, and other geriatric facilities will not only significantly reduce the risk of LTC admissions and re-admissions (and thus as targeted by REACH reduce overall healthcare cost) but also increase the elderly’s functional performance, social participation, independence, and quality of life.

Physical activity monitors (PAMs): activity trackers, also known as fitness trackers, is a device or application for monitoring and tracking fitness-related metrics such as distance walked or run, calorie consumption, and in some cases heartbeat. It is a type of wearable computer.

RCT: Randomised controlled trial

T: Task defined in the project proposal.

Touchpoints/Engine concept: structures the envisioned REACH product-service-system architecture, into manageable research and development clusters.

Touchpoints: The “Touchpoints” will act as “graspable” front ends towards the end users (elderly). The Touchpoints will serve as data gathering devices and as mediators of services and interventions coordinated by the Engine towards the end user. Each Touchpoint is modular and made up of several subsystems which allow adapting the system both for a particular person or setting, as well as over time.

WP: Work package defined in the project proposal.

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1 Introduction

REACH creates new market opportunities for European industry, including SMEs to capitalize on European high-tech-knowhow, to make Europe a market leader in prevention technologies, meanwhile tackling the ultimate cause of rising healthcare expenditures.

1.1 REACH overall hypotheses and goals

REACH develops, matures, and integrates products, processes, and solutions that seek to prevent older citizens from loss of function and decline as a major cause of physical inactivity. As such, the REACH system transforms clinical and care environments such as homes and everyday life, day care centres and other forms of care into highly personalized and data-driven early intervention systems that engage older people in preventative and rehabilitative activity, primarily physical activity but also with regard to cognitive, mobility, social and nutritional aspects (see Figure 1-1).

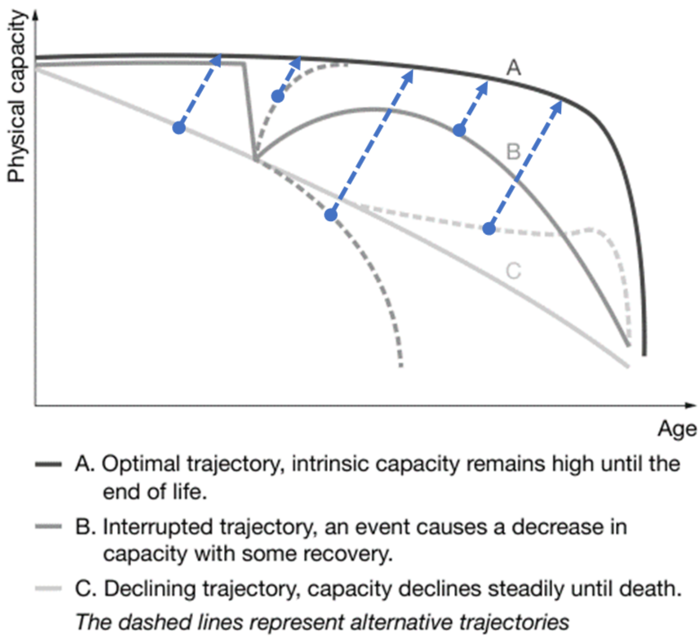

Figure 1-1: REACH solutions help to modify and optimize trajectories of physical capacity (image adapted from WHO “World Report on Ageing and Health”)

1.2 REACH toolkit and Touchpoints

The REACH toolkit guides the technical implementation of REACH. The toolkit comprises a series of partially independent components or “raw elements” developed by the partners, which can be classified into 11 categories (sensors, analytics and ML-tools, devices, smart furniture, exercise and behaviour change schematics, human-machine-interfaces, data storage platforms etc.). REACH has developed and refined a design methodology (Sensing-Monitoring-Intervention/SMI workflow) for the use case specific combination and integration of these elements (see Figure 1-2).

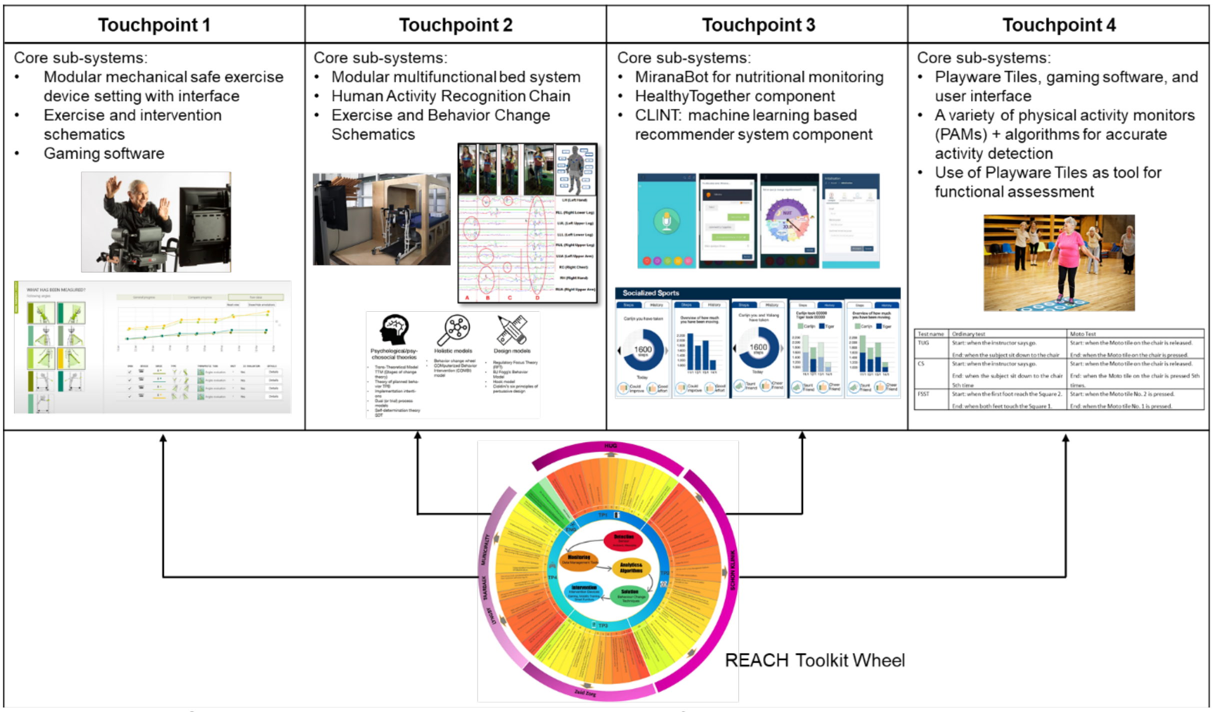

Figure 1-2: REACH Toolkit Wheel and its connection to the four Touchpoints

The REACH toolkit approach allows the tailoring of solutions that create value for end-users, care providers and health care payers alike. It does so through the combination, integration and adaptation/re-design of its elements towards the different contexts of different countries, different payment and reimbursement structures (e.g., insurance or tax-based), specific use case settings and processes and, most importantly, individual end-user needs and capabilities. (SK/Schön Klinik, HUG/Geneva Hospital, ZZ/Zui-dZorg, Lyngby/Lyngby Municipality). In this context, REACH demonstrates its ability to integrate, cross-integrate, share and interchange its elements (e.g. several Touch-points share standard elements that were, to a certain extent, adapted to the use case setting) and co-create (REACH believes that the ability to identify, incorporate and de-sign / develop new case-specific elements for each use case setting is important to the achievement of useful and appropriate solutions.).

1.3 Ecosystem approach and system verification and validation by trials

REACH achieves its objectives through highly integrated sensing-monitoring-intervention chains representing comprehensive solutions that are exemplarily and iteratively adapted in the project to the ecosystems of a series of care settings throughout Europe (homes, hospitals, care homes, day care facilities, communities, etc.) for older individuals. REACH implements, demonstrates, tests, and validates (by more than 27 small-to medium-sized trials) through those settings, customized and personalized instances of this chain. A unique feature of REACH is the integrated utilization of personalized behaviour change and engagement techniques informing about the development of the products and solutions (sensors, interfaces, devices, etc.).

REACH implements a combination of wearable and ambient sensors for each Touch-point along with a set of co-adapted Machine Learning elements. Machine Learning is used as a core element in multiple ways, e.g. to predict Activities of Daily Living (ADLs), recognize physical activity and behaviour trends, detect deviations of patterns and critical situations, cluster and profile people, and inform the effectiveness of the assignment of certain interventions. Personalised Intelligent Interior Units (PI²Us; smart furniture devices) are used to seamlessly integrate the above described functional elements into daily life in the different target use case settings. Last but not least, REACH has developed practices and schematics to assess the implications of the use of its solutions with regard to privacy, legal, and ethical aspects in order to ensure technology acceptance by end-users, caregivers, and other care and medical professionals (see Figure 1-3).

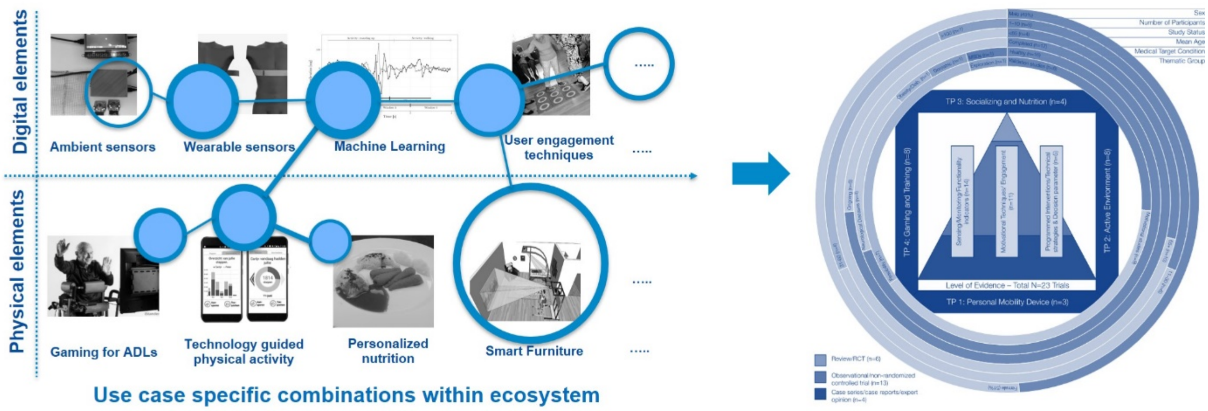

Figure 1-3: Ecosystem approach and system verification and validation by trials

1.4 REACH to market: a simplified structure

In order to work towards market implementation REACH needed to clarify and sharpen the medical purpose of its solutions, develop a regime for market segmentation, facilitate the preparation of medical certification and IPR protection activities, and define concrete business and marketing procedures.

1. **Medical purposes**
   - **Touchpoint 1:** System: Prevent, maintain, and restore balance, muscle strength, and muscle endurance. Patients: Patients who already have mild to moderate limitations due to polyneuropathy, stroke, advanced age, incomplete cross sections, or mild cognitive impairment. Environment: Care homes, rehabilitation institutions, day care environments, offices of occupational and physical therapists, etc. Use under the supervision of instructed personnel; no 1:1 care necessary.
   - **Touchpoint 2:** System: The system is intended to facilitate patient mobilization and help monitor vital signs and potentially dangerous situations. Simultaneously, it should recognize when a patient needs stronger nursing or therapeutic support and then support him or her in the partial takeover of activities. Patients: Patients with moderate to high restrictions of self-care (Activities of Daily Living) and / or with motor and / or cognitive impairment due to a neurological, medical or other disabling disease. Environment: Hospital or other nursing environments. System is able to alert a specialist, care professionals, or other skilled or semi-skilled personnel. Use in the absence of skilled or semi-skilled personnel, which only has to be available nearby.
   - **Touchpoint 3:** System: App for behaviour detection/monitoring, analysis, and modification. Patient: Healthy or not seriously ill people, especially in adulthood. The system can also be used under medical supervision to improve the treatment of chronic diseases (diabetes, sedentary lifestyle, obesity, etc.).

Environment: Everyday environment up to assisted living. Use if necessary, on the recommendation of a doctor.

- **Touchpoint 4:** System: A training guide to improve walking movement capability, gait safety, stability, endurance, and selective leg movements. The system is also able to capture and monitor parameters of gait safety (balance), walking speed, and endurance for functional assessment purposes and to detect physical activity trends and critical situations. Patient: People with gait and stability limitations while still able to walk. Environment: For groups of older people in sports groups and in day care facilities and for self-training. Can also be used for input measurement for allocation to suitable programs and groups.

2. **Market segmentation:** For business and marketing purposes, a simplified REACH structure includes and scales down the solutions developed as part of the Touchpoints in four major target market segments (see Figure 1-4):
   - For developers of new products
   - For health care institutions
   - For homes
   - For communities

   Techniques from the field of motivational segmentation and behaviour change are used to further sub-classify these segments and link them to REACH solutions.

Figure 1-4: Preliminary draft of the REACH consultancy firm website

3. **Technology management:** REACH develops products that are allocated at the intersection between medical and non-medical products. REACH therefore evaluates the market potential for each solution, classifies its solutions and develops associated roadmaps and regimes for medical certification. These

activities are supported by REACH's active involvement and lead in numerous standardization frameworks on national, European (CEN), and worldwide (ISO) levels.

- **Business and marketing**

REACH is currently preparing the formation of a "REACH Active Ageing GmbH" which will serve beyond the project as an integrator of REACH partner's individual products and services and a solution provider to above named market segments.

1.5 Tasks and goals of this deliverable

Deliverable 28 is an updated version of D27. It includes all changes and improvements made with respect to the testing activities presented in D27. The updated aspects are labelled as updated and further described in more detail. Detailed information on trials or tasks completed by the end of the D27 reporting period (M36) can be found in D27. D28 also refers to several associated deliverables (D12, D13, D23, D31, and D44).
D28 is related to the following tasks: **Task T6.5** focussed on the concretisation and adaptation of concept, subsystems, and larger stakeholder contexts, i.e., active user/ stakeholder involvement co-design, and **task T6.6** focussed on the final integration to demonstrators (prototypes) with other systems. The main tasks of this deliverable are the tasks T6.7 and T6.8. **Task T6.7** focussed on the final testing II and evaluation of the demonstrators in real world environments and larger stakeholder context, and task T6.8 focussed on the optimisation of the concept and subsystems and larger stakeholder contexts (active user/ stakeholder involvement/co-design).

- **Updated medical goals and hypotheses (including updated medical purposes and claims):** The hypothesis/ research questions of all trials reported are listed with respect to the Touchpoints.
- **Methodology – overview and classification of all testing activities:** Overview of the methodological characteristics of all REACH trials (n=30), including 10 practice case trials, are updated.
- **Results – Documentation of the testing activities and their outcomes:** Trials completed and performed in the REACH project months M36-M48 are described and results are reported when available.
- **Interpretation of the testing results and outcomes:** The REACH trials interpreted with respect to the importance to different touchpoints and several methodological aspects. A review on factors with co-factors and the Unified Theory of Acceptance and Use of Technology (UTAUT) are addressed.
- **Summary and Conclusion – Lessons learned, exploitation opportunities, project impact:** An reflection of the trial goals and the use of the trial results regarding the core user group of elder persons and patients is stated. Furthermore, the impact of the trial results on the REACH environment is described.

1.6 Reviewer Recommendations addressed in D28

This deliverable addressed the reviewer recommendations outlined in Appendix 2 as follows:

- **R15 - Factors and co-factors**: the reviewers commended that the differences between factors and co-factors in terms of prevention out of evidence based medical data should be addressed. A narrative literature review was performed focussing on factors and co-factors. The full review is attached as Appendix 1 to this deliverable.
- **R16 – Technical maturation with business aspects in mind for Touchpoint 2:** the reviewers commended that the consortium should further work towards the technical maturation and validation of the system. The full-scale TP2 system was evaluated in a real world scenario (real patient room in the SK hospital setting) with patients and elderly participants. Practical hands-on testing of the mobility and playful training components has been tested in patients and healthy elderly in order to receive “practice case” feedback.
- **R18 – Data analytics in Touchpoint 2 (and 3):** the reviewers recommended to prolong the planned duration of the final trials in realistic environments or to run them in 2 batches so that the analytics model construction can be trained on valid data. Data collection of in-domain user groups, i.e., active elderly and patients, was performed to improve the analysis.
- **R20 - Dissemination and market deployment:** the reviewer recommendation on this aspect was, inter alia, to better define the final users. To improve the description of the target user groups, more “practice case” trials were initiated.

2 Updated medical goals and hypotheses (including updated medical purposes and claims)

The ***overall hypothesis*** for the REACH system generated out of the diverse aims has to be the lowest common denominator:

*The **REACH system** is able to improve living conditions, foster autonomy, prevent adverse events of healthy elderly and patients by motivating them to improve physical status, cognitive abilities, and mental state by supporting a healthier life-style.*

This generalised hypothesis does not reflect important aspects of the REACH system.

Therefore, we defined **sub-hypotheses** for each Touchpoint:

1. **TP1**: The REACH system enables elder persons to prolong the time living at home in a healthier and more independent state, being ambulant also outside the home.
2. **TP2**: The REACH system enables patients to reduce the time being hospitalised, prevent decline after discharge, and readmission, being able to perform their ADL with as few supports from care givers as possible.
3. **TP3**: The REACH system enables elder persons and patients to improve their nutritional status and enhance their social environment.
4. **TP4**: The REACH system (A) enables elder persons and patients through individualised motivational strategies to engage in effective playful physical activity; and (B) care providers (professional and families) to monitor remotely frail elder persons living at home to detect critical events, bringing peace-of-mind and enhancing care security.

Separated with regards to the specific Touchpoints, the following four tables provide an overview of the testing activities of REACH, including the specific hypotheses or research questions. Those trials with an updated status are described in more detail in the Results. Descriptions of all other studies can be found in the preceding deliverable D27. Already published trials or those currently under review are highlighted in light green.

In reaction to the reviewers' comments we initiated additional trials focusing on practice cases which are included in the updated overview given in Chapter 3. Trials performed as practice trials are specifically ladled as such.

Five trials are still ongoing. The partners involved in these trials decided to continue the trials although the financing from the REACH project will be closed. Costs that will accrue after January 31, 2020 will be covered at one's own expense.

Trials mainly belonging to Touchpoint 1:

Table 2-1 Overview of trials that belong mainly to TP1

#	TP	Title	Keywords	Hypothesis/ Research questions	Status
10	1	ActivLife Test (**practice case**)	motivation, activity centre, RCT	H1: The motivation to do more PA is the same for seniors after using activLife and those after following the advices from physiotherapists. H2: Seniors remains in the same stage of change after using activLife. H3: Seniors remains in the same stage of change after following the advices from physiotherapists H4: The physical conditions (in terms of strength) remain unchanged for seniors after using activLife and those after following advices from physiotherapists. H5: The level of exertion of activLife exercise is the same as that of the exercise advised from the physiotherapists. H6: The strength measurement is the same as the Mobee Fitness measurement.	**Published**
17	1	HUG early testing (**practice case**)	Alreh Medical, elderly, safe standing, gaming platform,	1. iStander active device is a safe solution for the elderly. 2. iStander active has a good functionality for the elderly rehabilitation 3. Neuroforma gaming system is engaging tool for elderly rehabilitation. 4. Neuroforma interface is easy to use. 5. Fitbit HR sensor is comfortable, easy to use and valuable HR sensor.	**Published**
21	1	A personal mobility device for elderly physical rehabilitation: a study of acceptance and efficiency (**practice case**)	Rehabilitation; Serious games; Wearable Electronic Devices	- rehabilitation using the mobility equipment is as effective as the standard care - the usage of the mobility equipment will improve clinical outcomes such as physical strength, balance, and risk of falls - the use of the REACH concept adds value to the continuity of patient care, specifically in terms of engagement and motivation to be more active during the hospital stay and when returning home	Update: **under review**
24	1	activLife Test 3 (**practice case**)	Muscle strength; frailty; cognitive training	1. activLife device is a safe solution for the elderly 2. activLife has a good functionality for the elderly rehabilitation 3. Vast Rehab -gaming system is an engaging tool for elderly rehabilitation 4. Vast Rehab interface is easy to use.	Update: *new trial*, data acquisition finished
26	1	Welfare Home Trial (**practice case**)	Personalized training program; elderly;	- to assess the impact of the therapy (multimedia platform training) among senior people with Mild Cognitive Impairment - to assess the attractiveness of the activLife therapy in users 60+ living in a Social welfare home - to assess the functional change among the users after the activLife training (using standardized geriatric functional tests and questionnaires)	Update: *new trial*, ongoing
29	1	Geriatrii Trial (**practice case**)	Falls; balance; prevention; elderly	- to assess the effectiveness of multimedia training and traditional group exercises among older people at increased risk of falling. Research hypothesis: After training with activLife equipment, the balance in geriatric patients will be improved.	Update: *new trial*, data acquisition finished

Results of Trial 10 (Leś, Niedzielska, Piotrowska, Staniszewski, & Kozak, 2017) and Trial 17 (Kozak et al., 2017) were published Open Access in the special issue of the journal Gerontechnology. Trial 21 is under review in the Journal of Population Ageing (M. Randriambelonoro, Perrin, Blocquet, et al., under review), and in the journal Archives of Physical Medicine and Rehabilitation (M. Randriambelonoro, Perrin, Frangos, et al., under review).

Trials mainly belonging to Touchpoint 2:

Table 2-2 Overview of trials that belong mainly to TP2

#	TP	Title	Keywords	Hypothesis/ Research questions	Status
11	2	SmartCardia - Healthy Volunteer Testing	Wearable sensor; vital signs; validation against monitors; activity	Measurements with SmartCardia sensors (applied at chest and upper arm) during different activity levels and postures are reliable. Heart rate, respiration rate, blood pressure, oxygen saturation, blood pressure variations, skin temperature, activity and posture.	Finished
12	2	SmartCardia - Patient testing at CardioCentro Lugano	Vital signs; wearable; patient testing	To validate the parameters from the wearable against ICU monitor devices for vital signs measurement.	Finished
13	2	Coffee Demonstrator Experiment	time series analysis, time series clustering, pattern detection, change point detection	We analysed the data from two different perspectives. On the one hand, coffee drinking events might elevate (or decrease) the mean HR of a subject temporarily. This could be seen as shifts of the HR levels. On the other hand, the effect of caffeine consumption on the subject's HR could result in more complicated patterns of the time series. For example, caffeine could cause an instantaneous peak in the HR, before the HR starts to decrease again until if finally reaches the level from before. Patterns of this kind should be reflected in time series motifs centred around coffee drinking moments. To assess both hypotheses, i.e. HR mean shifts and conserved time series motifs, we performed a change points analysis.	Finished
14	2	Opportunities and challenges for self-monitoring technologies for healthy aging: An in-situ study	Health; behaviour change; activity monitoring; qualitative studies; older adults; physical activity	Senior individuals are ready and willing to accept such technology to manage their health, considering some challenges. Senior individuals will change their behaviour and will sustain the device usage at the end of the study.	**Published**
15	2	Activity recognition with wearables and ambient sensors - gathering of data sets for the empirical validation with neurological patients	Sensors; neurology; activity recognition; data sets; machine learning; algorithm	Explorative trial: With the sensor set used in the trial valid algorithms for activity detection can be generated, suitable for neurological patients and healthy subjects.	**Published**
19	2	Data Collection and Annotation Workshop Touchpoint 2	Data Collection, Data Annotation, Ambient Sensing, Wearable Sensing, Monitoring, Targeting Specific Activities (Eating, Drinking and etc.)	Collection of data to monitor activities of daily living (ADL) at home, such as eating, drinking, activity (sleep, walking and etc.) and hygienic aspects.	**Published**
20	2	The Transfer- und Training Device activLife with neurological patients.	activity, neurology, sit-to-stand, transfer, mobility, training	Explorative trial: with the sensors used in that trial a valid feedback is given during the three different transfer methods. The activity and kinematic detection can be used to show if the activLife is suitable as a transfer-support and muscular training in the	Update: ongoing

		Feasibility und Usability Study (**practice case**)		field of neurological rehabilitation. Moreover, a patient group with Alzheimer's disease and their relatives, will test the implementation of the device with its Software.	
23	2	Feasibility study - SmartCardia sensors with standard Holter system and activePal sensors	ECG, motion data, posture	ECG and motion data from SmartCardia are consistent with the ECG data from the standard Holter system and the motion data from the activePal sensors	Finished
25	2	Szpital PD Trial (**practice case**)	Parkinson's Disease; balance; elderly	-to evaluate a therapy using activLife among patients with Parkinson's Disease on balance outcome	Update: *new trial*, ongoing
27	2	IKARD Trial (**practice case**)	Physical activity; prevention; cardiac patients; gaming	The study aims to evaluate effectiveness and attractiveness of exercises carried out on activLife	Update: *new trial*, data acquisition finished
28	2	ANIN IKARD Trial (**practice case**)	Muscular strength; coordination; balance; cardiovascular diseases	The aim of the study was to assess the effectiveness, safety, and attractiveness of exergames with the Kinect camera and fall protection equipment (activLife) in trainings of patients with cardiovascular diseases	Update: *new trial*, data acquisition finished
30	2	BRS trial	Machine learning; behaviour change	Qualitative Study of a Behavior Recommender System. *(This trial is part of the confidential deliverables D12 and D13. It counts as a trial but details will not be reported with the analyses of the present deliverable.)*	Update: *new trial*, data acquisition finished

Results of Trial 14 (Mirana Randriambelonoro, Chen, Yuruten, & Pu, 2017) were published Open Access in a special issue of the journal Gerontechnology. Results of Trial 15 and Trial 19 will be published in a special issue of the Journal of Population Ageing (Schrader et al., accepted).

Trials mainly belonging to Touchpoint 3:

Table 2-3 Overview of trials that belong mainly to TP3

#	TP	Title	Keywords	Hypothesis/ Research questions	Status
1	3	Mirana: A conversational agent with a hybrid user interface to promote healthy eating	health; behaviour change; nutrition; obese; diabetes	"Mirana" app is able to assess the user's nutrition habits as efficiently or better than a health professional. "Mirana" is able to identify a key food items that needs to be reduced as efficiently as a health professional. Patient is more motivated and engaged to change their behaviour with the support of "Mirana" app.	Update: **Published + under review** & ongoing
16	3	Towards personalised persuasive strategies for active ageing	active ageing, behaviour change, persuasive strategies, personalisation, physical activity	Which persuasive strategies are preferred to motivate older adults to enhance activity level?	**Published**
18	3	REACH Eindhoven Continued testing	active ageing; personalising behaviour change; motivation; technology acceptance	H1: There is no correlation between the number of times seniors open the application and the number of steps seniors take. H2: There is no correlation between the number of calls made by seniors and the number of steps seniors taken.	Finished

				H3: Self-awareness motivates seniors to take the same number of steps as the measured baseline. H4: Peer-awareness motivates seniors to take the same number of steps as the measured baseline. H5: The relative difference in steps taken by seniors with high self-efficacy is the same as those taken by seniors with low self-efficacy when using peer-awareness strategy H6: The relative difference in steps taken by seniors with high self-efficacy is the same as those taken by seniors with low self-efficacy when using self-awareness strategy H7: The relative difference in steps taken by seniors with a promotion regulatory focus is the same as those taken by seniors with a prevention regulatory focus when using peer-awareness strategy H8: The relative difference in steps taken by seniors with a promotion regulatory focus is the same as those taken by seniors with a prevention regulatory focus when using self-awareness strategy	
22	3	Questionnaire for the investigation of motivational aspects for food intake by elderly people / […] by dysphagia patients	Dysphagia, pureed food, motivational aspects to eat, effects on appetite and mood	Current situations (living in a nursing home, dependency on others while eating, dependency of pureed food, ...) have influence on elderlies' mood and in context on their motivation to eat.	**Published**

Results of Trial 1 and Trial 22 are published or under review in the Journal of Population Ageing (M. Randriambelonoro, Perrin, Blocquet, et al., under review; Rusu et al., 2020). Results of Trial 16 are published in the journal Gerontechnology (Valk et al., 2017).

Trials mainly belonging to Touchpoint 4:

Table 2-4 Overview of trials that belong mainly to TP4

#	TP	Title	Keywords	Hypothesis/ Research questions	Status
2	4	Criterion validity for step counting in four consumer-grade physical activity monitors among 103 older adults with and without rollators	Validity: physical activity monitors: walking: technology:	Bilateral counts from the same model measured on the left and the right side of the body have good agreement, and we expected all PAMs, no matter the placement, to have moderate criterion validity for all participants, good criterion validity for participants walking without a rollator and poor criterion validity for participants walking with a rollator.	Update: **Published**
3	4	The MIPAM trial: A 12-week intervention with motivational interviewing and physical activity monitoring, to enhance the daily amount of physical activity in community dwelling older adults – a randomized controlled trial	physical activity monitoring: older adults: walking: wearables: motivational interview: behavioural change strategies	Motivational interviewing will enhance the effect from physical activity monitoring and consumer available monitors.	Update: Ongoing

4	4	Lyngby 2: Feasibility study conducted in preparation of the Lyngby 3 trial	Playware, behaviour change, gaming, elderly, exercise, physical activity, postural control	Primary hypothesis: Physical exercise during a 9-week period with older (65+) citizens: • Improves physical and functional abilities • Is accompanied by changes in physical activities outside exercise sessions Secondary hypotheses: • Activity tracking is perceived by elderly citizens as an acceptable monitoring technology used by care providers • Training on Moto tiles is adhered to and is perceived as acceptable by users over a 9-week period • Changes in performance on MOTO tiles over time correlates with changes in balance and functional measures	Finished
5	4	Lyngby 3: The effect of playware technologies on physical activity	Gaming; Physical activity; Functional ability	1) 12 weeks of playful physical exercise improves physical and functional abilities. 2) It is accompanied by changes in physical activities outside exercise sessions.	Update: **under review**
6	4	Lyngby 1: Effect of daily feedback on older adults' physical activity level	Physical activity monitoring; Sensors; wearables; behaviour change; Effect of feedback; activity tracking	1) Receiving feedback on physical activity level increases activity 2) 24/7 monitoring for 8 weeks generates concerns about privacy	Finished
7	4	Playful Body and Brain Test with the Moto Tiles	Playware; balance test; cognitive test ;fall risk	Calculation of a normative Moto Tiles game score for different age groups can be calculated with a bid data approach. There is a correlation between Moto Tiles game score and standard tests (Timed-Up-and-Go, Sit-to-Stand).	Finished
8	4	Lyngby 4: Developing a reliable technique for automatic counting of steps of older adults – a validation study	Accelerometer; pedometer; validation; physical activity; step count; algorithm	Algorithms can be developed and validated with machine learning techniques based on raw data from 3-axis accelerometers.	Update: Data analysis ongoing
9	4	Lyngby 5 Trial: Test of smart home technologies	Smart Home, age at place	Primary: Determine potential problems occurring related to smart homes and potential positive and negative outcomes after the implementation of smart home technologies. Secondary: -Acceptability of interior sensors by elderly citizens -Acceptability of 24/7 monitoring by elderly citizens	Update: Finished

Results of Trial 2 (Larsen et al., 2020) were published Open Access in the journal European Review of Aging and Physical Activity. Results of Trial 5 are under review in the Journal of Population Ageing (Ehrari, Larsen, Langberg, & Andersen, under review).

3 Methodology – overview and classification of all testing activities

As described in D27, the complexity of the overall REACH goals/hypothesis can't be tested in one single activity. The complexity of the REACH project required a subdivision of the overall goal in single sub-goals which can then be tested in separate testing activities. In the framework of REACH 30 testing activities (trials, studies) have been performed. These testing activities can be classified according to different relevant aspects. Classifications can, for example, be performed to illustrate the assignment to the different touch points or different testing instances. To structure the final presentation of the 29 REACH testing activities (29 plus one confidential not reported in detail here in D28), the same methodology is used as in D27.

From those 29 trials performed, data collection of 24 could be completed while five are ongoing (see Figure 3-1).

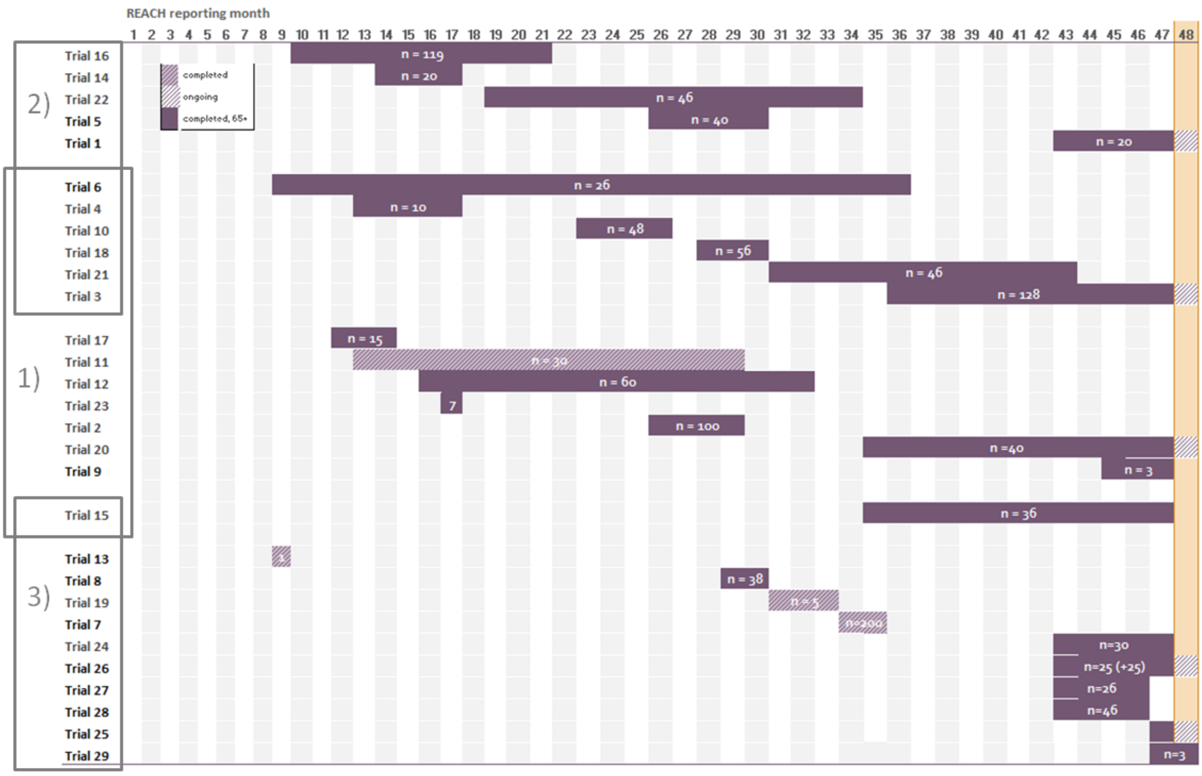

Figure 3-1 Time line for all testing activities (trials) performed within REACH. The order of the testing activities shows the affiliation of each trial to one of the 3 system instances: 1) Sensing and Early Detection, 2) Motivational Techniques, and 3) Programmed Interventions. The dark purple bars present those trials in which the REACH target population was investigated (age 65+), and the light purple those in which younger adults were investigated.

A graphical overview of some aspects on methodological classifications is given in
Figure 3-2. In addition, the figure also highlights the information on methodological aspects like a) the age group addressed in the specific trials, whether participants of the REACH focus group of adults 65+ (n=25) or younger (n=4) were recruited; b) the proportion of female and male participants in the completed trials, showing a nearly equal number for both sexes, i.e., 46% of participants were male and 54% female; or c) the medical condition investigated within the trials, whether healthy subjects, patients with diabetes, orthopaedic, and neurological diseases were included.

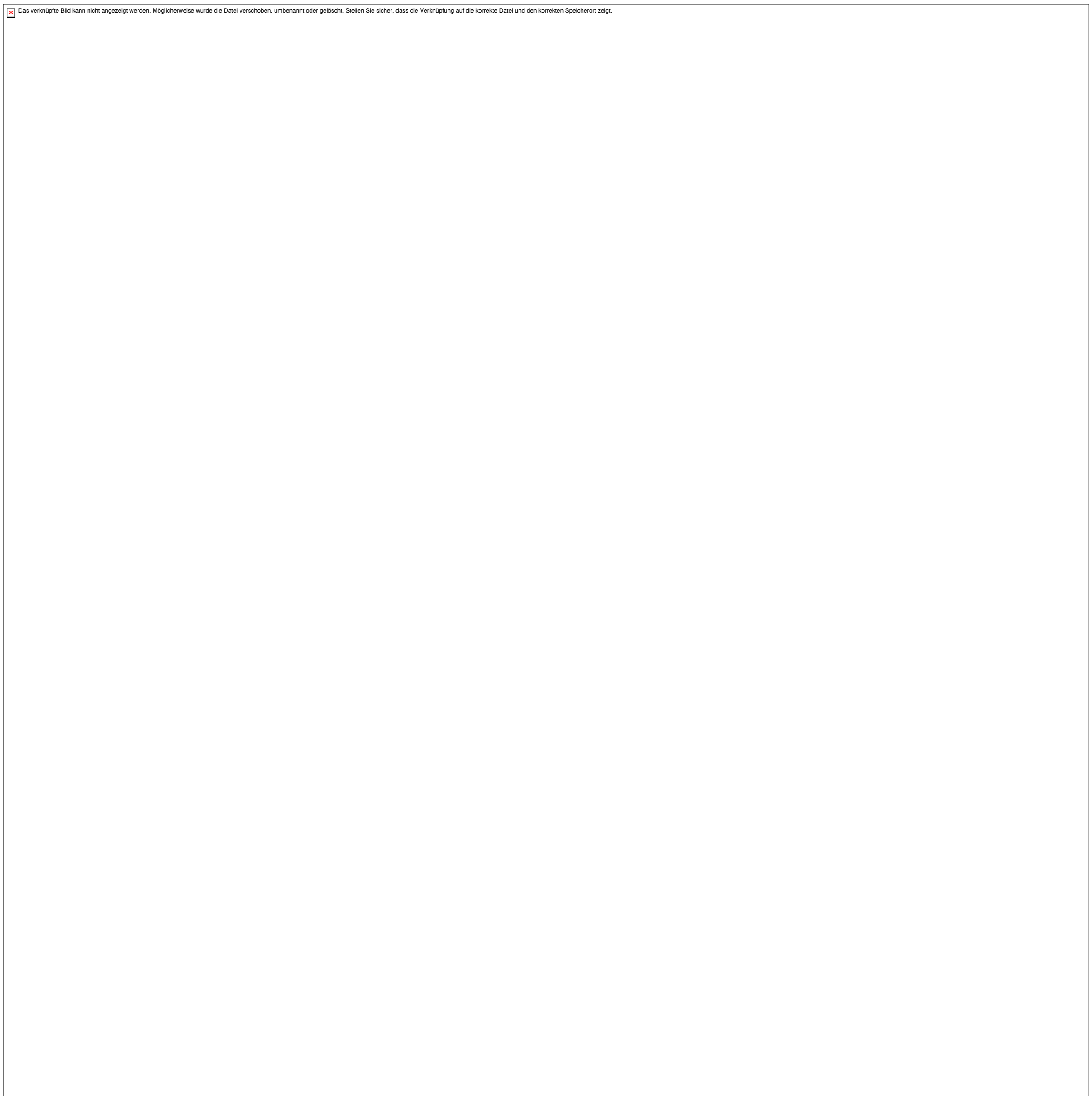

Figure 3-2 Overview of all testing activities (trials) performed within REACH. Descriptive analyses for several classification aspects are displayed, including the allocation of each trial to one of the touch points, the level of evidence, or the system instances

All trials performed in REACH were conducted in accordance with the ethical principles set by the Declaration of Helsinki and conforming regulations. The rights, safety, and well-being of the trial participants were the most important considerations and prevailed over all other interests, including but not restricted to scientific interest, personal ambition, or societal demands.
The clinical trials with patients did not commence until written approval/ favorable opinion from the EC and, if required, the permission of the relevant regulatory authorities had been received.
Data collection and processing were performed respecting the legal requirements about data protection (see D44). All aspects affecting the data protection rights of the participants were disclosed to the trial participants and explained in detail.

The ethical and data protection compliance in the REACH trials is outlined in detail in D44.

4 Results – Documentation of testing activities and their outcomes

A total of 30 testing activities were performed of which 29 are reported in this deliverable. A collection tool was created with survey monkey. The collection tool and the methods used in Survey Monkey are described in more detail in deliverable D 44. Overall, these 30 testing instances aim to solve the problems of caring for the ageing European society.

In this chapter, trials with an updated status compared to deliverable D27 (labelled as updated in Table 2-1, Table 2-2, Table 2-3, and Table 2-4) are further described. The order of trials is according to their appearance in Touchpoints 1 to 4.

Update on trials mainly belonging to Touchpoint 1:

4.1 Trial 21: Geneva 2 – A personal mobility device

The purpose of this trial was to use the activLife device (see Figure 4-1) in a hospital setting as a training option in geriatric patients. The impact of this therapeutic intervention on the activity of these patients after discharge from the hospital was also investigated.

Figure 4-1 Therapeutic intervention with the activLife device

The effectivity was evaluated within a randomized clinical trial in patients with musculoskeletal issues. Participants were seniors (65 +) with a minimal level of independence and strength (Functional Independence Measure >= 4 for the items regarding mobility and locomotion) and a minimal level of cognitive ability (MMSE >= 27) to be able to interact with the equipment. Participants had to be in need of specific exercise treatment and be hospitalized for at least 3 weeks in the hospital. Patients could not be recruited for the study when they were too weak to interact with the equipment.

Results showed that patients' step activity increased once they got home. Some patients kept the same number of steps and a few decreased their activity. Qualitatively, patients who were in the intervention group seemed more active than the control group, i.e., doing more indoor and outdoor activities. No significant difference could be found when we look at the number of steps. After 3 weeks at home the average increase in SPPB of the intervention group was even greater than the improvement of the control group. The standard rehabilitation intervention was non inferior to the device which engaged elderly in physical and cognitive activity as a simultaneous combination for the 3 chosen outcomes (SPPB, IHGS, number of steps).

4.2 Trial 24: ActivLife Test 3 - Wroclaw-Study

This study aimed at evaluating the safety and functionality of the activLife system which was applied to improve muscle strength, balance and memory in the elderly with frailty syndrome or those at risk of developing. A 6-week standardized training program was performed with components of endurance training, general development with elements of resistance and balance / balance exercises, as well as exercises of cognitive skills - memory and visual-spatial orientation.

Before and after the training program, patients underwent comprehensive geriatric assessments, with particular emphasis on cognitive ability and functional performance. Such parameters as weight, height, BMI, WHR index, calf and shoulder circumference were measured. Fried's criteria serve as a diagnostic tool in the direction of weakness syndrome. The functional efficiency of patients was measured using the ADL, IADL, Barthel scale and Fullerton tests, and the strength of the handshake - using a dynamometer. Risk of falls and balance were determined by means of the Tinetti test. The Moca test was used to measure memory and cognition. The goals and motivation of patients were examined by the KCAF test (Physical Activity Goals Questionnaire) and the quality of life by the SF-36 test. Each patient is also assessed for depression using the GDS test.

It could be concluded that a 6-week training program improved cognitive skills of seniors ($p<0.0001$), reduced BMI ($p<0.0001$), improved quality of life ($p<0.0001$) and reduced the level of depression measured by GDS test ($p<0.0001$). No effect was found on the functional efficiency ($p=0.037$), strength ($p=0.025$) and balance ($p=0.01$). The study showed a positive influence of a trainer led to a greater number of intended physical activities, and joy caused a greater readiness to undertake activities. The induction of joy led to greater physical activity and a tendency to increase the priority of goals.

4.3 Trial 26: Welfare Home Trial

In this trial, 25 elderly at the age of 60 + living in a social welfare home participated in a personalised training program with the activLife device. Training took place 3 times per week for 20 minutes over the duration of 8 weeks.

Following 6 assessments and 2 tests were collected:

1. SPPB: Short Physical Performance Battery
2. BIA: Bio-Impedance Analysis

3. Hand grip
4. MMSE: Mini-Mental State Examination
5. WHO-QOL: World Health Organization - quality of life test
6. SES: Self-efficacy scale
7. GDS: Geriatric Depression Scale
8. MNA-SF: Short from Mini Nutritional assessment

First observation showed that participants with lower cognitive functions are willing to do exercises with the activLife device and are unexpectedly good in performing the training programs. Based on this observation it was decided to recruit an additional 25 patients with lower cognitive function to analyze this subgroup of users in more depths. This study is still ongoing.

4.4 Trial 29: Geriatrii Trial

This trial used a single-case design. Three patients in a geriatric hospital setting qualified to participate in this trial. The three participants had a known increased risk of falling, and were aged over 60 years. The training was performed for a period of 2 weeks. Figure 4-2 shows an example of a measurement performed with the VASTRehab software that comes with the activLife device.

Figure 4-2 Screenshot of the VASTRehab software that comes with the activLife device

Patient A performed 6 training sessions with an active therapy time of (in total) 1.5 hours. Patient showed improvements in balance (+56.24%), functional movements (+46.43%), troubleshooting (+24.29%). Only speed could not be improved (-23.68%).

Patient B performed 6 training sessions with a total active training duration of 1.5 hours. In this patient all 4 tests showed an improvement: balance by 83.2%, functional movements by 2.66%, troubleshooting by 32.14%, and speed by 186.67%.

Patient C performed 6 training sessions with also 1.5 hours of total active training time. This patient also improved in all the tests: balance by 75.88%, functional movements by 9.73%, troubleshooting by 40%, and speed by 83.33%.

Update on trials mainly belonging to Touchpoint 2:

4.5 Trial 15: Activity Recognition

In trial 15, machine learning methods from the field of human activity recognition (HAR) to detect human activities were applied. These algorithmic methods need a large database with structured datasets that contain human activities. Compared to existing data recording procedures for creating HAR datasets, a novel approach was implemented, since our target group comprises of elderly and diseased people, who do not possess the same physical condition as young and healthy persons. Since our targeted HAR system aims at supporting elderly and diseased people, we focussed on daily activities, especially those to which clinical relevance is attributed, like hygiene activities, nutritional activities or lying positions. Therefore, we propose a methodology for capturing data with elderly and diseased people within a hospital under realistic conditions using wearable and ambient sensors. Table 4-1 gives an overview of the technical equipment used in this trial.

Table 4-1 Overview of data acquisition devices

Sensor type and amount	Specification	Ambient or wearable device
4 × Akaso Action Camera EK7000	Up to 4k resolution. 170° Wide Angle Lens. Micro SDHC Card for data storage. Micro USB & HDMI interface. Can be started with a remote control.	ambient 
1 × Tekscan Body Pressure Measurement System (BPMS)	940 × 640 cm² (three times). Using 34 × 52 sensors (three times). 0,3 sensels/cm². 100 Hz sampling frequency. 8 bit resolution.	ambient 
1 × Canon G11	3648 × 2736 resolution. SDHC Card for data storage. Micro USB interface. 5x optical zoom. 4x digital zoom.	wearable 
9 × activPAL micro (PAL Technologies Ltd, 2019)	3-axis accelerometer. 20 Hz sampling frequency. activePAL software allows to set recording time and to download recorded data via docking station.	wearable 
2 × Myo armband	3-axis accelerometer. 3-axis gyroscope. 3-axis compass. 8 EMG sensors. 50 Hz sampling frequency. Needs Bluetooth connection for storing the raw data.	wearable 

The applied approach was first tested in healthy young adults in a laboratory environment (see D 27) before it was transferred to the REACH target user groups (elderly people and patients in a hospital).

Two categories of target activities were defined: activities of daily life (ADL) and modes of locomotion. Ni, Garcia Hernando, and de la Cruz (2015) defined ADL as the self-care and domestic activities that a person performs in a daily living, e.g., feeding oneself, bathing, dressing, grooming work, homemaking, and leisure. These activities are typically the first ones that require outside support and it has been found that there is a progressive functional loss on them, with hygiene being an early-loss activity (i.e., this is one of the first ADL where it is likely that a person needs help from others), toilet-use a mid-loss activity, and eating a late-loss activity (Morris, Berg, Fries, Steel, & Howard, 2013). The measurement of ADLs allows conclusions to be drawn about the physical and cognitive status, provides information about frailty, and allows predictions about the risk of falling (Hellström et al., 2013; Nourhashemi et al., 2001; Tinetti et al., 1994). As modes of locomotion walking, sitting, and lying can be used as reference for the physical activity level of an individual. They can be useful for detecting hazardous situations such as falling (Ni et al., 2015).

The defined ADL activities and modes of locomotion were collected in a real-world environment (SK hospital setting). Figure 4-3 shows the final test setting in the hospital.

Figure 4-3 Patient room for final testing. Left: The bedroom. Right: The bathroom.

During the final data acquisition, data from both elderly people and patients were collected. Eligible elderly were aged 60+, while eligible patients were able to walk (with or without support) and had no terminal diseases.
Eight healthy elderly and seven neurological patients were recruited. The group of healthy elderly people consisted of 5 men and 3 women aged 67 to 86 years with a mean age of 74.4 years (SD 6.5). The patient group consisted of 5 men and 2 women aged 30 to 84 years with a mean age of 64.0 years (SD 17.5).

In order to classify the human activities, the training stage of an activity recognition chain (ARC) requires the availability of the ground truth labels (i.e., an annotation for each data point that indicates which activity was performed). Therefore, the data had to be annotated with the corresponding activities. An ARC is commonly used to analyse human activity data by means of machine learning methods and aims to detect activity patterns. Figure 4-4 shows an example of the annotation process.

Figure 4-4 Example of the annotation process. Left: a video snapshot which is used to create the annotation. Right: the corresponding annotation to the performed activity. The red vertical line indicates the time corresponding to the video snapshot.

Following the annotation process, the ARC was implemented to classify activities. An example of raw acceleration data taken with a Myo band is shown in Figure 4-6.

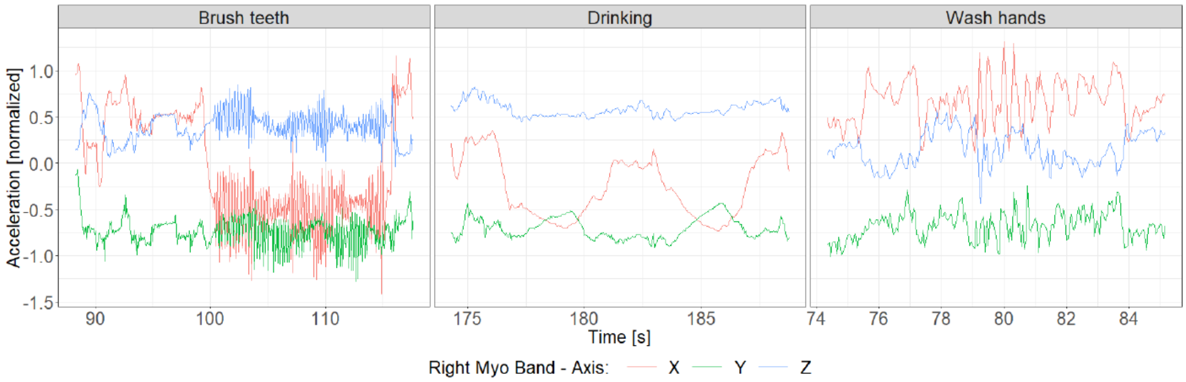

Figure 4-5 Acceleration data taken with a Myo band (RLA). The recordings show the triaxal acceleration measurements for the 3 exemplary.

The first versions of the ARC were trained and tested using the publicly available Opportunity dataset (Chavarriaga et al., 2013). The authors of the dataset released a public challenge to recognize hand gestures and locomotion activities. Table 4-2 shows the performance of the participants of the challenge, reported in (Chavarriaga et al., 2013), and the performance of our approach (all details of this implementation are to be found in (Vargas Toro, 2018)). These results show that our first ARC version already outperforms other approaches in terms of recognizing locomotion and hand gestures.

Table 4-2 Baseline results of the Opportunity challenge.

Opportunity challenge results (Chavarriaga, et al., 2013)		
Method	**F-score**	
	Locomotion	**Hand Gestures**
LDA	0.59	0.69
QDA	0.68	0.53
NCC	0.53	0.51
1-NN	0.84	0.87
3-NN	0.85	0.85
UP	0.60	0.64
NStar	0.61	0.84
SStar	0.64	0.86
CStar	0.63	0.88
NU	0.53	-
MI	0.83	-
MU	0.62	-
UT	0.52	-
NAGS	-	0.71
Our approach	0.87	0.90

To assess the potential acceptability of our HAR system, all participants filled out a standardized questionnaire on their general technical affinity. Therefore, the Affinity for Technology questionnaire (TA-EG) of electrical devices was used, which is one of a few scales that is not restricted to computer use (Attig, Wessel, & Franke, 2017; Karrer, Glaser, Clemens, & Bruder, 2009). The TA-EG is a 19-item questionnaire consisting of four dimensions, i.e., enthusiasm for technology, competence in dealing with technology, positive and negative attitudes towards technology. The responses to all items are categorized on a 5-point Likert scale, ranging from “fully agree” to “fully disagree” (transferred to a 5-point scale as shown in Figure 4-6). Although all healthy elderly persons were highly interested and motivated in participating in a study aiming at a monitoring or intervention system, their overall general technical affinity was only moderate with a mean value of 3.0 points (SD 0.6). Enthusiasm for technology resulted to be the lowest dimension, but nevertheless the participants’ ratings showed the highest value in positive attitude towards technology for each individual. Hence, the general acceptability of the system envisaged can be estimated to be high enough that elderly people are likely to use it. The implementation strategy, however, needs to be adapted to the users’ low enthusiasm to search and test new technological equipment.

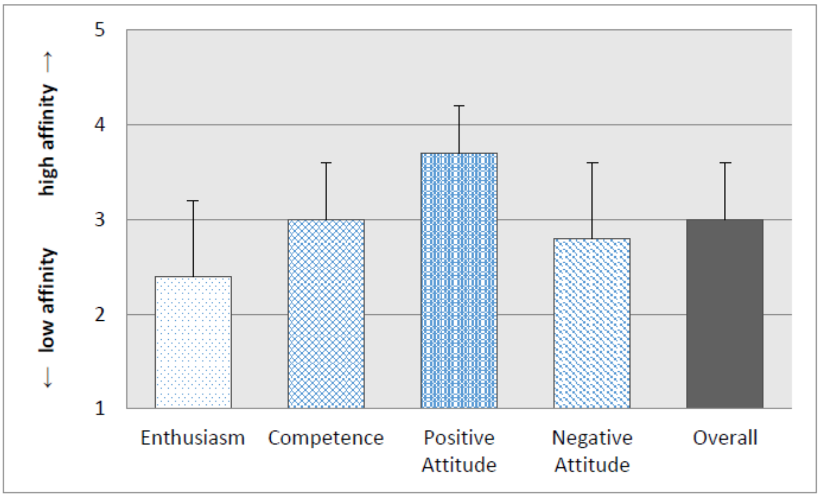

Figure 4-6 Technical affinity of healthy elderly persons (n=8) using the TA-EG questionnaire. (Note: The items of the dimension "negative attitude towards technology" were analysed with an inverted number encoding.)

First results of this trial are published in the Journal of Population Ageing (Schrader et al., accepted).

4.6 Trial 20: ActivLife 2 – Neurological patients

The aim of this trial is to investigate the feasibility, suitability, and the effectiveness of the transfer aid and training device activLife in healthy elderly and patients. The activLife is used as a transfer aid to support the patient to move from a sitting to a standing position.
It is important to evaluate if this device can be used in everyday clinical practice and after discharge for the benefit of neurological patients. The reduction of therapeutic activities after hospital discharge often leads to a decline in the acquired functions and thus a worsening of the general state of health. An intensive preparation for a high-frequency training starting during hospitalization could attenuate this negative effect.

The study protocol and pre-testing activities were performed to define several aspects of the study protocol (see deliverable **D23** for detailed description).

The study was designed in two parts (see Figure 4-7): a feasibility study (period A.1 and B), and an application observation study (period A.2 and C).

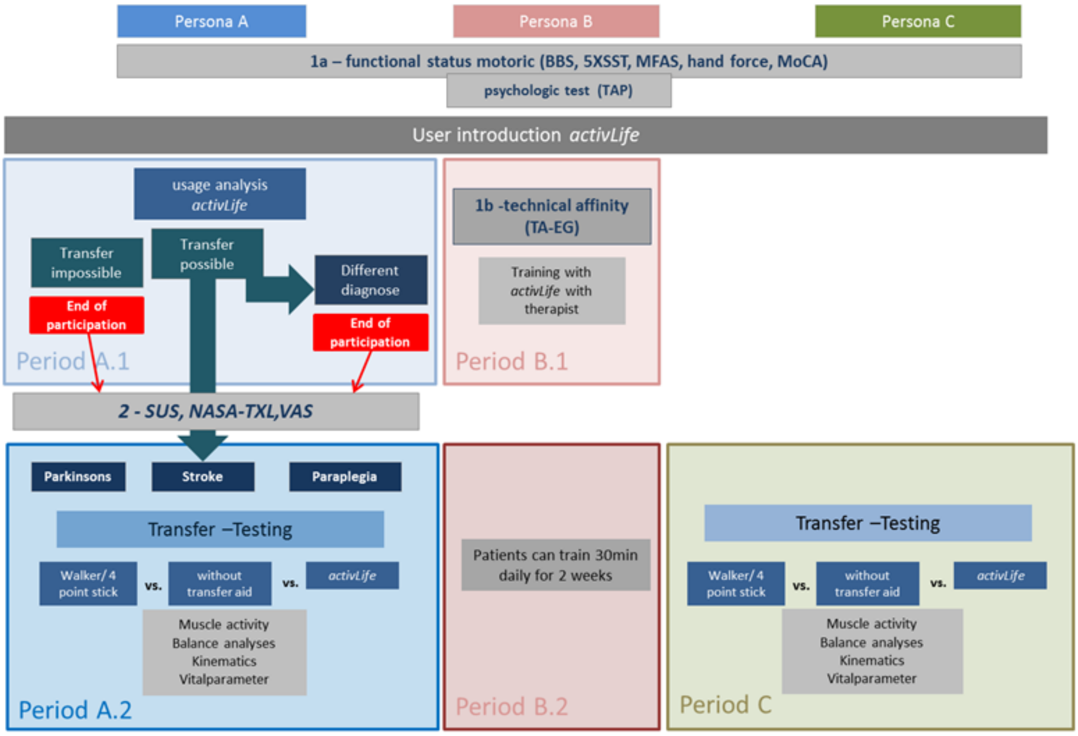

Figure 4-7 Protocol scheme for testing activities of bed add-on activLife device

The ethical documents were successfully submitted to the ethical committee of the Ludwig-Maximilians-University of Munich. The data collection started as soon as the approval was received in REACH project month M44.

Up to now, 50 patients were tested in phase A.1, of which 25 patients fulfilled the criteria for A.2. In total, 25 patients (diagnosis: Parkinson's disease (n=4), stroke (n=10), and 10 healthy participants over 65 completed the performance of the transition sequences, with and without the activLife device in phase A.2. The marker setting for the 3-D motion tracking was used as shown in Figure 4-8.
One patient with Alzheimer completed the 10 days Vast.Rehab-training together with his relatives (phase B).

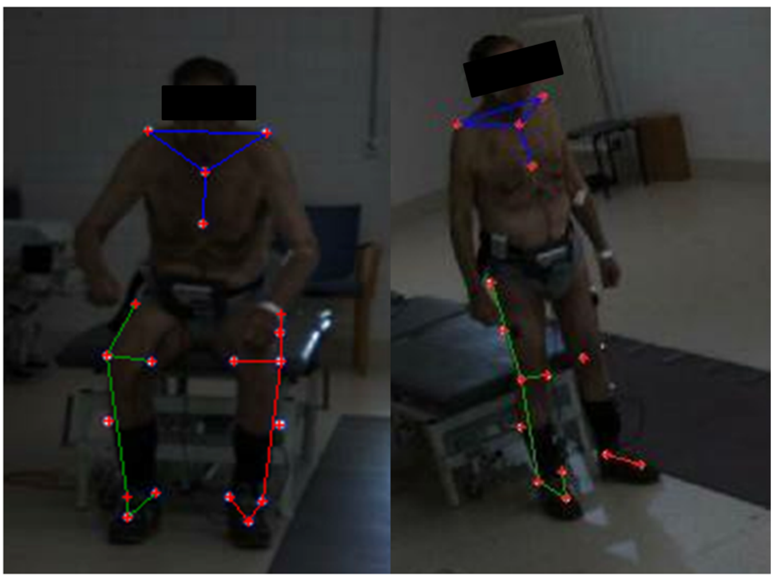

Figure 4-8 Marker tracking in Sit-to-Stand transitions (used to compare Sit-to-Stand transitions with and without the activLife).

Trial is ongoing to reach the target number of 10 healthy elderly and 40 neurological patients (10 participants per diagnosis Parkinson's disease, stroke, and paraplegia) and 10 patients with Alzheimer's disease.

4.7 Trial 25: Szpital PD Trial

Trial 25 was initiated in 2019 as a practice case with neurological patients. The aim of the trial is to evaluate a therapy with the activLife among patients with Parkinson's disease. In this trial the activLife therapy focusses on the balance function. Patients have been included in this trial when being between 55 and 70 years of age, and still have the ability to walk independently.
This trial is still ongoing.

4.8 Trial 27: IKARD Trial

Diversifying physical training and adapting it to existing trends helps to encourage cardiac patients to regularly perform physical activity. Trial 27 aims at evaluating effectiveness and attractiveness of exercises carried out on the activLife device.

The target group comprised of 26 cardiac patients: 9 female patients and 17 male patients, whose average age was 60 ± 12 years. The average body mass was 84 ± 19 kg and the average BMI was 28 ± 5. The patients took part in a standard inpatient Phase II of a cardiac rehabilitation (support and counselling from health specialists, breathing, stretching, strength exercises, cycle ergometer or treadmill training), enriched with the activLife.
The trainings were performed 5 times a week, once a day for 15 minutes, and included a set of 7 exercises. In this study, resting and exertional heart rate and blood pressure, as well as the Borg scale were measured and compared in the same patients depending on the method of physical training (activLife vs. cycle ergometer). After activLife, improvement in patients' range of motion (ROM) and speed of exercise completion were also evaluated.

Results showed statistically significant differences between the results of six following activLife trainings:

- increased speed of exercise completion in "Squats" exercise
- increased speed in "Boxer" exercise
- improved percentage of ROM: in left lower limb mobility exercise, in right lower limb mobility exercise
- improved balance exercise

The level of fatigue measured with the Borg scale didn't differ between trainings on activLife and the cycle ergometer. However, in following trainings using activLife, the level of fatigue significantly decreased. Exercise systolic blood pressure and diastolic blood pressure were significantly lower in sixth trainings on activLife in comparison to sixth trainings on a cycle ergometer.
For cardiac patients, the activLife is an interesting and safe device for individual trainings. Incorporating it in an inpatient and outpatient cardiac rehabilitation, patients may benefit in a good additive or a substitution of exercise therapy

4.9 Trial 28: ANIN IKARD Trial

The limited physical activity and aging of patients with cardiovascular disease (CVD) causes reduction of muscular strength, coordination, motion, and balance. Therefore there is a need for incorporating new rehabilitation forms covering those areas into cardiac rehabilitation. The aim of trial 28, therefore, was to assess the effectiveness, safety, and attractiveness of exergames with the Kinect camera and the fall protection equipment activLife as a training option in CVD patients.

The study group consisted of 46 patients with various CVD (after myocardial infarction, cardiosurgical procedure, with heart failure) admitted to a department of cardiac rehabilitation. All subjects participated in a four-week programme with standardized trainings (endurance training and general conditioning exercises with elements of resistance and balance exercises).
20 patients (group A) were offered additional trainings (five times per week) with the activLife. Before and after rehabilitation, all patients underwent tests assessing the strength of lower limbs, a 6-min timed walking test (6MWT), and the timed “Up and go” (TUG) test. Patients also filled out a questionnaire regarding the use of the activLife device.

Both groups significantly improved in all tests:

Strength of lower limbs [number of repetitions/30 sec]
- group A: 11.21 ± .61 vs 13.37 ± 3.96
- control group: 9.96 ± 3.34 vs 13.12 ± 3.99

6MWT [m]
- group A: 369.06 ± 129.1 vs 462.50 ± 104.88
- control group: 366.53 ± 121.76 vs 457.81 ± 102.2

TUG [sec]
- group A: 7.74 ± 2.75 vs 6.74 ± 1.8
- control group: 8.35 ± 2.75 vs 7.27 ± 3.51

There was also significant increase in the precision and speed of movements in subsequent trainings.
- 94.7% of patients evaluated activLife as “very good”
- 89.5% - “comfortable/very comfortable”
- 100% - safe,
- 79.0% - useful in achieving rehabilitation goals
- 68.4% assessed it as more attractive than standardized training

The conclusions drawn from this trial are that 1. Cardiac rehabilitation using exergames is seen by patients as attractive, safe, and useful in achieving their goals. 2. Although the test results have improved for both groups, there is a need for a longer observation and increased training time to reliably compare effectiveness of both forms of training. 3. The activLife device is safe and useful for cardiac rehabilitation.

Update on trials mainly belonging to Touchpoint 3:

4.10 Trial 1: MiranaBot

For this trial a conversational agent called “MiranaBot” (see that helps the elderly to be aware of their eating habits in terms of variety and regularity was developed. Rather than focusing on food quantity and nutritional value, the system targets the variety of the individuals’ diet. From a regular description of the elderlies’ meals during a certain period, "MiranaBot" is able to assess the quality of their nutrition, identify the foods they need to consume less and explain why and how to replace them. The system proposes personalized solutions tailored to the older adults’ needs and context.

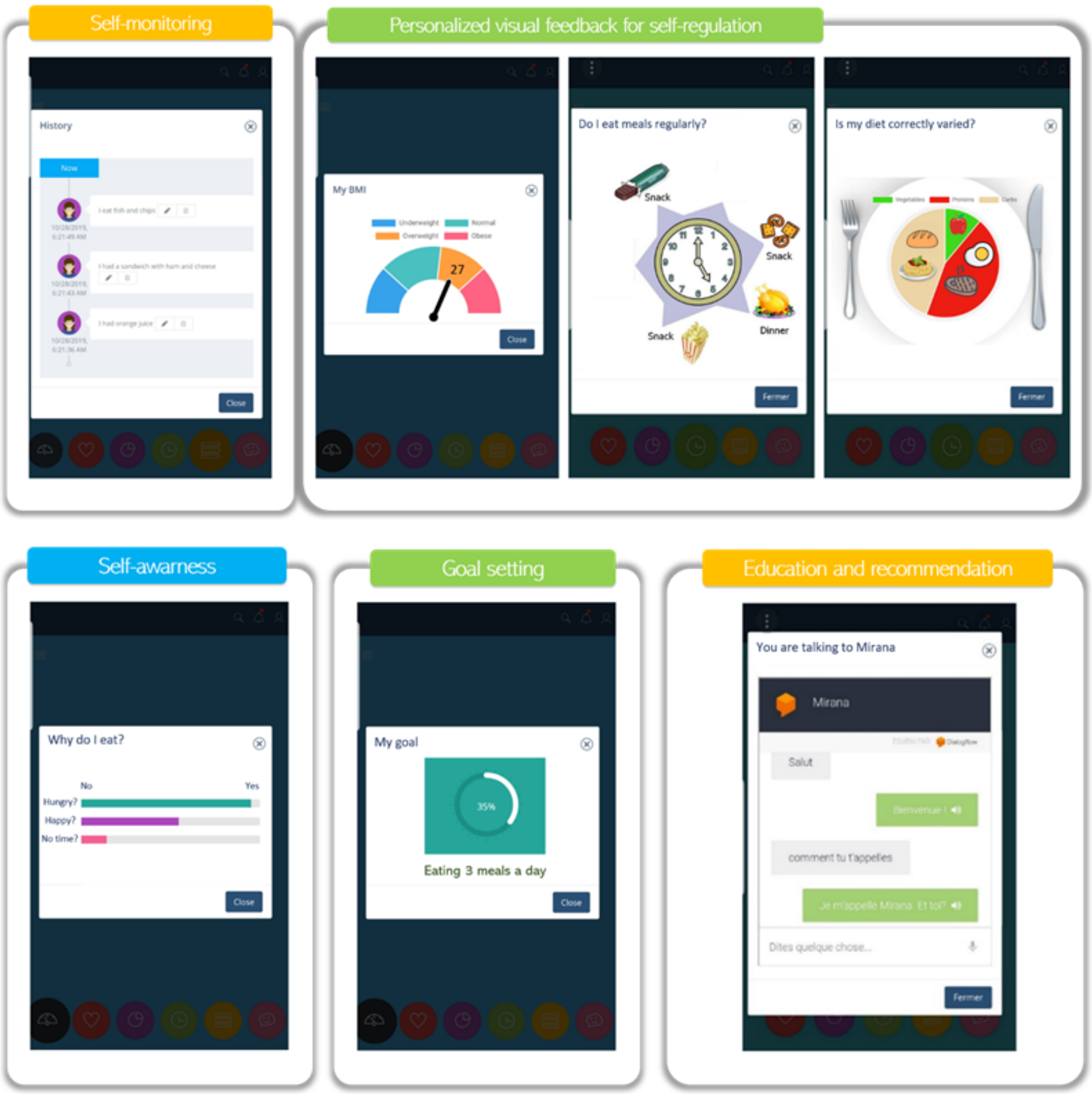

Figure 4-9 Graphical User-Interface - MiranaBot

A qualitative study with 10 obese and diabetic patients, 2 nutritionists, and 1 physician with a specific expertise on therapeutic education of chronically-ill patients was performed to understand patient’s barriers for adopting a healthy nutrition.

This study is still ongoing. Details of the procedure and the methodology used were already included in a previous deliverable (**D31**) and will not be reiterated here.

Update on trials mainly belonging to Touchpoint 4:

4.11 Trial 2: Criterion validity

A systematic review with meta-analysis (Larsen, Christensen, Juhl, Andersen, & Langberg, 2019) was performed within the framework of the REACH Touch Point 4 to estimate the effect of physical activity monitor-based interventions on physical activity behaviour in participants aged 65 and above. Subsequently the effect on body mass index, physical capacity, and health-related quality of life and finally the impact of patient- and intervention characteristics was explored. Searches in MEDLINE, EMBASE, SPORTDiscus, CINAHL, and CENTRAL were performed to seek for RCTs and cross-over RCTs investigating the effect of physical activity monitor-based interventions on physical activity. Twenty-one studies with 2783 participants were included in this review, showing a good effect to increase physical activity in older adults (Figure 4-10). Compared to intervention groups an average increase of 1297 steps per day was found when the elderly participants trained with support of PAMs.

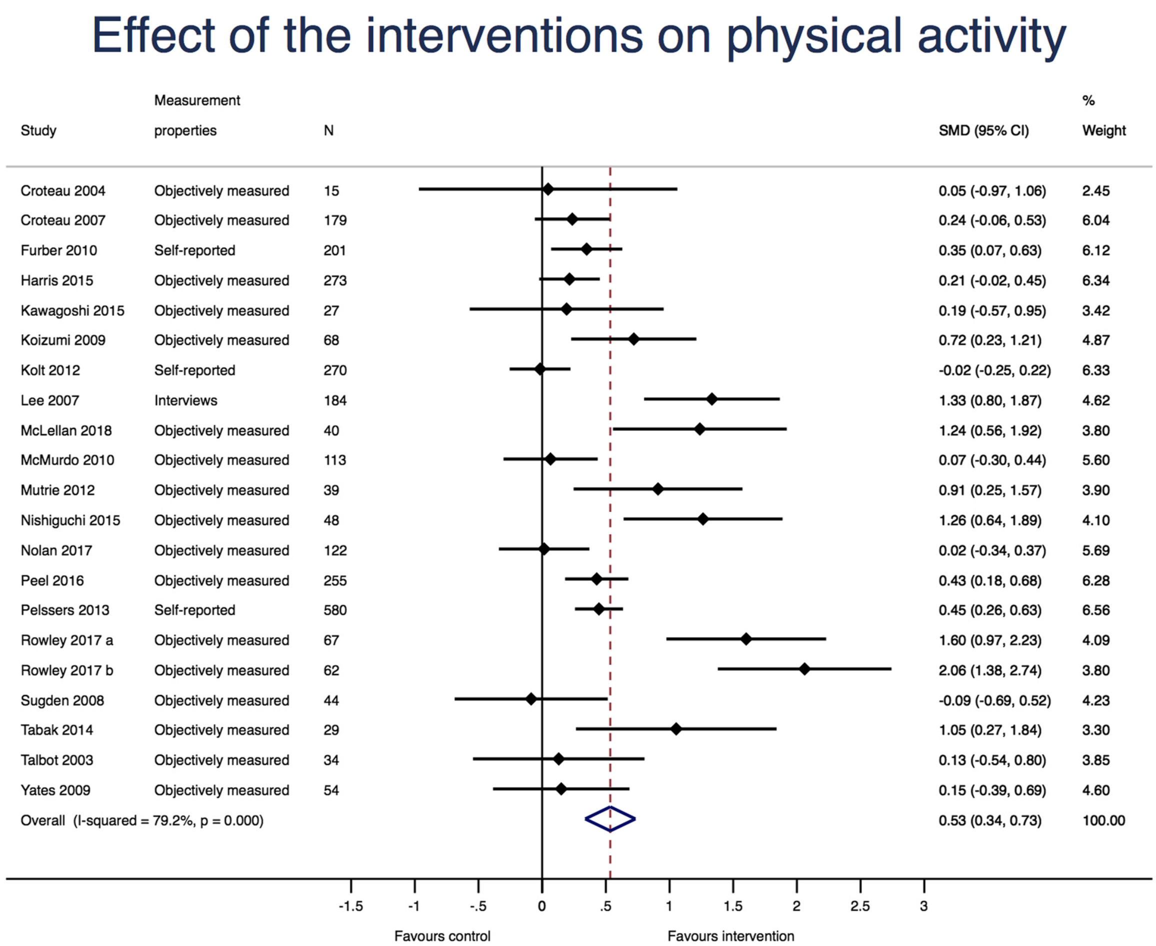

Figure 4-10 Random effects meta-analysis with effect of the interventions on physical activity using Hedges g. N: Number of participants; SMD; standardized mean difference. For each study, the diamond represents the standardized mean difference of the intervention (figure published in (Larsen et al., 2019))

Only a few studies, however, have investigated the measurement properties of consumer-grade physical activity monitors (PAMs) in older adults, and none of these has studied the measurement properties of a given PAM model worn on the hip and wrist. Therefore, Trial 2 aimed to investigate (a) the criterion validity of four consumer-grade PAMs in older adults performing a self-paced indoor walking test and (b) whether the measurement properties of the PAMs differed between older adults with and without rollators and comparing wrist-worn and hip-worn positions. Four consumer-grade wearable PAMs were identified which were available on the commercial market that met the predefined eligibility criteria: Misfit Shine, Nokia GO, Jawbone UP Move and Garmin Vivofit 3. Figure 4-11 shows the four included monitors used in this study.

a

b

Figure 4-11 a and b From left to right: Misfit Shine, Nokia GO, Jawbone UP Move and Garmin Vivofit 3 on paper with 10-mm grid lines. Figure a shows the hip-worn physical activity monitors and below figure b shows the wrist-worn physical activity monitors (figure published in (Larsen et al., 2020))

Three of these four included consumer-grade PAMs were analysed. They showed varying measurement properties related to criterion validity among older adults performing a self-paced walking task. The results show that wrist-worn PAMs cannot measure the number of steps in a population of older adults using rollators. The hip-worn PAMs were not significantly different in terms of measurement error or criterion validity, but when selecting a PAM for a clinical study, investigators should consider both the criterion validity and the rate of data loss as this also varied between monitors.

4.12 Trial 3: MIPAM trial

In several RCTs and in the systematic review with a meta-analysis performed within the REACH project (Larsen et al., 2019), physical activity monitors have been reported to effectively enhance the daily amount of physical activity in older adults. Some evidence suggests that increased feedback and focus on social barriers to physical activity might increase the effect. The aim of this RCT therefore is to investigate if bi-weekly motivational telephone interviews as an add-on intervention to the use of consumer-grade physical activity monitors is superior to the use of consumer-grade physical activity monitors alone. The hypothesis is tested that motivational interviewing enhances the effect from physical activity monitoring and consumer available monitors.
From the 128 participants planned, 69 (44 female/ 25 male) have been recruited for this trial so far. This study is ongoing and will be completed after the end of the REACH project.

4.13 Trial 8: Lyngby 4

The Lyngby 4 trial is a validation study conducted to validate algorithms for counting steps of slow walkers with machine learning techniques on raw data from 3-axis accelerometers.
For this trial, 26 participants (20 female and 6 male) between 67- 94 years (mean age 83.5) were recruited from homecare centers in Lyngby municipality to attend a 3x6 min walk testing session (see Table 4-3). Participants were eligible for inclusion if they were 65 or over and able to walk independently for at least 6 minutes with or without an assistive device.

Table 4-3 Participants' characteristics of Trial 8

Participants	N	Mean age	Walking ability
Walking without an assistive device	13	84	3 Shuffling 4 slow walkers 6 normal walker
Walking with an assistive device:	13	83,5	
– with cane	4	84	all slow walker
– with walker	9	83	5 normal walker

Each participant's 6-min gait performance during different walking conditions was collected. Each participant was monitored by five sensors (SENS intelligence) attached to following positions in their bodies: One in the thigh slightly above the knee (under a plaster), one on the chest (clipped to the shirt/blouse), one at the waist (clipped to the belt) and one on each ankle (under a Velcro strap). Device placement was standardized based on manufacturers' recommendations and previous validation studies. The exact positions are illustrated in Figure 4-12. All participants completed a 6MWT on the same track wearing the monitors

Figure 4-12 Device placement during the tests

Each Participant was asked to walk three different walking trials for six min: A) 6 min walk at their self-selected speed (natural speed of the participants) b) 12 min at the fastest speed they can walk (6 min inside and 6 min outside).

To accurately validate ankle sensors as ground truth activity, each session was video recorded. The video camera was angled so that the participants' feet were clearly visible in the video. A camera person walked behind the participant to capture each walk on camera.

The data collection phase for this trial is completed. Data analysis is still ongoing. We will, however, briefly describe some important aspects of the data analysis process and show some process steps exemplarily. In general, data analysis will be divided in to two parts, namely walk detection and step count estimation. Preliminary filtering and pre-processing of the data was done in the beginning to reduce noise.

Walking detection

Data analysis showed that many discontinuous walking sessions were detected. Filtering operations on the discontinuous part resulted in anomalous spikes due to the sharp transition in signal strength. This motivates the idea behind classifying each sampled signal from the sessions into two labels: "walking activity" and "non-walking activity". As can be seen from Figure 4-13, the green region is found using the detection method and was labelled as non-walking activity. An interesting thing to notice in the green region is the characteristics of the mixed filtered signal (denoted in blue). There are some false peaks in the green region, due to which it is important to discard these samples as our method is loosely based on counting peaks and crossing threshold measurements as feature extractor.

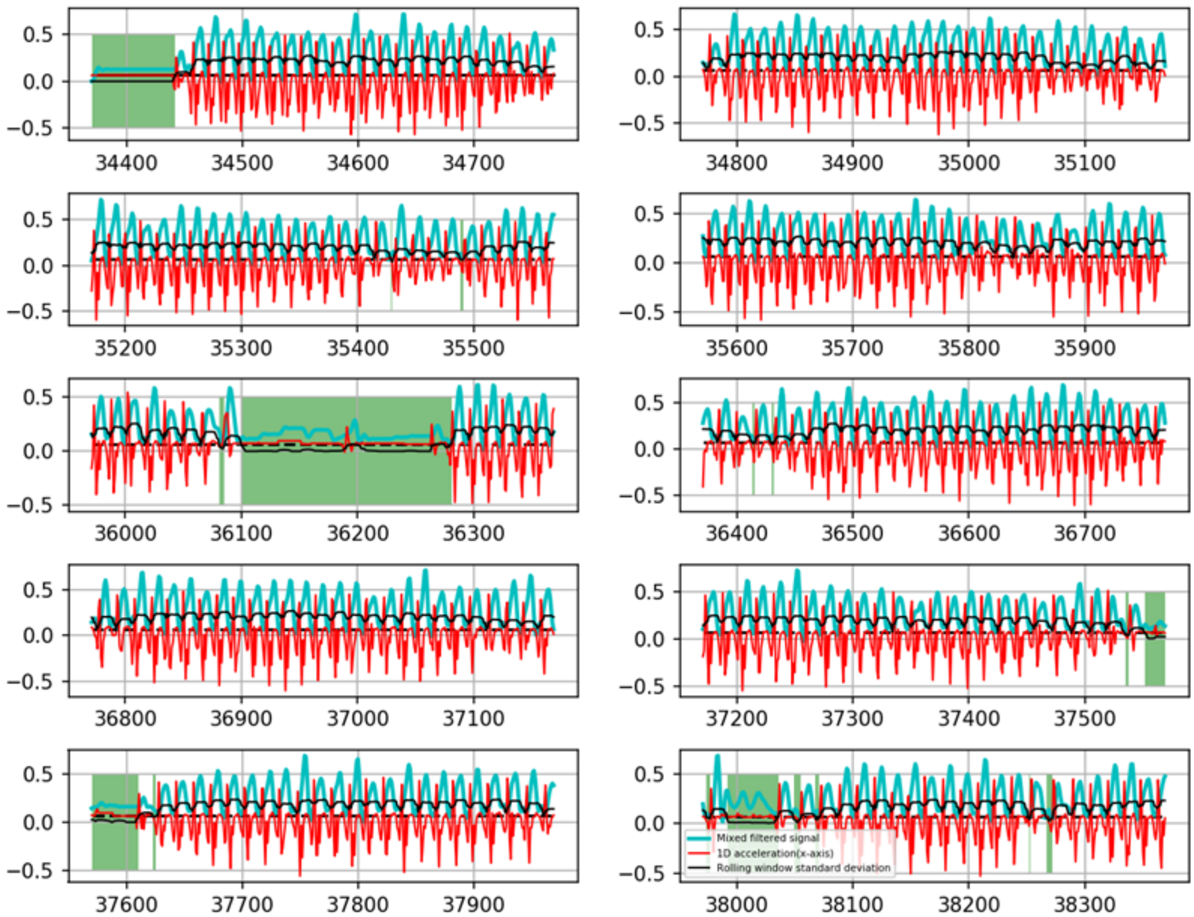

Figure 4-13 Example of a whole session with discontinuous walk. Red coloured signal represents the x-component of the accelerometer. The blue coloured signal is the corresponding mixed filtered signal. The black coloured signal represents the rolling window standard deviation to detect walk activity. The green region is detected as non-walking activity.

<u>Step count estimation</u>

The analysis to estimate step count is still ongoing. The step count estimation will be performed using a principal component regression analysis. Principle component analysis (PCA) is carried out in this data to find hidden structures of the data to better understand the modelling aspects. PCA can reveal how many attributes/dimensions are important to effectively model the data.

The following features will be used for the PCA:

- *Ratio of walk:* It is a ratio variable, which can take a maximum value of 1 and minimum value of 0. It is the ratio of the walking activity duration to total duration of the session.
- *Age:* Age of the participant. It is a discrete variable.
- *Distance:* Distance travelled by the participant for a given session. It is a continuous type variable.
- *BBS:* Berg Balance Scale is to objectively determine a patient's ability to safely balance during a series of predetermined tasks. It is a 14-item list with each item consisting of a five-point ordinal scale ranging from 0 to 4.
- *CST:* The chair stand test is similar to squat test to measure leg strength. The score is the number of completed chair stands in 30 seconds.

– *Support:* It is a 3 level discrete variable which can take values in “No Support”, “Cane” or “Rollator”. This explains what tools/help were used during the walk.
– *Location:* It is a 2 level discrete variable which explains whether the session took place indoors or outdoors.
– *Speed:* It is 2 level discrete variable which explains if the participants were told to either “walk fast” or “walk normal speed”.
– *Gender:* Binary variable, which explains gender of the participant.

This will reduce any redundancy thereby keeping only those attributes that explains the data most. This is done by projecting the data into a latent space which maximizes the variance of the projected data. The directions obtained are called the Principal directions and they are orthogonal to each other. The importance of each Principal Component (PC) can be seen in Figure 4-14 A, which shows how much variance is explained by each PC, both individually and cumulatively. It can be seen that to explain or retain 95% and 99% of variance in the data, only 8 and 10 PCs are enough respectively.
Figure 4-14 B shows how individual attributes will be spread out in different PCs. For example PC7 has a high negative projection of attribute 2 (ratio of walk) and 3 (age) and positive projection of attribute 5 (BBS) and 6 (CST). PC4 has high positive projection on attribute 8 (rollator) and high negative on attribute 9 (cane) which implies that this axis (principal direction) captures the information about the kind of support used during the walk. Similar interesting observation can be made about other PCs. As the original space in information is lost due to data projection in latent space, PCA can give insights about the importance of each PCs on individual attributes to draw meaningful conclusions.

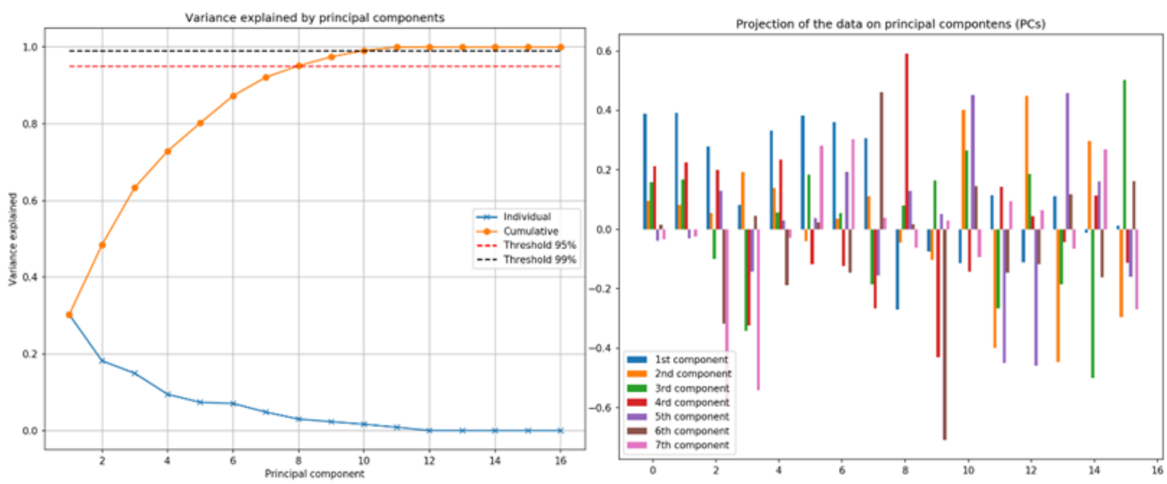

Figure 4-14 Variance explained by each PC (A: left plot). Influence of individual PCs on each attributes (B: right plot)

4.14 Trial 9: Lyngby 5 - Test of Smart Home Technologies

This feasibility study aimed at monitoring older adult’s daily activity throughout the day by in-home sensors. The monitoring aimed at capturing critical deviations, improving support and avoiding unnecessary hospitalization, and provided peace of mind for elderly persons and their family members. An interface for remote monitoring of daily activities of a home-dwelling frail elderly family member was developed and tested. A user-centred design and prototyping approach was used. Figure 4-15 shows the general concept of the Lyngby 5 trial.

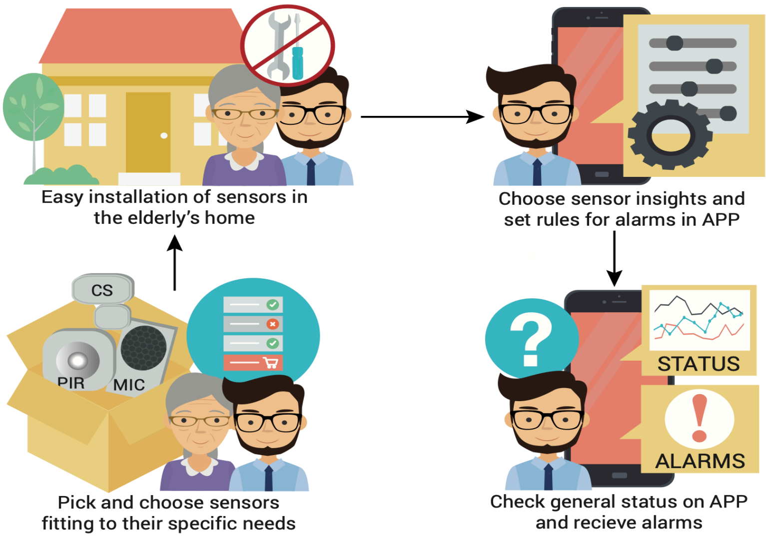

Figure 4-15 General concept of the components of the Lyngby 5 trial

Changes in performance, behaviour, and habits were detected by analysing patterns for deviation from baseline data. This study provides evidence about the positive and negative impacts related to smart home technologies. Furthermore, it sheds lights on ability and consequences of smart home implementation in the reality.
Family members of four older adults (3 female, 1 male) were included in this study. A total of 12 family members participated.
Data collection of this trial is completed and analysis of the qualitative feasibility study is in progress.

5 Interpretation of the testing results and outcomes

In this chapter we compare and interpret the results and outcomes of the 29 testing activities reported in this deliverable. Comparison and interpretation is in a first step done according to the structure used in D27. To address the reviewers' recommendation the literature review on factors and co-factors is added to this chapter, as well as an overview of user acceptance and the development of the so called UTAUT model, the Unified Theory of Acceptance and Use of Technology model.

5.1 Summary update on testing activities

According to D27, the 29 testing instances were categorized into 4 thematic groups: validation studies, motivational studies, feasibility studies, and exploration studies. Figure 5-1 shows the comparison of each thematic group.

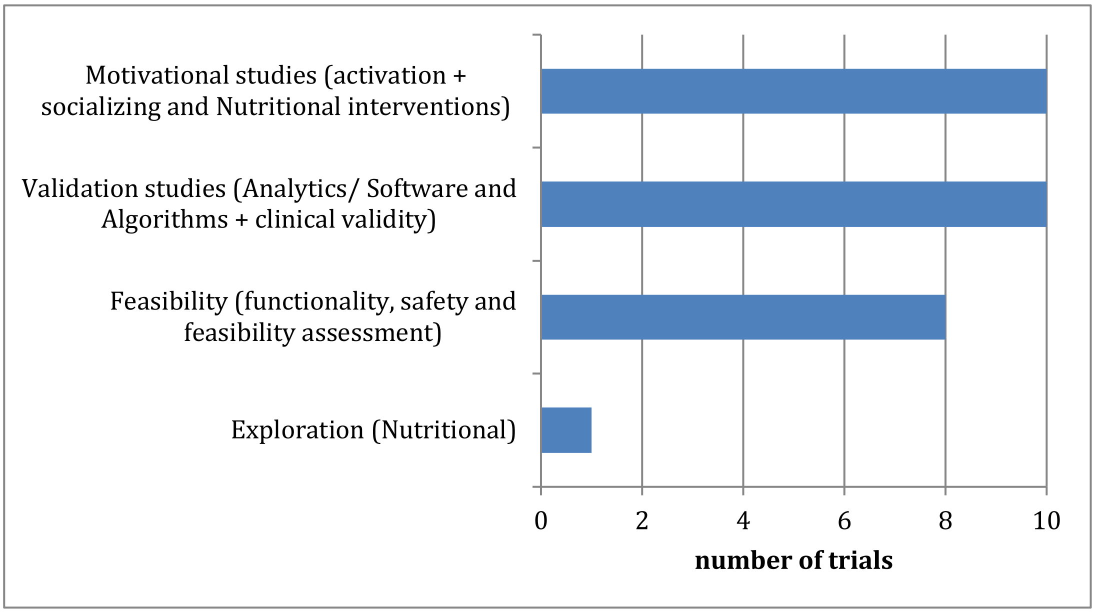

Figure 5-1 Number of trials per thematic group

5.1.1 Validation studies (Analytics/ Software and Algorithms + clinical validity)

Ten out of the 30 trials are categorized as validation studies (see Figure 5-1). The main objective of the validation studies was to test the clinical validation of personal mobility and wearable devices. Each trial aimed at testing and analysing the users' needs and gave direction for further improvement of a specific device. These trials belong to TP2 (Active environment) and TP4 (Gaming & Training). The trial focus is mostly on accurately measuring heart rate, activity level or number of steps. The sample size of the validation studies varies from 5 to 203 participants with a minimum age of 4 and a maximum age of 97). The mean age of participants in the validation trials was 88 years. For 3 trials the participating criteria were community-dwelling (living at home). However, four trials also involved younger participants. The health and ambulatory status criteria for validation studies different between REACH devices, like SmartCardia or activLife. They included patients with cardiovascular or neurological diseases.

5.1.2 Motivational studies (activation + socializing and nutritional interventions)

Ten of the 29 trials are categorized as motivational studies since the focus of the trials is on behaviour change strategies to promote healthy ageing (Figure 5-1). The strategies to motivate older adults to become more physically active correspond to providing feedback and gaming. The sample size varied from 18 to 58 participants; minimum age was 47 and maximum age 94 years. The age varied between 70 and 88 years. Only one trial included younger participants with a mean age of 64.4 years. Four trials corresponded to TP4, three corresponded to TP3, one to TP2 and one to TP1. The inclusion criteria were identical in almost all trials. One trial is divided into two parts, starting with a feasibility and then motivational test. As the main focus is on feasibility, it is not categorised under the thematic group ‘motivational studies’.

5.1.3 Feasibility (functionality, safety and feasibility assessment)

Eight out of 29 trials are categorized as applicability and safety assessment trials (Figure 5-1). The main objective of a feasibility study is to evaluate the logistic, functionality, usability and safety of the devices. The testing of the equipment is conducted to analyze the users’ needs and guide direction for further development of the devices so that it can be an accurate and efficient tool for promoting daily physical activity. Moreover, it is implemented to find out which requirements a neurological patient must fulfil in order to use the devices, and to potentially integrate it into the clinical routine. Each trial was designed as a pilot feasibility study. Two belong to TP4, four are associated with TP2 and two with TP1. The inclusion criteria were identical in almost all trials. The data collection included assessments related to activities of daily living, or focused on numbers of steps, numbers of sit-to-stand-transfers, heart rate pressure data, video recordings and interviews.

5.1.4 Exploration

One out of the 29 trials was categorized as exploration study (Figure 5-1). As mentioned already in D27, the researchers wanted to explore the effect of coffee on heart rate by collecting movement data and heart rate via a Fitbit tracker. The sample was based on one-person aged 38 years. The study was in correspondence to TP2.

The following figures give an overview of some methodological aspects of the REACH trials with respect to

- the Touchpoints addressed (Figure 5-2)
- the sample size of the trials completed (Figure 5-3)
- the amount of intervention sessions per participant (Figure 5-4)
- the assessments performed (Figure 5-5)

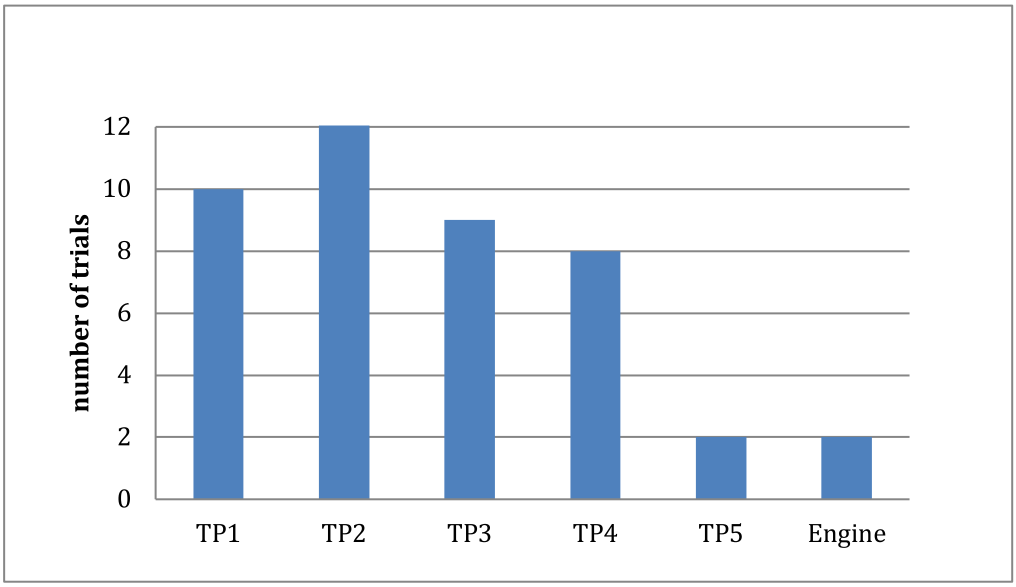

Figure 5-2 Distribution of trials across touchpoints

Figure 5-2 shows the distribution of the 29 REACH trials across the touchpoints (TPs). Five trials are associated to more than one TP. Two trials from TP 1 (Personal Mobility Device) are overlapping with TP 2 (Active Environment) as well as TP3 (Socializing & Nutritional Intervention). Two trials have main test activities in TP 2 but address also TP5; one trial from TP2 and two trials from TP4 (Gaming & Training) belong also to the Engine.

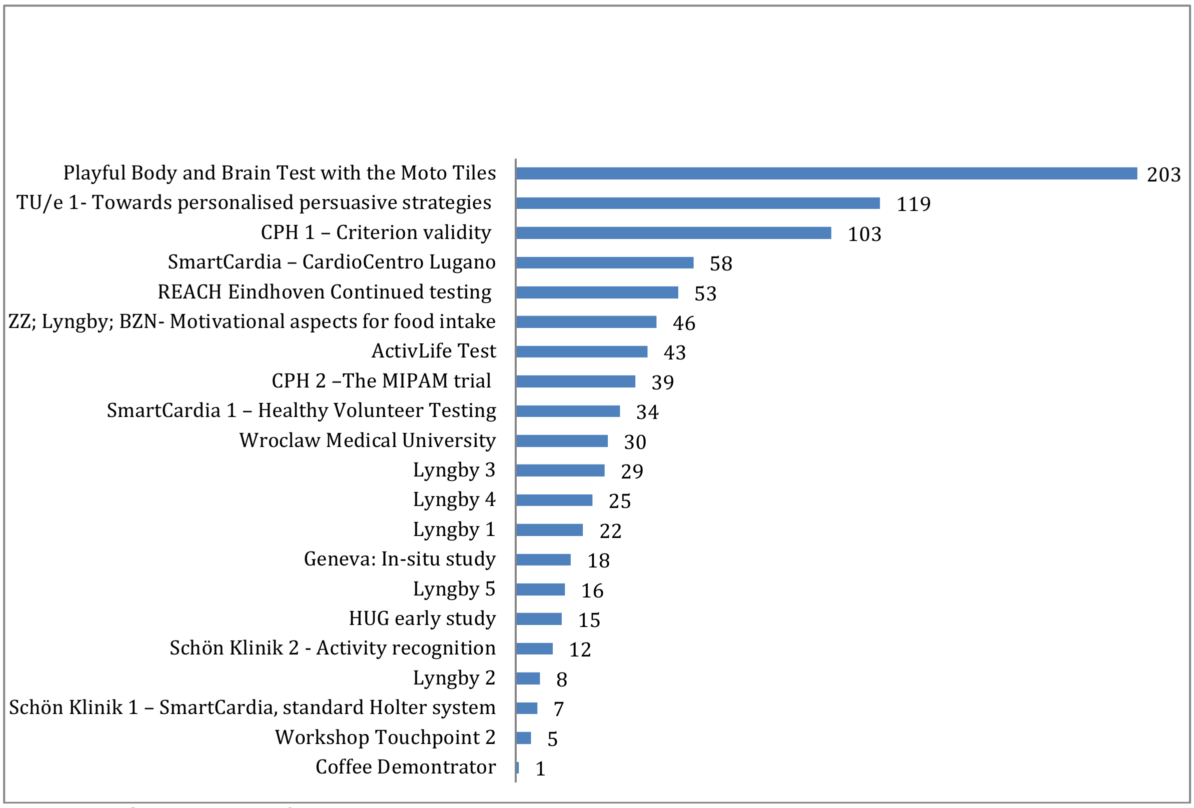

Figure 5-3 Sample size of completed trials

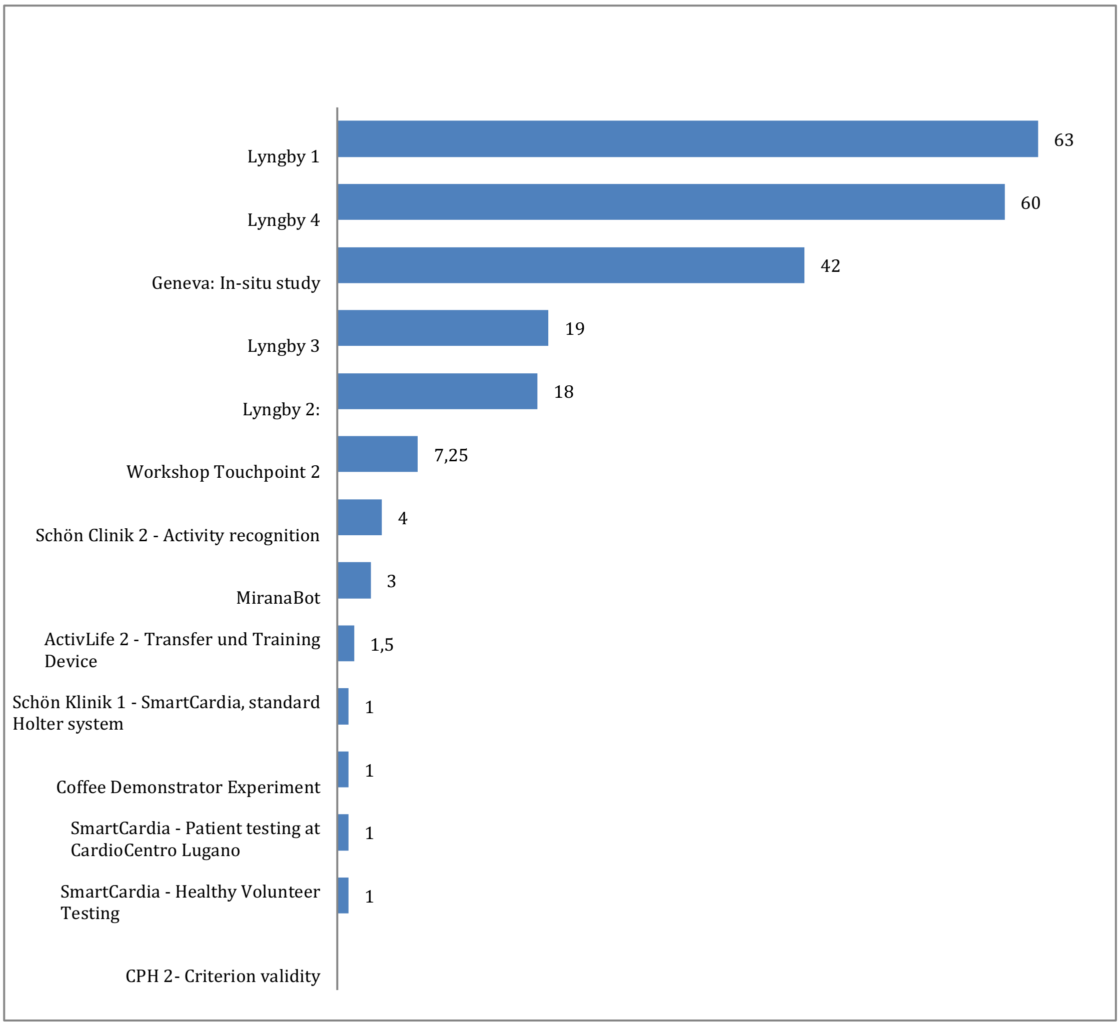

Figure 5-4 Mean amount of intervention sessions per participant

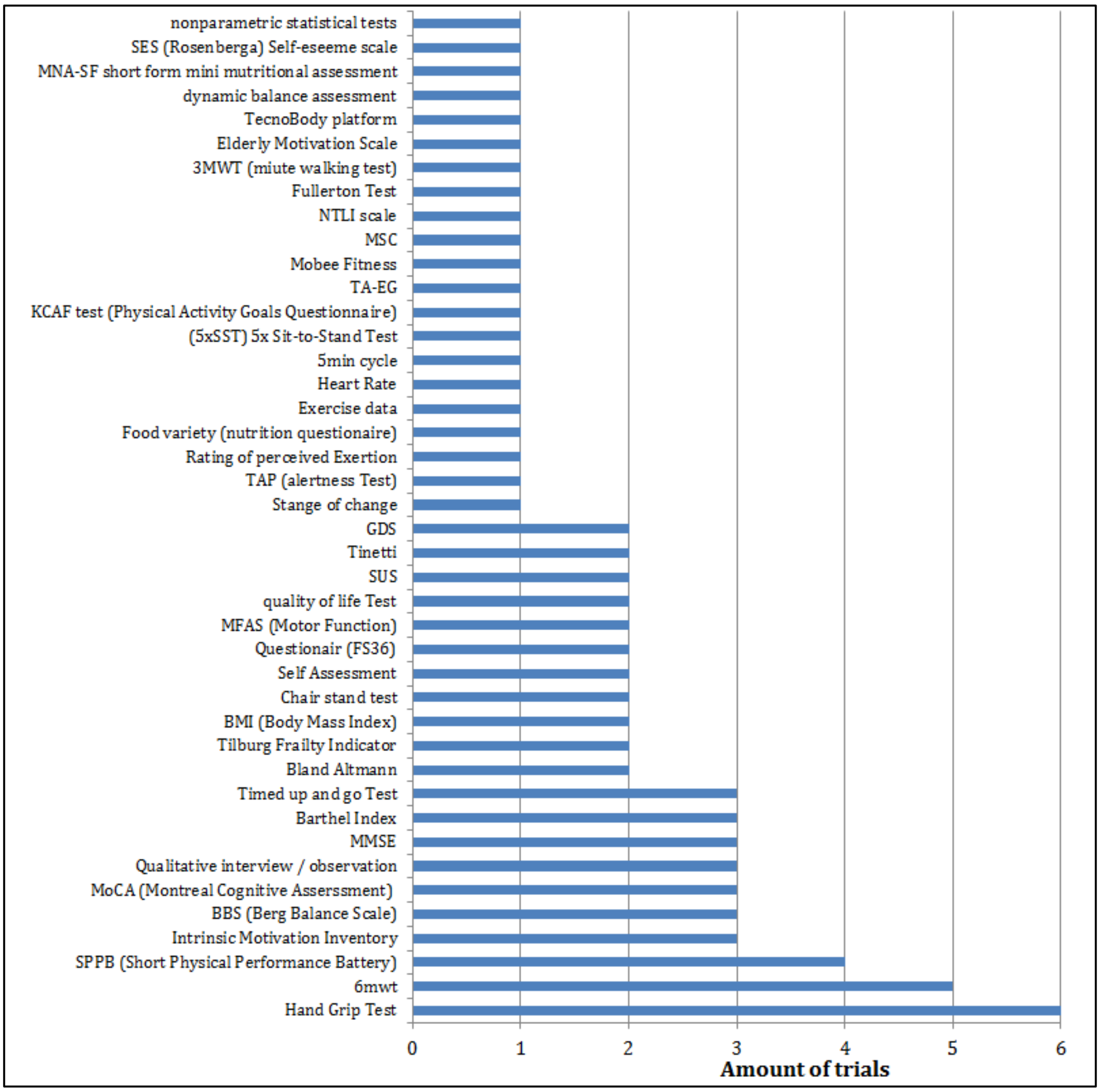

Figure 5-5 Assessments and tests performed in the REACH trials

As a valid instrument to collect information on frailty, the Hand-Grip-Test was the most used test (n=6) in all trials (Figure 5-5). Followed by a 6-minutes-walking test which was used in 5 trials, and the SPPB physical performance used in 4 trials. Other assessments and tests used were very specific to each hypothesis of the respective trial (e.g. SES, MNA-SF).

5.1.5 Strength & weaknesses of the results

The first stage of the data acquisition methodology used in Trial 19 showed that no technical difficulties are to be expected in the hospital environment. It also demonstrated that the most time-consuming task was storing the data. To optimize these procedures, two technical assistants were involved to manage the equipment as well as two (medical) assistants to prepare the participants and to guide them through the session according to the activity protocol. This stage also allowed improving the activity protocol, such that less relevant activities were removed to focus on core activities. Finally, this stage served to fine tune the methodology for the data recordings with elderly people and patients. From the core activities defined, the protocol conceded also a short-term adaptation option which allowed the study team to exclude such test scenarios from the testing procedure which were too strenuous for the individual elderly or patient.

5.2 Review on factors and co-factors

In an aging society, where the number of elder people in the world is growing at a fast pace it is getting more important to focus on challenges of this specific group. As living longer does not necessarily mean being healthy, increasing age is commonly related to certain so called 'geriatric' factors, representing common, serious conditions in elders that substantially affect functioning and quality of life. According to trials performed in the REACH project, several geriatric conditions were identified as highly prevalent:

- Falling
- Frailty
- Cognitive decline
- Sarcopenia
- Social isolation
- Malnutrition.

Those factors are covered by several testing activities. Figure 5-6 shows the number of trials that cover the specific factors.

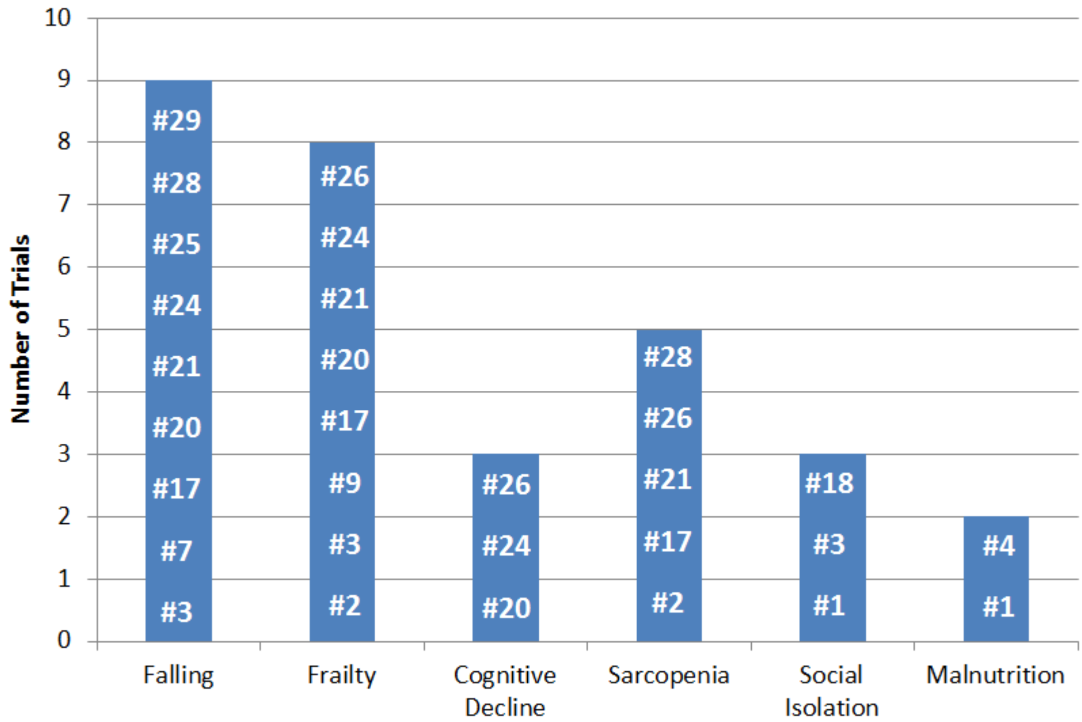

Figure 5-6 Amount of trials covering the different factors. Numbers represent the trial numbers.

In a narrative literature review (see Appendix 1: Factors & Co-factors) for the full review and the references of this section) that was done based on the reviewers' recommendations, risk factors regarding the above mentioned conditions (target factors) are being analysed, while by means of co-factors, the connection between those is attempted to be explained. Co-factors here describe the connection between both, as visible in Figure 5-7.

This report should be used as a guidance document for the technical, commercial, and non-medical scientific partnser in REACH to support the development of the sensingmointoring-intervention modules. The REACH system should aim to positively affect causes underlying an adverse event or condition and relevant risk factors being presumably associated with this causes.

In this report the term risk factor is used for an factor in causal relationship with a given condition or event. The co-factors are factors influencing or underlying the risk factors.

Risk factors and co-factors can either be influenced by the REACH system or being important to monitor. An example for an co-factor which can be targeted with an intervention is vitamin D deficiency, a risk factor for developing or worsening osteopenia and osteoporosis, cause osteomalacia and muscle weakness. These are conditions known to enhance the risk for falls. So the risk of falls can possibly be reduced by treating the vitamin D deficiency and avoiding the development of the above mentioned diseases.

On the other hand, female gender is a risk factor most strongly associated with the target factor sarcopenia. Gender cannot be influenced by an intervention, but the REACH system could monitor all female users very closely to detect first signs of sarcopenia and recommend interventions to prevent the decline of the physical status.

This report is not a comprehensive review which evaluated the causality of the risk and co-factors to the target conditions. A valid association was assumed when one best evidence trial was found in which the results supports an influence of risk factors or co-factors on the target condition.

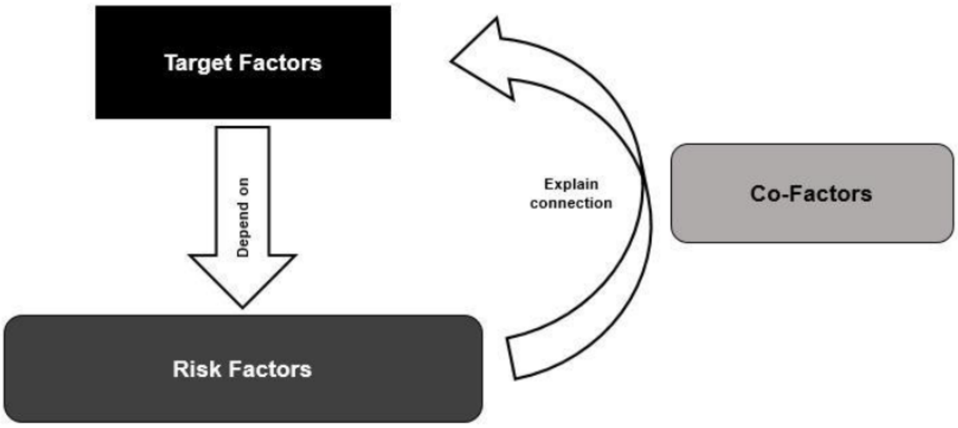

Figure 5-7 Relationship between target factors, risk factors and co-factors

The most important risk factors for each target factor as shown in Figure 5-8 are: 1. ‘orthostatic hypotension’ and ‘use of assistive devices’ for falls, 2. ‘malnutrition’ and ‘sedentary lifestyle’ for frailty, 3. ‘elevated plasma homocysteine’ and ‘anxiety’ for cognitive decline, 4. ‘female gender’ and ‘underweight’ for sarcopenia, 5. ‘male gender’ and ‘low income’ for social Isolation, and 6. ‘mental disorders’ and ‘poor oral and dental health’ for malnutrition.

Figure 5-8 Target factors and most important risk factors

To specifically address the reviewers' comments, the factor 'Falling' is presented here as an example in more detail.

According to the NANDA International (North American Nurse Diagnosis Association), the following categories have been identified in order to classify the factors resulting in such an event as falling (Herdman and Kamitsuru, 2014):

- Personal factors
- Physiological factors
- Cognitive factors
- Environmental factors
- Pharmacological factors

For this review, another category was added according to the findings of Sousa et al. (2017):

- Psychological factors

However, in their systematic review, Sousa et al. (2017) also proposed the category "socio-economic factors", including low education, low family income and black or ethnic minority group as risk factors for falling. Nevertheless, this category has not been added to this report due to lack of evidence. Moreover, the presence of such socio-economic factors might not directly represent a causal relationship to falling, but merely a correlation with other risk factors, whereby those lead to a higher risk of falling.

All risk factors for 'falling' elaborated within this review were matched to the NANDA International categories. Figure 5-9 shows the risk factors for the category 'Physiological factors'.

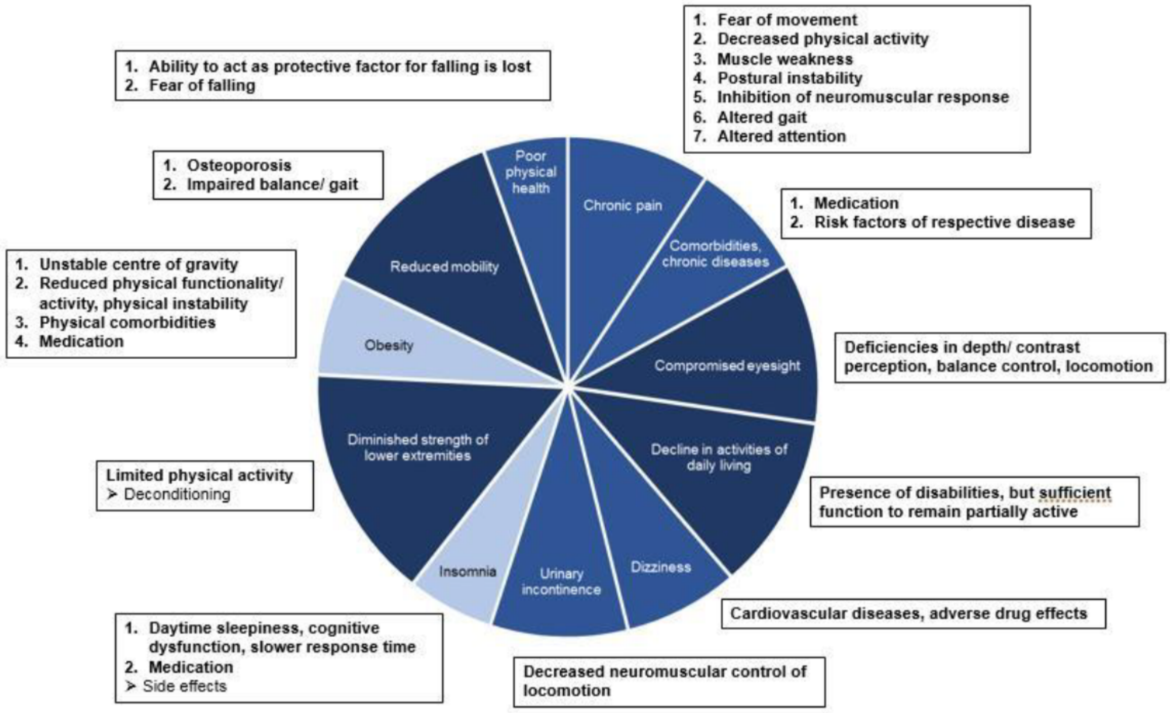

Figure 5-9 Physiological Factor with the co-factors found in literature

Figure 5-9 shows the representation of associations with the target factor 'falling'. Study types and means of odds ratios for the co-factors are listed here: 'Poor physical health': OR=1.1, cohort; 'Chronic pain': OR=1.88, cohort + cross-sectional; 'Comorbidities and chronic diseases': OR=1.555, cohort + cross-sectional; 'Compromised eyesight': OR=2.1, systematic review + cohort; 'Decline in activities of daily living: OR=2.3, systematic review; 'Dizziness': OR=1.5, cohort; 'Urinary incontinence': OR=1.8, cohort; 'Insomnia': OR=1.13, cross-sectional; 'Diminished strength of lower extremities': OR=3.08, systematic review + systematic review; 'Obesity': OR=1.3, cross-sectional; 'Reduced mobility': OR=2.5, systematic review.

Weakness of legs is common in older persons, with an estimation of 20% to 40% lower scores on strength tests compared to younger adults (Rubenstein and Josephson, 2006). This results in a strong association with an increased risk of falling (Moreland et al., 2004, Rubenstein and Josephson, 2006). Thus, according to a meta-analysis of Moreland et al. (2004), the combined odds ratio for lower extremity weakness and falling is 1.76 (95% CI: 5 1.31-2.37). This might be due to the fact that weakness is often subject to deconditioning, which is a result of limited physical activity (Rubenstein and Josephson, 2006).

There are two risk factors belonging to the 'Deficiency' category, Vitamin D deficiency and Hypoalbuminemia. Here, the risk factor 'Vitamin D deficiency' presents the strongest association with falling as shown in Figure 5-10.

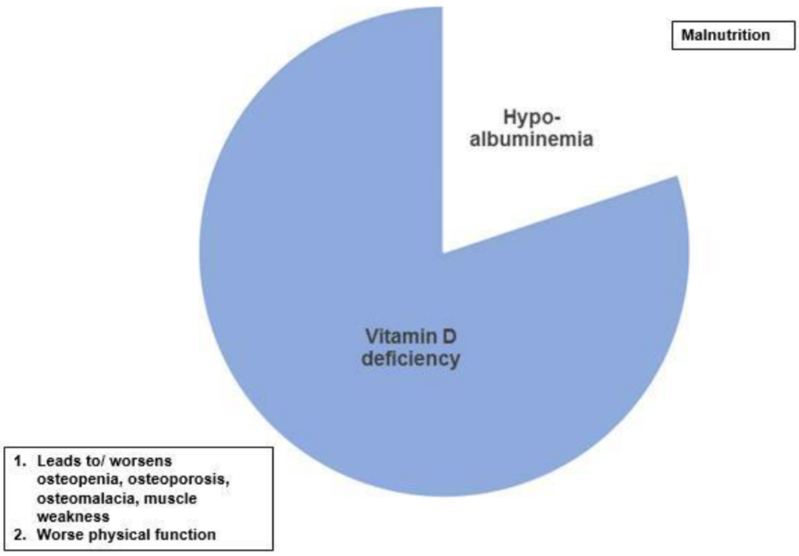

Figure 5-10 Physiological factors - Deficiencies: Representation of associations with the target factor 'falling'. Study types and means of odds ratios: 'Vitamin D deficiency': OR=4.03, case-control; 'Hypoalbuminemia': no study.

Vitamin D deficiency is common in adults, resulting from reduced sunlight exposure and limited dietary intake of vitamin D (Kotlarczyk et al., 2017). However, it can lead to or worsen osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and therefore increase the risk of falling (Holick, 2007, Aspray et al., 2014).
Furthermore, individuals with low vitamin D levels are more likely to have worse physical function in terms of slower gait, poor physical performance and balance and lower strength and thus increasing the risk as well (Kotlarczyk et al., 2017).
All in all, this suggests that vitamin D deficiency might influence the conditions predisposing to falls rather than the fall by itself (Duval et al., 2017).
Nevertheless, a case-control study of Duval et al. (2017) found a significant association between falling and vitamin D deficiency of OR=4.03 (95% CI: 1.33-12.27).

For all factors, recommendations for prevention are given in this review as well. As 'Falling' has been picked as an example to give an overview on the risk factors, the literature based recommendations are given for 'Falling' as well.

<u>Recommendations for the prevention of 'Falling'</u>
Falling counts to the geriatric syndromes due to its multifactorial nature and complex manifestations (Yamashita et al., 2012). Therefore, to prevent falls, also multifaceted interventions are needed in order to address multiple fall risk factors (Yamashita et al., 2012, Karlsson et al., 2013). Moreover, as the likelihood of falling also depends on the amount and type of risk factors a person has, fall prevention programmes should be tailored to personal characteristics, activities, and locations (Kuhirunyaratn et al., 2013, Kelsey et al., 2012).
According to a review of Karlsson et al. (2013) on RCT's for identifying programmes with fall-reductive effects, the most effective strategies include regular physical training with different training modalities. Furthermore, interventions according to a patient specific risk profile have been proven to decrease fall risk as well. This includes for example areas like adjustment of psychotropic medication, wearing anti-slip shoe devices when walking in icy conditions or supplementation of vitamin D (Karlsson et al., 2013).

5.3 The hierarchy of needs and the role of privacy in technology acceptance

The acceptance of technology has been a key subject in information systems research for decades. Early modern theories of technology acceptance include the theory of reasoned action, which explains the determinants of human behavior within a specific context and seeks to explain how pre-existing attitudes and intentions shape actions (Davis et al., 1989).

The Technology Acceptance Model (TAM) was inspired by the theory of reasoned action and was specifically designed to identify the determinants of computer usage behavior (Davis et al., 1989). Based on the psychological aspects of user's interaction with technology, TAM explains the user's intention to accept and use information technology through two constructs: *perceived usefulness* and *perceived ease of use* (Taherdoost, 2018). *Perceived usefulness* is about the benefits of the technology whereas *perceived ease of use* is about the efforts required to gain those benefits.

Venkatesh et al. (2003) extended TAM within a motivational framework to examine the influence of pre-training and training environment interventions. They formulated a *unified theory of acceptance and use of technology* (UTAUT) to explain facilitating conditions for behaviour intention. This model is explained in detail in deliverable D31 (D31: User Interfaces), where also the reference of this section can be found.

The importance of privacy has been investigated by many researchers. All describe privacy as a human's basic need and right to control others' access to themselves. Among the most notable of these existing approaches are the works by (Westin, 2003). It describes privacy as a dynamic process, where the importance of protecting it, is based on one's internal states and external conditions (Westin, 2003). Compared with other privacy theories, Westin's theory is a useful candidate in the context of the REACH studies of privacy as it provides an articulated foundation for understating the drivers of privacy as psychological concept (Trepte & Reinecke, 2011). This is important for our understating of users' behavioral intention towards use of technology and the balance between perceived usefulness of technology and need for protecting privacy. In Figure 5-11 we illustrate how the need for privacy becomes stronger when more invasive technologies appear and, similarly, how the need for care and monitoring becomes greater when frailty and disabilities are increased.

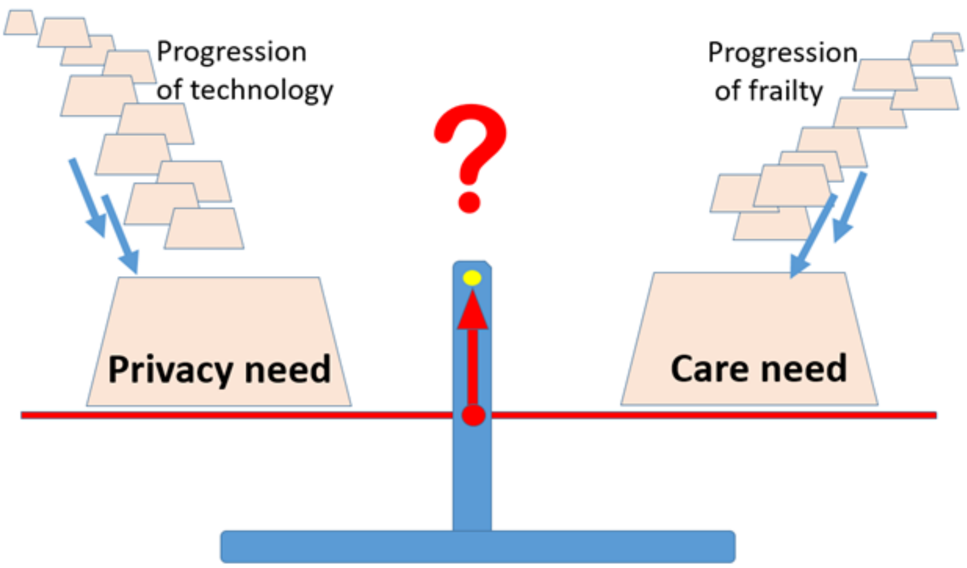

Figure 5-11 Balancing the need for privacy and the need for care and their drivers

The intention to accept technology is influenced by the compatibility between intrinsic and extrinsic needs. However, psychological needs vary over time and according to one's situation. As illustrated above, gradual increase in frailty will lead to greater care needs, and in general, a person's needs for care depend on state of health and day-to-day variations (Peek et al., 2016; Townsend et al., 2011).

People were willing to trade their privacy for the technological benefits that satisfied the needs, especially those benefits that were necessary for their health or independence. Hence, the balancing should be compared to the individual needs where the need to stay safe has a positive influence on technology acceptance despite the privacy issues imposed by the technology. Therefore, sensors and other technologies will be perceived as a tool that can satisfy the need for safety, care and peace of mind at an acceptable cost of privacy. This finding is in line with existing work within psychology that outlines safety and independence as a basic human need (Elliotet. al., 2001; Maslow, 1943; Thielke et al., 2012).

6 Summary and Conclusion – Lessons learned, exploitation opportunities, project impact

In REACH, our goal was to improve some aspect of the user's wellbeing by triggering an external event (intervention) which is suitable to have positive causal impact on the elderly. The interventions in trials were designed to be personalized because REACH users have diverse requirements, are varying in health status, and live in different environments. Therefore, during the design phase the targeted condition, represented in the different use cases, were taken into account.

All REACH trials have been implemented and realized as planned, and new trials (practice cases) were initiated as a reaction to the reviewers comments. As shown in

Figure 3-2 and Figure 5-2, all touchpoints are covered across the trials. Importantly, most of the trials, i.e., more than 86%, were performed for and with the target population, elderly aged 65+ and patients. Also about one third of the trials have been performed in a (near) real world setting to evaluated the effectiveness of the REACH system.

Relating the REACH trials to the most important factors that affect elderly people's life, we addressed all those factors within our trials (see Figure 5-6). Our review on factors and co-factors also verified the strong impact of physical activity on, for example, falling. As a results of the REACH review on physical activity monitors, we know that such sensors can be effectively used as they lead to a behavior change (Larsen et al., 2019). This proves the potential benefit of the REACH system and its modules. To be effectively used to induce behavior change, a system has to show sufficient simplicity and functioning, and people are willing to trade their privacy for the tehnological benefits zjat satisfied their needs, especially those benefits that are necessary for their health and independence (see 5.3).

The activity recognition procedures and the use of activity tracking algorithms have been proved as feasible technical solutionions with a overall high acceptance in elderly and patients. This was achieved also by using a participatory design approach to better include the use-cases' and stakeholders' needs and opinions.

The impact of the tesing activities on the consortium was an intensive information exchange between technical, scientific, medical, and commercial pertners. The non-technical partners had to learn what kind and quality of data is needed to qualitfy as data set for algorithm designing and what possibilities and boundaries are given in the respective machine learning methods. In return the technical partners had to learn about the limits and preferences of the end users. The impact on the system was a better understanding which sensors or sensor clases and equipment is suitable for the use in the REACH system, which data met the quality requirements, what kind of adaptations had to be done on software and hardware to create a seamless system.

With respect to the newly re-organized structure of the use-cases, eight trials were performed in a community setting, ten performed in a home setting, and 12 in an institutional setting.

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Appendix 1: Factors & Co-factors

Risk Factors Concerning Elder Ages – a Narrative Literature Review

for the European Project REACH – Responsive Engagement of the Elderly Promoting Activity and Customized Healthcare

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Abstract

In an aging society, where the number of elder people in the world is growing at a fast pace, it is getting more important to focus on challenges of this specific group. As living longer does not necessarily mean being healthy, increasing age is commonly related to certain, so called 'geriatric' factors, representing common, serious conditions in elders, that substantially affect functioning and quality of life. According to trials performed in the REACH project, several geriatric conditions were identified as highly prevalent: Falling, frailty, cognitive decline, sarcopenia, social isolation malnutrition.

Thus, in this narrative literature review, risk factors regarding the mentioned conditions (target factors) are being analysed, while by means of co-factors, the connection between those is attempted to be explained. Here, the database 'Pubmed' has been used for study search, while the selection of references was conducted according to certain rules.

In any case, the most important risk factors for each target factor are: 1. Falling: 'orthostatic hypotension' and 'use of assistive devices'; 2. Frailty: 'malnutrition' and 'sedentary lifestyle'; 3. Cognitive decline: 'elevated plasma homocysteine' and 'anxiety'; 4. Sarcopenia: 'female gender' and 'underweight'; 5. Social Isolation: 'male gender' and 'low income'; 6. Malnutrition: 'mental disorders' and 'poor oral and dental health'.

Lastly, as geriatric syndromes are generally assumed to have a multifactorial nature with complex manifestations, prevention strategies also need to show multifaceted implementations. Furthermore, as the development of such conditions is also subject to the amount and type of risk factors a person has, interventions need to be tailored to present risks factors, but also to general activities, characteristics or locations of an individual.

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1. Introduction

In an aging society, where the number of elder people (65+ years) in the world is growing at a fast pace (Crespo Cuaresma et al., 2016, Kannus et al., 2005) and is estimated to more than double between 2019 and 2050 (United Nations, 2019), it is getting more important to focus on challenges of this specific group. As living longer does not necessarily mean being healthy, increasing age is commonly related to certain, so called 'geriatric' factors (Lorenzo-Lopez et al., 2017). Thus, according to Inoue et al. (2016), geriatric factors or syndromes represent common, serious conditions in elders, that substantially affect functioning and quality of life. Due to the multifactorial nature, a large pattern of risk factors has been detected, including physiological, psycho-social or environmental issues (Inoue et al., 2016).

According to trials performed in the REACH project (see 0. REACH), several geriatric conditions were identified as highly prevalent:

- Falling
- Frailty
- Cognitive decline
- Sarcopenia
- Social isolation
- Malnutrition

In this report, the above-mentioned geriatric conditions are being analysed, as well as their respective risk factors.

2. Methods

In this narrative literature review, the association between the development of the main geriatric conditions, in this report called 'target factors', (falling, frailty, cognitive decline, malnutrition, social isolation and sarcopenia) and their dependence on specific risk factors is being analysed. Co-factors describe here the connection between both, as visible in Figure 1. Thus, co-factors intend to explain the increase in risk for a specific target factor through a risk factor.

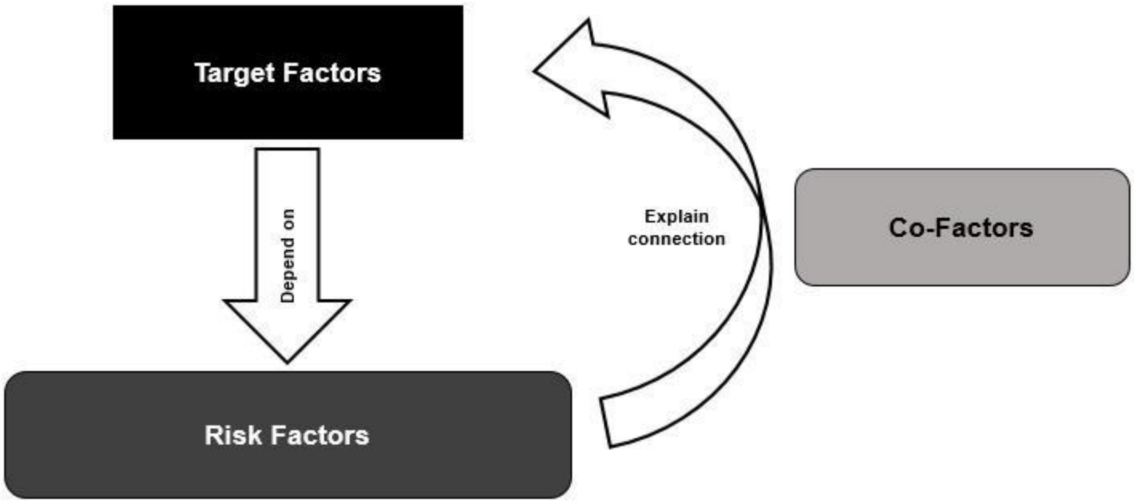

Figure 1: Relationship between target factors, risk factors and co-factors

For each specific risk factor, a sample of studies has been selected in order to present the strengths of associations between the risk factor and the target factor. The selection of studies has here been executed by adhering to certain rules:

1. *Quality*: For each risk factor, the most qualitative studies available (to the knowledge of the author) were selected. Here, systematic reviews were being favoured. However, if such study type was not to be found, cohort studies were included, case-control and also cross-sectional studies. Nevertheless, the decision on the inclusion was subjective to the author meaning that not necessarily all studies available were being considered.
2. *Contemporary work*: The selection of studies was focused on recently published work. Nevertheless, if such work was not available, older studies have been included as well.

In general, the search for studies has been performed via 'Pubmed'. However, 'Google Scholar' was used in order to consider other websites, as well.

Furthermore, in order to visualize the association between risk- and target factors, the mean of all odds ratios found for each risk factor were calculated and presented in respect to the other factors of this category. Thus, allowing for immediate grasp of importance of the respective risk factors in their specific category. Additionally, the colouring of the risk factor indicates the quality of the evidence. Here, darker colours indicate better quality in terms of the design; therefore, systematic reviews are represented by dark fields, whereby associations found by cross-sectional studies are brighter. If no study was available, this was indicated by a blank field.

Figure 2 shows a fictional example of the representation of associations between risk- and target factors. Here, the size of the field indicates the importance of the risk factor in terms of strength of the association.

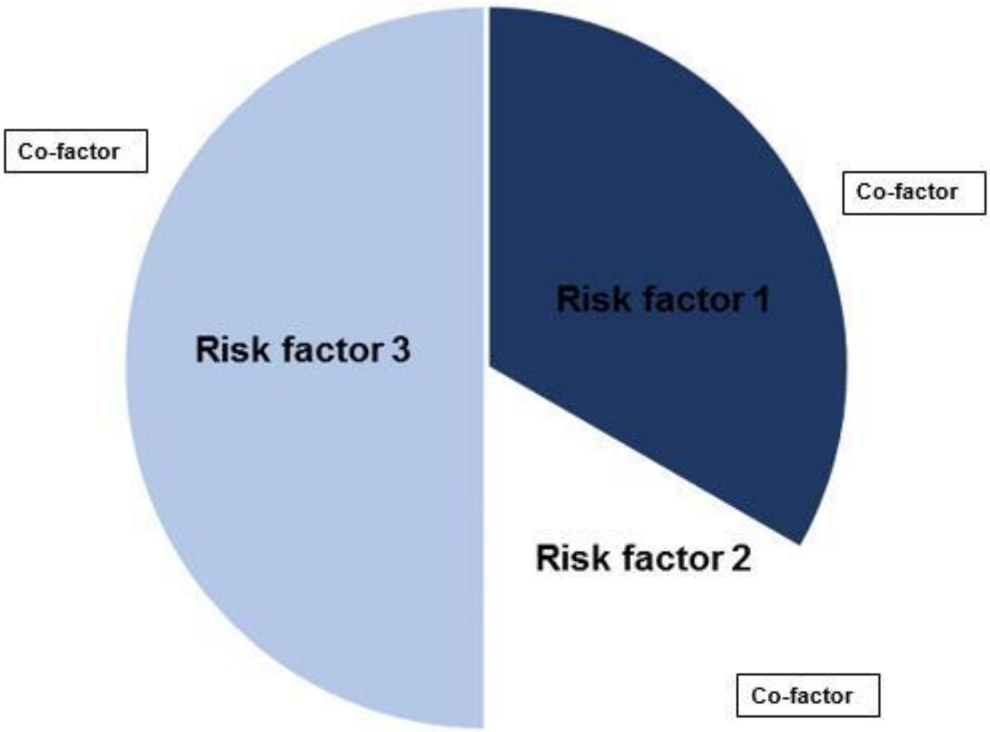

Figure 2: Example for the visualization of association between risk- and target factor

3. Falling

Falling accounts as the leading cause of injury-related mortality and morbidity among elderlies aged 65+ years and is also the most frequent cause of hospitalisation in this population (Cuevas-Trisan, 2017, Nevitt et al., 1991, Bergen et al., 2016, Sousa et al., 2017) Furthermore, it is estimated that one third of elderlies fall once a year, whereby more than half of those even fall several times (Cuevas-Trisan, 2017, Pirker and Katzenschlager, 2017, Voermans et al., 2007, Jansen et al., 2016). Also, approximately 10% to 20% of falls result in injury, hospitalisation or even death (Pirker and Katzenschlager, 2017, Rubenstein, 2006). Falling therefore represents a significant health and safety problem for adults (Verma et al., 2016).

According to Sousa et al. (2017), "a fall is an unexpected event, in which a person moves from a higher level to a lower level of the floor". This event can occur due to many different reasons and out of various circumstances and therefore has a complex and multifactorial nature (Sousa et al., 2017, Cuevas-Trisan, 2017). The nursing diagnosis "Risk for falls" is defined as "vulnerable to increased susceptibility to falling, which may cause physical harm and compromise health" (Herdman and Kamitsuru, 2014). Therefore, meaning that such susceptibility to falling depends on possible risk factors (Sousa et al., 2017).

According to the NANDA International (North American Nurse Diagnosis Association), categories have been identified in order to classify the factors resulting in such an event of falling (Herdman and Kamitsuru, 2014):

- Personal Factors
- Physiological Factors
- Cognitive Factors
- Environmental Factors
- Pharmacological Factors

For this review, another category has been added by the author according to the findings of Sousa et al. (2017):

- Psychological Factors

However, in their systematic review, Sousa et al. (2017) also proposed the category "socio-economic factors", including low education, low family income and black or ethnic minority group as risk factors for falling. Nevertheless, this category has not been added to this report due to lack of evidence. Moreover, the presence of such socio-economic factors might not directly represent a causal relationship to falling, but merely a correlation with other risk factors, whereby those lead to a higher risk of falling.

Finally, Figure 3 shows all categories of falling stated in this review. Here, the left figure presents the importance of the categories according to the number of risk factors, with the physiological group demonstrating the most risk factors. In contrast to this, the right figure presents the importance of the categories according to the strength of the associations. Here, for each category, the risk factor with the strongest association has been elected. Thus, the physiological group shows the strongest association.

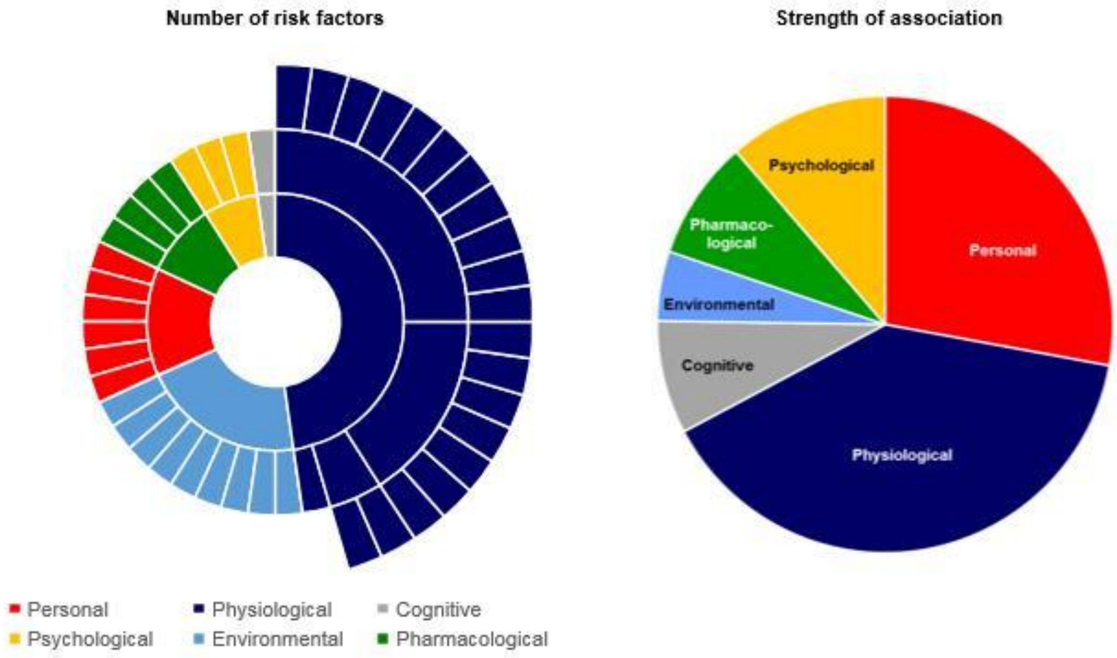

Figure 3: Categories of the target factor 'falling' according to importance

In the following, the risk factors of the target factor falling are going to be analysed in their respective categories.

3.1. Risks of 'Falling'

3.1.1. Personal Factors

Figure 4 shows all risk factors from the 'Personal Factors' category and their association with the target factor 'falling'. Here, the risk factor 'use of assistive devices' presents the strongest association with falling.

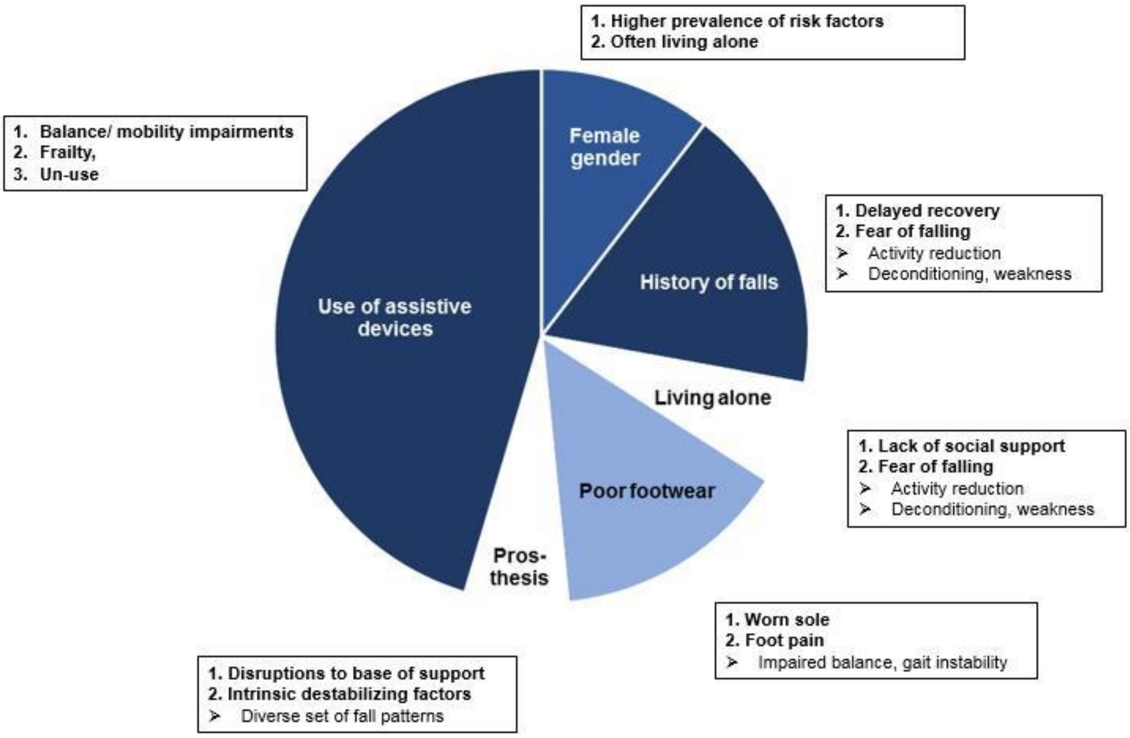

Figure 4: Personal factors: Representation of associations with the target factor 'falling'
Study types and means of odds ratios: 'Use of assistive devices': OR=7.3, systematic review+ cross-sectional; 'Female gender': OR=1.68, cohort+case-control+cross-sectional; 'History of falls': OR=2.8, systematic review+cohort; 'Living alone': no study; 'Poor footwear': OR=2.31, case-control; 'Prosthesis': no study

History of falls

According to the systematic review of Sousa et al. (2017), 'history of falls' is one of the most prevalent risk factors in the personal factors category. Thus, patients who have fallen in the last year are significantly more likely to fall again with a likelihood ratio of 2.3–2.8 (Ganz et al., 2007, Smith et al., 2017, Todd, 2004). This is supported by a systematic review of Rubenstein and Josephson (2006), who found an association between history of falling and recurrent falls of OR=3.0 (range: 1.7-7.0) and a cohort study of Tromp et al. (2001) with an association of OR=2.6 (95% CI:2.0-3.3).

This risk might result from the fact that recovery from fall injury is often delayed in older persons, which in turn might increase the risk of subsequent falls through deconditioning and weakness (Rubenstein, 2006). Furthermore, individuals often develop a fear of falling again and hereby increasing the risk further (see "Fear of Falling") (Rubenstein, 2006). As Rubenstein (2006) highlights, "the risk associated with previous fall history emphasizes the importance of avoiding fall events in order to reduce the risk of further falls."

Female gender

Another highly prevalent risk factor for falling is the 'female gender' (Sousa et al., 2017, Elliott et al., 2009, Chang and Do, 2015, Todd, 2004, Gale et al., 2016, Lin et al., 2011). Therefore, evidence suggests that women are more likely to fall than men, whereby Lin et al. (2011) found an association of OR=1.94 (95% CI:1.36-2.76) which is similar to the findings of Duval et al. (2017) with OR=1.70 (95% CI:0.64-4.48) and Tromp et al. (2001) with OR=1.4 (95% CI: 1.1-1.8).

The risk might be due to a higher prevalence of (age-related) risk factors among women, as, for example, women are compared to men less physically active, which in turn increases the risk of falling due to deconditioning and fear of falling (Chang and Do, 2015, Jeoung, 2015, Stahl and Albert, 2015).

Also, women tend to live alone more often compared to men (57% vs. 26%), which is a risk factor in itself (see "Living alone") (Elliott et al., 2009). However, men tend to underreport the incidence of falls, which in turn creates a wrong view on the fall proportion compared to women (Elliott et al., 2009, Cuevas-Trisan, 2017).

Nevertheless, it still is unclear whether risk factors for falls really vary between the sexes (Gale et al., 2016).

Living alone

According to the *Health Evidence Network Report* of the WHO, "living alone has been shown to be a risk factor for falls" (Todd, 2004, Wickham et al., 1989).

This might be due to several factors: First, evidence suggests that subjects living alone are more afraid of falling than those living with others (Elliott et al., 2009, Zijlstra et al., 2007), being a risk factor for falling in itself (see "Fear of falling"). Moreover, fear of falling especially leads to an activity reduction in those living alone, compared to those living with others, which might be due to the present social support for the latter, that in turn makes them less fearful (Elliott et al., 2009, Howland et al., 1998). Furthermore a reduction in activity might lead to deconditioning and weakness and therefore increases the risk of falling (Rubenstein and Josephson, 2006).

Poor footwear

Poor footwear can increase the risk of falling, for example when wearing slippers or too narrow shoes (Herdman and Kamitsuru, 2014, Kuhirunyaratn et al., 2013). According to a case-control study of Kuhirunyaratn et al. (2013) in Thailand, the odds ratios of falling with slippers are 2.31 (95% CI: 1.24-4.29) compared to non-slipper wearers. This is possibly due to the often already worn sole, causing the shoe to get even more slippery (Kuhirunyaratn et al., 2013).

Furthermore, too narrow shoes are a risk factor as well as they cause foot pain and, especially pain from the plantar fasciitis, increases the risk of falls (foot pain OR=2.5;

95% CI:1.03–6.12) as it often results in impaired balance and gait instability (Chaiwanichsiri et al., 2009).

Lower limb prostheses

Lower limb prostheses are generally a risk factor for falls (Herdman and Kamitsuru, 2014, Kim et al., 2019, Kulkarni et al., 1996, Wong et al., 2016). Evidence suggests that over 50% of adults with lower limb prostheses fall at least once a year (Miller et al., 2001, Kulkarni et al., 1996, Kim et al., 2019), whereby most falls occur from disruptions to the base of support, intrinsic destabilizing factors, and a diverse set of fall patterns (e.g. slips, trips, inadequate weight shift) (Kim et al., 2019). Regarding the disruptions of the base of support, environmental barriers (e.g. cracks in the sidewalk) or limitations in modern prosthetic components might be contributing factors (Kim et al., 2019). Furthermore, the reduced active ankle dorsiflexion in most prosthetic feet might limit the functional shortening of the prosthetic leg required during the swing phase to achieve sufficient toe clearance, resulting for example in trips (Kim et al., 2019).

Assistive devices

In 2013, 16.9% of elderlies reported using an assistive device (e.g. walker, cane, wheelchair) for mobility improvement, with an increasing tendency as the population ages (West et al., 2015). Although the use of assistive devices along multifaceted interventions has been proven in RCTs to be effective for fall reduction (Karlsson et al., 2013), it is listed as risk factor for falling in the NANDA International (Herdman and Kamitsuru, 2014). This is supported by a study of West et al. (2015), claiming that assistive device users were more likely to report a recent fall compared with non-users (OR=12.0; 95% CI:4.9-29.3), however presenting a cross-sectional design. Nevertheless, a systematic review of Rubenstein and Josephson (2006) found an association as well, with OR=2.6 (range: 1.2-4.6).

This connection might be due to the fact that elderlies using assistive devices usually have balance or mobility impairments and often are frail, which puts them at an increased risk of falling in general (West et al., 2015). Furthermore, according to a study of Luz et al. (2017), 57% of patients using assistive devices fell when they were not using them, indicating that the actual risk for falling is the un-use of assistive devices when they are needed.

3.1.2. Physiological Factors

3.1.2.1. General Health Status

Figure 5 shows all risk factors from the 'General Health Status' category and their association with the target factor 'falling'. Here, the risk factor 'diminished strength of lower extremities' presents the strongest association with falling.

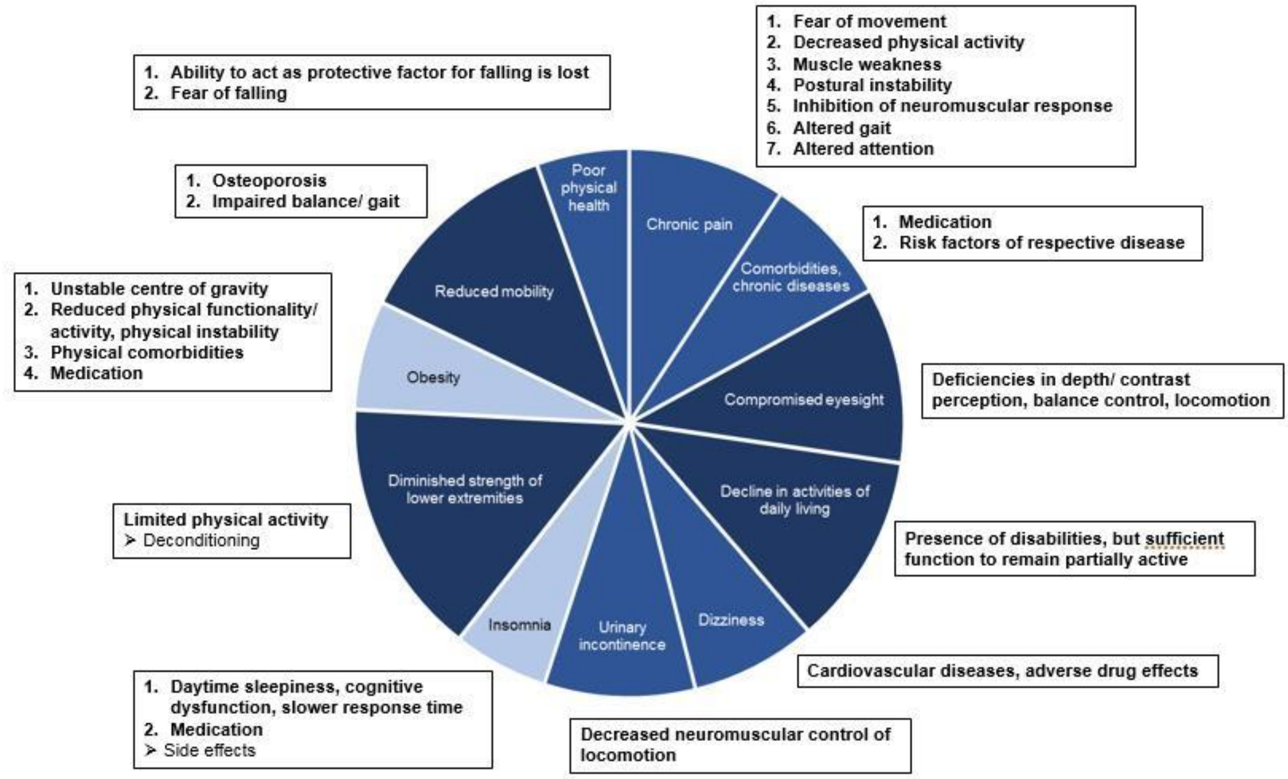

Figure 5: Physiological Factors, General health status: Representation of associations with the target factor 'falling'
Study types and means of odds ratios: 'Poor physical health': OR=1.1, cohort; 'Chronic pain': OR=1.88, cohort+cross-sectional; 'Comorbidities and chronic diseases': OR=1.555, cohort+cross-sectional; 'Compromised eyesight': OR=2.1, systematic review+cohort; 'Decline in activities of daily living: OR=2.3, systematic review; 'Dizziness': OR=1.5, cohort; 'Urinary incontinence': OR=1.8, cohort; 'Insomnia': OR=1.13, cross-sectional; 'Diminished strength of lower extremities': OR=3.08, systematic review+systematic review; 'Obesity': OR=1.3, cross-sectional; 'Reduced mobility': OR=2.5, systematic review

Urinary incontinence

According to a survey of Schreiber Pedersen et al. (2017), in Germany, 50% of women over 60 and 60% over 80 have experienced urinary incontinence in the last four weeks. However, urinary incontinence accounts as a significant risk factor for falls, with an association of OR=1.8 (95% CI: 1.4-2.4) (Morris and Wagg, 2007, Tromp et al., 1998, Tromp et al., 2001). This might be due to the fact, that urinary incontinence is associated with a decreased neuromuscular control of locomotion, and therefore possibly leading to falls (Tromp et al., 2001).

Decline in activities of daily living

Functional limitations in terms of decline in (instrumental) activities of daily living affect about 20% of persons older than 70 years and are significantly associated with a risk of falls, which is “doubled”, according to Rubenstein and Josephson (2006) (Herdman and Kamitsuru, 2014, Brown et al., 2014).

Activities of daily living can be defined as activities, essential for an independent life or necessary for survival and represent common everyday tasks required for self-care (e.g. bathing, dressing, eating, toileting) (van der Vorst et al., 2016).

They are usually divided in five stages, whereas the lowest stage (stage 0) implies that there is no difficulty (no, absent, or negligible limitation) and the highest (stage 4) means complete difficulty (total ADL limitation) (Henry-Sanchez et al., 2012). Evidence suggests that the highest risk for falls is at intermediate stages, which might be related to the individual being at a point when having significant disabilities, but still having sufficient function to remain partially active (Henry-Sanchez et al., 2012, Brown et al., 2014).

Brown et al. (2014) found the strongest association between falling and limitations in activities of daily living at stage 2 with a relative risk of 2.0 (95% CI: 1.5-2.6). This is similar to the findings of Rubenstein and Josephson (2006), who found a general association for impaired activities of daily living of OR=2.3 (range: 1.5-3.1).

According to van der Vorst et al. (2016), risk factors for developing limitations in activities of daily living, are higher age, female gender, diabetes, hypertension, and stroke.

Dizziness

Another important factor is ‘dizziness’, as it generally is a common symptom among elderlies (O'Loughlin et al., 1993, Rubenstein, 2006). Evidence suggests subjects with frequent dizziness are twice as likely to fall (O'Loughlin et al., 1993). Thus, in a prospective cohort study, Tromp et al. (2001) found an association between falling and dizziness of OR=1.5 (95%CI: 1.1-2.0).

According to Maarsingh et al. (2010), cardiovascular diseases are the most common major cause of dizziness in elderly patients in primary care. Furthermore, adverse drug effects contribute to causing dizziness as well (Maarsingh et al., 2010, Rubenstein, 2006).

Compromised eyesight

Moreover, another variable that is associated with risk of falls is ‘compromised eyesight’ (Sousa et al., 2017, Rubenstein, 2006), which is highly prevalent in elderlies, with 65% of visually impaired and 82% of blind people being over 50 years (Marks, 2014, Pascolini and Mariotti, 2012). According to Smith et al. (2017), having visual deficits increases in 1.929 times the chances of falls. This is similar to the findings of Rubenstein and Josephson (2006), who found an association of OR=2.5 (range: 1.6-3.5) and Tromp et al. (2001) with OR=1.7 (95% CI: 1.3–2.3).

As visual impairments are associated with deficiencies in depth and contrast perception, the ability to perceive objects in three dimensions and monocular cues implicating depth and motion cues is impaired, as well as the ability to detect stimuli of varying brightness against a background of given brightness (Marks, 2014).

Furthermore, vision also affects balance control and locomotion, as it regulates step length and speed, which may be reduced, disrupted, or compromised due to visual impairments and therefore might lead to falls as well (Marks, 2014).

Chronic pain

Chronic pain is common in community-dwelling older adults and is associated with an increased risk for falls (Eggermont et al., 2012, Sousa et al., 2017, Gale et al., 2016, Patel et al., 2014). According to Gale et al. (2016), the association between pain and risk of falling can be expressed in a dose response relationship, whereby the odds ratios for severe pain are OR=1.92 (95% CI: 1.26-1.94). Similar findings were observed by Lazkani et al. (2015), who found an association of severe pain and falling of OR=1.84 (95% CI:1.15-2.96).

According to Patel et al. (2014) , chronic pain might increase the risk of falling through several factors: fear of movement, decreased physical activity, postural instability, muscle weakness, inhibition of neuromuscular response and altered gait and attention.

Comorbidities and chronic diseases

Chronic diseases or comorbidities can, for example, be diseases of the circulatory system, chronic obstructive pulmonary disease, arthritis or even depression (Lawlor et al., 2003). Evidence suggests that chronic diseases are associated with a risk of falls, whereby the prevalence of falling is thought to increase with growing numbers of simultaneously occurring chronic diseases in a linear trend (Gale et al., 2016, Lawlor et al., 2003, Todd, 2004, Sousa et al., 2017). According to Lawlor et al. (2003), the population attributable risk of falling associated with having at least one chronic disease is 32.2% (OR=1.81, 95% CI: 1.42-2.31), with an odds ratio of OR=1.37 (1.25 to 1.49) for each additional disease.

This matches with the findings of Tromp et al. (2001), who found an odds ratio of OR=1.3 (95% CI: 1.0-1.7) for at least one chronic disease, but, however, included different conditions (i.e. chronic obstructive pulmonary disease, cardiovascular disease, stroke, urinary incontinence, diabetes mellitus, joint disorders and malignant neoplasms).

The increased risk of falling in chronic diseases might result from medication often used in such conditions, which acts as a risk factor itself (see ”Pharmacological Factors”) (Smith and Tett, 2009). The same applies for the respective chronic diseases themselves, who often are associated with increased risk as well.

Diminished strength of lower extremities

Weakness of legs is common in older persons, with an estimation of 20% to 40% lower scores on strength tests compared to younger adults (Rubenstein and Josephson, 2006). This results in a strong association with an increased risk of falling (Moreland et al., 2004, Rubenstein and Josephson, 2006). Thus, according to a meta-analysis of Moreland et al. (2004), the combined odds ratio for lower extremity weakness and falling is 1.76 (95% CI: 5 1.31-2.37).

This might be due to the fact that weakness is often subject to deconditioning, which is a result of limited physical activity (Rubenstein and Josephson, 2006)

Obesity

Obesity and larger waist circumference, which is basically an indicator of central obesity, are independent risk factors for falls (Lin et al., 2011, Herdman and Kamitsuru, 2014, Mitchell et al., 2014). A study of Lin et al. (2011) showed the odds ratio for falling when having a larger waist circumference are at 1.03 (95% CI:1.01-1.05), whereas obesity was associated with a 31% higher risk (RR 1.31, 95%CI 1.14-1.50) of having fallen in the previous 12 months compared to non-obese subjects (Mitchell et al., 2014).

This might be a consequence of an unstable centre of gravity, which can induce falls (Lin et al., 2011). Moreover, evidence suggests that obese individuals show reduced levels of physical functionality, activity and physical instability in general, which are factors contributing to fall risk, as well (Mitchell et al., 2014). Lastly, obese people often have certain physical comorbidities that are commonly associated with weight gain (e.g. Diabetes, cardiovascular diseases) and therefore use multiple medication, which in itself are all risk factors for falling (Mitchell et al., 2014).

Insomnia

Sleep problems are common among older adults, with 50% reporting to suffer of poor sleep, but nevertheless, are often undertreated (Chen et al., 2017, Min et al., 2016). However, Insomnia is associated with a greater risk of falls (OR=1.13; 95% CI: 1.01-1.25) (Min et al., 2016), whereby the extent of various insomnia symptoms, such as "falling asleep", "waking up during the night", and "waking up too early and not being able to fall asleep again", increases the risk in terms of a dose-response relationship (Chen et al., 2017, Min et al., 2016).

The incidence of falls might be due to several reasons: First, patients suffering from insomnia often take sleep medication which in turn can lead to falls due to their side effects (Chen et al., 2017). Second, poor sleep can cause daytime sleepiness, cognitive dysfunction and slower response time, and is therefore leading to falls (Min et al., 2016).

Reduced mobility

Evidence suggests that persons with impaired mobility have a higher risk for falling (Herdman and Kamitsuru, 2014, Forrest and Chen, 2016, Rubenstein and Josephson, 2006). Thus, according to a systematic review of Rubenstein (2006), the risk of falling is significantly associated with mobility impairments with 2.5 (range: 1.0–5.3).

Nevertheless, the risk of falling depends on the degree of mobility impairment, as highly impaired persons, for example bed-ridden elders, are unlikely to fall, but persons who are still mobile but show certain instabilities are most likely (Studenski et al., 1994)

This might be due to the fact that immobility promotes osteoporosis, which in itself increases the risk of falling (see ”Osteoporosis”) (Voermans et al., 2007). Furthermore, immobile persons often show altered or impaired gaits as well as impaired balance and is therefore increasing the risk as well (see “Balance and Gait”) (Sturnieks et al., 2008).

Lastly, a driving factor behind unnecessary immobility is a fear of falling which is regularly experienced by elderly fallers (Voermans et al., 2007).

Poor physical health

Poor physical performance such as leg extension strength, walking speed, lower extremity performance and balance is found to be associated with an increased risk of falling (Sousa et al., 2017, Chan et al., 2006). Nevertheless, according to a cohort study of Tromp et al. (2001), this association is rather weak, with OR=1.1 (95% CI: 1.0-1.1).

Still, the association might exist due to the fact that good physical performance acts as a protective factor for falling, whereby in poor performances this ability is lost (Chan et al., 2006).

Furthermore, if one’s physical health is perceived as poor, this can lead to a fear of falling, which in turn increases the risk of falling itself (see “fear of falling”) (Kumar et al., 2014, Chen et al., 2013).

3.1.2.2. Diseases and Disorders

Figure 6 shows all risk factors from the 'Diseases and Disorders' category and their association with the target factor 'falling'. Here, the risk factor 'orthostatic hypotension' presents the strongest association with falling.

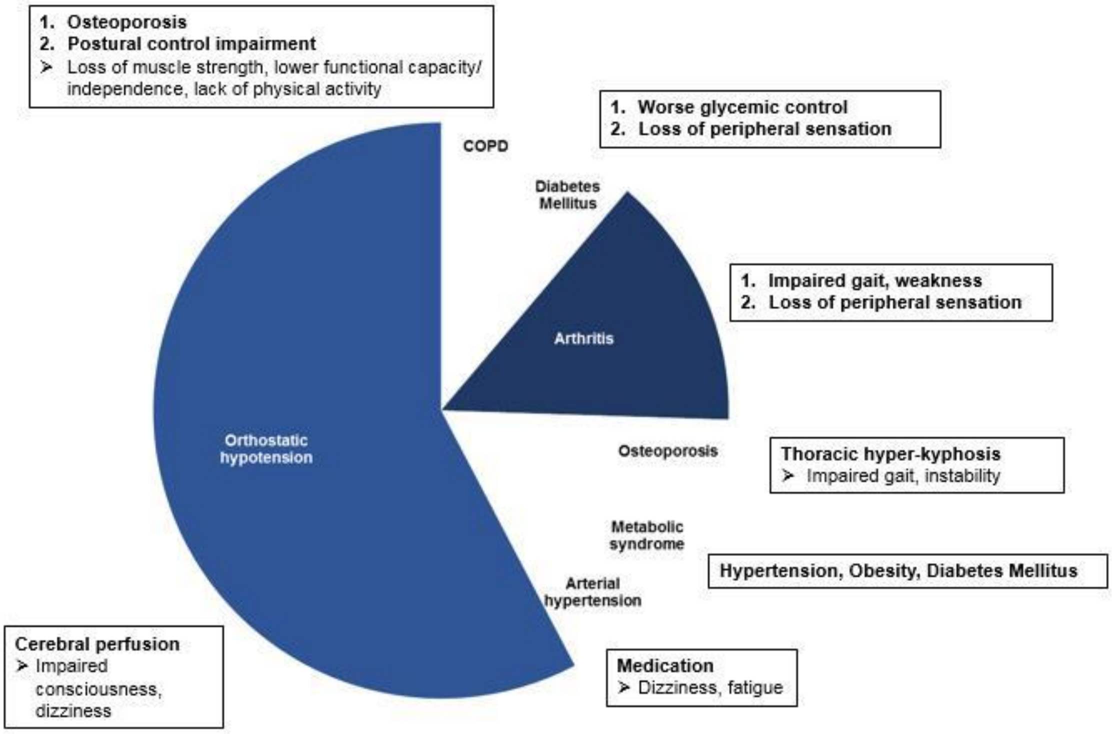

Figure 6: Physiological factors, diseases and disorders: Representation of associations with the target factor 'falling'
Study types and means of odds ratios: 'COPD': no study, 'Arthritis': OR=2.553, systematic review+cross-sectional+cross-sectional; 'Osteoporosis': no study; 'Metabolic syndrome': no study; 'Arterial hypertension': no study; Orthostatic hypotension': OR=10.299, cohort

3.1.2.2.1. General

COPD (chronic obstructive pulmonary disease)

COPD is a chronic inflammatory airway disease that is associated with various systemic comorbidities (Inoue et al., 2016). Evidence suggests that patients with COPD have a higher susceptibility to falls (Roig et al., 2011, Sousa et al., 2017, Oliveira et al., 2015) and that it is even one of the chronic conditions with the highest prevalence of falls (Lawlor et al., 2003). According to Hakamy et al. (2018) patients with COPD are 55% more likely to have an incident record of fall than non-COPD subjects. Nevertheless, Roig et al. (2011) estimates the fall incidence in people with COPD to range between 25–46%.

The higher incidence of falling might be a consequence of the often present postural control impairment in COPD patients (Porto et al., 2015, Oliveira et al., 2017). Contributing factors here are loss of muscle strength, lower functional capacity and independence and a lack of physical activity (Porto et al., 2015).

Furthermore, an often-occurring comorbidity is 'Osteoporosis'; here, the prevalence among COPD patients is assumed to be two- to five-fold higher than in age-matched subjects (Graat-Verboom et al., 2009, Inoue et al., 2016). As osteoporosis is a risk factor for falling itself (see "Diseases regarding skeletal system"), this might contribute to the higher risk of falling in COPD patients.

Diabetes Mellitus

The population of older adults with diabetes mellitus is rapidly growing worldwide (Strain et al., 2018), which is especially due to the prevalence of diabetes mellitus type 2 (T2DM), accounting for 90%-95% of diabetes cases (Cannon et al., 2018). T2DM is defined by relative insulin deficiency, peripheral insulin resistance, and high blood glucose levels, and therefore leads to an insufficient insulin secretion which is necessary to compensate for insulin resistance (Cannon et al., 2018).

According to a meta-analysis of Yang et al. (2016), older adults with diabetes mellitus are associated with a 64% greater risk of falling, with an annual incidence of falls of 39% (Tilling et al., 2006). Here, a poor control of the disease in terms of intensive or very loose glycaemic control may contribute to such risk (Yang et al., 2016). Furthermore, as diabetes can lead to a loss of peripheral sensation, this might increase the risk as well (Todd, 2004).

Metabolic Syndrome

The Metabolic Syndrome comprises of the presence of abdominal obesity, dyslipidaemia, hypertension, and glucose intolerance and is a worldwide health problem with increasing prevalence in age (Liao et al., 2012). The Metabolic Syndrome accounts furthermore as an independent risk factor for falling, with an annual incidence of 22.4%–80.9% in community-dwelling older adults in Western countries (Liao et al., 2012). Nevertheless, the relation between fall incidence and the metabolic syndrome needs further investigation (Liao et al., 2012). However, as the syndrome's components are by itself risk factors for falling, this might be the explanation.

3.1.2.2.2. Diseases regarding the skeletal system

Osteoporosis

According to Inoue et al. (2016), "osteoporosis is defined as a skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk of fracture". It has been estimated to be prevalent in more than 200 million people worldwide and is therefore the most common bone disease, with women being affected more often (Sözen et al., 2017). Hereby, Vitamin d deficiency might be a contributing factor as it is necessary for calcium absorption, bone health, muscle performance, and balance (Sözen et al., 2017, Aspray et al., 2014).

Evidence suggests that osteoporosis accounts as a predictive factor for the occurrence of falls (Smith et al., 2017, Sousa et al., 2017, Rubenstein, 2006).

As especially women with osteoporosis have weaker back extensor and lower extremity muscle strength than normal women of comparable age, this often leads to a Thoracic hyperkyphosis (excessive curvature of the spine). As a result, this might impair gait, lead to instability and therefore increase the risk of falls (Sinaki et al., 2005).

Arthritis

Osteoarthritis is the most common global chronic joint disease with an estimated prevalence of 9.6% in men and 18.0% in women aged over 60 years (Valdes and Stocks, 2018).

Evidence suggests that Arthritis increases the risk for falling about 2.4 times (range: 1.9-2.9) (Rubenstein and Josephson, 2006). Lawlor et al. (2003) found a similar association for women having an attributable risk of having had at least one fall in the previous 12 months of 17.4% with an odds ratio of 1.60 (95% CI: 1.33-1.93), whereas Ou et al. (2013) found an association of OR=3.66 (95%CI: 1.15-11.64) in men.

The increased fall risk might be due to gait impairments and weakness that are common in patients with arthritis (Rubenstein and Josephson, 2006, Barbour et al., 2014). Furthermore, arthritis can lead to a loss of peripheral sensation and therefore might increase the risk as well (Todd, 2004).

3.1.2.2.3. Vascular diseases

Vascular diseases (e.g. arrhythmia, hypertension, heart failure) are generally associated with an increased risk of falling (Herdman and Kamitsuru, 2014, Jansen et al., 2016). Thus, it is estimated that they are responsible for 77% of patients in emergency and accident departments with unexplained or recurrent falls that are associated with unexpected loss of consciousness (Carey and Potter, 2001).

Arterial Hypertension

As hypertension is especially common among elderlies, and due to the issue of aging societies, it is estimated to be an “ever-increasing public health problem” (Setters and Holmes, 2017). Furthermore, older adults with hypertension have a significantly higher prevalence of falls (Liao et al., 2012). This might be due to specific medications used to lower blood pressures as well as the low pressures themselves causing dizziness, fatigue and falls (Setters and Holmes, 2017).

Orthostatic Hypotension

Orthostatic hypotension reflects a significant decrease of systolic blood pressure (over 20 mmHg) when switching between a lying and standing position and is estimated to be prevalent in 10-30% of elderly people (Rubenstein, 2006). The condition can result from several factors such as autonomic dysfunction (frequently related to age, diabetes or brain damage), hypovolaemia, low cardiac output, Parkinsonism, metabolic and endocrine disorders and medications (e.g. sedatives, antihypertensives and antidepressants) (Rubenstein, 2006). Furthermore, the orthostatic drop can be stronger in the morning as the baroreceptor response is diminished after lying for a longer period (Rubenstein, 2006).

All in all, the risk of falling can be increased through orthostatic hypotension (Herdman and Kamitsuru, 2014, Shaw and Claydon, 2014); Juraschek et al. (2017) found in a prospective study a hazard ratio of HR=1.30 (95% CI: 1.10-1.54) and McDonald et al. (2017) found an even higher hazard ratio of 3.017 (95% CI: 1.291-7.050). Furthermore, the general association between the risk of falling and orthostatic hypotension is OR=10.299 (95% CI: 1.703-61.43), according to McDonald et al. (2017).

As Shaw and Claydon (2014) state, decreases in blood pressure can reduce cerebral perfusion which impairs consciousness, leads to dizziness, and therefore might lead to falls.

3.1.2.3. Balance and Gait

Balance and gait disorders are especially common in elder individuals and are a major cause of falls (Salzman, 2010, Rubenstein and Josephson, 2006). As they are usually multifactorial in their origin, several factors are contributing to such impairment (Cuevas-Trisan, 2017). Thus, common causes include arthritis and orthostatic hypotension, however, it is often caused by age- and disease-related changes in the central and peripheral nervous system, leading to an impaired sensorimotor functioning (Viswanathan and Sudarsky, 2012, Cuevas-Trisan, 2017, Ganz et al., 2007, Salzman, 2010, Pirker and Katzenschlager, 2017).

Nevertheless, most changes in gait or balance occurring in older adults are related to underlying medical conditions, as visible in Figure 7 shows both risk factors from the ‘Balance and Gait’ category and their association with the target factor ‘falling’. Here, both risk factors present nearly similar associations with falling.

Table 1 (Salzman, 2010, Cuevas-Trisan, 2017)

Figure 7 shows both risk factors from the ‘Balance and Gait’ category and their association with the target factor ‘falling’. Here, both risk factors present nearly similar associations with falling.

Table 1: Medical Conditions and Risk Factors Associated with Gait and Balance Disorders

Affective disorders and psychiatric conditions
Depression
Fear of falling
Sleep disorders
Substance abuse

Cardiovascular diseases
Arrhythmias
Congestive heart failure
Coronary artery disease
Orthostatic hypotension
Peripheral arterial disease
Thromboembolic disease

Infectious and metabolic diseases
Diabetes mellitus
Hepatic encephalopathy
Human immunodeficiency virus–
associated neuropathy
Hyper- and hypothyroidism
Obesity
Tertiary syphilis
Uremia
Vitamin B12 deficiency

Musculoskeletal disorders
Cervical spondylosis
Gout
Lumbar spinal stenosis
Muscle weakness or atrophy
Osteoarthritis
Osteoporosis
Podiatric conditions

Neurologic disorders
Cerebellar dysfunction or degeneration
Delirium
Dementia
Multiple sclerosis
Myelopathy
Normal-pressure hydrocephalus
Parkinson disease
Stroke
Vertebrobasilar insufficiency
Vestibular disorders

Sensory abnormalities
Hearing impairment
Peripheral neuropathy
Visual impairment

Other
Other acute medical illnesses
Recent hospitalization
Recent surgery
Use of certain medications (i.e., antiarrhythmics, diuretics, digoxin, narcotics, anticonvulsants, psychotropics, and antidepressants), especially four or more

Source: (Salzman, 2010)

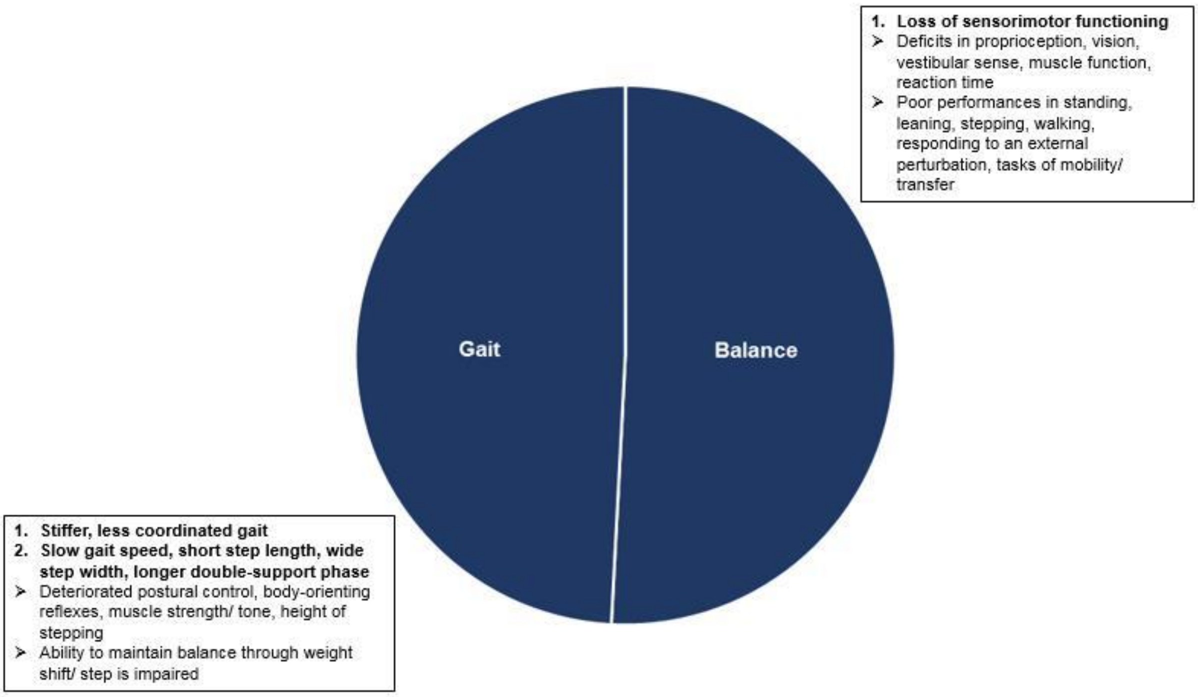

Figure 7: Physiological factors, balance and gait: Representation of associations with the target factor 'falling' Study types and means of odds ratios: 'Gait': OR=2.95, systematic review+pooled analysis; 'Balance': OR=3.05, systematic review+pooled analysis

Balance

Balance disorders are common in advancing age, with 13% of patients reporting to experience balance difficulties at age 65 and 46% at age 85 (Viswanathan and Sudarsky, 2012, Sturnieks et al., 2008). According to a systematic review of Rubenstein and Josephson (2006), the association between such impairments and falling is OR=2.9 (range: 1.6–5.4), with Rubenstein (2006) reporting similar findings in a pooled analysis of OR=3.2 (range: 1.6-5.4).

Sturnieks et al. (2008) state, that “good balance requires the complex integration of sensory information regarding the position of the body relative to the surroundings and the ability to generate appropriate motor responses to control body movement”. In order to prevent falling, those cognitive and physiologic systems need to allow for rapid and precise changes, engaging in a complex relationship (Cuevas-Trisan, 2017).

Therefore, balance disorders can establish through the progressive loss of sensorimotor functioning, which is especially present at increasing age (Sturnieks et al., 2008). This loss is characterised by deficits in proprioception, vision, vestibular sense, muscle function and reaction time and thus manifests in poor performances in standing, leaning, stepping, walking, responding to an external perturbation and tasks of mobility and transfer (Sturnieks et al., 2008).

Gait

Similar to balance disorders, the prevalence of abnormal gait increases with age as well and is estimated to occur in 8% to 19% of elder individuals in total, whereby it is estimated that more than 60% of persons aged over 80 years are affected (Cuevas-Trisan, 2017, Viswanathan and Sudarsky, 2012, Sturnieks et al., 2008, Pirker and Katzenschlager, 2017). According to a systematic review of Rubenstein and Josephson (2006), the association between impaired gait and falling is OR=2.9 (range: 1.3-5.6), with Rubenstein (2006) reporting similar findings of OR=3.0 (range: 1.7-4.8).

This often results from neurological disorders, like polyneuropathy, which leads to sensory ataxia, subcortical vascular encephalopathy leading to frontal gait disorders and parkinsonism, but also disorders associated with dementia (Pirker and Katzenschlager, 2017). However, also non-neurological disorders can affect gait, especially hip and knee osteoarthritis (Pirker and Katzenschlager, 2017).

Moreover, according to Rubenstein (2006), “older people have stiffer, less co-ordinated and more dangerous gaits than do younger people”, which might also be due to deteriorated postural control, body-orienting reflexes, muscle strength and tone, and height of stepping. Thus, in the event of an unexpected trip or slip, the ability to maintain balance through weight shift or a quick step is impaired or even lost, causing the individual to fall (Rubenstein, 2006).

Furthermore, older adults often show a decreased gait speed with a shorter step length and a wider step width and spend more time in the phase were both feet are in contact with the ground (Sturnieks et al., 2008). These gait patterns are more common in fallers and especially a gait speed below 1.0 m/s is a strong predictor for falls in the elderly (Sturnieks et al., 2008, Kyrdalen et al., 2019).

3.1.2.4. Deficiencies

Figure 8 shows both risk factors from the 'Deficiencies' category and their association with the target factor 'falling'. Here, the risk factor 'Vitamin D deficiency' presents the strongest association with falling.

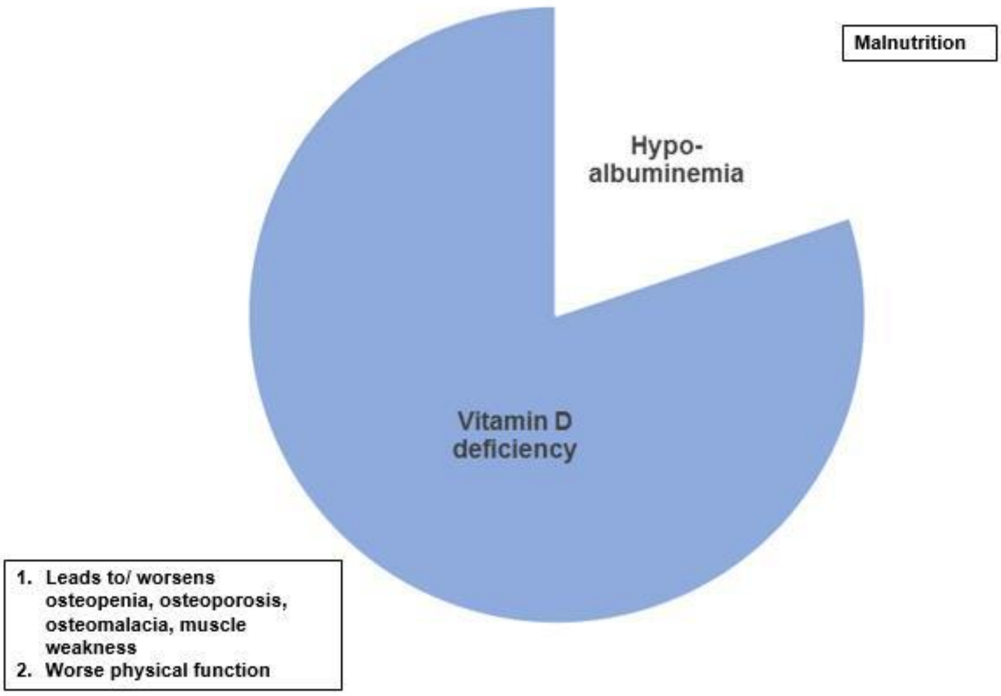

Figure 8: Physiological factors, deficiencies: Representation of associations with the target factor 'falling'
Study types and means of odds ratios: 'Vitamin D deficiency': OR=4.03, case-control; 'Hypoalbuminemia': no study

Vitamin D deficiency

Vitamin D deficiency is common in adults, resulting from reduced sunlight exposure and limited dietary intake of vitamin D (Kotlarczyk et al., 2017). However, it can lead to or worsen osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and therefore increase the risk of falling (Holick, 2007, Aspray et al., 2014).

Furthermore, individuals with low vitamin D levels are more likely to have worse physical function in terms of slower gait, poor physical performance and balance and lower strength and thus increasing the risk as well (Kotlarczyk et al., 2017).

All in all, this suggests that vitamin D deficiency might influence the conditions predisposing to falls rather than the fall by itself (Duval et al., 2017).

Nevertheless, a case-control study of Duval et al. (2017) found a significant association between falling and vitamin D deficiency of OR=4.03 (95% CI:1.33-12.27).

Hypoalbuminemia

Hypoalbuminemia (low serum albumin level) is an independent risk factor for falls (Sousa et al., 2017, Lin et al., 2011). This might be due to the fact that a low serum albumin level is a marker of malnutrition, which in turn is a risk factor for falls (Lin et al., 2011, Bauer et al., 2007). Furthermore, Hypoalbuminemia is influenced by infections, liver and renal diseases (Lin et al., 2011).

3.1.3. Cognitive Factors

Evidence suggests that neurocognitive functions have a great influence on fall risk (Cuevas-Trisan, 2017, Kearney et al., 2013). Therefore, older people with changes or impairments in cognitive function, such as dementia, are at increased risk (Shaw, 2002, Smith et al., 2017, Kearney et al., 2013). According to Shaw (2002) and Kearney et al. (2013) the annual incidence of falls is estimated to be between 60% and 85%, representing an approximate doubling of fall risk compared with that of cognitively not impaired older people. Moreover, Rubenstein (2006) found in a pooled analysis of a specific sample of studies an association between cognitive impairment and fall risk of OR=2.4 (range: 2.0-4.7). Also, Rubenstein and Josephson (2006) found in a systematic review an association of OR=1.8 (range: 1.0-2.3).

The clinical term 'dementia' includes various neurodegenerative diseases, characterized by the progressive loss of mental faculties, with Alzheimer's disease being the most common type (Darby and Dickerson, 2017). Here, specific cognitive processes can be impaired, such as memory, language, behaviour, or executive functions (Darby and Dickerson, 2017). Executive functions are responsible for the decision-making process, including abilities to reason and solve problems and initiate and maintain tasks (Kearney et al., 2013). Furthermore, attention, working memory and abstract reasoning are a part, as well as a general cognitive flexibility in order to adapt to changing contingencies (Kearney et al., 2013).

According to a systematic review of Shaw (2002), the most common risk factors for falls in patients with cognitive impairment and dementia are postural instability, medication, neurocardiovascular instability (e.g. orthostatic hypotension) and environmental hazards.

Figure 9 shows the 'Cognitive Factors' category and its association with the target factor 'falling'.

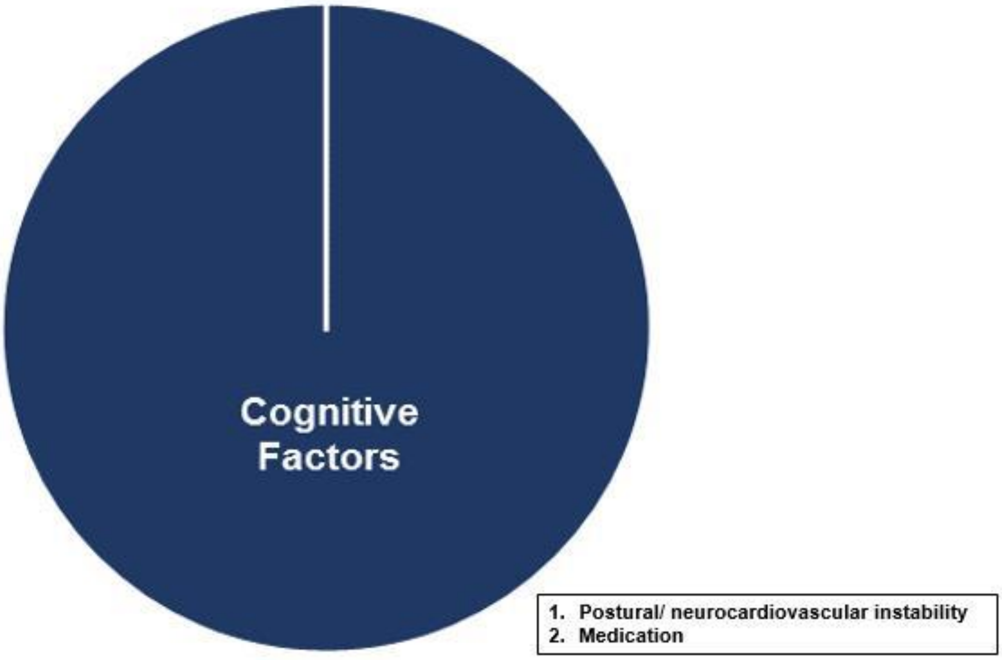

Figure 9: Cognitive Factors: Representation of associations with the target factor 'falling'
Study types and mean of odds ratios: OR=2.1, systematic review+systematic review

3.1.4. Psychological Factors

Figure 10 shows the risk factors from the 'Psychological Factors' category and their association with the target factor 'falling'. Here, the risk factor 'fear of falling' presents the strongest association with falling.

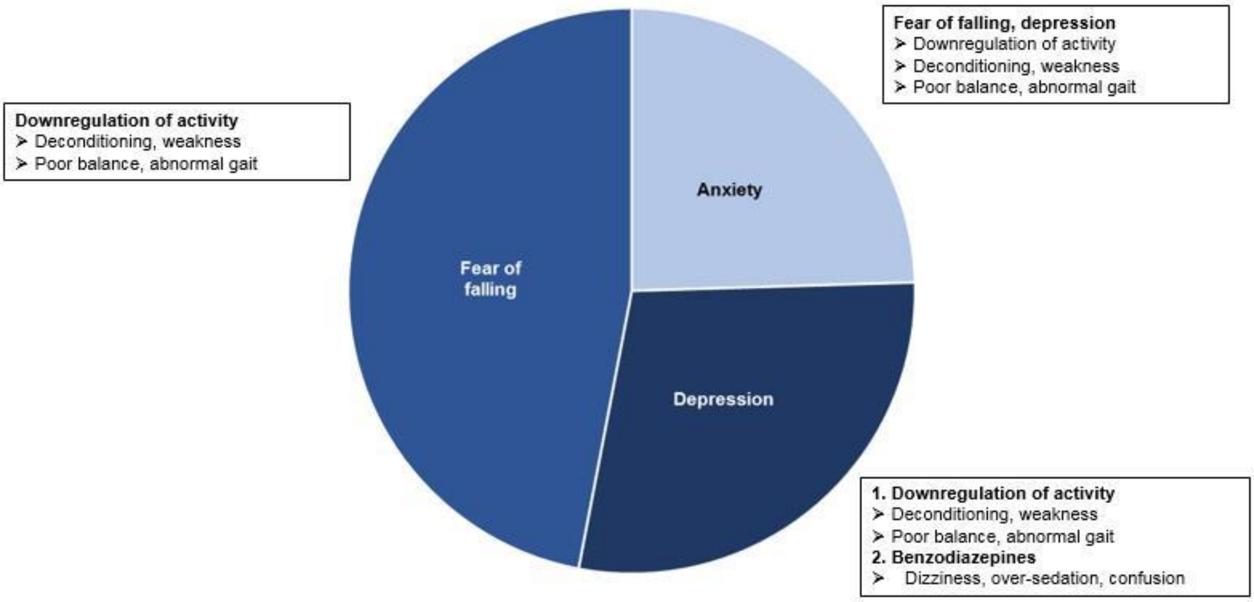

Figure 10: Psychological Factors: Representation of associations with the target factor 'falling' Study types and means of odds ratios: Anxiety: OR=1.55, cross-sectional; Depression: OR=1.8, cohort+systematic review; Fear of falling: OR=2.97, cohort+cross-sectional

Anxiety

About 8% to 18% of community-dwelling older adults experience anxiety, which is affecting physical and psychosocial functions (Painter et al., 2012). Also, anxiety is thought to be a risk factor for falling (Sousa et al., 2017, Painter et al., 2012, Chen et al., 2013), whereby Chen et al. (2013) found an association of OR=1.55 (95% CI:1.12-2.13).

This might result from the fact that anxiety is significantly associated with fear of falling and with depression, both being risk factors in itself (see "Fear of Falling" and "Depression") (Gagnon et al., 2005, Painter et al., 2012). Furthermore, anxious persons often restrict activities, which is also a risk factor for falling as it leads to deconditioning and weakness and therefore to poor balance and abnormal gait (see "Decline in activities of daily living") (Painter et al., 2012).

Depression

Depression is common in elderlies with an estimated prevalence of around 13%-23%, and is more frequent in women (Eggermont et al., 2012, Byers et al., 2010).

Evidence suggests, depressive symptoms are associated with an increased risk for falls in community-dwelling older adults (Eggermont et al., 2012, Sousa et al., 2017, Smith et al., 2017). According to Smith et al. (2017), having depression increases in 1.867 times the chances of falls, which is similar to Rubenstein and Josephson (2006) findings in a systematic review (OR=2.2, range: 1.7-2.5) and a cohort study of Tromp et al. (2001) (OR=1.4; 95% CI:1.0-2.0). This might result from a reduced willingness to carry out tasks, which causes muscle weakness and possibly leads to walking difficulties (Smith et al., 2017). Furthermore, the intake of certain medication such as benzodiazepines is common in patients with depression, and therefore might contribute to the fall incidence, as well, being a risk factor in itself (see "Benzodiazepines") (Smith et al., 2017).

Fear of falling

Fear of falling is prevalent in 35-55% of older people and is associated with serious physical and psychosocial consequences (Kumar et al., 2014, Painter et al., 2012, Zijlstra et al., 2007). Furthermore, research indicates that 'fear of falling' and risk for falling is associated with OR=1.8 (95% CI:1.3-2.3) (Tromp et al., 2001). Gazibara et al. (2017) even found an association of OR=4.14 (95% CI: 1.22-14.08), however presenting a cross-sectional study design.

An explanation for the increased risk of falling is, that the individual might down-regulate activity in order to prevent falls, which however can in turn lead to the exact opposite as it contributes to deconditioning, weakness, poor balance and abnormal gait (Rubenstein and Josephson, 2006, Rubenstein, 2006, Painter et al., 2012)). This corresponds with past research, estimating that 20% to 60% of older adults limit activity due to fear of falling (Zijlstra et al., 2007, Painter et al., 2012).

Furthermore, especially women are prone to fear of falling (OR=3.23; 95% CI: 2.76-3.79), individuals with poor perceived general health (OR=6.93; 95% CI: 4.70-10.21) and a history of falling (OR=5.72; 95% CI: 4.40-7.43) (Zijlstra et al., 2007).

3.1.5. Environmental Factors

Evidence suggests that a significant proportion of falls in older people occur at home or in the immediate environment (Pighills et al., 2011). Thus, 44% of falls result of environmental hazards, such as tripping over objects on the floor or loose rugs and missing handrails (Pighills et al., 2011, Tinetti et al., 1988). Nevertheless, more recent evidence suggests that elderlies with one or more environmental hazards within their homes are only 1.20 times more likely to experience a fall (OR=1.20, 95% CI:1.01-1.43) according to a cross-sectional study of (Fletcher and Hirdes, 2002). Furthermore, in a systematic review of Letts et al. (2010), the association was similarly low with OR=1.38 (95% CI: 1.03-1.87) when only including qualitative studies. This might be due to already implemented changes to the direct environment in terms of elimination of such hazards over time. Therefore, elderlies now might not be exposed to such number of environmental hazards, leading to a smaller percentage of falls. This is also visible in the study of Fletcher and Hirdes (2002), where most people reported to only be exposed to one (7.69%) or no environmental hazards (88.4%) and only 3.47% to two or more.

However, in the NANDA International, several environmental factors increasing the risk of falling have been identified (Herdman and Kamitsuru, 2014):

- Cluttered environment
- Exposure to conditions of insecurity related to weather conditions (e.g., wet floor, ice)
- Insufficient lighting
- Insufficient anti-slip material in bathroom
- Unfamiliar setting
- Use of restraints
- Use of throw/scatter rugs

This list has been extended by Sousa et al. (2017):

- External areas without grab bars and handrails/obstacle of the doorway
- Toilets without grab bars

Figure 11 shows the risk factors from the 'Environmental Factors' category and their collective association with the target factor 'falling'.

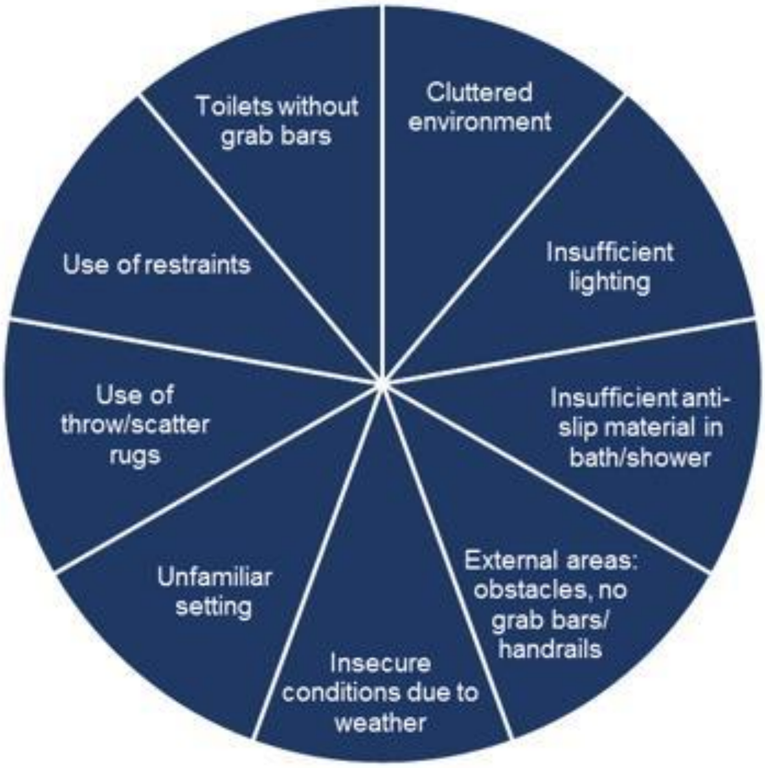

Figure 11: Environmental Factors: Representation of associations with the target factor 'falling'
Study types and mean of odds ratios: OR=1.29, systematic review+cross.sectional

3.1.6. Pharmacological Factors

Figure 12 shows the risk factors from the 'Pharmacological Factors' category and their association with the target factor 'falling'. Here, the risk factor 'general medication use' presents the strongest association with falling.

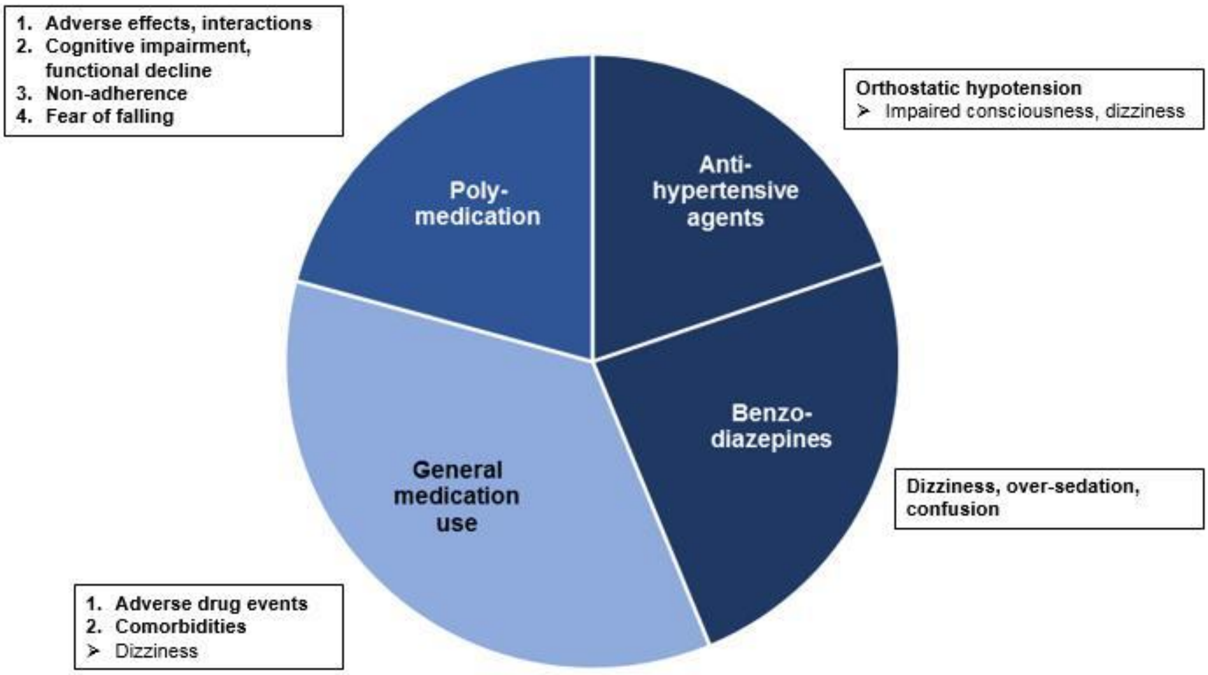

Figure 12: Pharmacological Factors: Representation of associations with the target factor 'falling'
Study types and means of odds ratios: 'Antihypertensive agents': OR=1.24, meta-analysis; 'Benzodiazepines': OR=1.5, meta analysis+cohort+cohort; 'General medication use': OR=2.22, case-control; 'Poly-medication': OR=1.3, cohort

General medication use

According to the NANDA-International, the general use of medication is a risk factor for falling (Herdman and Kamitsuru, 2014). This is supported by a study of Kuhirunyaratn et al. (2013), who found an association between falling and regular medication use of OR=2.22 (95%CI: 1.19-4.12). Furthermore, 'The National Health and Aging Trends Study' in the US found that 22.82% of medication users had a fall in the past year, compared with 13.15% of non-medication users (Watanabe, 2016).

As the medication metabolism is affected by age-related pharmacokinetic and pharmacodynamic changes and therefore increases drug half-life and drug free fraction, this might lead to adverse drug events (Berdot et al., 2009) Furthermore, coexisting diseases can interact with medications as well, causing the same effect and therefore increase the risk of falling, for example due to dizziness (Berdot et al., 2009, Maarsingh et al., 2010, Enderlin et al., 2015).

Benzodiazepines

Benzodiazepines are the most common used psychotropic medication in the general population and the intake is still increasing worldwide (Smith and Tett, 2009, Rossat et al., 2011). Nevertheless, it is associated with an increased risk of falls (Seppala et al., 2018, Sousa et al., 2017). According to a study of Ensrud et al. (2002), women taking benzodiazepines were 34% more likely to fall at least once (OR=1.34; 95% CI: 1.09-1.63) than non-users. Similar findings were reported by Woolcott et al. (2009), with an association of OR=1.57 (95% CI: 1.43-1.72) and Tromp et al. (2001) with OR=1.6 (95% CI: 1.2-2.3)

As the intake of Benzodiazepines can cause problems such as dizziness, over-sedation and confusion, this might be the indicator of the increased fall risk (Smith and Tett, 2009).

Antihypertensive agents

Antihypertensive agents are commonly used to treat hypertension in the elderly and are the most widely prescribed medications for this age group (Butt et al., 2013). This includes for example diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers and beta-adrenergic blockers (Butt et al., 2013, Sousa et al., 2017).

The use of antihypertensive agents is associated with an increased risk of falling, whereby this accounts especially for new users (Butt et al., 2013, Sousa et al., 2017). According to a study of Butt et al. (2013), new users had a 69% increased risk of having an injurious fall during the first 45 days following antihypertensive treatment (IRR=1.69; 95 % CI: 1.57-1.81). This is similar to the findings of Woolcott et al. (2009), who found in a meta-analysis an association between antihypertensive agents and fall risk of OR=1.24 (95% CI:1.01-1.50).

The reason for the increased risk might be, that the initiation of antihypertensive drugs is associated with sudden drops in blood pressure, which is a risk factor for falls itself (see “orthostatic hypotension”) (Butt et al., 2013).

Poly-medication

Approximately 40% of older people take more than five prescription medications (Park et al., 2015). However, evidence suggests that the simultaneous intake of several drugs (irrespective of type) significantly increases the risk of falling (Tromp et al., 2001, Herdman and Kamitsuru, 2014, Todd, 2004, Ganz et al., 2007, Park et al., 2015). According to Tromp et al. (2001), the association between the intake of more than four drugs and falling is OR=1.3 (95% CI: 1.0-1.7). This matches the findings of Dhalwani et al. (2017), who estimated the rate of falls to be 18% higher in people with polypharmacy compared to people without (IRR 1.18, 95% CI: 1.08-1.28).

Furthermore, Freeland et al. (2012) estimated a 14% increase in fall risk with the addition of each medication beyond a four-medication regimen (OR 1.14; 95% CI 1.02 to 1.27; p = 0.027).

The intake of multiple medications might be associated with falls through the adverse effects of drug to drug or drug to disease interactions (Zia et al., 2015). Also, poly-medication has been associated with cognitive impairment, functional decline, non-adherence and a higher rate of fear of falling which are also risk factors in itself (Todd, 2004, Dhalwani et al., 2017, Park et al., 2015).

However, newer studies suggest that poly-medication only is threat if it includes medication that increases the risk for falls in itself, such as sedatives, antidepressants or benzodiazepines (Pirker and Katzenschlager, 2017).

3.2. Consequences of ‘Falling’

Falls in the elderly are a major health problem with various consequences, as listed in Figure 13. First of all, a total of 25% of elderly fallers require medical attention after falling with approximately 10% to 15% of falls leading to serious injuries such as traumatic brain injury or hip fractures (Pirker and Katzenschlager, 2017, Voermans et al., 2007). Further results are also soft tissue injuries, longstanding pain, functional impairment, reduced quality of life, increased mortality, and excess in healthcare costs (Karlsson et al., 2013).

Moreover, falls might reduce life expectancy, either directly (for example, subdural haematoma following head trauma) or indirectly due to complications of the fall (Voermans et al., 2007). Furthermore, 20% to 30% of fallers suffer injuries that reduce mobility and independence and therefore increase the risk of premature death, as well (Todd, 2004). Evidence shows that injuries in general are the fifth most common cause of death in elderly persons, whereby most of them are related to falls (Kannus et al., 2005, Pirker and Katzenschlager, 2017).

Furthermore, falling and such related injuries often are the reason for nursing home admission and hereby might reduce the individual’s quality of life (Voermans et al., 2007).

Another problem is that up to 50% of elderly fallers are unable to get up afterwards, which is often not only due to injury, but rather because of physical frailty and muscle weakness (Voermans et al., 2007, Fleming and Brayne, 2008). By lying on the ground for a long time, this can lead to dehydration, pressure sores, rhabdomyolysis, hypothermia or pneumonia and therefore being not seldom fatal (Voermans et al., 2007, Fleming and Brayne, 2008).

Also, falling and related injuries can cause severe depression or anxiety; especially when the individual fears of consequences in terms of loss of independence and confidence or admission to a long-term care facility or social withdrawal (Kannus et al., 2005).

Figure 13: Consequences of the target factor 'falling'

3.3. Recommendations for the Prevention of 'Falling'

Falling counts to the geriatric syndromes due to its multifactorial nature and complex manifestations (Yamashita et al., 2012). Therefore, to prevent falls, also multifaceted interventions are needed in order to address multiple fall risk factors (Yamashita et al., 2012, Karlsson et al., 2013). Moreover, as the likelihood of falling also depends on the amount and type of risk factors a person has, fall prevention programmes should be tailored to personal characteristics, activities, and locations (Kuhirunyaratn et al., 2013, Kelsey et al., 2012).

According to a review of Karlsson et al. (2013) on RCT's for identifying programmes with fall-reductive effects, the most effective strategies include regular physical training with different training modalities, as visible in Figure 14. Furthermore, interventions according to a patient specific risk profile have been proven to decrease fall risk as well. This includes for example areas like adjustment of psychotropic medication, wearing anti-slip shoe devices when walking in icy conditions or supplementation of vitamin D (Karlsson et al., 2013).

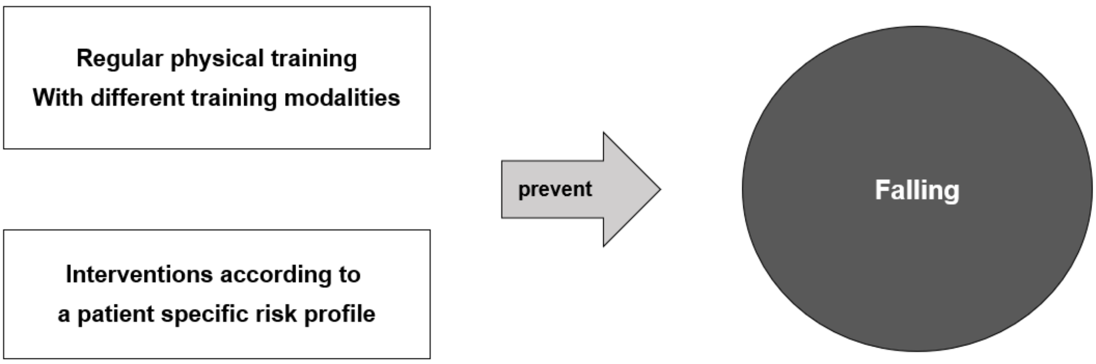

Figure 14: Recommendations for the prevention of 'falling'

4. Frailty

Another common negative consequence of ageing is frailty, which is considered a high risk factor for disability, hospitalization, and mortality (Fried et al., 2001, Wilson et al., 2017). Thus, it often affects multiple domains of human functioning, including gait, balance, muscle strength, mobility, cognition, motor processing, endurance, physical activity, and nutrition (Lorenzo-Lopez et al., 2017, Gobbens et al., 2010a). Furthermore, it is characterized by a condition of extreme vulnerability to stressors and therefore exposes individuals to an increased risk of negative health-related outcomes (Cesari et al., 2017, Collard et al., 2012, Guyonnet and Rolland, 2015). This is possibly due to a decreased reserve capacity of physiological systems, being at a critically low point in the state of frailty and therefore leading to complications even through small disturbances (Collard et al., 2012).

According to a systematic review of Collard et al. (2012), the prevalence of frailty in elderlies is 10.7%, whereby another 41.6% are found to be prefrail. However, as the exact definition of frailty differs substantially, prevalence rates might change accordingly. Therefore, studies, investigating frailty as a purely physical condition, are found to report lower prevalence rates, and studies with broader definitions, higher rates, respectively (Collard et al., 2012).

A prominent (physical) definition for frailty is the phenotype definition according to Fried et al. (2001). Here, three of five central components need to be present:

1. Unintentional weight loss
2. Slow walking speed
3. Self-reported exhaustion
4. Low energy expenditure (physical activity)
5. Weakness (measured in grip strength)

However, in this review, frailty is defined rather broad by inclusion of psychological and social aspects, as well, according to the *North American Nursing Diagnosis Association* (NANDA) (Herdman and Kamitsuru, 2014). Here, the frail elder syndrome is defined as:

"Dynamic state of unstable equilibrium that affects the older individual experiencing deterioration in one or more domain of health (physical, functional, psychological, or social) and leads to increased susceptibility to adverse health effects, in particular disability" (Herdman and Kamitsuru, 2014).

Evidence suggests, that the development of frailty is caused by multiple factors, listed in NANDA (Herdman and Kamitsuru, 2014). In this review, several categories have been identified in order to classify such factors leading to frailty:

- Personal Factors
- Physiological Factors
- Cognitive Factors

- Psychological Factors
- Environmental Factors
- Social Factors

However, several risk factors from NANDA were not included in this report: Low educational level, ethnicity, economically disadvantaged.

This is due to the fact that such factors might not directly influence the development of frailty, but rather likely co-exist with other lifestyle factors increasing the risk alone (Espinoza and Fried, 2007).

Furthermore, the NANDA-factor "suppressed inflammatory response", was changed to "inflammatory response", as evidence suggests that an upregulated response increases the risk for frailty, rather than a suppressed one (Leng et al., 2004, Morley, 2001).

Finally, Figure 15 shows all categories of frailty stated in this review. Here, the left figure presents the importance of the categories according to the number of risk factors, with the physiological group demonstrating the most risk factors. In contrast to this, the right figure presents the importance of the categories according to the strength of the associations. Here, for each category, the risk factor with the strongest association has been elected. Thus, the personal group shows the strongest association.

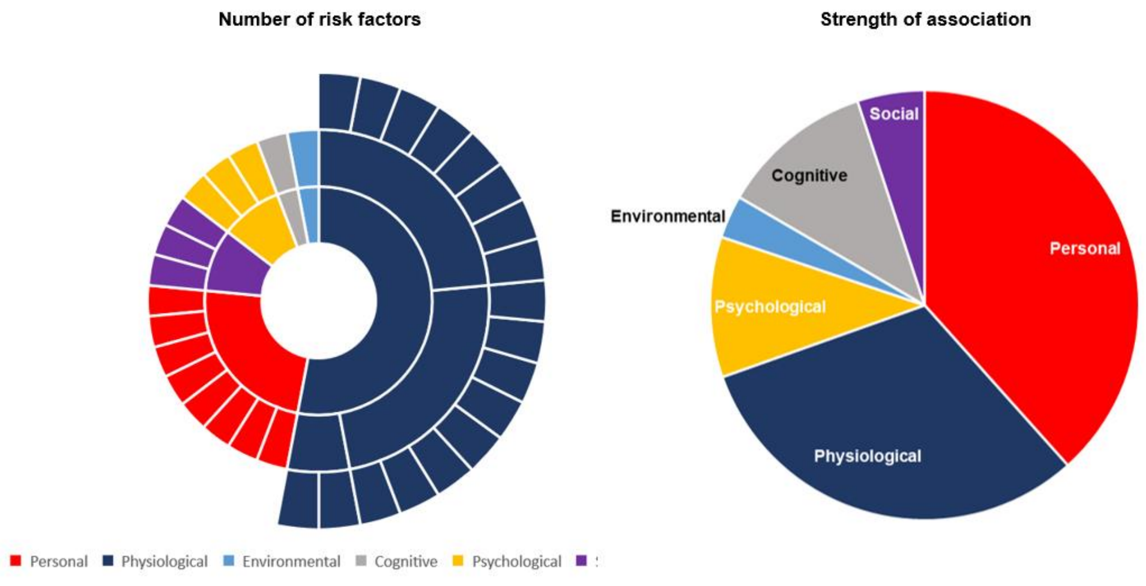

Figure 15: Categories of the target factor 'frailty' according to importance

In the following, the risk factors of the target factor frailty are going to be analysed in their respective categories.

4.1. Risks of 'Frailty'

4.1.1. Personal Factors

Figure 16: Personal factors: Representation of associations with the target factor 'frailty' shows all risk factors from the 'Personal Factors' category and their association with the target factor 'frailty'. Here, the risk factor 'sedentary lifestyle' presents the strongest association with frailty.

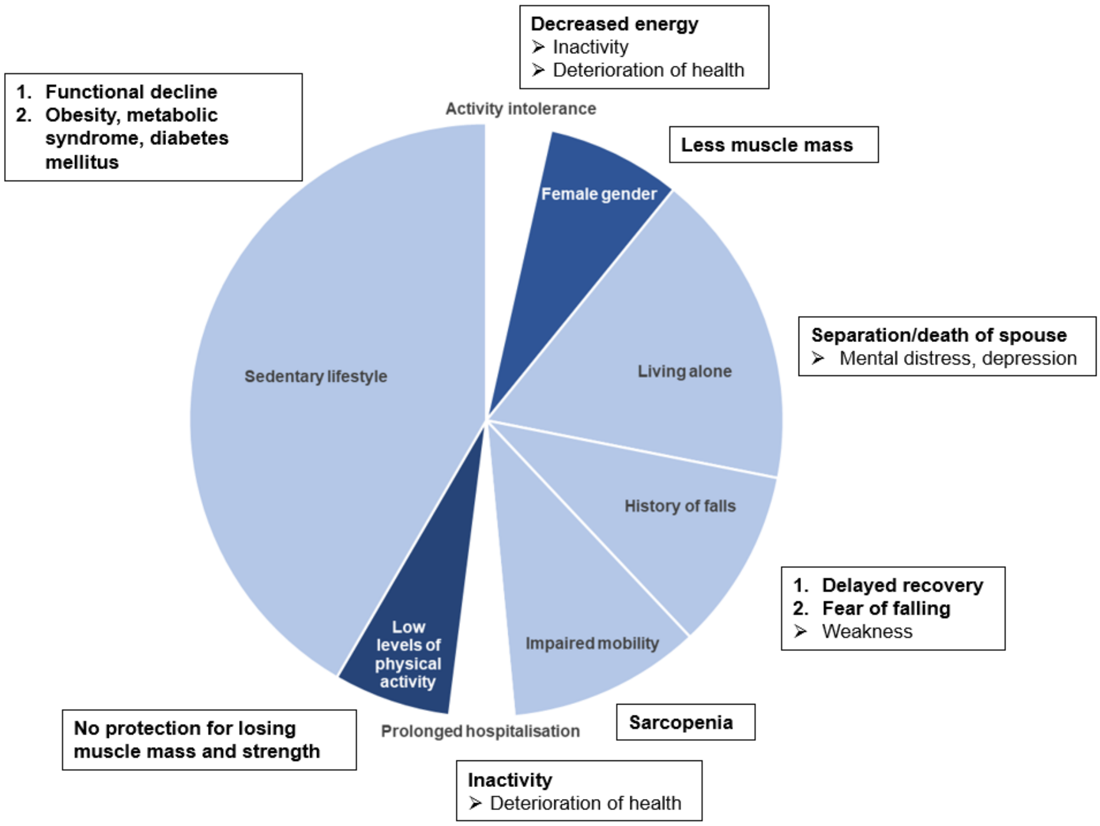

Figure 16: Personal factors: Representation of associations with the target factor 'frailty'
Study types and means of odds ratios: 'Sedentary lifestyle': OR=11.88, cross-sectional; 'Activity intolerance': no study; 'Female gender': OR=2.096, cohort+cross-sectional; 'Living alone': OR=4.93, cross-sectional+cross-sectional, 'History of falls': OR=2.82, cross-sectional+cross-sectional; 'Impaired mobility: OR=3.0, cross-sectional; 'Prolonged hospitalisation': no study; ' Low levels of physical activity': OR=1.825, cohort+cohort

Activity intolerance

Activity intolerance is defined as "a state in which an individual has insufficient physiologic or psychological energy to endure or complete required or desired daily activities" (Hur et al., 2005). According to NANDA, it shows an increased risk for the development of frailty (Herdman and Kamitsuru, 2014). However, no studies investigating this association were to be found by the author.

Nevertheless, the definition already includes the presence of a state of decreased energy, which is a risk factor for frailty in itself (see "Decrease in energy") and also is part of the definition of frailty according to Fried et al. (2001). In addition, this decreased energy leads to lower engagement in activities, which is associated with an increased risk for frailty, as well (Morley et al., 2002).

Female gender

The female gender is associated with a higher risk for frailty (Espinoza and Fried, 2007, Myers et al., 2014, Feng et al., 2017, Eyigor et al., 2015). Thus, in a systematic review of Theou et al. (2015), women had a 2.1-16.3% higher frailty prevalence than men. Moreover, the association was found to be significant in a cohort study of Myers et al. (2014), with OR=1.67 (95% CI:1.10-2.55) and also in a cross-sectional study of Eyigor et al. (2015), with OR=2.522 (95% CI: 1.772-3.588).

This might be due to the fact that women generally have less muscle mass than age-matched men, which might therefore confer an intrinsic risk for the development of frailty (Espinoza and Fried, 2007).

History of falls

About one third of elder individuals fall each year (Cuevas-Trisan, 2017). However, having a history of falls increases the risk for frailty (Guaraldi et al., 2017). According to a cross-sectional study of Valencia et al. (2018), having had a fall in the previous year was associated with an increased risk for frailty, with OR=2.54 (95% CI: 1.60-4.03). Still, the study was conducted on patients with diabetes mellitus, which might have influenced the outcome, whereby this is not considered a risk factor in this review.

Furthermore, Zazzetta et al. (2017) reported similar findings on the occurrence of two or more falls within 12 months and the association with frailty, with OR=3.1 (95%CI: 1.4-7.1).

This relationship might be due to the fact that having a history of falls is strongly associated with a fear of falling, which is a risk factor in itself (see “fear of falling”) (Rubenstein, 2006). Additionally, recovery from fall injury is often delayed in older persons, which in turn might lead to weakness, which is basically part of the definition for frailty by Fried et al. (2001) (Rubenstein, 2006).

Impaired mobility

Impaired mobility can be described as “a state in which an individual experiences a limitation in independent physical movement or is at risk of experiencing limitations but is not immobile” (Hur et al., 2005).

Evidence suggests that immobile elder persons are at increased risk for the development of frailty (Davis et al., 2011, Ahmed et al., 2007, Xue, 2011). Thus, Zazzetta et al. (2017) found in a cross-sectional study an association of OR=3.0 (95%CI: 1.5-5.8).

This relationship might be due to the fact that impaired mobility and resulting immobility might lead to sarcopenia (Gale et al., 2018).

Living alone

Evidence suggests thatlLiving alone increases the risk for frailty (Yamanashi et al., 2015, Gobbens et al., 2010b). Thus, according to a study of Yamanashi et al. (2015)

in Japan, the association is significant for men, with OR=3.85 (95% CI: 1.94-7.65), however not for women with OR=1.08 (95% CI:0.72-1.63).

This connection might result from the fact that living alone is possibly due to separation or death of a spouse, which can lead to mental distress and depression and increases hereby the risk of frailty (Yamanashi et al., 2015).

Prolonged Hospitalisation

According to NANDA, prolonged hospitalisation shows an increased risk for the development of frailty (Herdman and Kamitsuru, 2014). However, no studies investigating this association were to be found by the author.

Nevertheless, as repeated or long hospital admissions can lead to deteriorations in general health, for example due to inactivity, this might increase the risk for frailty (Abdelhafiz et al., 2015, Morley et al., 2002).

Low levels of physical activity

Low levels of physical activity are a risk factor for developing frailty (Woo et al., 2005, Yuki et al., 2019). Thus, Yuki et al. (2019) investigated in a cohort study the relationship between frailty and physical activity and between frailty and steps per day as further activity criterion, whereby the association was as follows: Frailty was associated with low moderate- to vigorous-intensity physical activity (MVPA; <7.5 minutes/d) with OR=1.80 (95% CI: 1.05-3.09) and with walking less than 5000 steps per day with OR=1.85 (95% CI: 1.10-3.11).

However, this relationship might be more related to the fact that physical activity acts as a protective factor. As exercise increases skeletal muscle mass and improves muscle strength in older adults, it therefore reduces frailty symptoms and might contribute to the prevention of it (Yuki et al., 2019). In individuals with low levels of physical activity, this protection is not given and thus, exposes the person to an increased risk of losing muscle mass and strength.

Sedentary lifestyle

Evidence suggests a strong relationship between daily sedentary time and the development of physical frailty (Eyigor et al., 2015, Song et al., 2015). Thus, according to a cross-sectional study of Eyigor et al. (2015), living a sedentary lifestyle increases the risk for frailty with an association of OR=11.880 (95% CI: 5.415-26.065).

Moreover, Song et al. (2015) found in a cohort study that the risk of physical frailty increased 36% (HR=1.36 (95% CI: 1.02-1.79) for each additional hour spent in sedentary behaviour during daily waking time.

As living a sedentary lifestyle increases the risk of functional decline and such conditions as obesity, metabolic syndrome and diabetes mellitus, this might be the reason for an increase in frailty (Song et al., 2015).

4.1.2. Physiological Factors

4.1.2.1. General

Figure 17 shows all risk factors from the 'General' category and their association with the target factor 'frailty'. Here, the risk factor 'malnutrition' presents the strongest association with frailty.

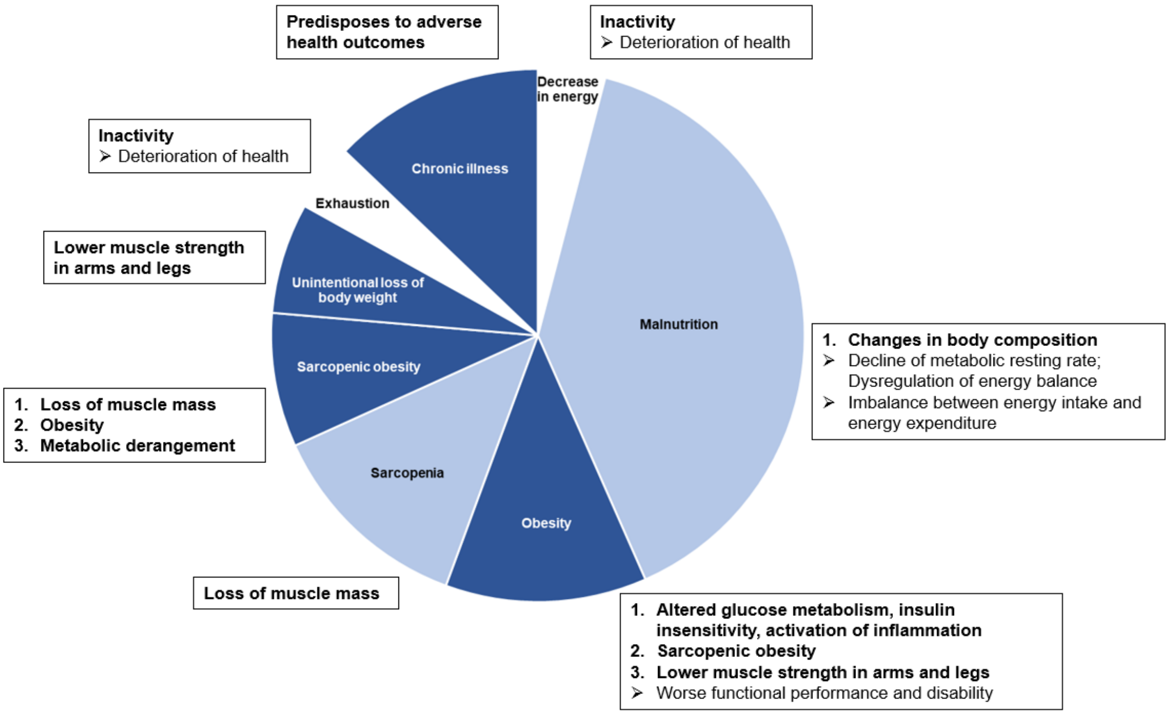

Figure 17: Physiological Factors, General: Representation of associations with the target factor 'frailty' Study types and means of odds ratios: 'Malnutrition': OR=9.665, cross-sectional+cross-sectional; 'Obesity': OR=3.0, cohort+cohort; 'Sarcopenia': OR=3.1, cross-sectional; 'Sarcopenic obesity': OR=2.0, cohort; 'Unintentional loss of body weight': OR=1.65, cohort; 'Exhaustion': no study; 'Chronic illness': OR=3.16, cohort+cross-sectional; 'Decrease in energy': no study

Chronic illness

The presence of comorbidities has been suggested to increase the risk of frailty (Espinoza and Fried, 2007, Ottenbacher et al., 2009, Guaraldi et al., 2017, Lee et al., 2018, Ahmed et al., 2007). This includes, for example, cardiovascular disease, diabetes mellitus, hypertension, arthritis, cancer and chronic obstructive pulmonary disease (Espinoza and Fried, 2007). According to a cohort study of Myers et al. (2014), the presence of comorbidities was associated with frailty with OR=1.12 (95% CI: 0.75-1.66). Moreover, Jurschik et al. (2012) found an even higher association of OR=5.20 (95% CI: 1.78-15.16).

This relationship might result from the fact that the accumulation of medical illnesses predisposes to adverse health outcomes and therefore increases the risk for frailty (Espinoza and Fried, 2007).

Decrease in energy

As a decrease in energy is already included in the definition of frailty by Fried et al. (2001), the mere presence of it might also increase the development of such condition. Thus, it is also listed in NANDA as risk factor for frailty (Herdman and Kamitsuru, 2014).

Furthermore, Xue (2011) found in a cohort study that decreased energy production might be involved in the threshold transition towards frailty.

As the individual is not able to engage in (long-lasting) tasks anymore due to low levels of energy, this might lead to inactivity, which, according to Morley et al. (2002), increases the risk for frailty through deteriorations in general health.

Exhaustion

As exhaustion is according to Fried et al. (2001) already part of the characteristics of frailty, the mere presence of such might also indicate a higher risk for the development of it. Thus, it is also listed in NANDA as a risk factor for frailty (Herdman and Kamitsuru, 2014). Furthermore, Xue (2011) found in a cohort study, that exhaustion might act as a threshold to the state of frailty, as exhaustion was involved in 80% of transitions.

This might be due to the fact that exhaustion leads to lower engagement in (long-lasting) tasks or inactivity, which, according to Morley et al. (2002), increases the risk for frailty through deteriorations in general health.

Malnutrition

Evidence suggests that malnutrition is an important determinant of the development of frailty (Lorenzo-Lopez et al., 2017, Li et al., 2017a, Artaza-Artabe et al., 2016). Here, a poor nutritional status arises through quantitative (energy intake) and qualitative (nutrient quality) factors of nutrition (Lorenzo-Lopez et al., 2017). Furthermore, the prevalence of malnutrition depends on the setting and therefore increases as the level of care increases, with approximately 23% to 60% of elderly patients in the acute care setting being malnourished and 5% to 30% of community-dwelling older adults (Guyonnet and Rolland, 2015).

Regarding the relationship between frailty and malnourishment, Li et al. (2017a) found in a cross-sectional study that 26.5% of participants who were malnourished were also frail, and 64.2% were prefrail. Furthermore, the association was found to be OR=17.4 (95% CI: 6.68-45.3) when using the *The Mini Nutritional Assessment-short form (MNA-SF)* method and OR=1.93 (95% CI: 1.09-3.43) when using the *Nutritional Screening Index (NSI),* both being widely used nutritional screening scales (Li et al., 2017a). However, the NSI reflects the impact of food intake in relation to the nutritional risk and as particularly the intake of inadequate food is considered the main cause of malnutrition, this might provide a more realistic view (Li et al., 2017a).

As aging is accompanied by changes in body composition (decrease in lean body mass and bone mineral density, lesser extent of fat mass, loss of muscle mass), the resting metabolic rate declines and the energy balance is dysregulated (Yannakoulia et al., 2017). Therefore, an imbalance between energy intake and energy expenditure emerges, especially with people tending to undernutrition, decreased energy intake and macro- and micro-nutrient deficiency and is thus leading to frailty (Yannakoulia et al., 2017).

Obesity

Obesity is a general health problem, especially concerning older adults, as they are significantly more overweight (42.4%) and obese (20.9%) than middle age and younger adults (Marques et al., 2018). Furthermore, obesity, classified by a Body Mass Index (BMI, kg/m2) of ≥30.0, is associated with a higher risk for frailty (Feng et al., 2017, Woods et al., 2005, Espinoza and Fried, 2007, Myers et al., 2014, Lee et al., 2018). Thus, according to a cohort study of Woods et al. (2005), the relationship is significant, with OR=3.95 (95% CI: 3.50-4.47). Similar findings are stated by Myers et al. (2014), who found an association of OR=2.05 (95% CI: 1.43-2.93).

This relationship might be due to several factors: First, high extremes of body fat are associated with lower muscle strength in arms and legs and worse functional performance and disability (Woods et al., 2005). Also, sarcopenic obesity is especially common in older women who are significantly overweight, being a risk factor in itself (see “Sarcopenic obesity”) (Woods et al., 2005). Finally, as obesity contributes to an altered glucose metabolism, insulin insensitivity and an activation of inflammation, the risk for frailty is increased, as well (Espinoza and Fried, 2007).

Sarcopenia

Sarcopenia, with a prevalence from 6% to 12% in persons older than 60 years, is the age-dependent loss of muscle mass and function, leading to decreased strength and weakness (Marzetti et al., 2017, Morley et al., 2002). However, it is related to an increased risk for frailty (Marzetti et al., 2017, Greco et al., 2019). Thus, Frisoli et al. (2011) showed in a cross-sectional study that sarcopenia is associated with frailty, with OR=3.1 (95% CI: 0.88-11.1), though this is not statistically significant.

As sarcopenia is part of the (physical) definition of frailty, and both conditions share many common points, this explains the effect of sarcopenia on the risk for frailty (Cruz-Jentoft and Michel, 2013).

Sarcopenic obesity

As sarcopenia is the loss of muscle mass, sarcopenic obesity describes a condition, where fat masks this state (Woods et al., 2005, Espinoza and Fried, 2007). Therefore, lean muscle mass can predispose individuals to the development of frailty even in the presence of obesity (Greco et al., 2019, Espinoza and Fried, 2007). Thus, Hirani et al. (2017) found in a cohort study an association between sarcopenic obesity and frailty of OR=2.00 (95% CI: 1.42-2.82).

A possible explanation is that the mismatch between lean muscle mass and fat results in a metabolic derangement (Espinoza and Fried, 2007). Furthermore, individuals with sarcopenic obesity suffer from loss of muscle mass, but in addition have to deal with the challenges associated with obesity (see “Obesity”).

Unintentional loss of body weight

Underweight, classified by a Body Mass Index (BMI, kg/m2) of <18.5, presents an increased risk for the development of frailty (Espinoza and Fried, 2007, Woods et al., 2005). Thus, Woods et al. (2005) found in a cohort study an association of OR=1.65 (95% CI: 1.11-2.45).

This relationship might be due to the fact that low extremes of body fat (similar to high extremes) are associated with lower muscle strength in arms and legs (Woods et al., 2005).

4.1.2.2. Diseases and Disorders

Figure 18 shows all risk factors from the 'Diseases and Disorders' category and their association with the target factor 'frailty'. Here, the risk factor 'endocrine regulatory dysfunction' presents the strongest association with frailty.

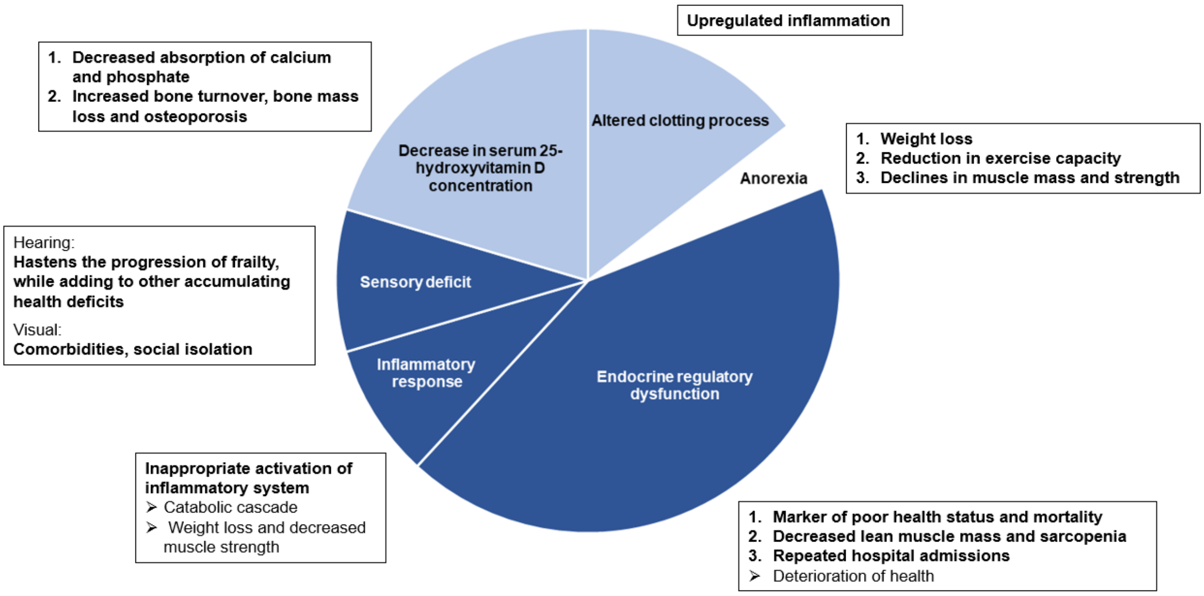

Figure 18: Physiological factors, diseases and disorders: Representation of associations with the target factor 'frailty' Study types and means of odds ratios: 'Endocrine regulatory dysfunction': OR=9.57, cohort+cohort+cohort; 'Inflammatory response': OR=1.92, cohort+cross-sectional; 'Sensory deficit': OR=2.04, cohort+cross-sectional+cross-sectional; 'Decrease in serum 25-hydroxyvitamin D concentratin: OR=4.56, cross-sectional+cross-sectional+cross-sectional; 'Altered clotting process': OR=3.24, cross-sectional; 'Anorexia': no study

Altered clotting process

Increased markers of coagulation, including factor VIII and D-dimer are suggested to increase the risk for frailty (Espinoza and Fried, 2007, Walston et al., 2002). Thus, Walston et al. (2002) found in a cross-sectional study an association between factor VIII (>16800 mg/dL) and frailty of OR=3.24 (95% CI: 1.84-569).

Evidence suggests that coagulation is often due to an upregulated inflammation and therefore increases the risk for frailty (Espinoza and Fried, 2007, Walston et al., 2002).

Anorexia

As the appetite decreases with aging, Anorexia is often present in elderlies, with a prevalence of 15% to 30%, whereby women are more affected (Tsutsumimoto et al., 2018, Malafarina et al., 2013). However, evidence suggests that Anorexia increases the risk of frailty (Tsutsumimoto et al., 2018, Tsutsumimoto et al., 2017, Sanford, 2017, Morley, 2012). Thus, Tsutsumimoto et al. (2017) found in a cohort study a hazard ratio of HR=2.44 (95% CI:2.00–4.59).

As sensory perception in terms of taste and smell leads to a reduced enjoyment of food, it therefore contributes to the development of anorexia (Somekawa et al., 2017). Furthermore, this causes a reduction in exercise capacity, weight loss, declines in muscle mass and strength and puts the individual hereby at an increased risk of frailty (Martone et al., 2013).

Decrease in serum 25-hydroxyvitamin D concentration

Vitamin D, which is hydroxylated in the liver into 25-hydroxyvitamin D (25(OH)D), increases the absorption of calcium and phosphate needed for mineralization of the skeleton (Chang et al., 2010). However, low 25(OH)D levels are common in the elderly due to decreased vitamin synthesis in the skin, insufficient sunlight exposure, and deficient dietary supplementation and therefore promotes frailty (Boxer et al., 2008, Chang et al., 2010, Ensrud et al., 2010). In a cross-sectional study, Chang et al. (2010) found a strong dose-response relationship between low serum 25-hydroxyvitamin D levels and frailty with an association of OR=10.74 (95% CI 2.60–44.31). However, elsewhere, in two cross-sectional studies, the association between low levels of 25(OH)D was found to be weaker with OR=1.47 (95% CI:1.19–1.82) in women (25(OH)D:<15.0 ng/ml) and OR=1.47 (95% CI:1.07-2.02) in men (25(OH)D:<20.0 ng/mL) (Ensrud et al., 2011, Ensrud et al., 2010).

As a low 25(OH)D concentration is associated with a decreased absorption of calcium and phosphate from the gut, this leads to increased bone turnover, bone mass loss and osteoporosis and therefore increases the risk of frailty (Chang et al., 2010).

Endocrine regulatory dysfunction

Evidence suggests that alterations in the endocrine system increase the risk of frailty (Espinoza and Fried, 2007, Maggio et al., 2010). This includes decreased levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulphate (DHEAS), whereby both hormones are associated with decreased lean muscle mass and sarcopenia and therefore increase the risk of frailty (Espinoza and Fried, 2007, Leng et al., 2004, Voznesensky et al., 2009).

Furthermore, hypoglycaemia (plasma glucose level of <3.9mmol/l) is common in elder individuals with diabetes mellitus and might increase the risk of frailty, as well (Abdelhafiz et al., 2015). According to Abdelhafiz et al. (2015), this relationship is bidirectional, with both conditions promoting the other. Thus, Chao et al. (2019) found in a cohort study a significantly higher risk of frailty for hypoglycaemia with HR=1.443 (95% CI 1.01-2.05). As repeated hospital admissions result of frequent hypoglycaemia, this can lead to even further deteriorations in general health and, thus, leads to frailty (Abdelhafiz et al., 2015).

Finally, high levels of cortisol are a risk factor frailty, as well (Serra–Prat et al., 2017). Thus, according to the findings of Serra–Prat et al. (2017) in a cohort study, high levels of cortisol (>14.5 µg/dL) were associated with frailty, with OR= 2.43 (95% CI: 0.69-8.61) and in women alone, with OR=6.00 (95% CI:0.75-48.2). However, a cohort study of Baylis et al. (2013) suggests that the association is weaker with OR=1.14 (95% CI: 0.60, 2.16).

All in all, evidence suggests that frailty increases as the number of hormonal dysregulations increases, as it is generally a marker of poor health status and mortality (Serra–Prat et al., 2017, Maggio et al., 2010).

Sensory deficit

Age-related hearing loss is the most prevalent sensory deficit in the elder individuals, and is associated with an increased risk of frailty (Bowl and Dawson, 2019). Therefore, Liljas et al. (2017b) found in a cross-sectional analysis an association of OR=1.66 (95% CI: 1.37-2.01) and OR=1.43 (95% CI = 1.05-1.95) in a longitudinal analysis of the same study. Moreover, Ng et al. (2014) and Eyigor et al. (2015) found in cross-sectional studies associations of OR=2.34 (95% CI:1.21-4.52) and OR=1.983 (95% CI: 1.211-3.247), respectively.

This connection might exist, since hearing impairment hastens the progression of frailty, while adding to other accumulating health deficits in increasing the risk of frailty (Liljas et al., 2017b).

Furthermore, poor vision might increase the risk of frailty, as well, while affecting many elder individuals (Liljas et al., 2017a). Here, Liljas et al. (2017a) found in a cross-sectional analysis and association of OR=2.53 (95% CI: 1.95–3.30) and OR=2.07 (95% CI: 1.32-3.24) in a longitudinal analysis of the same study. Moreover, Ng et al. (2014) found in a cross-sectional study an association of OR=1.52 (95% CI:1.19-1.95).

A possible explanation for the relationship is, that vision impairment is associated with a range of comorbidities known to be associated with frailty such as cardiovascular diseases and diabetes mellitus (Liljas et al., 2017a). Furthermore, visual deficits have also been associated with social isolation, which is a risk factor for frailty, as well (see “Social isolation”) (Liljas et al., 2017a).

Inflammatory response

High levels of C-reactive protein (CRP; >5.77 mg/L), a reliable marker of inflammation, is generally associated with frailty (Espinoza and Fried, 2007), with OR=2.80 (95% CI: 1.55-5.05), according to a cross-sectional study of Walston et al. (2002). However, Baylis et al. (2013) found no association of such (OR=1.04 (95% CI: 0.49-2.18)).

Furthermore, increased levels of interleukin-6 (IL-6), an inflammatory cytokine, are also associated with frailty (Leng et al., 2004, Morley, 2001), with OR=1.64 (95% CI: 0.71-3.76) according to a cohort study of Baylis et al. (2013).

Here, Kanapuru and Ershler (2009) suggest, that the increased risk for frailty is due to an inappropriate activation of the inflammatory system, hereby producing a catabolic cascade, and resulting in weight loss and decreased muscle strength (Morley, 2001).

4.1.2.3. Balance and Gait

As for none of two risk factors of the 'Balance and Gait' category associations in terms of odds ratios were found, no graphical representation with the target factor 'frailty' was possible.

Balance

Balance disorders are common in advancing age, with 13% of patients reporting to experience balance difficulties at age 65 and 46% at age 85 (Viswanathan and Sudarsky, 2012, Sturnieks et al., 2008). However, impaired balance is associated with an increased risk for frailty (Lee et al., 2018, Ahmed et al., 2007, Davis et al., 2011).

This might be due to the fact that impaired balance is generally common in adults with frailty and even adds to the characteristic of it (Davis et al., 2011). Thus, early signs of impaired balance might also indicate a progression into a frail status. Furthermore, impaired balance results in an increased risk of falling, which is associated with frailty, as well (see "History of falls") (Chkeir et al., 2016, Salzman, 2010, Rubenstein and Josephson, 2006).

Slow gait speed

A decrease in gait speed is generally associated with an increased risk for frailty (Silveira et al., 2015, Parentoni et al., 2015, Xue, 2011, Thiede et al., 2016).

Thus, according to a study of Thiede et al. (2016), gait speed was significantly associated with (pre-) frailty, next to other parameters: Gait cycle time, double support, anterior-posterior and medial-lateral sway, and mid-swing speed.

Therefore, gait speed and trunk sway in the anterior-posterior and medial-lateral direction were larger during walking in the non-frail group compared to pre-frails, with 21%, 80% and 47%, respectively. Also, gait cycle time was 11% and double support percentage 22% smaller in the non-frail group (Thiede et al., 2016).

As those parameters represent a higher level of weakness or exhaustion in lower extremities, this might increase the risk for frailty, with both being defining factors of frailty in itself, according to Fried et al. (2001), to which also decreased speed counts, itself. Furthermore, exhaustion is specifically included as risk factor in this report (see "Exhaustion") (Thiede et al., 2016).

Moreover, decreased gait speed might lead to a loss of muscle mass and strength and results in an increased risk of falling which is associated with frailty, as well (see “Sarcopenia”, “History of falls”) (Salzman, 2010, Rubenstein and Josephson, 2006, Gale et al., 2018).

4.1.3. Cognitive Factors

Cognitive impairment

Cognitive impairment is common among older people and refers to a decline in intellectual functions (e.g. thinking, remembering, reasoning and planning) (Robertson et al., 2013). However, the effects range widely between mild forms of forgetfulness to debilitating dementia (Robertson et al., 2013).

Nevertheless, cognitive impairment is generally associated with an increased risk for frailty (Albala et al., 2017, Espinoza and Fried, 2007). Thus, Albala et al. (2017) found in a cohort study a strong association between frailty and mild cognitive impairment, with OR=3.93 (95% CI: 1.41-10.92). Similar findings were reported by Jurschik et al. (2012), with OR=3.22 (95% CI: 1.48-7.02).

This relationship might be due to several factors: First, frailty might result of a decreased food intake due to forgetting which leads to weight loss and sarcopenia (Espinoza and Fried, 2007, Morley et al., 2002, Jurschik et al., 2012). Moreover, a decreased cognitive processing speed is associated with a decline in physical performance and therefore predisposes to frailty, as well (Binder et al., 1999). Finally, cognitive impairment due to alterations in the central nervous system can result from cerebrovascular diseases which is associated with an upregulated inflammation (Morley et al., 2002).

Figure 19 shows the ‘Cognitive Factors’ category and its association with the target factor ‘frailty’.

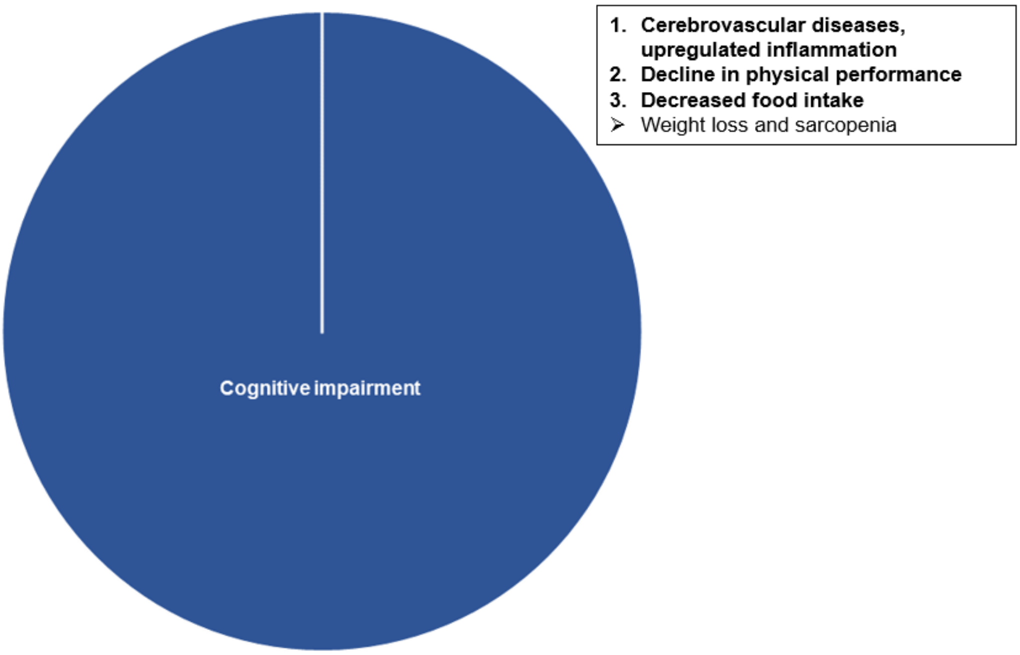

Figure 19: Cognitive Factors: Representation of associations with the target factor ‘frailty’
Study types and mean of odds ratios: OR=3.575, cohort+cross-sectional

4.1.4. Psychological Factors

Figure 20 shows the risk factors from the ‘Psychological Factors’ category and their association with the target factor ‘frailty’. Here, the risk factor ‘depression’ presents the strongest association with frailty.

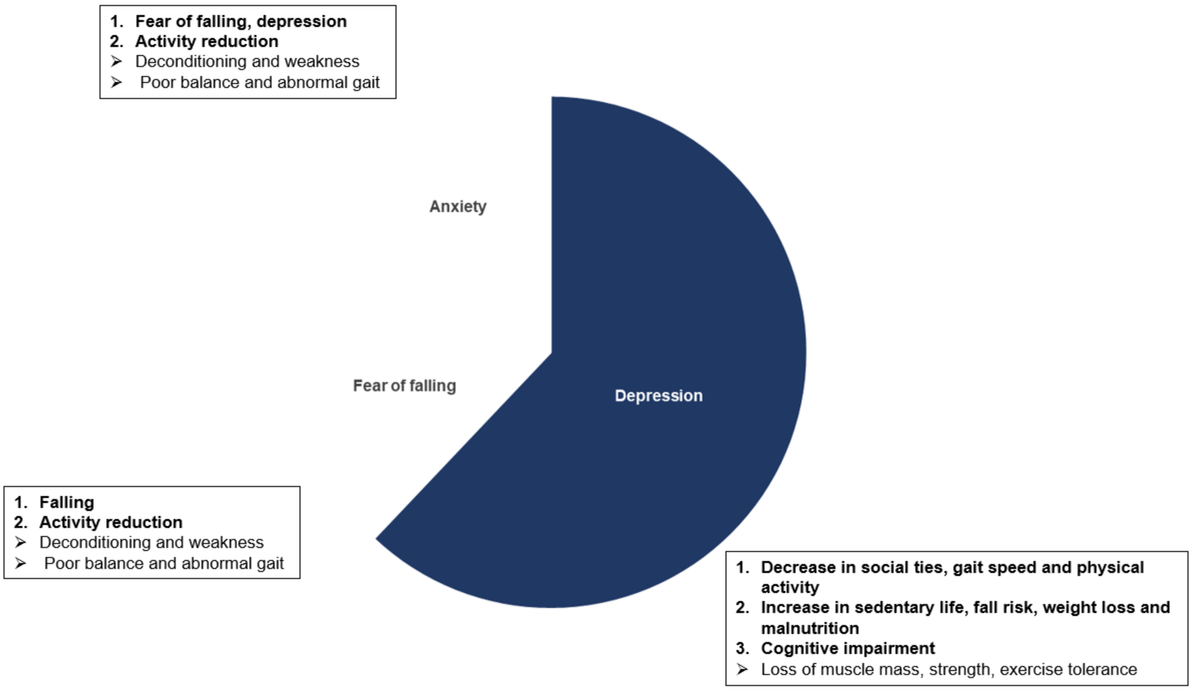

Figure 20: Psychological Factors: Representation of associations with the target factor ‘frailty’
Study types and means of odds ratios: ‘Depression’: OR=3.273, systematic review+cross-sectional+cross-sectional; ‘Fear of falling’: no study: ‘Anxiety’: no study

Anxiety

Anxiety is common in elder adults, as, with one in four patients reporting severe emotional problems, this mostly results of anxiety and depression (Ní Mhaoláin et al., 2012). Also, women are generally at higher risk for developing this condition (Ní Mhaoláin et al., 2012).

Furthermore, anxiety is associated with frailty and is included as risk factor in NANDA (Herdman and Kamitsuru, 2014). However, no studies investigating this association were to be found by the author.

Nevertheless, some studies report of a higher prevalence of anxiety in frail patients (Ní Mhaoláin et al., 2012, Bourgault-Fagnou and Hadjistavropoulos, 2009). Thus, with increasing frailty, also higher anxiety scores were found (Ní Mhaoláin et al., 2012, Bourgault-Fagnou and Hadjistavropoulos, 2009), indicating a dose-response relationship.

If this relationship also exists in the other direction, with anxiety predisposing to frailty, is unclear. However, as anxious persons often restrict activities, which leads to deconditioning and weakness and therefore to poor balance and abnormal gait, this might increase the risk for frailty (Painter et al., 2012). Furthermore, anxiety is significantly associated with fear of falling and with depression, which are also risk factors for frailty in itself (see “Fear of Falling” and “Depression”) (Gagnon et al., 2005, Painter et al., 2012).

Depression

Depression is common in elder individuals, with a prevalence of 10% to 20% (Barua et al., 2011). However, evidence suggests that it is associated with an increased risk for frailty (Ko and Choi, 2017, Mezuk et al., 2012, Soysal et al., 2017, Feng et al., 2017, Espinoza and Fried, 2007), whereby Mezuk et al. (2012) speaks of a bidirectional relationship. This is supported by the findings of Soysal et al. (2017), stating that “each condition is associated with an increased prevalence and incidence of the other, and may be a risk factor for the development of the other”. According to a meta-analysis of Soysal et al. (2017), people with depression were at increased odds of having frailty with an association of OR=3.72 (95%CI: 1.95-7.08). This is supported by cross-sectional studies of Ng et al. (2014) and Jurschik et al. (2012), who found associations of OR=2.97(95% CI:1.16–7.62) and OR=3.13 (95% CI: 1.37-7.13), respectively.

Depression might lead to frailty due to several factors: Decrease in social ties, gait speed and physical activity and increase in sedentary life, fall risk, weight loss, and malnutrition (Soysal et al., 2017). Additionally, depression is associated with cognitive impairment, which might contribute to the development of frailty, as well (Soysal et al., 2017). Finally, according to Espinoza and Fried (2007), individuals suffering from depression often become less active, resulting in loss of muscle mass, strength and exercise tolerance, and are more prone to acute illness.

Fear of falling

Fear of falling is prevalent in 35-55% of older people and is generally associated with an increased risk for frailty (Silveira et al., 2015, Painter et al., 2012, Arfken et al., 1994, Morley et al., 2002).

This relationship might result from the fact that persons with a fear of falling tend to decrease activities, which in the long term may have negative effects on physical health, such as deconditioning, weakness, poor balance and abnormal gait (Rubenstein, 2006, Rubenstein and Josephson, 2006, Painter et al., 2012). Here, some are risk factors for frailty, in itself (see “Balance”, “Gait”), whereby ‘weakness’ even is a criterion for frailty after Fried et al. (2001).Furthermore, a fear of falling is also associated with an increased risk for falling, which predisposes to frailty as well (see “History of falls”) (Tromp et al., 2001, Gazibara et al., 2017).

4.1.5. Environmental Factors

Life-space constriction

Life space, a measure of spatial mobility, is defined as “the size of the spatial area people purposely move through in their daily life as well as the frequency of travel within a specific time frame” (Xue, 2011). According to a cohort study of Xue (2011) individuals living in constricted spaces are at an increased risk for frailty.

Evidence suggests that constricted life space is a marker of declines in physiologic reserves (Xue, 2011). Furthermore, it leads to decreased physical activity and social engagement and accelerates deconditioning, hereby increasing the development of frailty (Xue, 2011).

As no association in terms of odds ratios was found for the risk factor in the ‘Environmental Factors’ category, no graphical representation with the target factor ‘frailty’ was possible.

4.1.6. Social Factors

Figure 21 shows the risk factors from the 'Social Factors' category and their association with the target factor 'frailty'. Here, the risk factor 'social isolation' presents the strongest association with frailty.

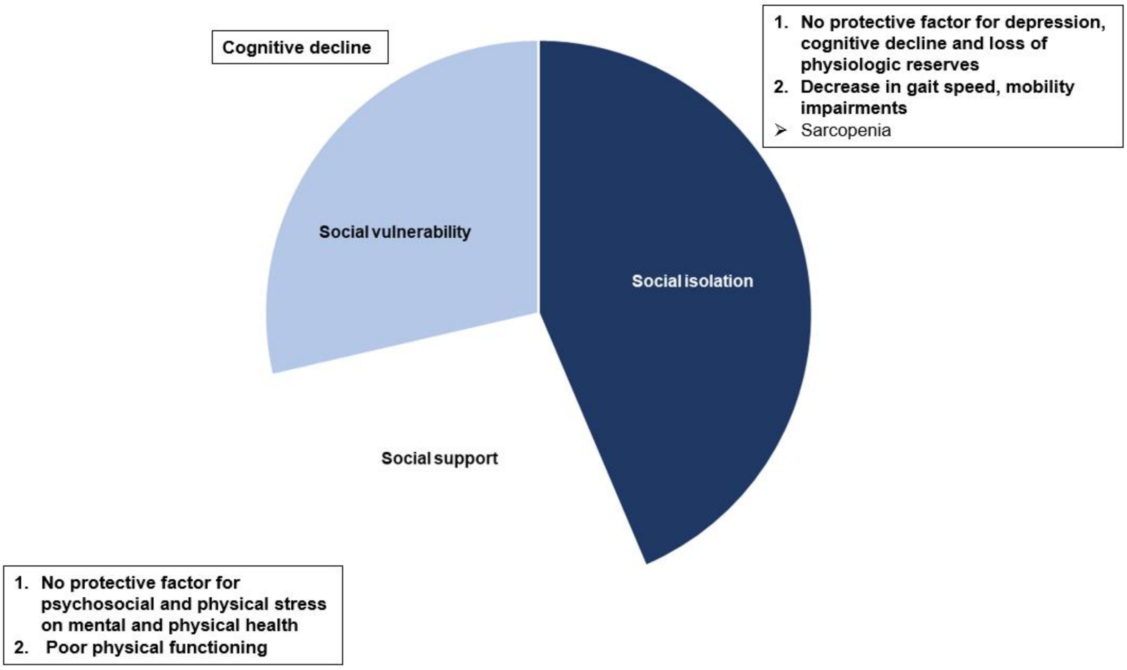

Figure 21: Social Factors: Representation of associations with the target factor 'frailty'
Study types and means of odds ratios: 'Social isolation': OR=1.57, cohort; 'Social support': no study; 'Social vulnerability': OR=1.03, cross-sectional

Social isolation

According to a cross-sectional study of Chon et al. (2018), people who maintain less frequent contact with others are at greater odds of prevalent frailty compared to people who maintain better contact frequency. Thus, Strawbridge et al. (1998) found in a cohort study an association of long-term social isolation and frailty of OR=1.57.

As social contact has a positive effect on health in terms of decreasing depression and cognitive decline, this might act as a protective factor for frailty, as both are considered risks for frailty (see "Depression", "Cognitive impairment") (Chon et al., 2018). Furthermore, being socially engaged might reduce a loss of physiologic reserves, which also might predispose to frailty (Liljas et al., 2017a).

On the other hand, social isolation might also lead to a decrease in gait speed and mobility impairments, which in turn can increase the likelihood of sarcopenia, all being risk factors for frailty in itself (see "Slow gait speed", "Impaired mobility", "Sarcopenia") (Shankar et al., 2017, Perissinotto et al., 2012).

Insufficient social support

Social support is important in elderlies, as it acts as a protective factor for frailty, however it is generally decreasing with age (Woo et al., 2005, de Labra et al., 2018).

Therefore, factors, like number of relatives and neighbours, frequency of participation in helping others, frequency of contact with relatives and participation in religious activities are associated with lower frailty (Woo et al., 2005). This is also supported by a cross-sectional study of Jurschik et al. (2012), who found that poor social ties are significantly associated with frailty, whereby sufficient support acts protective, with OR=0.57 (95% CI: 0.43–0.77).

Social support has a direct positive effect on health status and decreases effects of psychosocial and physical stress on the mental and physical health of the individual (Broadhead et al., 1983). Therefore, in individuals with no/ insufficient social support, the risk for developing such conditions is increased and thus, exposes them to a higher risk for frailty. Furthermore, in a cohort study of Stansfeld et al. (1998), low social support was also associated with a risk for poor physical functioning, hence leading to frailty, as well.

Social vulnerability

Social vulnerability can be defined as “the degree to which a person’s overall social situation leaves him or her susceptible to further insults (either health-related or social)” (Andrew, 2015) and is thus, associated with a risk for frailty (Andrew et al., 2008, Manrique-Espinoza et al., 2016). Prominent examples for social vulnerability are here ‘disempowerment’ or ‘decreased life control’ (Herdman and Kamitsuru, 2014).

According to a cross-sectional study of Manrique-Espinoza et al. (2016), social vulnerability was associated with frailty, however only with OR=1.03 (95% CI: 0.73-1.45).

Nevertheless, this relationship might be due to the fact that social circumstances particularly impact health (Andrew et al., 2008). Therefore, social vulnerability is associated with increased cognitive decline, which is considered a risk factor for frailty (see “Cognitive impairment”) (Andrew, 2015).

4.2. Consequences of 'Frailty'

Frailty is an important geriatric syndrome associated with a greater risk of adverse health outcomes, as it is a precursor of functional deterioration (see Figure 22) (Collard et al., 2012, Fried et al., 2001, Morley et al., 2002). Thus, an apparently small insult (e.g. new drug, “minor” infection, “minor” surgery) results in a dramatic and disproportionate change in health state (Clegg et al., 2013). Because of this, frailty has also been referred to as “unstable disability” to reflect the often marked changes in functional ability (Clegg et al., 2013).

Consequently, frailty leads to decreased strength, weakness, and worsening motor performance, which in turn increases the risk for falls, less mobility, less independence, hospitalization and disability (Collard et al., 2012, Fried et al., 2001, Morley, 2012, Fhon et al., 2018).

Furthermore it is also associated with decreased survival rates (Shamliyan et al., 2013, Collard et al., 2012, Fried et al., 2001). Thus, survival rate is reduced in a dose-response relationship per increasing number of frailty criteria (Shamliyan et al., 2013).

Finally, frailty also affects social areas, as frail persons have a decrease in social activity, which is often due to the association with incontinence (Morley et al., 2002).

Figure 22: Consequences of the target factor 'frailty'

4.3. Recommendations for the Prevention of ‘Frailty’

According to a systematic review of Shamliyan et al. (2013), it is estimated that 3-5% of deaths among older adults could be delayed if frailty was prevented.

Furthermore, evidence suggests that frailty and prefrailty are reversible as they are dynamic processes (Serra–Prat et al., 2017, Fhon et al., 2018). Thus, interventions such as physical exercise can reverse this state and lead to a decrease in falls and improve mobility, balance, and muscle strength (Fhon et al., 2018).

This has been demonstrated in a randomized, controlled trial of Fiatarone et al. (1994), where strength training increased lower-extremity strength, gait velocity, stair climbing power and improved mobility in frail older adult residents of a nursing facility.

All in all, the complexity and heterogeneity of the frailty syndrome requires a multidimensional clinical approach, based on several factors: Healthy nutrition, psychosocial well-being, regular physical exercise and pharmacological measures (Greco et al., 2019). Thus, preventing and controlling chronic diseases, which affect life expectancy and quality of life, and thereby reducing mortality (Greco et al., 2019).

Figure 23 shows all recommendations regarding the target factor ‘frailty’.

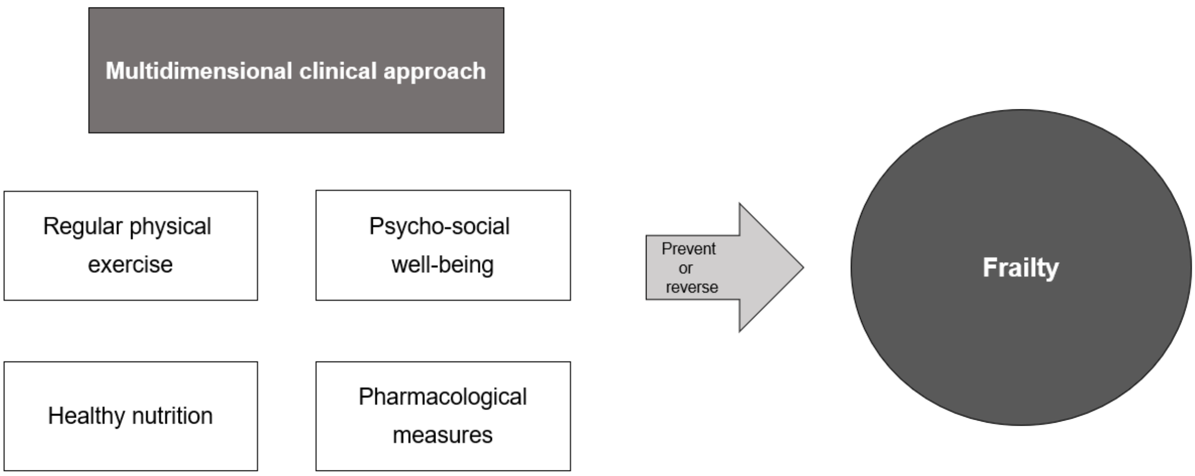

Figure 23: Recommendations for the prevention of ‘frailty

5. Cognitive Decline

As aging is accompanied by structural and neurophysiological changes in the brain, this can lead to various degrees of cognitive decline, which has emerged as one of the greatest health threats of old age (Bishop et al., 2010). Thus, in elder ages, separate brain regions, usually interacting to sub-serve higher-order cognitive functions, show less-coordinated activation, which leads to poor performance in several cognitive domains (Bishop et al., 2010). Furthermore, neural activity also becomes less localized in some brain regions, especially the prefrontal cortex, in response to executive tasks (Bishop et al., 2010).

Especially so called 'fluid' mental abilities are generally thought to decline in increasing ages (Deary et al., 2009). This includes aspects of memory, executive functions, processing speed and reasoning, which is important for carrying out everyday activities and living independently (Deary et al., 2009, Prince et al., 2015). Thus, Dementia and cognitive decline are the leading chronic disease contributors to disability and dependence among elderlies worldwide, often making a caregiver indispensable (Prince et al., 2015).

Dementia is a group of disorders characterized by a decline from a previously attained cognitive level, whereby Alzheimer's disease is the most common form (World Health Organization, 2019, Johansson et al., 2015). Furthermore, the term 'mild cognitive impairment' involves cognitive decline beyond that normally expected in a person of the same age, with preservation of function, whereby 'Dementia' is defined as cognitive decline in one of several cognitive domains, along with difficulty in functional abilities as visible in Figure 24 (Naqvi et al., 2013).

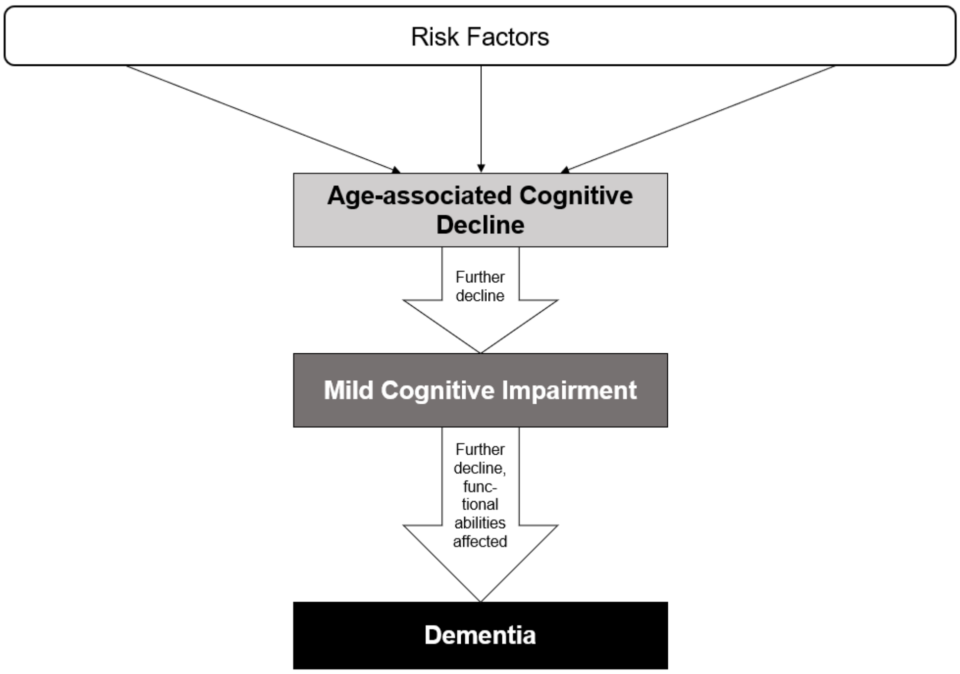

Figure 24: Cognitive decline and Dementia

As life expectancy increases worldwide, so does the prevalence of cognitive decline, as age is the greatest risk factor (Bishop et al., 2010). According to the World Health Organization, in 2015, 47.47 million people lived with dementia worldwide, and is estimated to reach 75.63 million in 2030 and 135.46 million in 2050 (Prince et al., 2015). Furthermore, 37% of people living with dementia are from high-income countries and 63% live in low and middle-income countries, where access to social protection, services, support and care are limited (Prince et al., 2015).

Mild cognitive impairment on the other hand is estimated to affect 10% to 25% of people over the age of 70 years (Naqvi et al., 2013).

Finally, regarding the development of cognitive decline, evidence suggests that it is caused by multiple factors. Thus, according to the *WHO Guidelines on risk reduction of cognitive decline and dementia* (World Health Organization, 2019) and a systematic review of Baumgart et al. (2015), several risk factors regarding cognitive decline were identified and classified into the following categories:

- Personal Factors
- Physiological Factors
- Cognitive Factors
- Psychological Factors
- Social factors

However, the risk factor "Education", from the systematic review of Baumgart et al. (2015) was not included in this report. This is due to the fact that such factor might not directly influence the development of cognitive decline, but rather likely co-exist with other lifestyle factors increasing the risk alone.

Nevertheless, the risk factor "Anxiety" has been included in this report, as it was found to show a strong association with cognitive decline (Potvin et al., 2011).

Finally, Figure 25 shows all categories of cognitive decline stated in this review. Here, the left figure presents the importance of the categories according to the number of risk factors, with the physiological group demonstrating the most risk factors. In contrast to this, the right figure presents the importance of the categories according to the strength of the associations. Here, for each category, the risk factor with the strongest association has been elected. Thus, the psychological group shows the strongest association.

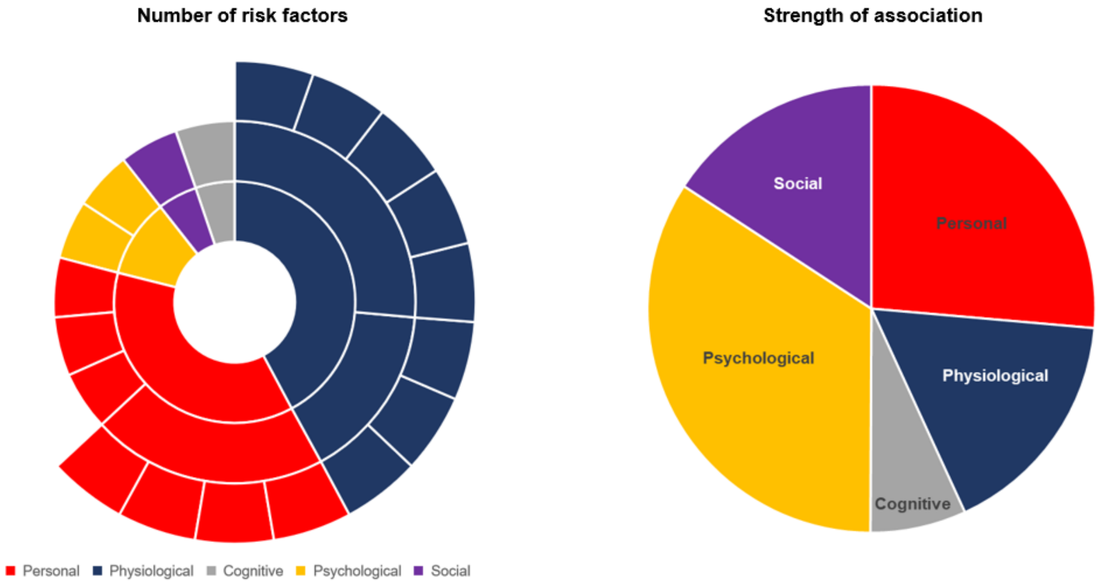

Figure 25: Categories of the target factor ‘cognitive decline’ according to importance

In the following, the risk factors of the target factor cognitive decline are going to be analysed in their respective categories.

5.1. Risks of 'Cognitive Decline'

5.1.1. Personal Factors

Figure 26 shows all risk factors from the 'Personal Factors' category and their association with the target factor 'cognitive decline'. Here, the risk factor 'elevated plasma homocysteine' presents the strongest association with cognitive decline.

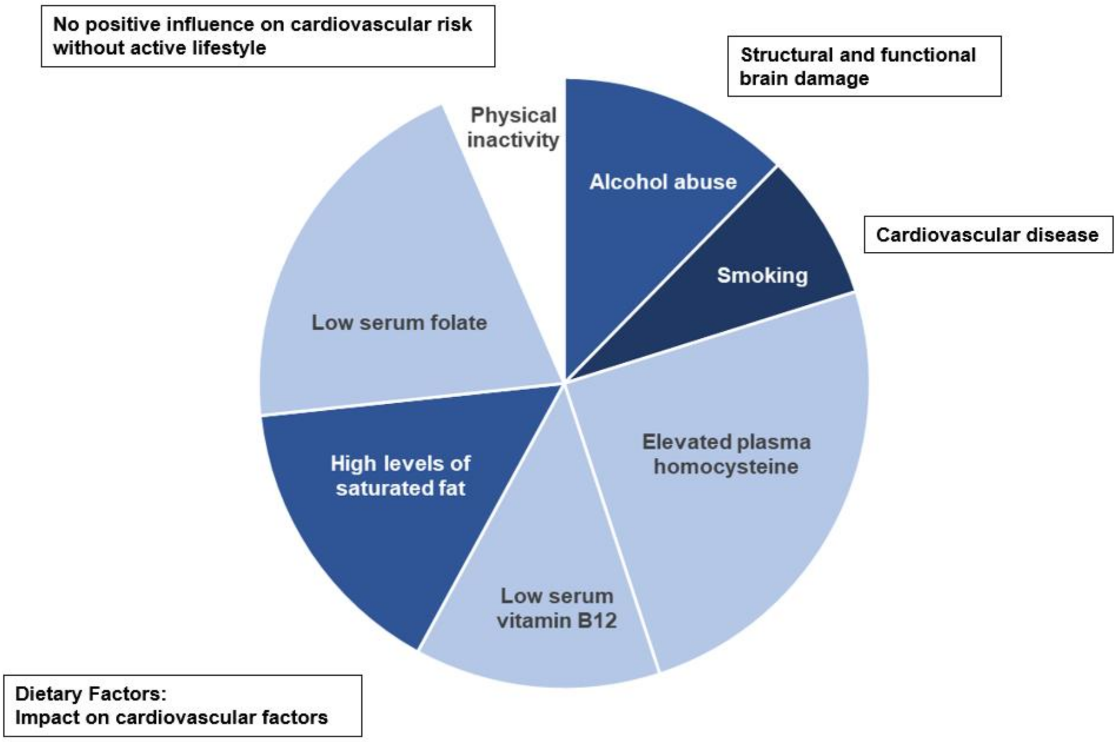

Figure 26: Personal factors: Representation of associations with the target factor 'cognitive decline'
Study types and means of odds ratios: 'Elevated plasma homocysteine': OR=3.81, cross-sectional; 'Low serum vitamin B12': OR=2.0, cross-sectional; 'High levels of saturated fat': OR=2.36, cohort; 'Low serum folate': OR=3.1, cross-sectional; 'Physical inactivity': no study; 'Alcohol abuse': OR=1.895, cohort+cross-sectional; 'Smoking': OR=1.2, systematic review

Alcohol abuse

Excessive alcohol consumption is common in many countries, whereby it is one of the leading causes of general disability (World Health Organization, 2019). Also, in 2012, 5.9% of all deaths worldwide (about 3.3 million) were directly attributable to the harmful use of alcohol (World Health Organization, 2019). Furthermore it is a direct cause of more than 200 diseases including cognitive decline and dementia (World Health Organization, 2019, Topiwala et al., 2017). Thus, Langballe et al. (2015) found in a cohort study that drinking alcohol frequently was significantly associated with an increased dementia risk, with HR=1.40 (95% CI: 1.07-1.84).

Furthermore, similar findings were reported by Mukamal et al. (2003), who found in a case-control study an association of heavy drinking and dementia, with OR=1.22 (95% CI: 0.60-2.49) and Anttila et al. (2004), with OR=2.57 (95% CI: 1.19-5.52) in a cohort study.

Lastly, according to a study of Topiwala et al. (2017), higher alcohol consumption especially predicted greater decline in lexical fluency.

As the prolonged and excessive use of alcohol might lead to structural and functional brain damage, this increases the risk for cognitive decline (Sachdeva et al., 2016).

Dietary factors

Dietary factors might be involved in the development of cognitive decline, either directly or indirectly through their impact on other risk factors, such as cardiovascular changes (World Health Organization, 2019). Furthermore, a healthy diet, for example the *Mediterranean Diet,* might even have preventive potential for cognitive impairment (World Health Organization, 2019).

Dietary risk factors, increasing the risk for cognitive decline include:

- Low serum vitamin B12 (<150 ρmol/L), with OR=2.0 (95% CI. 1.1-4.09) in a cross-sectional study of Argyriadou et al. (2001)
- High levels of saturated fat, with OR=2.36 (95% CI: 1.17-4.74) in a cohort study by Eskelinen et al. (2008).
- Low serum folate (<13.5 nmol/L), with OR=3.1 (95% CI: 1.2-8.1) in a cross-sectional study of Quadri et al. (2004)
- Elevated plasma homocysteine (>15 μmol/L), with OR=3.81 (95% CI: 1.9-7.5) in a cross-sectional study of Ravaglia et al. (2003)

Physical inactivity

Physical activity is generally thought to act as a protective factor for cognitive decline (Sofi et al., 2011, World Health Organization, 2019). Thus, according to a meta-analysis of Sofi et al. (2011) high levels of physical activity were significantly protective (-38%), with HR=0.62 (95% CI: 0.54-0.70), as well as low-to-moderate levels with -35% and HR=0.65 (95% CI 0.57-0.75), respectively.

However, if no physical activity might act as a risk factor for cognitive decline, has, to the knowledge of the author, not yet been proven. Nevertheless, a relationship with cognitive decline might be indirect, such that with physical inactivity, the positive influence on cardiovascular risk factors that an active lifestyle has, is not given (World Health Organization, 2019). Therefore, especially high levels of physical activity have positive effects on hypertension, insulin resistance or cholesterol levels, as well as on other biological mechanisms, including the immune system function, anti-inflammatory properties and increasing neurotrophic factors (World Health Organization, 2019). Thus, due to the (possible) increase in cardiovascular diseases, which is a risk factor in itself (see “Cardiovascular disease”), the relationship with cognitive decline might be given.

Smoking

Evidence suggests that current smoking increases the risk of cognitive decline (Baumgart et al., 2015, Plassman et al., 2010, Whitmer et al., 2005).

Thus, Peters et al. (2008) found in a meta-analysis a combined ratio of odds and risks of 1.20 (95% CI: 0.90–1.59).

This relationship might result of the fact that smoking increases the cardiovascular risk, which in turn is associated with cognitive decline (see “Cardiovascular disease”) (Peters et al., 2008).

5.1.2. Physiological Factors

5.1.2.1. General

Figure 27 shows all risk factors from the 'General' category and their association with the target factor 'cognitive decline'. Here, the risk factor 'obesity' presents the strongest association with cognitive decline.

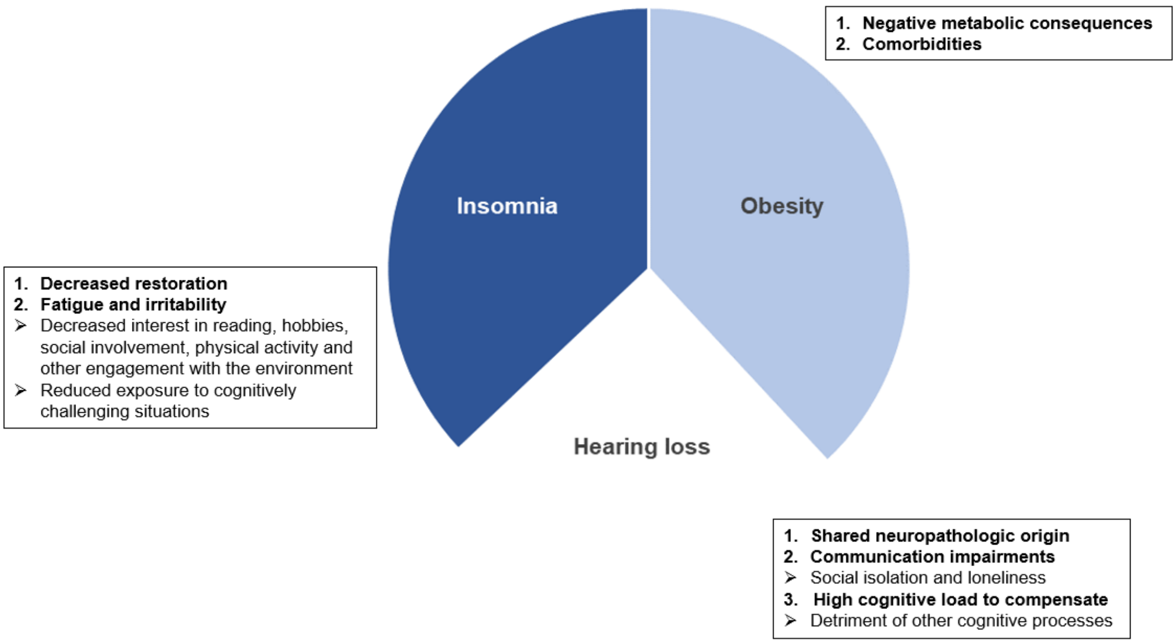

Figure 27: Physiological Factors, General: Representation of associations with the target factor 'cognitive decline' Study types and means of odds ratios: 'Obesity': OR=1.532, cross-sectional; 'Hearing loss': no study; 'Insomnia': OR=1.49, cohort

Hearing loss

Age-related hearing loss if one of the most common health conditions affecting older adults, with a prevalence of almost two-thirds in over 70 year olds (Uchida et al., 2019). However, it is associated with accelerated cognitive decline and incident cognitive impairment in community-dwelling older adults (Uchida et al., 2019, Lin et al., 2013). Thus, in a cohort study of Lin et al. (2013), individuals with hearing loss demonstrated a 30% to 40% accelerated rate of cognitive decline and a 24% increased risk for incident cognitive impairment during a 6-year period compared with individuals having normal hearing.

This relationship might result of several factors: First, evidence suggests that both, hearing loss and cognitive decline, have a shared neuropathologic origin underlying and therefore increasing the risk for each other (Lin et al., 2013). Furthermore, communication impairments caused by hearing loss can lead to social isolation and loneliness, which are associated with cognitive decline, as well (see "Social disengagement") (Lin et al., 2013). Finally, the effect of hearing loss on cognitive load might be a reason for the increase in cognitive decline, as well. Thus, under conditions where auditory perception is difficult (as in the case of hearing loss), greater cognitive resources are needed for auditory perceptual processing, however to the detriment of other cognitive processes such as working memory (Lin et al., 2013).

Insomnia

Sleep problems are common among older adults, with 50% reporting to suffer of poor sleep, but are nevertheless often undertreated (Chen et al., 2017, Min et al., 2016). However, symptoms of insomnia are assumed to be a risk factor for cognitive decline (Cricco et al., 2001, Lim et al., 2013). Thus, Cricco et al. (2001) found in a cohort study an association of insomnia and cognitive decline in men, with OR=1.49 (95% CI: 1.03-2.14), but not in women. This gender discrepancy might result of men having a higher threshold of reporting sleep complaints, and therefore, those men reporting insomnia might have significantly more disturbed sleep than women (Cricco et al., 2001).

The cognitive decline might be a result of decreased restoration due to poor sleep (Cricco et al., 2001). As sleep is important in terms of increasing anabolic activity in order to allow for repairs in the central nervous system and peripheral tissues, this might affect cognitive functions (Cricco et al., 2001).

Furthermore, chronic poor sleep can lead to fatigue and irritability and thus, results in decreased interest in reading, hobbies, social involvement, physical activity and other engagement with the environment (Cricco et al., 2001). As involvement in intellectually stimulating activities helps maintain cognitive abilities, reduced exposure to cognitively challenging situations might increase the risk for cognitive decline (Cricco et al., 2001)

Obesity

Obesity is a general health problem, especially concerning older adults, as they are significantly more overweight (42.4%) and obese (20.9%) than middle age and younger adults (Marques et al., 2018). Furthermore, obesity, classified by a Body Mass Index (BMI, kg/m2) of ≥30.0, is associated with a higher risk of cognitive decline (Dye et al., 2017, Smith et al., 2011). Thus, Hou et al. (2019) found in a cross-sectional study that abdominal obesity was significantly associated with an increased risk of cognitive impairment, with OR=1.532 (95% CI:1.037-2.263). However, in contrast to that, overweight (25<BMI<30) was found to be a protective factor, with OR=0.458 (95% CI:0.298-0.703) (Hou et al., 2019).

This is supported by the World Health Organization (2019) as well, suggesting that overweight has a protective factor in terms of overall mortality, whereby an excess of fat is considered a risk factor for cognitive decline or dementia.

Obesity is especially related to impaired performance on tasks of episodic memory and visual modality, verbal learning and working memory (Dye et al., 2017). This relationship possibly results of the negative metabolic consequences and comorbidities of obesity, like diabetes mellitus or hypertension, which are risk factors in itself (see “Diabetes mellitus”, “Hypertension”) (Dye et al., 2017, World Health

Organization, 2019). As in persons with overweight only, the metabolic consequences are probably lower, this might be the reason for the protective function of it, as compared to obesity.

5.1.2.2. Diseases and Disorders

Figure 28 shows all risk factors from the 'Diseases and Disorders' category and their association with the target factor 'cognitive decline'. Here, the risk factor 'hypertension' presents the strongest association with cognitive decline.

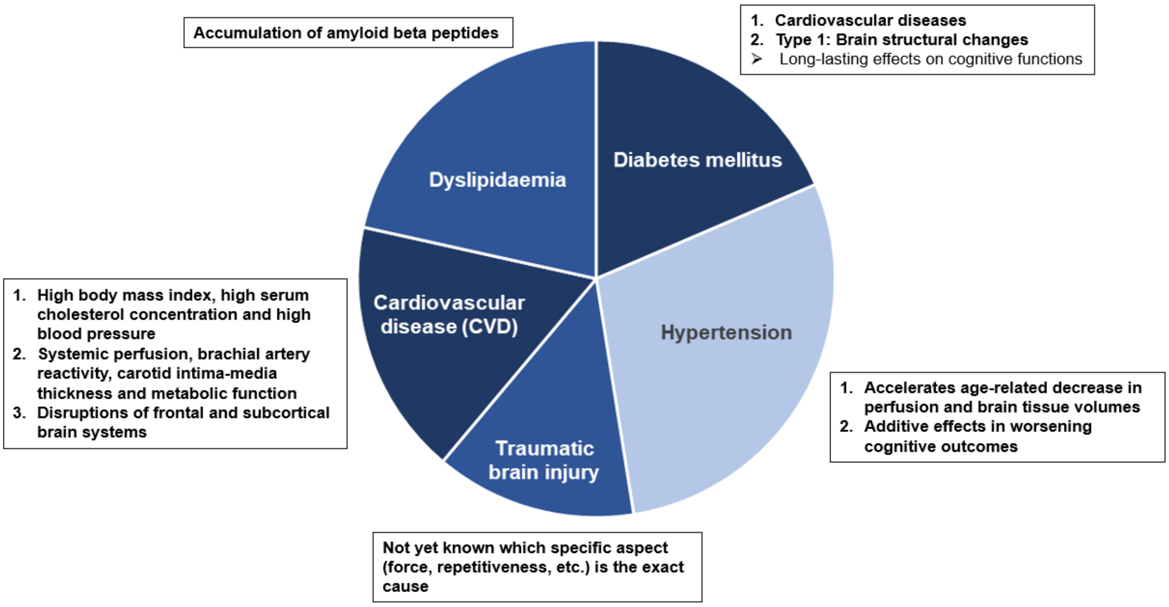

Figure 28: Physiological factors, diseases and disorders: Representation of associations with the target factor 'cognitive decline'
Study types and means of odds ratios: 'Hypertension': OR=2.42, cross-sectional; 'Traumatic brain injury': OR=1.14, cohort; 'Cardiovascular disease': OR=1.45, systematic review; 'Dyslipidaemia': OR=1.8, cohort; 'Diabetes mellitus': OR=1.55, systematic review+ cross-sectional

Cardiovascular disease (CVD)

Evidence suggests that cardiovascular disease is associated with a decline in cognitive function, even in the absence of major cardiac events or clinically relevant stroke (Okonkwo et al., 2010, Dregan et al., 2012). One prominent example of CVD is 'coronary heart disease', which was found to be associated with an increased risk of cognitive impairment or dementia in a meta-analysis, with OR=1.45 (95% CI: 1.21-1.74) (Deckers et al., 2017).

CVD is especially thought to lead to deficits in attention, executive functions, psychomotor speed and information processing, which might result of disruptions of frontal and subcortical brain systems (Okonkwo et al., 2010). Furthermore, specific factors, associated with CVD are itself thought to increase the risk of cognitive decline: Body mass index, serum cholesterol concentration and high blood pressure. This also applies for indices of vascular integrity: Systemic perfusion, brachial artery reactivity, carotid intima-media thickness and metabolic function (e.g. C-reactive protein and brain natriuretic peptide) (Okonkwo et al., 2010).

Diabetes mellitus

The population of older adults with diabetes mellitus is rapidly growing worldwide (Strain et al., 2018), which is especially due to the prevalence of diabetes mellitus type 2 (T2DM), accounting for 90%-95% of diabetes cases (Cannon et al., 2018).

However, T2DM is associated with an increased risk of cognitive dysfunction (Bordier et al., 2014, Ebady et al., 2008, Whitmer et al., 2005). Thus, Cukierman et al. (2005) found in a systematic review an association of OR=1.2 (95% CI: 1.05-1.4). Similar findings were reported by Ebady et al. (2008) in a cross-sectional study, with OR=1.9 (95% CI: 1.01-3.6).

This relationship might be due to the fact that T2DM is associated with vascular diseases, which are a risk factor for cognitive decline in itself (see "Cardiovascular diseases") (Umegaki, 2014).

Furthermore, as another subtype of diabetes, type 1 diabetes mellitus (T1DM) accounts for about 5% of all diabetic cases and is also associated with an increased risk for cognitive decline (Li et al., 2017b). This is possibly du to long-lasting effects on cognitive functions, resulting of associated brain structural changes due to early onsets of the disease (Li et al., 2017b).

Dyslipidaemia

High levels of blood cholesterol are especially prevalent in high-income countries, with more than 50% of adults being affected, which is more than twice the rate of low-income countries (World Health Organization, 2019). However, it is associated with an increased risk for cognitive decline (Ma et al., 2017, Whitmer et al., 2005).

Thus, according to a cohort study of Ma et al. (2017), higher concentrations of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) were associated with faster cognitive decline.

Furthermore, Solomon et al. (2007) found in a cohort study that an increase of cholesterol from midlife to late life was associated with cognitive decline, with OR=1.8 (95% CI: 0.7-4.5).

This relationship might be due to the fact that high cholesterol plays a role in the accumulation of amyloid beta peptides, which accelerates the development of cognitive impairment (Burns and Duff, 2002).

Hypertension

Hypertension affects more than a third of the population worldwide and is especially prevalent in over 65 year olds (65%-75%) (Novak and Hajjar, 2010, Pereira et al., 2009, Kearney et al., 2005). However, it is suggested to increase the risk for cognitive decline (Sharifi et al., 2011, Whitmer et al., 2005). Thus, Sharifi et al. (2011) found in a cross-sectional study an association between cognitive decline and diastolic blood pressure of OR=2.42 (95% CI: 1.01-5.78).

This might result of the fact that hypertension accelerates age-related decrease in perfusion and brain tissue volumes and has additive effects in worsening cognitive outcomes (Novak and Hajjar, 2010).

Traumatic brain injury (TBI)

Traumatic brain injury is an important public health problem, with more than 10 million individuals being affected every year (Moretti et al., 2012). However, having a history of TBI, might lead to exacerbated cognitive decline in older adults (Moretti et al., 2012, Luukinen et al., 1999, LoBue et al., 2016). Especially those experiencing repeated head injuries (e.g. boxers, football players and combat veterans) might be at an even higher risk (Baumgart et al., 2015).

Thus, LoBue et al. (2016) found in a cohort study an association between TBI and cognitive impairment of OR=1.14 (95% CI=0.94-1.37), which is however rather weak.

According to Arciniegas et al. (2002), disturbances of attention, memory and executive functioning are the most common neurocognitive consequences of TBI and therefore might lead to a general cognitive decline. However, it is not yet known which specific aspect (force, repetitiveness, etc.) is the exact cause (Baumgart et al., 2015).

5.1.3. Cognitive Factors

Low cognitive engagement

Evidence suggests that mental engagement or cognitive training interventions show improvements in immediate and delayed recall and therefore improve cognitive functions (Baumgart et al., 2015). In addition, a reverse association might exist, as well, with decreased participation in cognitive activities leading to cognitive decline (Doi et al., 2013).

However, this relationship might be more related to the fact that high cognitive activity acts as a protective factor. As having a cognitive reserve protects against cognitive decline, in individuals with low cognitive activity, this protection from cognitive decline is not given and might therefore increase the progression.

As no association in terms of odds ratios was found for the risk factor in the ‘Cognitive Factors’ category, no graphical representation with the target factor ‘cognitive decline’ was possible.

5.1.4. Psychological Factors

Figure 29 shows the risk factors from the 'Psychological Factors' category and their association with the target factor 'cognitive decline'. Here, the risk factor 'anxiety' presents the strongest association with cognitive decline.

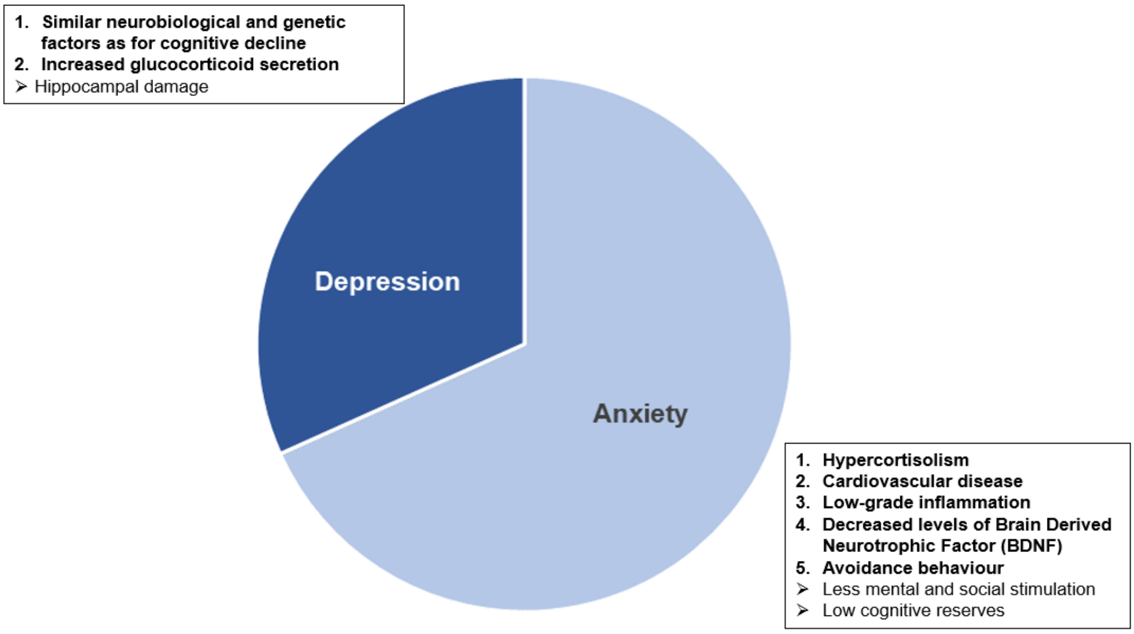

Figure 29: Psychological Factors: Representation of associations with the target factor 'cognitive decline'
Study types and means of odds ratios: 'Anxiety': OR=4.93, cross-sectional; 'Depression': OR=2.29, cohort

Anxiety

About 8% to 18% of community-dwelling older adults experience anxiety (Painter et al., 2012). However, anxiety is associated with an increased risk for cognitive impairment and dementia (Gulpers et al., 2016, Bierman et al., 2005, Beaudreau and O'Hara, 2008, Sinoff and Werner, 2003). Thus, according to a meta-analysis of Gulpers et al. (2016), anxiety predicted incident cognitive impairment, with RR=1.77 (95% CI: 1.38-2.26). Furthermore, Potvin et al. (2011) found in a cross-sectional study an association of OR=4.93 (95% CI: 1.84-13.23).

According to Gulpers et al. (2016), several factors might be causal to the development of cognitive decline due to anxiety: Hypercortisolism, cardiovascular disease, low-grade inflammation, Brain Derived Neurotrophic Factor (BDNF) suppression and low cognitive reserves.

First, regarding hypercortisolism, anxiety will lead to stress and therefore to higher levels of cortisol, which is suggested as risk factor for cognitive decline in itself (see " Dyslipidaemia") (Gulpers et al., 2016).

Furthermore, anxiety is related to cardiovascular diseases, as the mental stress might trigger physiological reactions like an increased heart rate, blood pressure, vasoconstriction and platelet activity and therefore increases the risk for cognitive decline (see "Cardiovascular disease") (Gulpers et al., 2016).

Moreover, elevated levels of cytokines (IL-6, TNF), responsible for inflammation, are found in stress-related disorders, including anxiety, and are associated with negative effects on cognitive functioning (Gulpers et al., 2016).

Anxiety disorders have also been associated with decreased levels of BDNF, which is essential for synaptic plasticity, learning and memory and neuronal repair (Gulpers et al., 2016).

Finally, anxiety is frequently accompanied with avoidance behaviour, which leads to lowered cognitive reserves due to less mental and social stimulation (Gulpers et al., 2016).

Depression

Depression is common in elder individuals, with a prevalence of 10% to 20% (Barua et al., 2011). However, depressive symptoms are associated with poor cognitive functioning and cognitive decline (Dotson et al., 2008, Ng et al., 2009). Thus, Ng et al. (2009) found in a cohort study an association of OR=2.29 (95% CI: 5 1.05-5.00).

Depression is especially thought to affect attention, visuospatial abilities, memory processing, concept formation, information processing speed and overall cognitive functioning (Dotson et al., 2008). This might result of several factors:

First, the risk for cognitive decline might be due to hippocampal damage, caused by depression pathology such as increased glucocorticoid secretion (Dotson et al., 2008).

Furthermore, it is suggested that both conditions underly the same common risk factors or neurodegenerative processes (Dotson et al., 2008). Thus, both are associated with frontal pathology, disruption of frontosubcortical circuits, neurotransmitter changes, vascular changes and finally, they are also thought to share the same genetic links (Dotson et al., 2008).

5.1.5. Social Factors

Social disengagement

Social engagement is defined as “the maintenance of many social connections and a high level of participation in social activities” (Bassuk et al., 1999). However, decreased social interaction, and instrumental social support increase the risk for a decline in cognitive performance (Dickinson et al., 2011). Thus, Bassuk et al. (1999) found in a cohort study that social disengagement is associated with cognitive decline, with OR=2.24 (95% CI: 1.40-3.58) after 3 years, OR=1.91 (95% CI: 1.14-3.18) after 6 years and OR=2.37 (95% CI: 1.07-4.88) after 12 years.

Furthermore, Khan et al. (2016) found in a cross-sectional study that elderlies with poor social support almost have a threefold higher odds of being cognitively impaired (OR=2.6; 95% CI: 1.2-5.4).

Social support has a direct positive effect on health status and decreases effects of psychosocial and physical stress on the mental and physical health of the individual (Broadhead et al., 1983). Thus, low levels of social support are associated with greater depression severity and therefore might lead to declines in cognition (see “Depression”) (Steffens et al., 2005).

This is also true the other way around, as greater social resources are associated with reduced cognitive decline in old age (Barnes et al., 2004).

Figure 30 shows the ‘Social Factors’ category and its association with the target factor ‘cognitive decline’.

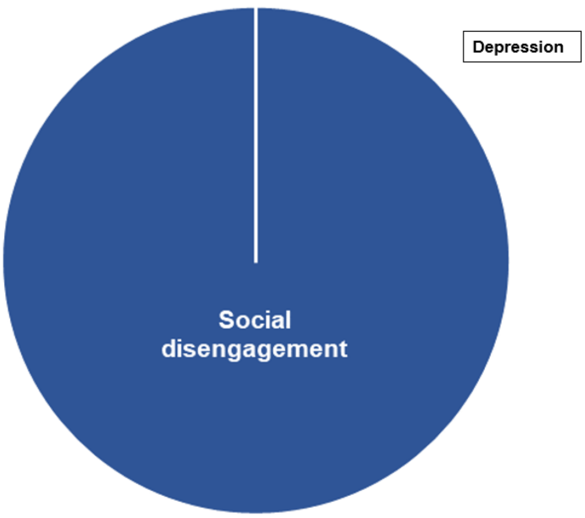

Figure 30: Social Factors: Representation of associations with the target factor ‘cognitive decline’
Study types and mean of odds ratios: OR=2.28, cohort+cross-sectional

5.2. Consequences of 'Cognitive Decline'

Mild cognitive impairment is considered a precursor to dementia and basically is the boundary between normal aging and dementia (Johansson et al., 2015). In people aged 65 years and older, the risk for developing a major neurocognitive disorder or dementia is approximately 10 percent (Small, 2016), whereby many different types of dementia exist, with Alzheimer's disease being the most common one (about 50%-70%) (Johansson et al., 2015).

Dementia and cognitive decline are the leading chronic disease contributors to disability and dependence among elderlies worldwide (Prince et al., 2015). As, cognitive decline also affects functional ability, this leads to impairments in instrumental activities of daily life (Johansson et al., 2015). Therefore, the individual might experience impairments in using the telephone and public transportation or management of medications and finances (Johansson et al., 2015). In later stages of dementia, even more basic activities of daily living such as bathing, dressing, toileting, transferring, continence, and feeding are affected (Johansson et al., 2015). Thus, with impaired ability to carry out essential tasks in daily life, making a caregiver indispensable (Prince et al., 2015).

Furthermore, evidence suggests that impairments in cognitive functioning have a great influence on fall risk (Cuevas-Trisan, 2017, Kearney et al., 2013). Thus, the annual incidence of falls is estimated to be between 60% and 85%, representing an approximate doubling of fall risk compared with that of cognitively not impaired older people (Shaw, 2002, Kearney et al., 2013).

Moreover, as decision making is a complex behaviour, even small changes in cognition have effects on judgment, leading to poor decision making (Boyle et al., 2012). Thus, elder people with cognitive decline frequently make suboptimal financial and healthcare choices and are often vulnerable to frauds (Boyle et al., 2012).

However, consequences of cognitive decline are individual and differ among people with cognitive impairments or dementia (Johansson et al., 2015).

Figure 31 shows the most important consequences of cognitive decline.

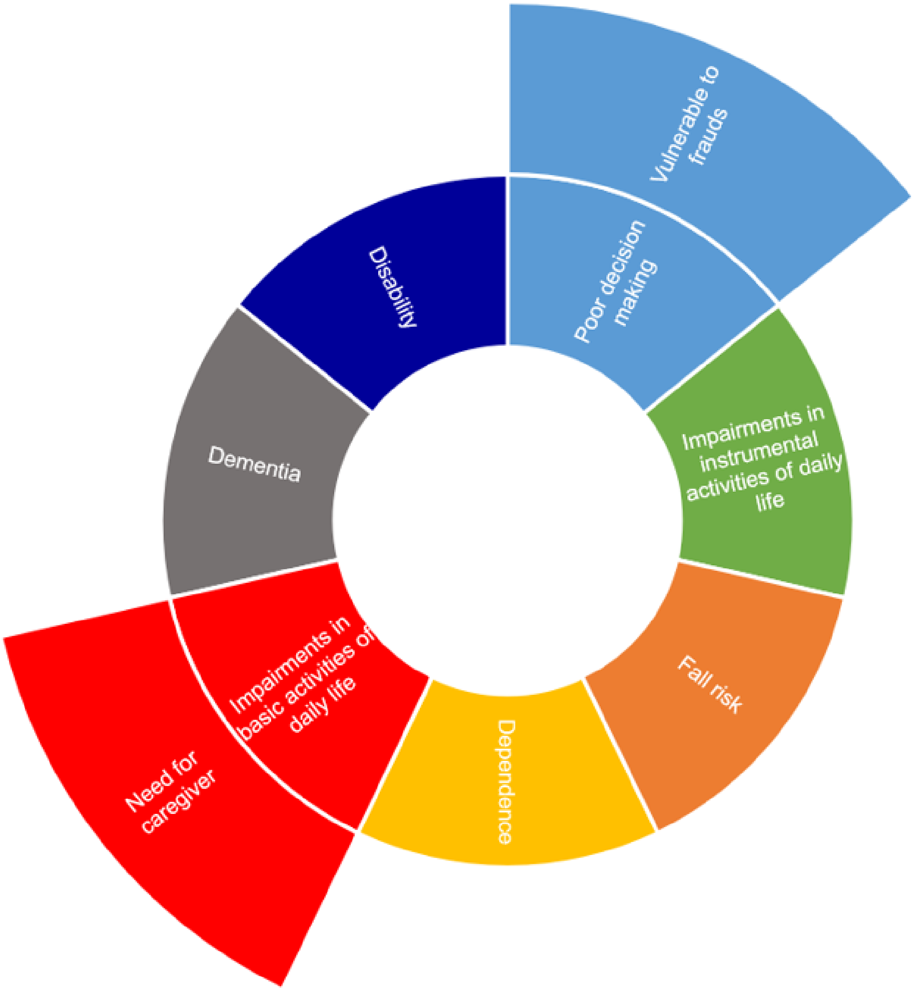

Figure 31: Consequences of the target factor 'cognitive decline'

5.3. Recommendations for the Prevention of 'Cognitive Decline'

In order to identify any curable conditions, it is important to investigate cognitive decline or dementia at an early stage and to provide appropriate support and assistance (Johansson et al., 2015). Furthermore, some interventions thought to prevent cognitive decline were identified and listed in the following:

First, evidence suggests that lifelong learning and cognitive training are effective at preventing cognitive decline (Naqvi et al., 2013, Baumgart et al., 2015). Thus, for example exercises triggering processing speed, memory or reasoning might reduce the risk (Naqvi et al., 2013, Willis et al., 2006).

Also, physical exercise might have a positive benefit, as well (Naqvi et al., 2013). This is supported by a meta-analysis of Sofi et al. (2011), suggesting a significant and consistent protection for all levels of physical activity against the occurrence of cognitive decline.

Moreover, according to a review of Baumgart et al. (2015), a healthy diet is suggested to have a protective effect on cognitive decline. Thus, especially the Mediterranean diet (low amount of red meat, emphasis on whole grains, fruits, vegetables, fish, nuts, and olive oil) might have a positive impact on the risk (Baumgart et al., 2015). However, evidence is limited and conflicting and thus this finding needs to be treated with caution (Baumgart et al., 2015).

Finally, the appropriate management of risk factors, especially of cardiovascular ones (e.g. diabetes, obesity, smoking, and hypertension) are thought to reduce the risk of cognitive decline and dementia, as well (Baumgart et al., 2015).

Figure 32 shows all recommendations for the prevention of the target factor 'cognitive decline'.

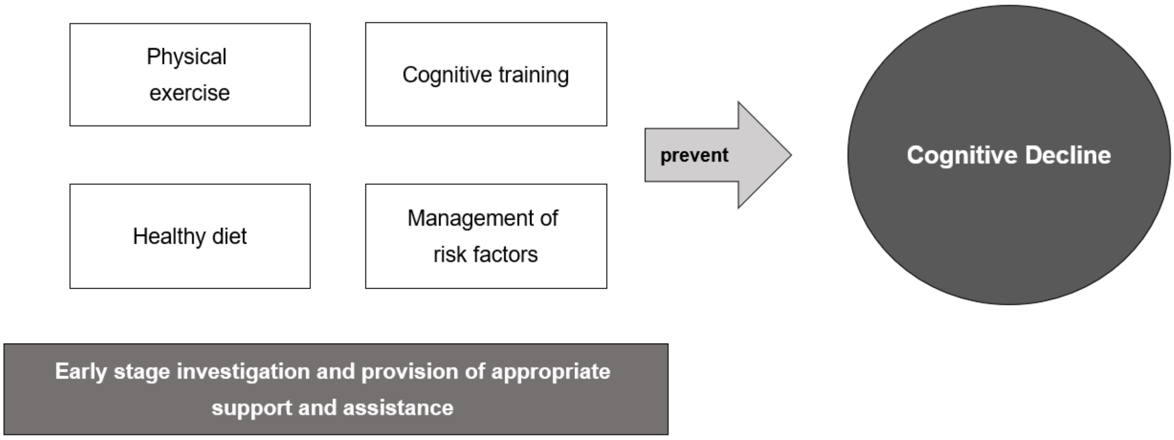

Figure 32: Recommendations for the prevention of 'cognitive decline'

6. Sarcopenia

Sarcopenia is a major health problem among older adults as it is associated with serious health consequences in terms of frailty, disability, morbidity and mortality (Tsekoura et al., 2017). The syndrome generally describes a decline in muscle mass and function occurring with advancing age and is diagnosed according to *The European Working Group on Sarcopenia in Older People (EWCSOP)* when at least two of three criteria are present (Tsekoura et al., 2017, Shafiee et al., 2017):

1. Low muscle mass
2. Low muscle strength
3. Low physical performance

This syndrome especially affects elder people, as the balance between muscle protein breakdown and -synthesis seems to be disturbed in age (Dalle et al., 2017). However, a balanced regulation is highly important in muscle protein metabolism and if not provided, this progressively increases the loss of skeletal muscle mass (Dalle et al., 2017).

Thus, according to a meta-analysis of Shafiee et al. (2017), a substantial proportion of old people is affected by sarcopenia, with a prevalence of 10% in both men and women worldwide.

Finally, regarding the development of sarcopenia, evidence suggests that it is caused by multiple factors. Thus, according to a report of Marzetti et al. (2017), several risk factors regarding sarcopenia were identified and classified into the following categories:

- Personal Factors
- Physiological Factors
- Cognitive Factors
- Psychological Factors

Here, the categorisation has slightly been changed by the author.

Furthermore, the risk factor ‘genetic characteristics’ has not been included in this report, as it is not a modifiable risk factor.

However, the factor ‘underweight’ has been added, as evidence suggests it to be a strong risk factor for sarcopenia (Lee et al., 2018, Szulc et al., 2004, Lau et al., 2005, Khongsri et al., 2016).

Finally, Figure 33 shows all categories of sarcopenia stated in this review. Here, the left figure presents the importance of the categories according to the number of risk factors, with the personal group demonstrating the most risk factors. In contrast to this, the right figure presents the importance of the categories according to the strength of the associations. Here, for each category, the risk factor with the strongest association has been elected. Thus, the personal group shows the strongest association, as well.

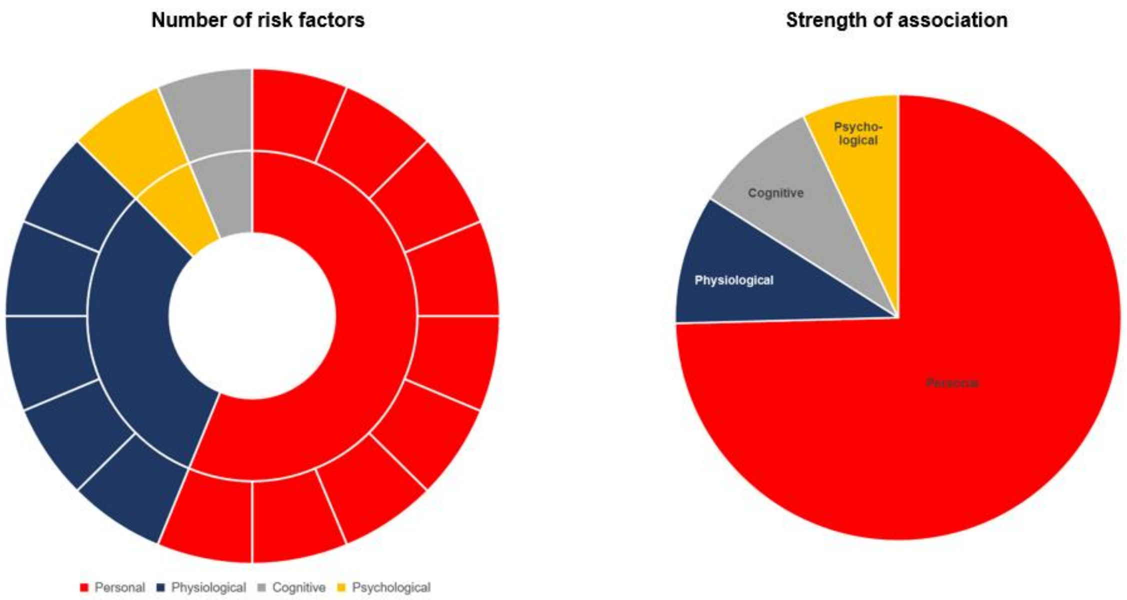

Figure 33: Categories of the target factor 'sarcopenia' according to importance

In the following, the risk factors of the target factor sarcopenia are going to be analysed in their respective categories.

6.1. Risks of ‘Sarcopenia’

6.1.1. Personal Risk Factors

Figure 34 shows all risk factors from the ‘Personal Factors’ category and their association with the target factor ‘sarcopenia’. Here, the risk factor ‘underweight’ presents the strongest association with sarcopenia.

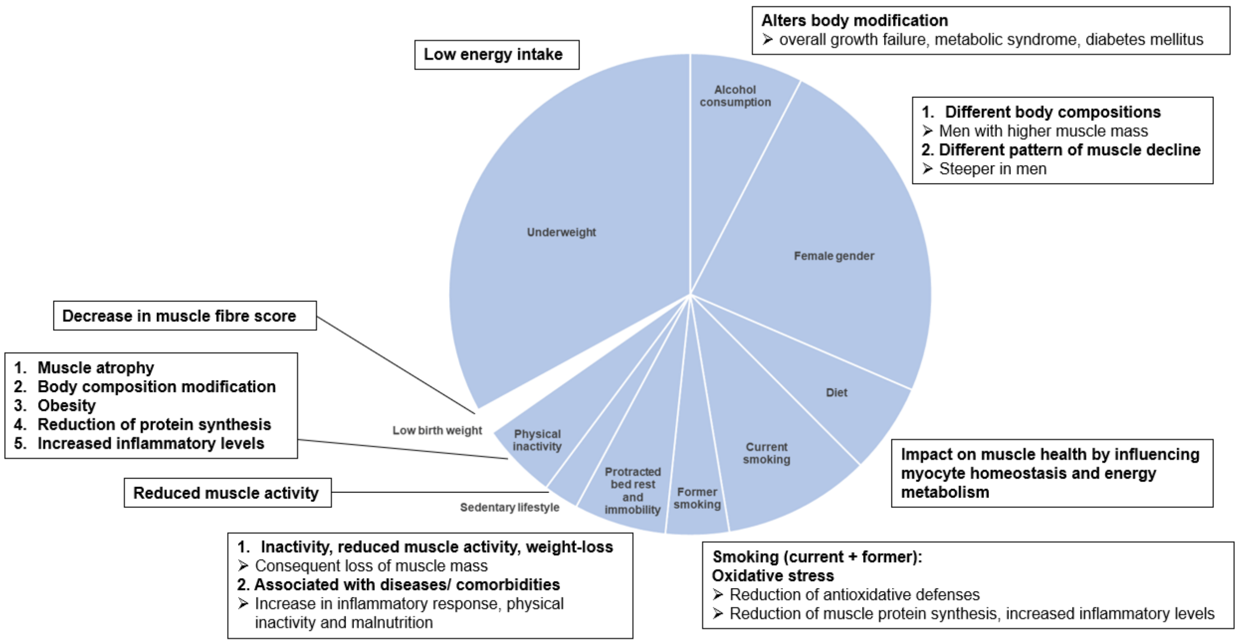

Figure 34: Personal factors: Representation of associations with the target factor ‘sarcopenia’
Study types and means of odds ratios: ‘Underweight’: OR=18.62, cross-sectional+cross-sectional; ‘Alcohol consumption’: OR=4.29, cross-sectional; ‘Female Gender’: OR=13.5, cross-sectional; ‘Diet’: OR=3.425, cross-sectional+cross-sectional; ‘Current smoking’: OR=5.57, cross-sectional+cross-sectional; ‘Former smoking’: OR=2.4, cross-sectional; ‘Protracted bed rest and immobility’: OR=3.49, cross-sectional; ‘Sedentary lifestyle’: OR=1.33; ‘Physical inactivity’: OR=2.876, cross-sectional+cross-sectional+cross-sectional; ‘Low birth weight’: no study

Alcohol consumption

Excessive alcohol consumption is common in many countries, whereby it is one of the leading causes of general disability (World Health Organization, 2019). Also, in 2012, 5.9% of all deaths worldwide (about 3.3 million) were directly attributable to harmful use of alcohol (World Health Organization, 2019). Furthermore, it is associated with an increased risk for sarcopenia (Maddalozzo et al., 2009, Kwon et al., 2017). Thus, Kwon et al. (2017) found in a cross-sectional study an association of OR=4.29 for high and OR=2.25 (95% CI: 1.06-4.77) for intermediate alcohol consumption and sarcopenia (95% CI: 1.87-9.82).

This relationship might be due to the general effects of alcohol, as it alters the whole body composition and leads to an overall growth failure which predisposes to sarcopenia (Maddalozzo et al., 2009). However those findings were observed in a trial with rats only and therefore might not be transferable to humans (Maddalozzo et al., 2009). Furthermore, alcohol consumption is also associated with the metabolic syndrome and type 2 diabetes mellitus, which increases the risk for sarcopenia, as well (see "Diabetes Mellitus") (Kwon et al., 2017).

Diet

Malnutrition in terms of decreases in energy and protein intake is generally assumed to improve the development of sarcopenia, however it is an extremely frequent issue in older adults (Marzetti et al., 2017, Limpawattana et al., 2015, Tay et al., 2015). Thus, approximately 32 to 41% of women, and 22 to 38% of men do not reach the recommended dietary allowance for protein (International Osteoporosis Foundation, 2017). Also, food intake tends to decrease with aging due to several reasons (e.g. early satiety, hormonal modifications, sensory reduction, increased inflammatory status, depression, chronic clinical conditions, higher medications use, disability, social issues) (Cesari and Pahor, 2008).

In any case, Tay et al. (2015) found in a cross-sectional study that malnutrition in general conferred significantly higher odds for sarcopenia in women, with OR=5.71 (95% CI: 1.13-28.84). Furthermore, Atkins et al. (2014) found in a cross-sectional study that low energy intake (% kcal) was associated with low midarm muscle circumference and fat-free mass, with OR=1.14 (95% CI: 0.89-1.46).

As nutrition has a great impact on muscle health by influencing myocyte homeostasis and energy metabolism, this might explain the possible risk for sarcopenia through malnutrition (Marzetti et al., 2017).

Female gender

Sarcopenia is equally prevalent in men and women with 10% (Shafiee et al., 2017). However, it is generally assumed that women show a higher risk for developing sarcopenia compared to men (Sayer et al., 2013, Tramontano et al., 2017, Cesari and Pahor, 2008). Thus, Tramontano et al. (2017) found in a cross-sectional study an association of OR=13.5 (95% CI: 1.3-108.5).

This might result from the fact that men and women have different body compositions, with men having higher levels of muscle mass (Cesari and Pahor, 2008). Therefore, due to the greater starting capacity, it takes longer to cross the threshold to clinically evident sarcopenia (Cesari and Pahor, 2008). Furthermore, men and women also show different patterns of muscle decline (Cesari and Pahor, 2008). Thus, the age-related decline in skeletal muscle might be steeper in men compared to women (Cesari and Pahor, 2008).

Low birth weight

Low birth weight is suggested to increase the risk for developing sarcopenia in later life (Patel et al., 2011, Sayer et al., 2004, Yliharsila et al., 2007, Dodds et al., 2012).

Evidence suggests that early environmental conditions can induce permanent changes in tissue structure and function that have long-term effects on human health (Patel et al., 2011). Thus, lower birth weight is associated with a significant decrease in muscle fibre score and might therefore explain the association with sarcopenia (Patel et al., 2011).

Physical inactivity

Physical inactivity, especially a lack of resistance training is associated with an increased risk for sarcopenia (Lee et al., 2007, Szulc et al., 2004, Castillo et al., 2003, Rom et al., 2012, Steffl et al., 2017, Sayer et al., 2013). Thus, Atkins et al. (2014), Martinez et al. (2015) and Tramontano et al. (2017) found in cross-sectional studies associations of OR=1.43 (95% CI: 1.15-1.76), OR=3.4 (95% CI: 1.1-10.9) and OR=3.80 (95% CI: 1.30-10.90), respectively.

This relationship might be due to several factors: First, physical inactivity can lead to muscle atrophy and thus promotes sarcopenia (Cesari and Pahor, 2008). Furthermore, it can modify the body composition or lead to obesity due to the positive energy balance (Cesari and Pahor, 2008). Lastly, it is associated with a reduced protein synthesis and increased inflammatory levels, all of which being associated with sarcopenia (see "Chronic low-grade inflammation") (Cesari and Pahor, 2008).

Sedentary lifestyle

Greater overall sitting time or prolonged activities that do not substantially increase energy expenditure above resting levels, are associated with an increased risk of sarcopenia (Gianoudis et al., 2015, Marzetti et al., 2017, International Osteoporosis Foundation, 2017). Thus, Gianoudis et al. (2015) found in a cross-sectional study that for each additional hour of sitting, the risk for sarcopenia increases by 33%, with OR=1.33 (95% CI: 1.05-1.68).

This connection might be related to reduced muscle activity which therefore predisposes to sarcopenia (Marzetti et al., 2017).

Tobacco use

Smoking is generally associated with an increased risk for sarcopenia (Lee et al., 2007, Szulc et al., 2004, Castillo et al., 2003). Thus, Jo et al. (2019) found in a cross-sectional study an association between former smoking and sarcopenia in men of OR=1.74 (95% CI: 0.66-4.57) and of OR=3.06 (95% CI: 0.71-13.14) in women. However, current smoking was only significant for men, with OR=3.34 (95% CI: 1.09-10.26).

Furthermore, Martinez et al. (2015) found an even higher association between current smoking and sarcopenia of OR=7.8 (95% CI: 1.5-39.9).

As components of cigarette smoke increase oxidative stress, this activates signalling pathways that are related to the imbalance between protein synthesis and breakdown and lead to a reduction of antioxidant defences (Cesari and Pahor, 2008, Rom et al., 2012). As a result, muscle protein synthesis is reduced and inflammatory levels are increased, leading to fibre loss and atrophy and eventually to sarcopenia (Rom et al., 2012, Cesari and Pahor, 2008).

Protracted bed rest and immobility

Evidence suggests that protracted bed rest and resulting immobility increase the risk for sarcopenia (Rom et al., 2012).

According to a study of Dutra et al. (2015), hospital admission during the previous 12 months was associated with an increased risk for sarcopenia, with OR=3.49 (95% CI: 1.37-8.89).

This results of the fact that a protracted bed rest leads to inactivity, reduced muscle activity and weight loss and therefore to the consequent loss of muscle mass (Sayer et al., 2013, Dutra et al., 2015, Marzetti et al., 2017). Furthermore, hospitalisation usually is associated with diseases and comorbidities, which can trigger sarcopenia through the increase in inflammatory response, physical inactivity and malnutrition (Martinez et al., 2015).

Underweight

Underweight is associated with an increased risk for sarcopenia (Lee et al., 2007, Szulc et al., 2004). Thus, Khongsri et al. (2016) found in a cross-sectional study that low BMI (<18.5 kg/m2) is associated with sarcopenia, with OR=12.84 (95% CI: 3.85-42.82). Furthermore, Lau et al. (2005) found an even higher association with OR=39.1 (95% CI: 11.3-134.6) in men and OR=9.7 (95% CI: 2.8-33.8) in women.

This relationship might be due to the fact that underweight generally establishes through low energy intake, which is, according to Atkins et al. (2014), a risk factor for sarcopenia (see “Diet”).

6.1.2. Physiological Factors

Figure 35 shows all risk factors from the 'Physiological Factors' category and their association with the target factor 'sarcopenia'. Here, the risk factor 'Diabetes Mellitus' presents the strongest association with sarcopenia.

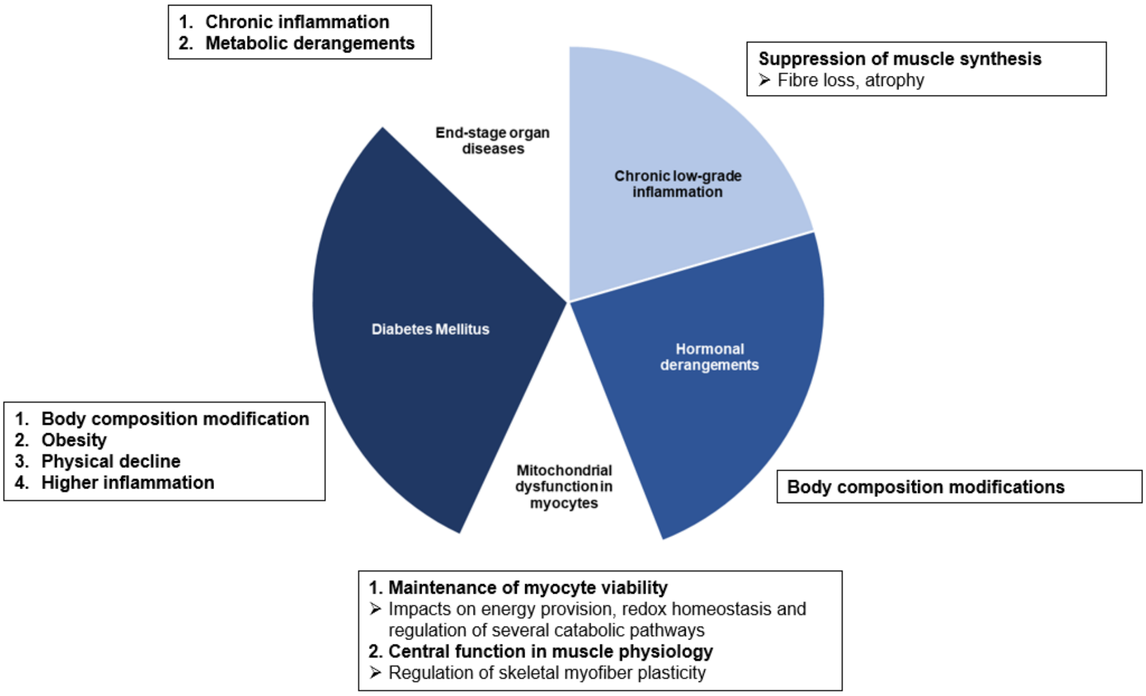

Figure 35: Physiological Factors: Representation of associations with the target factor 'sarcopenia'
Study types and means of odds ratios: 'Diabetes Mellitus': OR=2.3475, systematic review+cross-sectional; 'End-stage organ diseases': no study; 'Chronic low-grade inflammation': OR=1.593, cross-sectional+cross-sectional; 'Hormonal derangements': OR=1.8296, cohort; 'Mitochondrial dysfunction in myocytes': no study

Chronic low-grade inflammation

Increased inflammatory activity, as measured by C-reactive Protein (CRP) , fibrinogen or cytokines such as interlukin-6 (IL-6) and tumor necrosis factor- (TNF-), is associated with an increased risk for the development of sarcopenia (Atkins et al., 2014, Dalle et al., 2017, Rom et al., 2012, Rong et al., 2018, Limpawattana et al., 2015). Thus, Atkins et al. (2014) found in a cross-sectional study an association between sarcopenia and the inflammatory markers CRP and fibrinogen, with OR=1.94 (95% CI: 1.48-2.54) and OR=1.52 (95% CI: 1.17-1.96), respectively, however not for IL-6.

Nevertheless, Rong et al. (2018) found in a cross-sectional study an association between IL-6 and sarcopenia of OR=1.32 (95% CI: 1.07-1.55).

Inflammation has direct and indirect detrimental effects on skeletal muscle quality and quantity, as it impacts muscle protein catabolism and thus suppresses muscle synthesis, leading to fibre loss and atrophy (Bano et al., 2017, Dalle et al., 2017, Cesari and Pahor, 2008, Rom et al., 2012).

Hormonal derangements

Derangements of several hormonal pathways (e.g. testosterone, oestrogens, growth hormone (GH), insulin-like growth factor-1 (IGF-1)) are associated with an increased risk for sarcopenia (Rom et al., 2012, Morley, 2017, Limpawattana et al., 2015).

As hormones play a role in the development of muscle mass and in the regulation of muscle strength, changes can lead to body composition modifications and thus, predispose to sarcopenia (Morley, 2017, Cesari and Pahor, 2008).

Serum testosterone levels generally decline at a rate of about 1% per year from the age of 30-40 years in healthy men (Vitale et al., 2016). However, especially a decline of the free fraction of testosterone is associated with an increased risk of muscle loss (Renoud et al., 2014, Vitale et al., 2016, Szulc et al., 2004). Thus, Yuki et al. (2019) found in a cohort study an association of sarcopenia and free testosterone of OR=1.8296 (95% CI: 1.0391-3.2215).

This might result from the fact that testosterone is the main physiological anabolic hormone able to increase protein synthesis in skeletal muscle and to promote muscle regeneration via satellite cell activation (Vitale et al., 2016).

Furthermore, menopause is associated with a reduction in oestrogen levels (Vitale et al., 2016). However, such a decline increases the risk of sarcopenia, as well (Vitale et al., 2016). As oestrogen influences muscle strength and mitigates inflammatory responses and post-injury disruption in skeletal muscle through satellite cell activation and proliferation, with low levels this beneficial effect is not given and might therefore predispose to sarcopenia (Vitale et al., 2016)

Moreover, low serum IGF-1 is associated with an increased risk of sarcopenia as it leads to an anabolic resistance, causing a blunting of the response of muscle protein synthesis (Tay et al., 2015, Ryall et al., 2008, Limpawattana et al., 2015).

Finally, GH begins to progressively decline at the age of forty and thus, predisposes to sarcopenia, as it usually stimulates bone and muscle anabolism (Roubenoff and Hughes, 2000, Ryall et al., 2008, Borba et al., 2019).

Diabetes Mellitus

The population of older adults with diabetes mellitus is rapidly growing worldwide which is especially due to the prevalence of diabetes mellitus type 2 (T2DM), accounting for 90%-95% of diabetes cases (Strain et al., 2018, Cannon et al., 2018). T2DM is defined by relative insulin deficiency, peripheral insulin resistance, and high blood glucose levels, and therefore leads to an insufficient insulin secretion which is necessary to compensate for insulin resistance (Cannon et al., 2018).

Furthermore, diabetes mellitus is associated with an increased risk of sarcopenia (Cesari and Pahor, 2008). Thus, in a cross-sectional study of Kim et al. (2010) patients with diabetes mellitus had a threefold higher risk of sarcopenia, with OR=3.06 (95% CI: 1.42-6.62). Furthermore, Veronese et al. (2019) found in a systematic review an association of OR=1.635 (95% CI: 1.204-2.220).

This relationship might be due to several factors: First, the disease is associated with higher inflammation and physical decline, each predisposing to sarcopenia (Cesari and Pahor, 2008). Moreover, the body composition is modified in terms of lower appendicular lean mass and higher truncal and hepatic fat mass, leading to obesity and therefore to sarcopenia, as well (Cesari and Pahor, 2008).

End-stage organ diseases

Advanced organ failure of heart, lung, liver, kidney or brain is associated with an increased risk for sarcopenia (Marzetti et al., 2017, Cruz-Jentoft et al., 2010).

As it generally is a long-lasting health condition, it promotes the development of sarcopenia through chronic inflammation and metabolic derangements due to decreased levels of physical activity (Marzetti et al., 2017, Cesari and Pahor, 2008).

Mitochondrial dysfunction in myocytes

Mitochondria possess a central position in the maintenance of myocyte viability due to their functions in the context of energy provision, redox homeostasis and regulation of several catabolic pathways (Marzetti et al., 2013). Furthermore, they are involved in the regulation of skeletal myofiber plasticity and therefore have a central function in muscle physiology (Marzetti et al., 2013). Thus, if such function is impaired, this can lead to the development of sarcopenia (Marzetti et al., 2013, Rom et al., 2012).

6.1.3. Cognitive Factors

Cognitive impairment

Cognitive impairment is common among older people and refers to a decline in intellectual functions (e.g. thinking, remembering, reasoning and planning) (Robertson et al., 2013). However, the effects range widely between mild forms of forgetfulness to debilitating dementia (Robertson et al., 2013).

Having a cognitive impairment is assumed to increase the risk of sarcopenia (Chang et al., 2016). Thus, Chang et al. (2016) found in a meta-analysis an association of OR=2.246 (95% CI: 1.210-4.168).

This relationship might be due to the fact that both, sarcopenia and cognitive decline, share a similar aetiology (Chang et al., 2016). Thus, oxidative stress, inflammation, cardiovascular factors and insulin resistance (diabetes mellitus) are also associated with cognitive impairment (Chang et al., 2016).

Figure 36 shows the 'Cognitive Factors' category and its association with the target factor 'sarcopenia'.

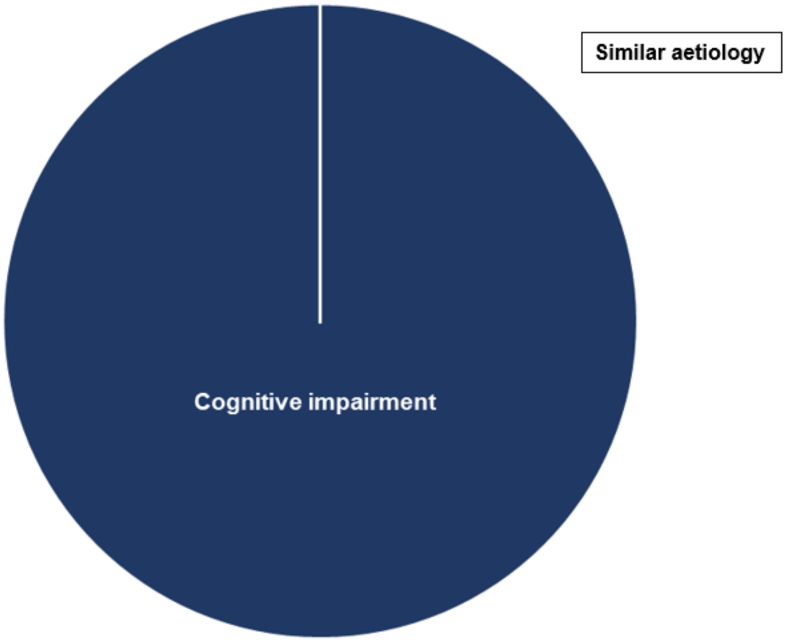

Figure 36: Cognitive Factors: Representation of associations with the target factor 'sarcopenia'
Study types and mean of odds ratios: OR=2.246, systematic review

6.1.4. Psychological Factors

Mood disturbances

Depression, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration, is one of the most frequent mood disorders in later life, with a prevalence of 10% to 20% in over 65 year olds (Wang et al., 2018, Barua et al., 2011). However, it is associated with an increased risk of sarcopenia (Confortin et al., 2018, Wang et al., 2018, Chang et al., 2017).Thus, Confortin et al. (2018) found in a cohort study an association between sarcopenia and depressive symptoms (history or present) in women, with OR=1.38 (0.60-3.17) and men, with OR=1.01 (0.25-4.05). Similar results were reported by Wang et al. (2018) in a cross-sectional study, with OR=2.23 (95% CI: 1.06-4.92) and by Chang et al. (2017) in a meta-analysis, with OR=1.821 (95% CI: 1.160-2.859).

As individuals with depressive moods are likely to be physically inactive, this might predispose to sarcopenia (see "Physical inactivity") (Chang et al., 2017). Furthermore, both conditions share similar risk factors, like upregulation of inflammatory cytokines and dysregulation of hormones and might therefore increase the development of each other (see "Chronic low-grade inflammation", "Hormonal derangements") (Chang et al., 2017).

Figure 37 shows the 'Psychological Factors' category and its association with the target factor 'sarcopenia'.

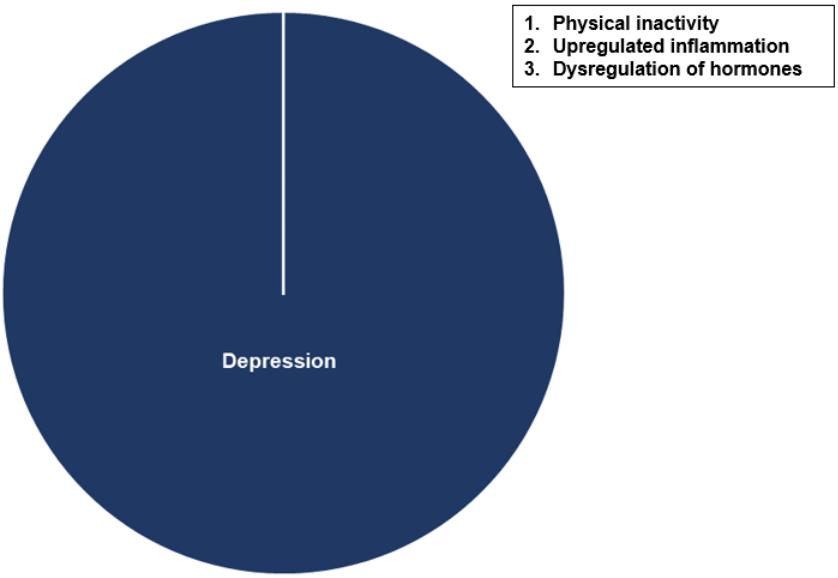

Figure 37: Psychological Factors: Representation of associations with the target factor 'sarcopenia'
Study types and mean of odds ratios: OR=1.7486, systematic review+cohort+cross-sectional

6.2. Consequences of 'Sarcopenia'

Sarcopenia is a major clinical problem concerning the health of older people, with a range of adverse outcomes (see Figure 38) such as (physical) disability, poor quality of life, functional decline and increased risk of death (Shafiee et al., 2017, Mohanty and Sahoo, 2016, Tsekoura et al., 2017, Beaudart et al., 2017).

Furthermore, it is associated with a decreased function of lower limbs, mobility limitations and falls and fall-related injuries (Mohanty and Sahoo, 2016, Tsekoura et al., 2017, Senior et al., 2015, Beaudart et al., 2017, Marzetti et al., 2017). Consequently, it can also lead to hospitalisation and a loss of independence, where assistance with daily living activities may be required (Senior et al., 2015, Szulc et al., 2004, Gianoudis et al., 2015, Beaudart et al., 2017, Marzetti et al., 2017).

Moreover, sarcopenia has severe metabolic effects, such as reduced metabolic rate due to lower muscle mass or physical inactivity, leading to a range of chronic diseases (Cesari and Pahor, 2008): Increased insulin-resistance and diabetes mellitus, dyslipidaemia, hypertension, obesity and osteoporosis (Sayer et al., 2013, Gianoudis et al., 2015, Cesari and Pahor, 2008, Marzetti et al., 2017).

Finally, sarcopenia is also related to an increased risk for frailty, as both conditions share many common points and sarcopenia is even included in the (physical) definition of frailty (Marzetti et al., 2017, Morley et al., 2002, Cruz-Jentoft and Michel, 2013).

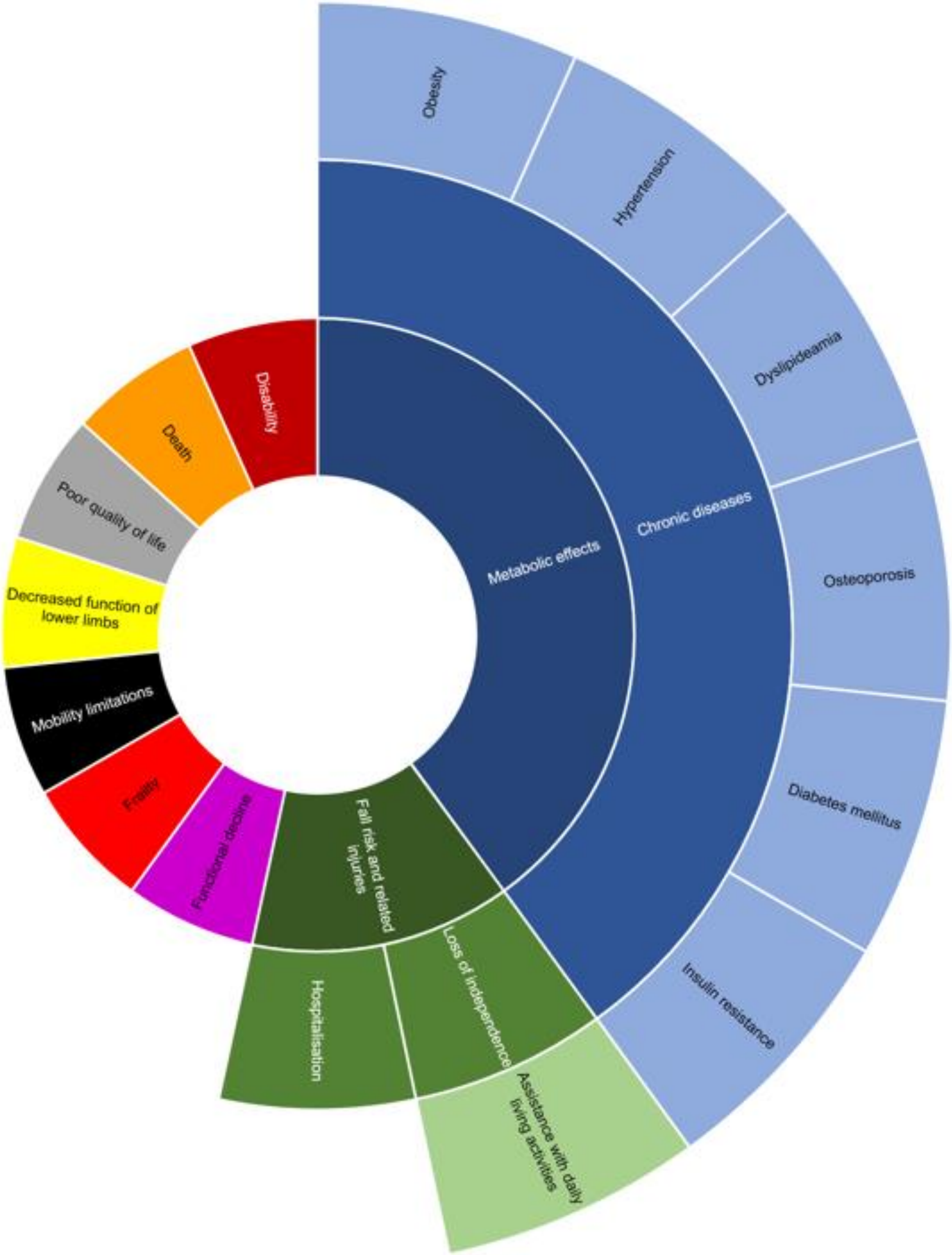

Figure 38: Consequences of the target factor 'sarcopenia'

6.3. Recommendations for the Prevention of ‘Sarcopenia’

Physical activity is one of the most important intervention methods for the prevention of sarcopenia (Atkins et al., 2014, Marzetti et al., 2017). Thus, it is generally assumed to have positive effects on metabolic and cardiovascular outcomes and oncologic diseases (Marzetti et al., 2017). Here, especially resistance exercise training increases muscle strength and mass and improves protein accretion in skeletal muscles; but also aerobic exercise training has positive effects through its influence on insulin sensitivity (Marzetti et al., 2017, Landi et al., 2014). In any case, according to a meta-analysis of Steffl et al. (2017), physical activity reduces the odds of acquiring sarcopenia in later life, with OR=0.45 (95% CI: 0.37-0.55).

Furthermore, interventions regarding the correction of nutritional deficits is important for the prevention of sarcopenia, as well (Marzetti et al., 2017, Bloom et al., 2018). Thus, according to a systematic review of Bloom et al. (2018), “healthy” diets, indicating a conformity to dietary recommendations, are suggested to lower the risk for sarcopenia. Also, Atkins et al. (2014) found in a cross-sectional study that a high percentage energy intake from carbohydrates is associated with decreased odds of low muscle mass. This coincides with the *World Health Organization’s* dietary recommendations of a low-fat high-carbohydrate diet, with 55-75% energy from carbohydrates (World Health Organization, 2003).

Moreover, the consumption of dairy products by older people may reduce the risk of sarcopenia, as well, by improving skeletal muscle mass through the addition of nutrient-rich dairy proteins (Cuesta-Triana et al., 2019).

Finally, the prevention of insulin resistance and reduction of inflammation and endothelial dysfunction might reduce the risk of low muscle mass, as well (Atkins et al., 2014).

Figure 39 shows all recommendations for the prevention of the target factor ‘sarcopenia’.

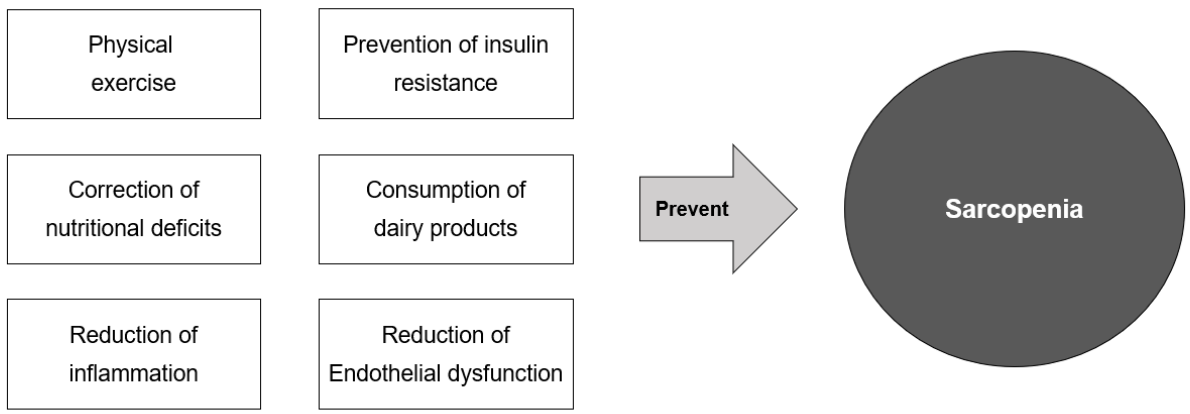

Figure 39: Recommendations for the prevention of ‘sarcopenia’

7. Social Isolation

According to Dury (2014), the term ‘social isolation’ is defined as “an individual lacking a sense of belonging, social engagement and quality relationships with others”. ‘Loneliness’ however, as a result, is thought to be subjective and defined as “involving feelings of loss of companionship” (Dury, 2014).

In any case, elder people are particularly vulnerable to both conditions, which is assumed to carry a potential health risk in itself (Dury, 2014, Pitkala et al., 2009, Malcolm et al., 2019, Courtin and Knapp, 2017). Thus, it is associated with a poor quality of life, cognitive decline, poor subjective health, disability, increased use of health and social services and increased mortality among older individuals (Pitkala et al., 2009, Malcolm et al., 2019, Courtin and Knapp, 2017).

However, social isolation and loneliness are especially problematic in old age due to decreasing economic and social resources, functional limitations, facing the death of relatives and spouses and possible changes in family structures and mobility (Courtin and Knapp, 2017).

Furthermore, according to Victor et al. (2000), older people might experience social isolation in four ways:

1. In comparison to their contemporaries (peer-group isolation)
2. By comparison with younger people (generation-contrasted isolation)
3. In comparison with themselves at a younger age group (age-related isolation)
4. In comparison with older people from preceding generations (preceding cohort isolation)

Here, especially the extent of a person’s network is implicitly seen as indicative of social isolation (Victor et al., 2000). Thus, the network of an older person is generally assumed to range between five to seven, as compared with 20+ for younger age groups, and is predominantly made up of family and relatives (Victor et al., 2000).

Moreover, evidence suggests that loneliness factors in elderly increased since 1940, with 8% to 9% of older adults being affected then, and 13% in 2011 (Dury, 2014). This corresponds to an analysis of Iliffe et al. (2007), where 15% of elder people were at risk of social isolation.

Finally, regarding the development of social isolation, evidence suggests that it is caused by multiple factors. Thus, according to the *Senior Report on Risk of Social Isolation* of the United Health Foundation (2019) and a report of Iliffe et al. (2007), several risk factors regarding social isolation were identified. However, due to the low amount, they were not classified into categories.

In the following, the risk factors of the target factor social isolation are going to be analysed.

7.1. Risks of 'Social Isolation'

Figure 40 shows all risk factors and their association with the target factor 'social isolation'. Here, the risk factor 'low income' presents the strongest association with social isolation.

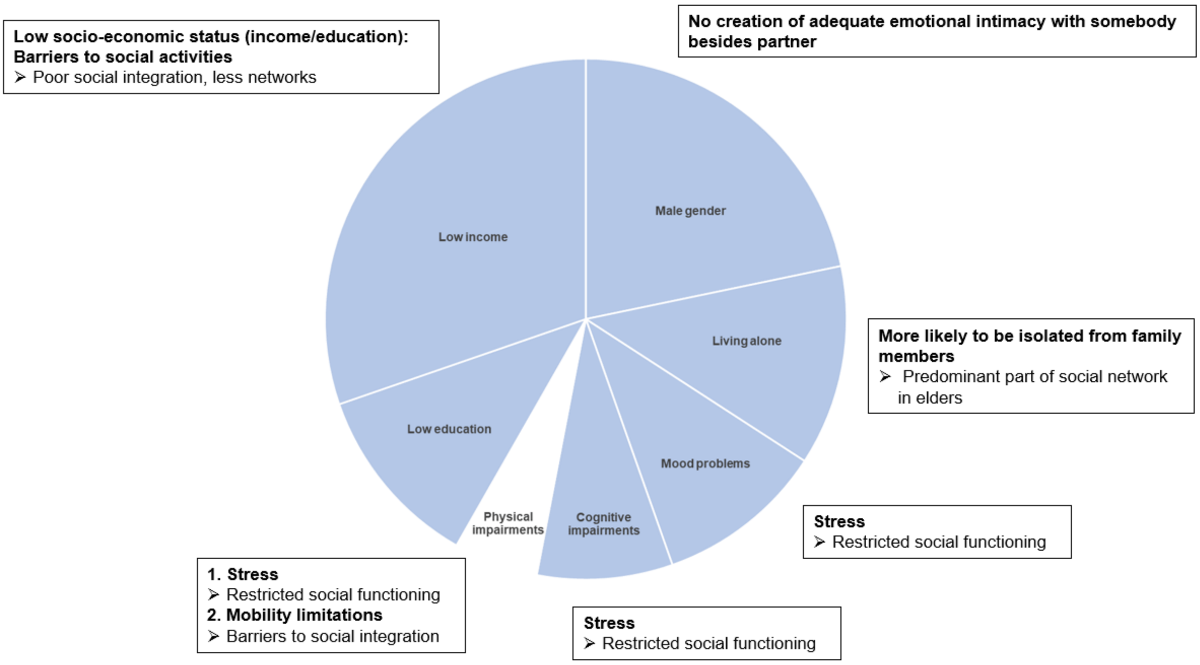

Figure 40: Risk factors: Representation of associations with the target factor 'social isolation'
Study types and means of odds ratios: 'Low income': OR=5.7725, cross-sectional+cross-sectional; 'Male gender': OR=4.14, cross-sectional; 'Living alone': OR=2.37, cross-sectional; 'Mood problems': OR=1.99, cross-sectional; 'Cognitive impairments': OR=1.6, cross-sectional; 'Physical impairments': no study; 'Low education': OR=2.18, cross-sectional

Male gender

Evidence suggests that the male gender is associated with an increased risk for social isolation, compared to being female (Iliffe et al., 2007, Vandervoort, 2012, Cudjoe et al., 2020). Thus, Iliffe et al. (2007) found in a cross-sectional study the female gender to be protective of social isolation, with OR= 0.69 (95% CI: 0.53-0.92).

Furthermore, Cudjoe et al. (2020) found in a cross-sectional study that being male is associated with severe social isolation and social isolation, with OR=4.14 (95% CI: 3.095.55) and OR=2.60 (95% CI: 2.20-3.06), respectively.

Evidence suggests that men generally get their emotional needs met by their partners, while women often turn to their female friends (Vandervoort, 2012). Thus, when being single, men tend to isolate them socially as they do not create adequate emotional intimacy with somebody else (Vandervoort, 2012).

Living alone

In 2015, 36% of women and 20% of men aged 65 and older lived alone in the United States (United Health Foundation, 2019). However, living alone is generally assumed to increase the risk for social isolation (Iliffe et al., 2007, United Health Foundation, 2019). Therefore, Iliffe et al. (2007) found in a cross-sectional study an association of OR=2.37 (95% CI: 1.81-3.10).

Still, evidence on the connection between living alone and social isolation is inconclusive (Victor et al., 2000). Thus, nearly everyone who is isolated lives alone, however, not everyone who lives alone is isolated (Victor et al., 2000). Also, living alone does not necessarily mean being lonely due to the positive aspects of such housing situation (Victor et al., 2000). Moreover, living in a larger household does not prevent from loneliness or isolation (Victor et al., 2000). Nevertheless, living with somebody else might still act protective, as evidence suggests that people, living in a single person household, are more likely to be isolated from family contact, which is important due to the fact that the social network of elders mostly constitutes of family members and relatives (Victor et al., 2000, Banks et al., 2009).

Mood impairments

Depression, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration, is one of the most frequent mood disorders in later life, with a prevalence of 10% to 20% in over 65 year olds (Wang et al., 2018, Barua et al., 2011). However, it is associated with an increased risk of social isolation (Iliffe et al., 2007). Thus, Iliffe et al. (2007) found in a cross-sectional study an association of OR=1.99 (95% CI: 1.46-2.72).

As conditions affecting mental functioning can also restrict social functioning by causing stress, this therefore might predispose to social isolation (United Health Foundation, 2019).

Cognitive impairments

Cognitive impairments are common among older people and refer to a decline in intellectual functions (e.g. thinking, remembering, reasoning and planning) (Robertson et al., 2013). However, the effects range widely between mild forms of forgetfulness to debilitating dementia (Robertson et al., 2013).

In any case, having a cognitive impairment is assumed to increase the risk of social isolation (Iliffe et al., 2007, United Health Foundation, 2019). Thus, Iliffe et al. (2007) found in a cross-sectional study an association with memory impairment of OR=1.60 (95% CI: 1.11-2.32).

Cognitive impairments can cause stress and lead to a restriction of social functioning. However, such conditions generally require a special need for social, emotional and physical support, which, if not given, leads to even more perceived loneliness (United Health Foundation, 2019).

Physical impairments

Having a physical impairment is generally associated with an increased risk for social isolation (United Health Foundation, 2019, Pitkala et al., 2009).

This might be due to the fact that such conditions are generally associated with higher levels of stress and restricted social functioning (United Health Foundation, 2019). Also, physical impairments that limit mobility can bring out barriers to social integration, resulting in fewer social contacts and greater feelings of loneliness (United Health Foundation, 2019).

Low socio-economic status

Having a low income or education is assumed to increase the risk for social isolation (United Health Foundation, 2019, Cudjoe et al., 2020, Gouda and Okamoto, 2012). Thus, according to two cross-sectional studies of Gouda and Okamoto (2012), low income was associated with social isolation, with OR=9.33 (95% CI: 1.66-52.39) in 2007 and OR=9.56 (95% CI: 1.02-89.83) in 2010.

Furthermore, Cudjoe et al. (2020) found in a cross-sectional study that low education was associated with severe social isolation and isolation, with OR=2.18 (95% CI: 1.40-3.40) and OR=2.15 (95% CI: 1.71-2.70), respectively. Moreover, lower income showed similar associations, with OR=2.10 (95% CI: 1.08-4.07) and OR=1.79 (95% CI: 1.39-2.31) for severe and normal social isolation (Cudjoe et al., 2020).

As socio-economic constraints can present barriers to social activities and thus, lead to poor social integration and less networks, this might be the reason for the increased risk (United Health Foundation, 2019).

7.2. Consequences of 'Social Isolation'

Being socially isolated or being lonely is associated with a range of adverse outcomes, such as impaired health, poor quality of life, disability and mortality, as visible in Figure 41 (Pitkala et al., 2009, Pitkala 2003, Holt-Lunstad et al., 2015).

Furthermore, it has an adverse impact on mental health, including outcomes such as depression, anxiety and schizophrenia and thus, often leads to suicide (Malcolm et al., 2019). Also, it predisposes to cognitive decline and dementia (Pitkala 2003, Pitkala et al., 2009, Malcolm et al., 2019).

Moreover, it is linked to physical diseases, such as cancer, infectious diseases or cardiovascular conditions, like coronary heart disease, stroke or hypertension (Malcolm et al., 2019, Hawkley et al., 2010, Holt-Lunstad and Smith, 2016). Long-term social isolation is even suggested to be associated with frailty (Strawbridge et al., 1998).

Finally, social isolation also leads to an increased use of health and social services among older individuals and predisposes to a greater need for institutional care or nursing home admission (Pitkala 2003, Pitkala et al., 2009).

Figure 41: Consequences of the target factor 'social isolation'

7.3. Recommendations for the Prevention of 'Social Isolation'

In their *Social Determinants of Health* document, the World Health Organization (2011) highlights the positive effects of social support networks in the promotion and maintenance of good health in the individual.

Evidence suggests that educational or focused social activities, such as interest groups that encourage individuals to increase their participation in activities and also involve them in the planning and delivery of the activities, appeared to be effective for the prevention or reduction of social isolation (Dury, 2014, Cattan et al., 2005).

Furthermore, the so called 'Mentoring' and 'Befriending' models, aiming to support socially isolated persons, have been explored in several government-lead research projects and have shown to be effective for the prevention or reduction of social isolation (Dury, 2014, Gardiner et al., 2018).

First, the 'Mentoring' model seeks to form a relationship between a volunteer and an individual on a short-term basis in order to support the individual in agreed positive life changes (Dury, 2014).

Second, in the 'Befriending' model, so called 'befrienders' visit elder people in their homes and provide a range of services, including transport provision, medication delivery and shopping (Dury, 2014, Gardiner et al., 2018). This is especially important for individuals who are unable to leave their homes, for example due to illness, and therefore cannot join social meetings (Dury, 2014).

Moreover, according to a review of Gardiner et al. (2018), other effective intervention strategies are:

Social facilitation interventions, describing interventions with the primary purpose of facilitating social interaction with others via group-based activities, such as charity-funded friendship clubs, shared interest topic groups, day care centres and friendship enrichment programmes

Psychological interventions, such as humour therapy, mindfulness and stress reduction interventions, reminiscence group therapy and cognitive and social support interventions

Health and social care provision, describing interventions involving support of social care professionals and the enrolment in a formal programme of care, either in a nursing home or community setting

Animal interventions, such as solitary pet interventions

Leisure or skill development interventions, such as solitary interventions involving technology, like videoconference and computer or Internet use

All in all, according to Gardiner et al. (2018), common features of successful interventions include adaptability, community participation and activities involving productive engagement.

Figure 42 shows all recommendations for the prevention of the target factor ‘social isolation’.

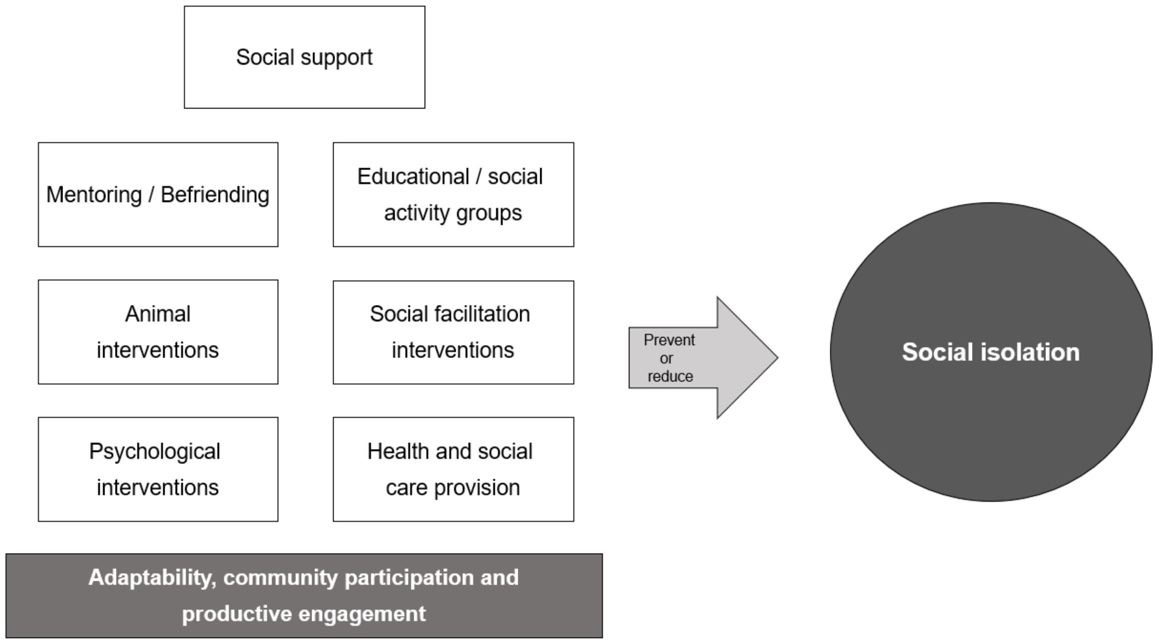

Figure 42: Recommendations for the prevention of ‘social isolation’

8. Malnutrition

Despite medical advances over the past decades, malnutrition remains a significant and highly prevalent public health problem of developed countries (Guyonnet and Rolland, 2015). Here, particularly older adults are affected, as the risk for malnutrition increases with age and level of care (Guyonnet and Rolland, 2015).

Especially protein-energy malnutrition is highly prevalent in elders, with, however, varying estimates, as methods for detection are not standardized (Guyonnet and Rolland, 2015). Nevertheless, it is generally estimated that 5% to 30% in elderly persons living at home are affected, 16% to 70% of those in institutional care and 20% to 60% of hospitalised elderly patients (Guyonnet and Rolland, 2015).

Protein-energy malnutrition is generally caused by an imbalance between the body's requirements and actual intake, causing tissue loss, especially of muscle tissue, with harmful functional consequences (Guyonnet and Rolland, 2015). Thus, malnutrition significantly increases morbidity and mortality and compromises the outcomes of other underlying conditions and diseases (Guyonnet and Rolland, 2015).

Furthermore, the term 'malnutrition' not only describes factors leading to underweight or normal weight with a shortage on vitamins or micro-nutrients, such as vitamin D or iron, but also to overweight (Leslie and Hankey, 2015).

All in all, aging is accompanied by many changes and thus leads to an increasingly diverse pattern in nutritional requirements (Leslie and Hankey, 2015). However, in most cases, malnutrition is based on insufficient food intake and less frequently on a higher need of nutrients or on a problem of malassimilation (Prell and Perner, 2018).

Finally, regarding the development of malnutrition, evidence suggests that it is caused by multiple factors (Evans, 2005). Thus, according to reports of Guyonnet and Rolland (2015) and Evans (2005), several risk factors regarding malnutrition were identified and classified into the following categories:

- Physiological Factors
- Cognitive Factors
- Psychological Factors
- Pharmacological Factors
- Social and Environmental Factors

However, the risk factors 'depression', 'anxiety' and 'dysphoria' were summarised to the risk factor 'mental disorders'. Furthermore, the risk factor 'lost ability to shop for and prepare food' is included in the factor 'impaired activities of daily living skills', as it generally is accounted to such functions. Lastly, for the same reason, the risk factor "lack of interactions with others at mealtime" is included in the factor 'isolation and loneliness".

Finally, Figure 43 shows all categories of malnutrition stated in this review. Here, the left figure presents the importance of the categories according to the number of risk factors, with the physiological group demonstrating the most risk factors. In contrast to this, the right figure presents the importance of the categories according to the strength of the associations. Here, for each category, the risk factor with the strongest association has been elected. Thus, the physiological group shows the strongest association, as well.

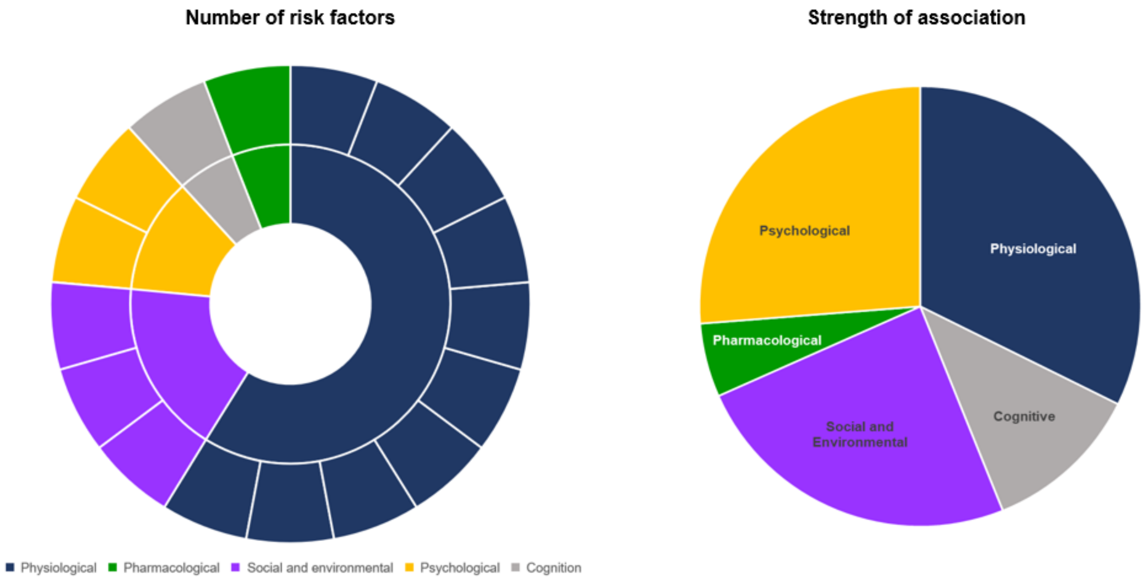

Figure 43: Categories of the target factor 'malnutrition' according to importance

In the following, the risk factors of the target factor malnutrition are going to be analysed in their respective categories.

8.1. Risks of 'Malnutrition'

8.1.1. Physiological Risk Factors

Figure 44 shows all risk factors from the 'Physiological Factors' category and their association with the target factor 'malnutrition'. Here, the risk factor 'Poor oral and dental health' presents the strongest association with malnutrition.

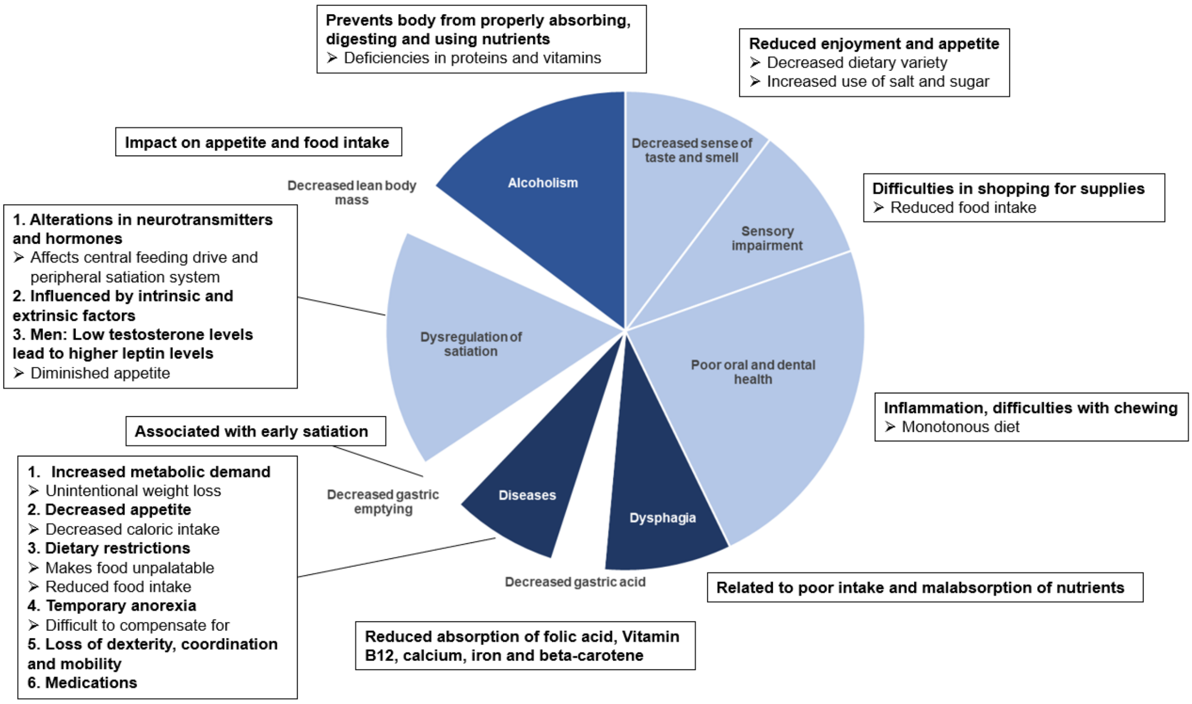

Figure 44: Physiological Factors: Representation of associations with the target factor 'malnutrition'
Study types and means of odds ratios: 'Poor oral and dental health': OR=6.54, cross-sectional; 'Dysphagia': OR=2.425, systematic review; 'Decreased gastric acid': no study; 'Diseases': OR=2.02225, systematic review+cohort+cross-sectional+cross-sectional; 'Decreased gastric emptying': no study; 'Dysregulation of satiation': OR=4.52, cross-sectional; 'Decreased lean body mass': no study; 'Alcoholism': OR=4.12, cohort+cross-sectional; 'Decreased sense of taste and smell': OR=2.9, cross-sectional; 'Sensory impairment': OR=2.61, cross-sectional+cross-sectional

Alcoholism

Excessive alcohol consumption is common in many countries, whereby it is one of the leading causes of general disability (World Health Organization, 2019). Also, in 2012, 5.9% of all deaths worldwide (about 3.3 million) were directly attributable to the harmful use of alcohol (World Health Organization, 2019). Furthermore, it is associated with an increased risk for malnutrition (Evans, 2005). Thus, Nicolas et al. (2003) found in a cohort study an association between the consumption of >1600 kg ethanol throughout life and protein malnutrition, with OR=4.2 (95% CI: 1.4-12.7). Similar findings were reported by Damayanthi et al. (2018), who found an association of OR=4.06 (95% CI: 1.17-14.07).

As alcohol and its metabolism prevent the body from properly absorbing, digesting, and using those nutrients, this can lead to deficiencies in proteins and vitamins, especially vitamin A, which might contribute to liver disease and other serious alcohol-related disorders (Lieber, 2003). Furthermore, it can also contribute to weight gain through the additional consumption of ethanol calories (De Aguiar, 2013).

Delayed gastric emptying

With ageing, there is a general decline in gastric emptying (Stanga, 2009). However, it is suggested a risk factor for malnutrition, as it is associated with weight loss and vitamin- and mineral deficiencies. (Evans, 2005, Parkman et al., 2011).

Since a decline in gastric emptying rate of large meals has been associated with early satiation, this might predispose to malnutrition (see “Dysregulated satiation”) (Stanga, 2009).

Decreased gastric acid

Changes in the aging gastrointestinal tract decrease the ability to provide the organism with adequate levels of nutrients, thus contributing to the development of malnutrition (Rémond et al., 2015). Therefore, a decline in gastric acid, which is often due to a helicobacter pylori infection or atrophic gastritis, is associated with an increased risk for malnutrition (Evans, 2005).

In any case, low levels of gastric acid are associated with a reduced absorption of folic acid, vitamin B12, calcium, iron and beta-carotene (Brownie, 2006).

Decreased lean body mass

A decline in lean body mass in terms of low muscle strength and muscle mass are especially prevalent in older hospitalized adults (Pierik et al., 2017). However, evidence suggests that a decreased lean body mass might increase the risk for malnutrition (Evans, 2005).

This relationship might be due to the fact that a loss of lean body mass is accompanied by a reduced basal metabolic rate, which might influence appetite and food intake (Evans, 2005, Brownie, 2006).

Diseases

Prevalence of acute or chronic diseases, such as congestive heart failure, chronic obstructive pulmonary disease (COPD), Parkinson’s disease, cancer and thyroid- or cardiovascular diseases, are assumed to increase the risk of malnutrition (Evans, 2005, Prell and Perner, 2018, Han et al., 2009, Brownie, 2006).

Thus, Hébuterne et al. (2014) found in a cross-sectional study an association between malnutrition and regional or metastatic cancer, with OR=1.96 (95% CI: 1.42-2.70) and OR=2.97 (95% CI: 2.14-4.12), respectively. Furthermore, Pirlich et al. (2006) found in a cohort study an association of malnutrition and general malignant disease of OR=1.509 (95% CI: 1.180-1.930).

Moreover, Parkinson’s disease was associated with malnutrition, with OR=2.450 (95% CI: 1.006-5.965) in a systematic review (Fávaro-Moreira et al., 2016).

According to a cross-sectional study of Chavarro-Carvajal et al. (2015), comorbidities in general were associated with malnutrition, with OR=1.16 (95% CI: 1.04-1.30).

As many diseases often are accompanied by an increased metabolic demand and decreased appetite and caloric intake, this can lead to unintentional weight loss and malnutrition (Evans, 2005).

Also, according to Prell and Perner (2018), acute diseases can lead to temporary anorexia resulting in loss of weight, which often cannot be compensated.

Furthermore, chronic illnesses often are treated with dietary restrictions, which can make the food unpalatable and therefore leads to a reduced intake (Evans, 2005). As a second treatment, the use of medication is often necessary, which is a risk factor in itself (see “Medications”) (Evans, 2005).

Finally, certain diseases such as cancer are associated with loss of dexterity, coordination and mobility, which leads to problems with food intake (Brownie, 2006).

Dysregulation of satiation

A dysregulated satiation is often due to alterations in neurotransmitters and hormones, affecting the central feeding drive and the peripheral satiation system (Evans, 2005). However, it is thought to increase the risk for malnutrition (Evans, 2005, Wong et al., 2019, Prell and Perner, 2018).

Thus, Wong et al. (2019) found in a cross-sectional study an association of malnutrition and bad appetite, with OR=4.52 (95% CI: 1.92-10.62).

In elderly men, general declines in testosterone levels and a reciprocal rise in leptin, reversible by testosterone administration, might contribute to diminished appetite (Stanga, 2009). Furthermore, as “appetite” is a complicated process composed of many intrinsic (perception of internal signals, e.g. sense of olfaction, taste, vision, hearing, hormones) and extrinsic factors (e.g. social and emotional problems, medications), changes in such factors can lead to a loss in appetite, as well (Stanga, 2009).

Dysphagia

Problems with swallowing, which can be a consequence of stroke, are generally associated with an increased risk for malnutrition (Evans, 2005). Thus, Foley et al. (2009) found in a systematic review an association of OR=2.425 (95% CI: 1.264-4.649).

As dysphagia is related to a poor intake and malabsorption of nutrients, this might predispose to malnutrition (Evans, 2005, Foley et al., 2009).

Poor oral and dental health

Poor oral health is common in older adults, involving tooth loss, poor oral hygiene, high prevalence of dental caries and periodontal disease, defective prosthetic appliances or absence of prosthetic rehabilitation, hyposalivation and oral lesions (Kossioni, 2018). However, oral health is important for well-being, as problems are associated with pain, infection, xerostomia, problems with chewing, swallowing, speaking, smiling, communicating, and socializing (Kossioni, 2018).

Furthermore, poor oral health and dental problems are associated with an increased risk for malnutrition (Evans, 2005, Guyonnet and Rolland, 2015, Burks et al., 2017, Prell and Perner, 2018, Brownie, 2006).

Thus, Mesas et al. (2010) found in a cross-sectional study an association between nutritional deficits and:

- Absence of posterior occlusion, with OR=2.18 (95% CI: 1.06-4.45)
- Stimulated salivary flow rate (<0.7 ml/minute), with OR=2.18 (95% CI: 1.06-4.50)
- Advanced periodontal illness, with OR=6.54 (95% CI: 2.03-21.00)
- Negative self-perception of oral health, with OR=3.41 (95% CI: 1.59-7.33)

As poor oral health and dental problems can lead to inflammation and difficulties in chewing and thus, to a monotonous diet that is poor in quality, this might increase the risk for malnutrition (Guyonnet and Rolland, 2015).

Sensory impairment

Impairments of vision or hearing are common in elder adults, but are, however associated with an increased risk for malnutrition (Guyonnet and Rolland, 2015, Brownie, 2006).

Thus, Wong et al. (2019) found in a cross-sectional study an association between malnutrition and unclear vision of OR=2.71 (95% CI: 1.68-4.35). Here, results indicate, the poorer the visual ability, the higher the odds of being malnourished. Similar findings were also reported by Muurinen et al. (2014), with OR=2.51 (95% CI: 1.80-3.51).

As poor vision reduces the functional status of older people, shopping for supplies might be difficult and thus, causing reduced food intake and malnutrition (Wong et al., 2019).

Decreased sense of taste and smell

Impairments in terms of a decreased sense of taste and smell are common in elder adults, but are, however assumed to increase the risk for malnutrition (Guyonnet and Rolland, 2015, Prell and Perner, 2018, Brownie, 2006).

Thus, Toffanello et al. (2013) found in a cross-sectional study in hospitalised elders an association of low citric acid sensitivity (which is one of the four basic tastes) and malnutrition of OR=2.9 (95% CI: 1.0-9.6).

This relationship is due to the fact that a decreased sense of taste and smell might result in reduced enjoyment of the food and less appetite, leading to a decreased dietary variety and promoting increased use of salt and sugar for compensation (Guyonnet and Rolland, 2015, Evans, 2005, Brownie, 2006).

8.1.2. Cognitive Factors

Dementia

Cognitive impairments are common among older people and refer to a decline in intellectual functions (e.g. thinking, remembering, reasoning and planning) (Robertson et al., 2013). However, the effects range widely between mild forms of forgetfulness to debilitating dementia (Robertson et al., 2013).

In any case, dementia is generally thought to increase the risk for malnutrition (Evans, 2005, Guyonnet and Rolland, 2015, Rodriguez-Tadeo et al., 2012, Meijers et al., 2014, Johansson et al., 2009). Thus, Rodriguez-Tadeo et al. (2012) and Meijers et al. (2014) found in cross-sectional studies associations of cognitive impairment and malnutrition, with OR=1.470 (95% CI: 1.076-2.009) and OR=1.462 (95% CI: 1.404-1.523), respectively. Furthermore, Johansson et al. (2015) found in a cohort study an association of OR=4.3 (95% CI: 1.8-10.0) and lastly, Fávaro-Moreira et al. (2016) found in a systematic review an association of OR=2.139 (95% CI: 1.343-3.407).

This link might result of the fact that cognitive impairments affect a person's ability to shop for food and to prepare meals (Evans, 2005). Furthermore, dementia generally is accompanied by a loss of appetite and thus, reduced food intake (Prell and Perner, 2018).

Figure 45 shows the 'Cognitive Factors' category and its association with the target factor 'malnutrition'.

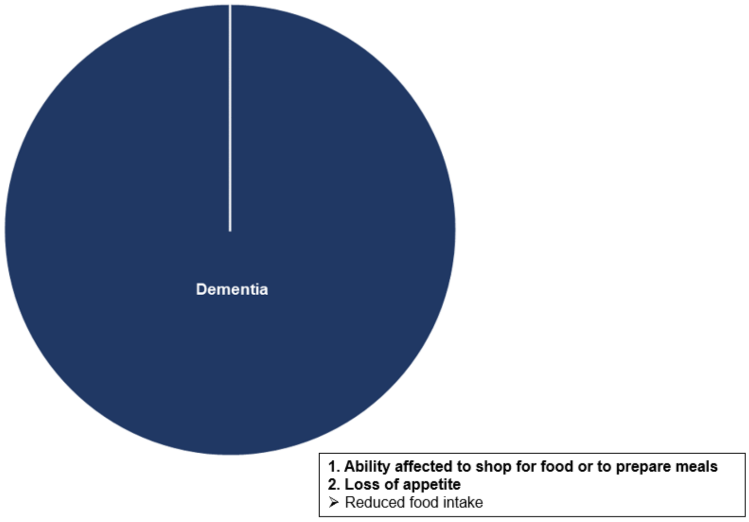

Figure 45: Cognitive Factors: Representation of associations with the target factor 'malnutrition'
Study types and mean of odds ratios: OR=2.34275, systematic review+cohort+cross-sectional+cross-sectional

8.1.3. Psychological Factors

Figure 46 shows the risk factors from the ‘Psychological Factors’ category and their association with the target factor ‘malnutrition’. Here, the risk factor ‘Mental disorders’ presents the strongest association with malnutrition.

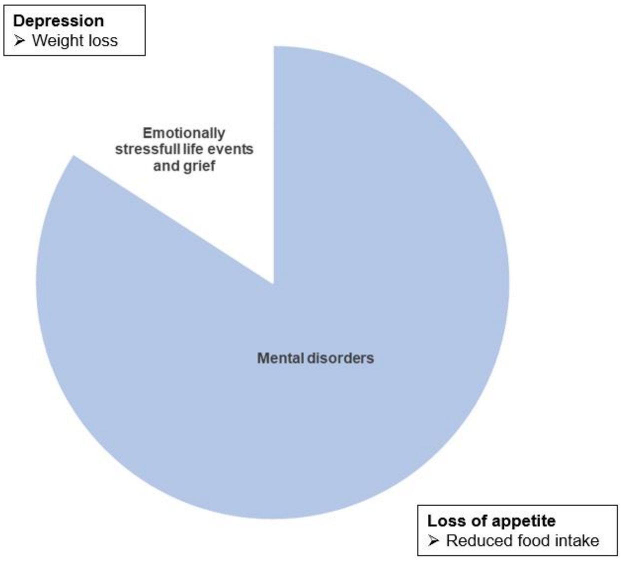

Figure 46: Psychological Factors: Representation of associations with the target factor ‘malnutrition’
Study types and means of odds ratios: ‘Mental disorders’: OR=5.3103, cross-sectional+cross-sectional+cross-sectional; ‘Emotionally stressful life events and grief’: no study

Mental disorders

Mental health problems are among the most prevalent conditions in elderly people, whereby anxiety and depression are the most frequent ones (Kvamme et al., 2011). About 8% to 18% of community-dwelling older adults experience anxiety, which is affecting physical and psychosocial functions (Painter et al., 2012). Depression, on the other hand is characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration and has a prevalence of 10% to 20% in over 65 year olds (Wang et al., 2018, Barua et al., 2011).

Furthermore, conditions, affecting mental health are associated with an increased risk for malnutrition (Guyonnet and Rolland, 2015, Evans, 2005, Rodriguez-Tadeo et al., 2012). Thus, according to a cross-sectional study of Kvamme et al. (2011), having significant mental health problems are associated with malnutrition, with OR=3.9 (95% CI: 1.7-8.6) in men and OR=2.5 (95% CI: 1.3-4.9) in women.

Furthermore, Rodriguez-Tadeo et al. (2012) found in a cross-sectional study an association of malnutrition and depression, with OR=2.936 (95% CI: 2.164-3.983). Moreover, Vafaei et al. (2013) even found an association of malnutrition and severe and mild depression of OR=15.49 (95% CI: 2.9-82.59) and OR=4.1 (95% CI: 0.80-20.93, respectively

This link might result from the fact that depression or problems with mental health generally are accompanied by a loss of appetite or nausea and thus, lead to reduced food intake (Prell and Perner, 2018, Brownie, 2006).

Emotionally stressful life events and grief

Late life can be a time of multiple losses and changes due to the death of friends or family or changes through retirement or disability (Evans, 2005). In any case, such stressful life events or resulting grief due to bereavement are related to an increased risk for malnutrition (Evans, 2005, Brownie, 2006).

As changes or bereavement often are accompanied with depression, this puts the individual at an increased risk for weight loss (see “Depression”) (Evans, 2005).

8.1.4. Pharmacological Factors

Medication

Approximately 40% of older people take more than five prescription medications (Park et al., 2015). Especially, antihypertensive agents are commonly used to treat hypertension in the elderly and are the most widely prescribed medications for this age group (Butt et al., 2013). This includes for example diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers and beta-adrenergic blockers (Butt et al., 2013).

However, evidence suggests the use of such drugs increases the risk for malnutrition (Evans, 2005, Brownie, 2006). Also, dopamine agonists, antidepressants, antibiotics and antihistamines are thought to have predisposing effects (Evans, 2005).

Thus, Pirlich et al. (2006) found in a cohort study an association between malnutrition and polypharmacy, with OR=1.096 (95% CI: 1.060-1.134) for each additional drug. However, this finding was not significant.

As drugs often are accompanied by side effects (e.g. anorexia, nausea and altered taste perception) and alter nutrient absorption, metabolism and excretion, this predisposes to malnutrition (Evans, 2005, Brownie, 2006).

Figure 47 shows the 'Pharmacological Factors' category and its association with the target factor 'malnutrition'.

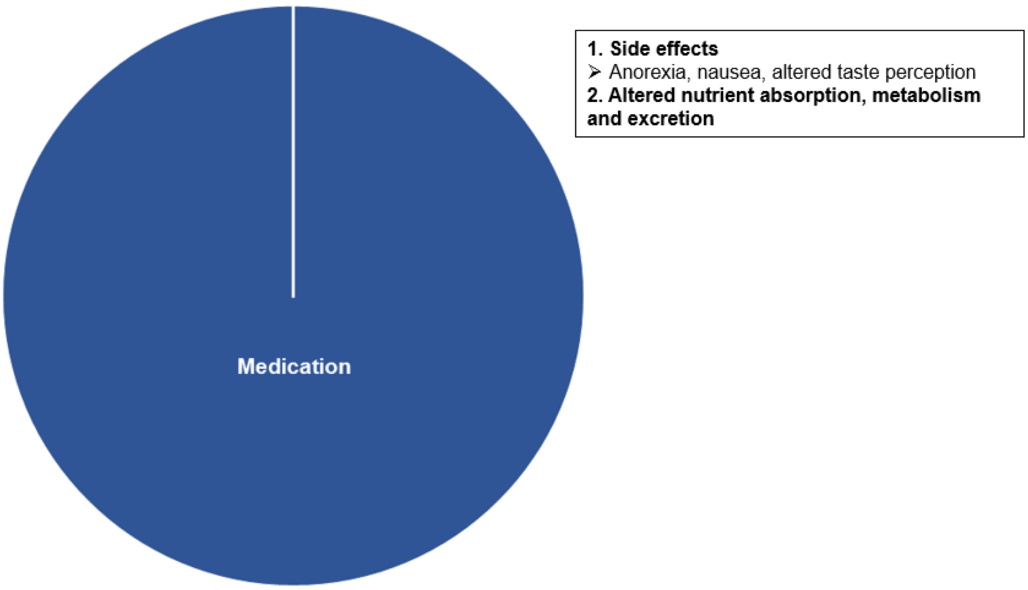

Figure 47: Pharmacological Factors: Representation of associations with the target factor 'malnutrition'
Study types and mean of odds ratios: OR=1.096, cohort

8.1.5. Social and Environmental Factors

Figure 48 shows the risk factors from the 'Social and Environmental Factors' category and their association with the target factor 'malnutrition'. Here, the risk factor 'Low socio-economic status' presents the strongest association with malnutrition.

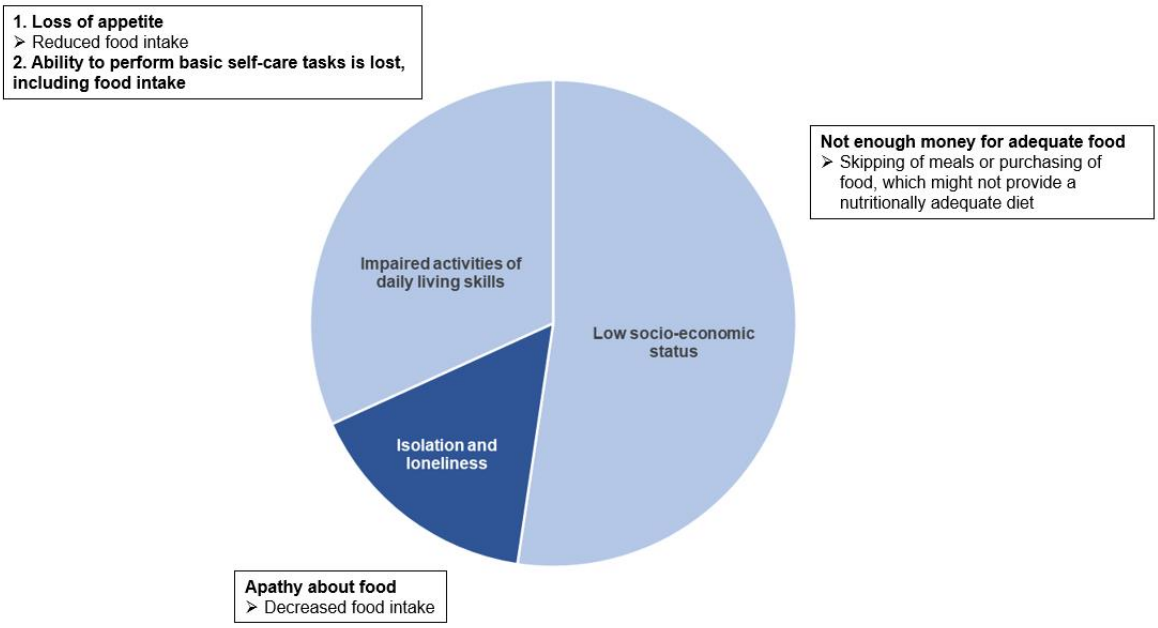

Figure 48: Social and Environmental Factors: Representation of associations with the target factor 'malnutrition' Study types and means of odds ratios: 'Low socio-economic status': OR=4.945, cross-sectional; 'Isolation and loneliness': OR=1.4975, cohort+cross-sectional; 'Impaired activities of daily living skills': OR=3.002, cross-sectional

Impaired activities of daily living skills

Older adults with low scores in both basic and instrumental daily living activity are assumed to confer a higher risk for malnutrition (Rodriguez-Tadeo et al., 2012, Evans, 2005, Agarwalla et al., 2015, Han et al., 2009).

Thus, Rodriguez-Tadeo et al. (2012) found in a cross-sectional study an association of malnutrition and impaired functional ability, with OR=3.002 (95% CI: 2.028-4.445).

As the functional status determines the ability to perform basic self-care tasks and live independently, which also includes food intake, such impairments can predispose to malnutrition (Agarwalla et al., 2015). Furthermore, functional impairments in activities are generally accompanied with a loss of appetite and thus, lead to a reduced food intake, as well (Prell and Perner, 2018).

Isolation and loneliness

Elder people are especially vulnerable to social isolation or a feeling of loneliness compared to younger adults (Dury, 2014). However, it is assumed to increase the risk for malnutrition (Evans, 2005, Prell and Perner, 2018, Brownie, 2006).

Thus, Boulos et al. (2016) found in a cross-sectional study an association between malnutrition and social isolation and loneliness of OR=1.58 (95% CI: 1.11-2.25) and OR=1.15 (95% CI: 1.02-1.30), respectively.

Similar findings were also reported by Eskelinen et al. (2016), who found an association between malnutrition and frequent feelings of loneliness, with OR=1.63 (95% CI: 1.09-2.45).

Inadequate social support networks and resulting social isolation is commonly thought to lead to apathy about food and therefore decreased intake and malnutrition (Evans, 2005).

Low socio-economic status

Evidence suggests that a low socio-economic status, especially in terms of low income is associated with an increased risk for malnutrition (Evans, 2005, Han et al., 2009, Brownie, 2006). Thus, Mathew et al. (2016) found in a cross-sectional study an association of OR=4.945 (95% CI: 1.194-11.144).

As finances often have to be used predominantly for housing or medical expenses, sometimes not enough money is left for adequate food, leading to skipping of meals or purchasing of food, which might not provide a nutritionally adequate diet (Evans, 2005).

8.2. Consequences of 'Malnutrition'

Malnutrition is generally associated with a range of adverse outcomes, such as increased morbidity and mortality, as visible in Figure 49, and is assumed to generally compromise the outcomes of other underlying conditions and diseases (Guyonnet and Rolland, 2015).

Elder people are especially vulnerable to protein-energy malnutrition and its consequences (Guyonnet and Rolland, 2015). Therefore, prolonged length of stay in hospital, admission to higher level care, decreased physical function, poorer quality of life and increased risk of life-threatening complications are important problems due to malnutrition (Guyonnet and Rolland, 2015). Also, pressure ulcers are twice as likely to develop in malnourished hospital patients compared to well-nourished patients, and the risk of surgical site infections is three times higher (Guyonnet and Rolland, 2015).

Furthermore, sarcopenia and frailty account to the consequences of malnutrition, as well (Esquivel, 2017). Here, the prevalence of such chronic conditions contributes to fall risk and dependency (Leslie and Hankey, 2015, Esquivel, 2017, Guyonnet and Rolland, 2015).

Further consequences of malnutrition include: Vulnerability to infection, loss of energy and mobility, poor wound healing, progressive decline in health, reduced cognitive functioning and confusion (Leslie and Hankey, 2015, Evans, 2005).

Lastly, due to the high amount of consequences, malnourished elders often require health and social services and have higher hospitalisation- and premature institutionalisation rates (Guyonnet and Rolland, 2015, Pichard et al., 2004, Evans, 2005).

Figure 49: Consequences of the target factor 'malnutrition'

8.3. Recommendations for the Prevention of ‘Malnutrition’

According to Prell and Perner (2018), the prevention and treatment of malnutrition depends on its aetiology. Thus, a divers pattern of interventions is required, such as correction of environmental and pharmacological risk factors, treatment of underlying medical causes and diseases or energy supplementation (Prell and Perner, 2018).

Furthermore, for the prevention of malnutrition, early detection is highly important, as this leads to earlier intervention with improved outcomes and a better quality of life (Guyonnet and Rolland, 2015). Also, the use of an appropriate and validated nutritional screening tool is necessary for the identification of etiologic factors, as it otherwise can negatively influence the patient care and risks misdiagnosis (or missed diagnosis) of nutrition-related problems (Guyonnet and Rolland, 2015).

The following tools are valid malnutrition screening tools for the identification of nutritional risks (Guyonnet and Rolland, 2015):

- Mini Nutritional Assessment (MNA)
- Malnutrition Screening Tool (MST)
- Malnutrition University Screening Tool (MUST)
- Nutritional Risk Screening 2002 (NRS 2002)
- Subjective Global Assessment (SGA)
- Simplified Nutritional Assessment Questionnaire (SNAQ)

Furthermore, for elders with protein-energy malnutrition or those at nutritional risk, oral nutritional supplements and dietary counselling are generally recommended, as it can increase dietary intake and improve quality of life (Guyonnet and Rolland, 2015).

All in all, evidence suggests, that early identification and appropriate nutrition support might even help to reverse or halt the malnutrition trajectory and the negative outcomes associated with poor nutritional status (Guyonnet and Rolland, 2015). Evans (2005) even highlights the need of nutritional assessment and treatment being a routine part of care for older adults.

Figure 50 shows all recommendations for the prevention of the target factor ‘malnutrition’.

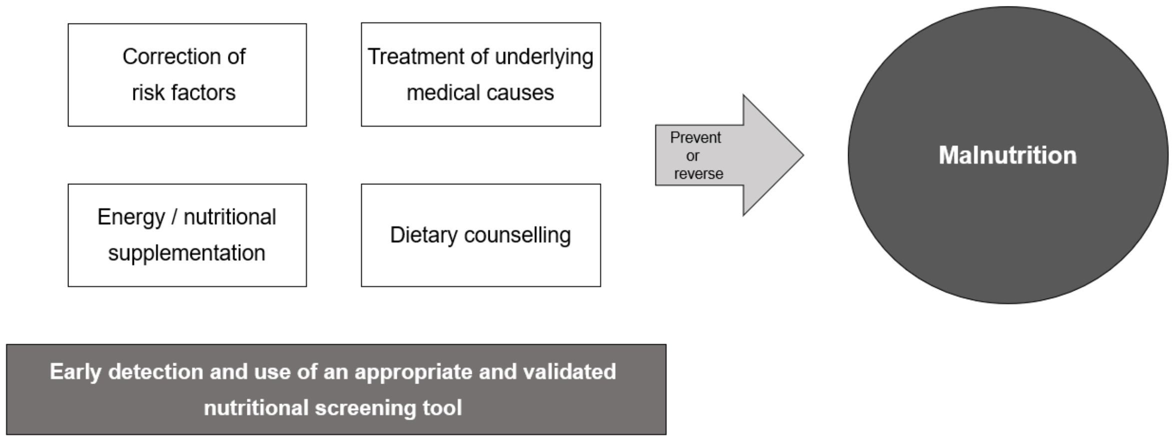

Figure 50: Recommendations for the prevention of 'malnutrition'

9. REACH

9.1. General Project Description

The REACH project (Responsive Engagement of the Elderly promoting Activity and Customized Healthcare) is a European project, aiming to develop a sensing-monitoring-intervention system that can be placed in an unobtrusive manner in various care settings and living environments of elderly citizens.

This includes:

1. A set of sensors to detect selected vital signs, behavioural/care patterns and health states
2. Early prediction of future health states, risks or events (e.g. loss of function, frailty, stroke)
3. Proactive provision and coordination of a set of customized services and products

Early intervention by REACH should enable to increase the time spent in a desirable health state (baseline health) and to reduce time spent in Long-Term Care (LTC) facilities.

In that context, REACH strives for improving and speeding up the physical and cognitive rehabilitation of elderly citizens in deteriorated health states, preventing readmissions, and detecting sudden adverse events and deterioration as early as possible.

Furthermore, REACH can be utilized in home or home care contexts in order to extend (as long as possible) a desired base-line health state of an individual, to mitigate the risk of deterioration and finally to slow down or prevent deterioration.

In order to develop the mentioned features in a target-oriented manner, several stakeholders were integrated in REACH into a joint developmental team:

- Knowledge providers (research, universities)
- Technology providers (sensors, prediction, intervention mechanisms)
- Multiplicators (e.g. insurances, standardization organizations)
- Solution operators (clinics, rehabilitation centres, home and home care providers)

Finally, regarding the solution operators, which are also called “use cases”, since they reflect concrete application scenarios for the REACH system, the following four were identified:

- Geneva Hospital (HUG)
- Schön Klinik Bad Aibling (SKBA)
- ZuidZorg (ZZ)
- Lyngby-Taarbæk Municipality (Lyngby)

9.2. Touchpoints and Engine Concept

REACH aims to systematically engage older adults in target-oriented physical activity, exercise and rehabilitation in a variety of environments and contexts, in order to counteract risk factors, such as inactivity or sedentary behaviour and its negative consequences.

Here, REACH provides value proposition and user acceptance throughout its digital-technological core and shares data strictly through case sensitive adaptation and insertion into the ecosystem of a specific country, use case setting, and/or individual user's needs.

The goal of the interventions, techniques, products, services, and programs developed by REACH is to improve the health outcomes of the elderly target population. This includes improvement of functional abilities according to the International Classification of Functioning, Disability and Health (ICF), enhancement of ADL performance and empowerment for social participation in communities. Consequently, this should lead to an ultimate increase in Quality of Life and risk reduction regarding the need for permanent and costly care, e.g. in a day care facility.

With the "Touchpoints and Engine concept" (see Figure 51), REACH´s so-called product-service-system architecture is divided into a set of manageable research and development clusters:

- Four clusters of "Touchpoints (TPs)": Representation of tangible connections between users (seniors, informal/formal caregivers) and the REACH system
- One "Engine" cluster: Digital toolkit (e.g. analytics and Machine Learning elements, data transformation and platform solutions, privacy and security tools, software applications)
- One "Interface" cluster: Set of elements, allowing for Touchpoint connection/interaction with each other, engine elements or the user

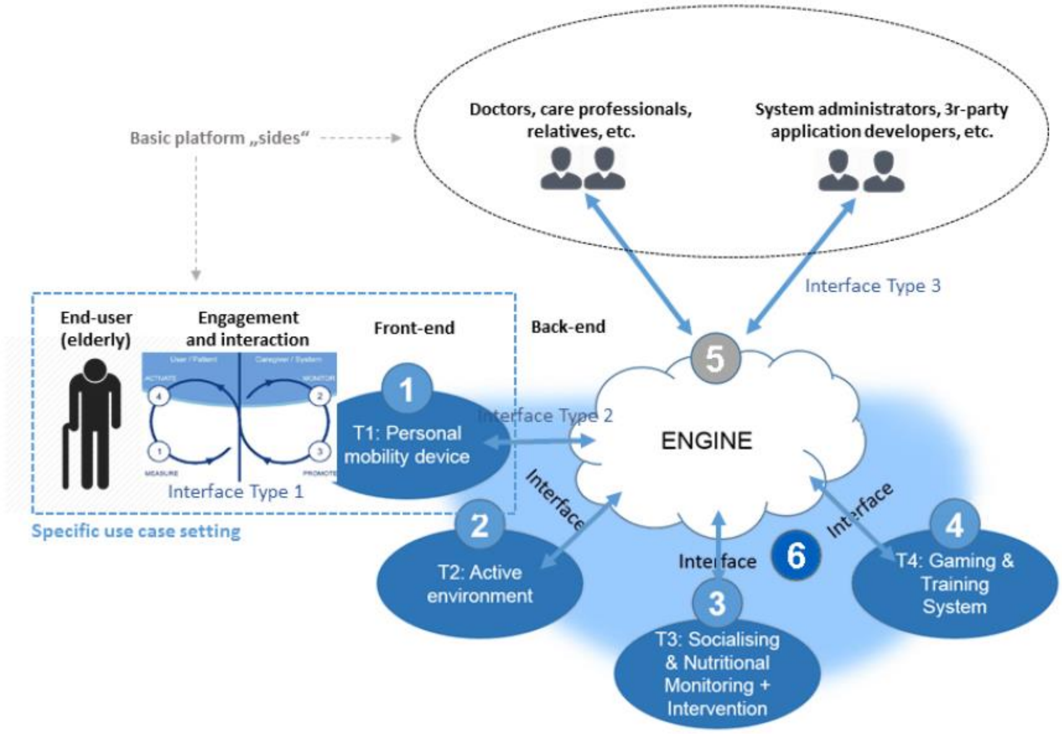

Figure 51: REACH Touchpoints and Engine Concept

In the following, each Touchpoint and its respective implementation will be described.

9.2.1. Touchpoint 1: Personal Mobility Device

In TP1, the REACH system enables older adults to prolong their time living independently through cost efficient, highly engaging, and safe community-integrated exercise technology. Specifically, the REACH system increases and maintains cardiopulmonary health (aerobic fitness), balance (and thus, reduces risk of falls through target-oriented muscle strengthening activity) and cognitive fitness.

Sensing and Monitoring:

By using additional sensing wearables (HR monitoring, activity tracker, activLife solution), TP1 provides valuable data for monitoring and early detection signs of physical decline among elderly.

Wearable: For quantitative data collection; physical activity is measured by activity trackers (Stepwatch or Invis Care)

HR tracking: Including ECG (Electrocardiogram) heart rate recording during exercises for monitoring of desired intensity (Polar OH2 and Invis Care)

Kinect: An IR camera reads position of 25 human bones, recorded with 3-dimensional position data and allows for precise anatomy movement mapping and performance improvement monitoring. Further, a depth camera allows accurate full-body motion capture in real time without the need of attaching sensors to the patient's body.

Data Analysis

Based on data analytics, the intervention programme can be personalised and adjusted to the respective user.

Dashboard: Philips data dashboard; visualisation of incoming user data enables researchers to personalise motivational strategies, which are aimed to increase the engagement in physical activity.

Stand-up counter: Supports training function of mobility device. Recognises executed stand-ups by a small sensor, installed within mobility device and thus encourages the user to be more active.

Personalisation -VAST.Rehab: Motivates to participate in physical activities and the rehabilitation process via various parameters and levels of tasks. Automatic tracking of patient's progress and synchronisation of data in the cloud-based server.

Intervention Concepts

The activLife intervention concept integrates sensing-monitoring, analysing and personalising in the intervention (see Figure 52).

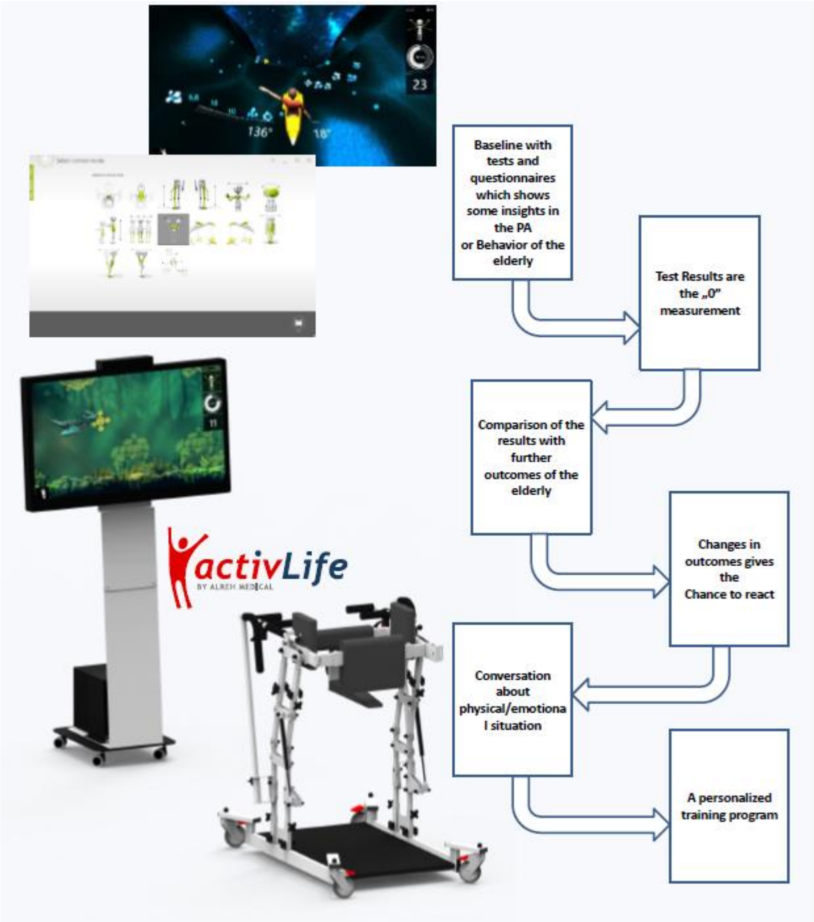

Figure 52: acivLife intervention concept

Behaviour Change Techniques

Activating training programmes in terms of computer games are effective, as they increase motivation through the aspect of gamification. Also, social interactions can be a trigger point, as well, as through sharing of goals and achievements, elders are involved in social networks, which motivates them to be active in everyday life. Table 2 shows the motivating strategies applied in TP1.

Table 2: REACH motivating strategies applied in Touchpoint 1

Gamification	Gaming platform
Social support	Sports coach
Performance support	Feedback, rewards

9.2.2. Touchpoint 2: Active Environment

In TP2, the REACH system enables patients to reduce the duration of hospitalisation, the decline after discharge and the risk of readmission. Further, it enables to perform ADL with reduced support from professional caregivers.

Sensing and Monitoring:

A series of sensing technologies are integrated in the prototypes of TP2 in order to monitor the patients' biometric signals.

Pressure Mattress: The pressure mattress monitors the peak pressure points of a person lying on the bed and informs the care personnel via the REACH Engine of the need for repositioning, in order to prevent the development of decubitus.

Thermal Camera: Two major objectives: 1. Breath frequency monitoring via nostrils during sleep, 2. Body temperature detection/monitoring via eyes.

Kinect for MiniArc and SilverArc: The Kinect sensors, integrated into the PI2U-MiniArc and PI2U-SilverArc, are used for gesture recognition by considering hand motions from the user side.

ECG Sensors: Measurement of the patient's heart activity during sleep via ECG (Electrocardiogram) sensors. Early detection of disorders possible.

Activity Monitoring Sensors: Activity monitoring sensors are integrated in the Alreh Medical iStander device, including stand-up counter for activity monitoring and EMG (Electromyography) sensors for electrical muscle activity monitoring.

Data Analysis

Based on the data analytics, the intervention concepts can be personalised and adjusted to certain users.

Data Collection Workshops: Two Data Collection Workshops were held at TUM's br2 laboratory, where a series of tests was carried out regarding data acquisition, data annotation and sensing system validation.

Data Analysis: Exploration and declaration of classifiers with the use of the collected dataset. Subsequently, design of classifiers to implement machine learning algorithms.

REACH Engine: 1. CARP: CACHET Platform (Copenhagen Center for Health Technology) for data management of sensing data. Establishment of initial communication and detailing of data format and -storage. 2. HSDP: HealthSuite Digital Platform developed by Philips. Initialisation of the first data communication and coordination between partners.

Interconnection to the REACH System: To link the investigated and developed technologies, each Touchpoint transfers as many technologies as possible to the prototypes, by communicating via a local server of the REACH Engine.

Intervention Concepts

In Touchpoint 2, the Personalized Intelligent Interior Unit (PI^{2}U), developed as a special type of smart furniture, integrates the REACH concepts and functionality seamlessly into the different REACH use case settings. The relevant PI^{2}Us for intervention consist of PI^{2}U-SilverArc, PI^{2}U-MiniArc, PI^{2}U-SilverBed, and PI^{2}U-ActivLife.

PI^{2}U-SilverArc: The SilverArc (see Figure 53) was developed for use in a large kitchen or dining space (e.g. a community kitchen). Thus, it offers an interactive projection area in the kitchen, where recipes and games can be displayed. Also, via a foldaway projection area, a training program can be displayed. Here, an ultra-short projector is fixed above the projection screen. It was purposely decided against a mounting under the projection surface, since the dust load for the projection lens would increase. Finally, depth cameras are attached to a sliding system so that positioning can be adjusted.

Figure 53: SilverArc

PI^{2}U-MiniArc: The MiniArc (see Figure 54) can be considered as a flexible and smaller variant of the SilverArc, which is designed to assist in the training and moving of elderly who are hospitalised or live in smaller apartments. An ultrashort projector can project the user interface on its foldaway table or on a separate table as needed. In addition, a motion-sensing camera (Microsoft Kinect) is integrated to detect the user's gestures, thus enabling the interactive gaming function. Further, another projector on top of the device can project extra information onto a wall. This prototype is equipped with wheels and is therefore mobile.

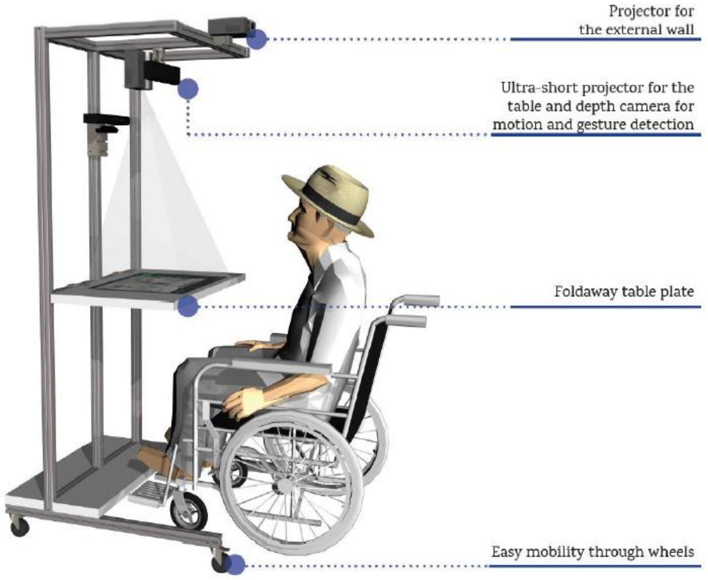

Figure 54: MiniArc

PI²U-iStander and ActivLife: The iStander (see Figure 55) is designed to activate the physical and mental activity of elderly, whose daily activity level has reduced in a safe manner. The device is equipped with a mechanism to assist the elder user to stand up and to perform movement exercises of the ankles, knees, hip joints and relevant muscles. It also allows the user to maintain a safe, upright standing position and to perform physical and cognitive exercises using the ActivLife gaming platform. Due to its flexibility and reasonable size, the system can be easily deployed in spaces such as bedrooms and bathrooms, thus serving as a mobility device between them.

Figure 55: iStander and ActivLife

PI²U-SilverBed: The SilverBed (see Figure 56 and Figure 57) resembles a normal bed for private use with an arc-shaped frame that covers the entire length of the bed. This allows for an easy integration of sensors, such as a thermal camera for breath detection and a projector for the bed. The height of the bed can be adjusted, and it can be set to both a sitting and a vertical position. The sitting position allows the bed to support the patient and the nurse in many tasks such as eating, while the vertical position is especially apt for patients in an Intensive Care Unit (ICU), where it must be able to perform the transfer from lying to vertical position. A modular docking system has been added to the design, providing additional functions such as a toilet, physical training, transfer and mobility.

Figure 56: SilverBed (hospital version)

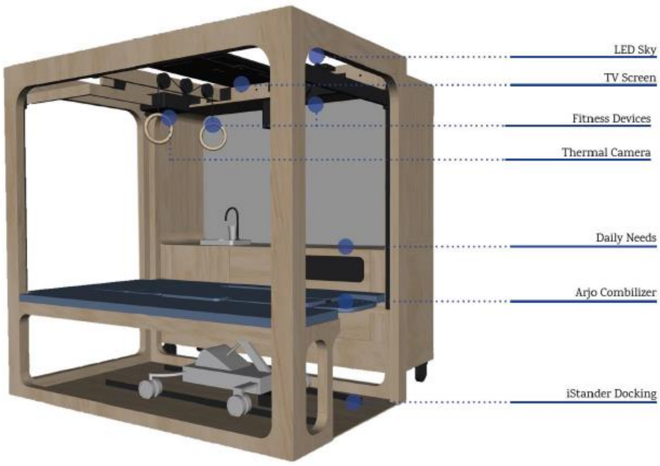

Figure 57: SilverBed (home version)

9.2.3. Touchpoint 3: Socialising and Nutritional Monitoring

In TP3, the REACH system enables older adults to improve nutritional intake and physical activity levels through social engagement and community participation. The context is here ‘home’ or ‘community centre’.

Nutrition Intake Monitoring

The REACH application monitors nutrition intake through self-reporting and photo analysis: Users can track nutrition intake in several ways, such as taking photos of their plate or using a voice recording option to track the respective kinds of food they are consuming.

Motivation towards Physical activity: The REACH application provides increased awareness and provides suggestions for physical activity: The REACH application creates highly personalised physical activity goals from the measured step data.

Physical activity Monitoring

The REACH application is connected to off-the shelf physical activity trackers: The off-the-shelf wearable activity sensors collect data on the user’s physical activity and send this information to the accompanying REACH application.

Highly personalised food: Provision of required nutrition via highly personalised food: After tracking the nurturance being consumed by the user, the system provides highly personalised food, infused with all required nutrients.

Method

REACH draws on the advantages of a sensing and monitoring system, which supports choices to personalise behaviour change strategies and thus motivates user to improve physical activity levels and healthy diets.

Data Measurement and Profiling: Through a co-design process with older adults, the research team at the TU/e adapted the original HealthyTogether application from EPFL (École Polytechnique Fédérale de Lausanne) to be usable by older adults. The application is designed to implement either personal or social reflection strategies in order to motivate users to engage in more physical activity. Further, the application provides users with an individual daily step goal and visualises the progress towards this. Finally, it enables users to send custom or pre-typed messages.

9.2.4. Touchpoint 4: Gaming and Training

In TP4, the REACH system enables early detection of critical changes in physical activity of older adults (either short-term or long-term changes) and supports increased physical activity through individualised motivational strategies and playful social or solitary activities.

Sensing and Monitoring

TP4 draws on elements of the REACH toolkit in order to co-create active environments, aiming to encourage older adults towards an active lifestyle.

Sens-motion sensor: Counting steps of slow walkers, implemented via a Sens-motion sensor and valid algorithm and machine learning techniques. The outcomes of this study ensure a convenient and easy way to estimate the changes in physical activity in older adults, with and without rollator.

Wearable: The assessment of physical activity and sedentary behaviour was conducted through the use of motion detectors, such as Sens-motion sensors, Fitbit, Germin vivofit Misift Shine, Nokia Go and Jawbone UP.

Moto Tiles: Moto Tiles is a valid and effective tool used for physical and cognitive training. Two new usage implementations of the Moto Tiles tool are proposed: Playful physical tests and body and brain age tests (BBA). The playful physical tests are similar to standardised traditional tests, but instead of traditional stopwatch measurement performed manually by an operator, Moto Tiles provides an automatic time measurement. Further, the BBA tests include a series of standardised Moto Tiles games.

Indoor sensors: Collection of raw data from two to three homes, equipped with different indoor sensors mounted in walls, furniture and daily objects to deduce older adults' daily activities. Here, monitoring can detect when a person falls or engages in activities such as opening the refrigerator or a door.

Data Analysis

Based on data analysis, the intervention programme can be personalised and adjusted to the respective user.

Machine learning: Based on the observed number of steps, machine learning is used to develop reliable algorithms for counting steps of different types of gait.

Smart home: Interior sensors are used to monitor older adults' daily activity. The collected data is then used to map patterns of behaviours and detect critical deviations.

Motivation, engagement and programme intervention: A systematic review is conducted in order to estimate the effect of monitor-based physical activity interventions on physical activity behaviour. Further, intervention studies are conducted to estimate the effect of motivational strategies on physical activity levels.

Intervention Concepts

TP4 proposes serval intervention concepts, which integrate sensing-monitoring, analysing and personalising abilities.

First step:

- Guidance for selection of activity tracker
- Valid algorithm for counting of steps
- Moto tiles as early detection device

Second step:

- Identification of best practice strategy to increase physical activity levels
- Testing of ability of gaming technology to motivate older adults for physical activity
- Testing of effects of daily feedback and bi-weekly interviews on older adults' physical activity levels

Third step:

- Quantitative data collection of physical activity via in-home sensors from smart home environments
- Early administration of playful physical and cognitive tests in naturalistic environments by moto tiles

Fourth step:

- Motivational interviewing as an add-on intervention to a monitor-based physical activity programme

Behaviour change techniques

TP4 focuses on motivation, engagement and user acceptance as those topics are highly related to gaming, motivational feedback and socialising (see Table 3).

Table 3: REACH motivating strategies applied in Touchpoint 4

Gaming	Playful exercise
Feedback	Bi-weekly interviews, daily calls
Performance support	Motivational interviewing, self-efficacy and social cognitive therapy

9.3. Connection of Target Factors with REACH

9.3.1. Use Cases

Table 4 shows the connection between the use cases and the target factors, identified in the REACH-trials and analysed in this report. The solution operators, or also called “use cases”, are as follows: Geneva Hospital (HUG), Schön Klinik Bad Aibling (SKBA), ZuidZorg (ZZ) and Lyngby-Taarbæk Municipality (Lyngby).

Thus, the target factor ‘falling’ is covered at all institutions, as well as the target factors ‘frailty’, ‘sarcopenia’ and ‘malnutrition. The target factor ‘cognitive decline’ however, is covered at Schön Klinik Bad Aibling, ZuidZorg and Lyngby-Taarbæk Municipality and the target factor ‘social isolation’ at the latter two.

Table 4: Use cases and target factors: Connection and Relevance

Target Factors	**HUG**	**SKBA**	**ZZ**	**Lyngby**
Falling				
Frailty				
Sarcopenia				
Malnutrition				
Cognitive Decline				
Social Isolation				

9.3.2. Touchpoints

Table 5 shows all target factors (falling, frailty, cognitive decline, sarcopenia, social isolation and malnutrition) and their relevance in the respective touchpoints. Thus, the target factor ‘frailty’ is strongly associated with all touchpoints, as well as the target factor ‘falling’, which only lacks relevance in TP3. ‘Sarcopenia’ on the other hand is strongly associated with TP1 and weakly with all others. ‘Malnutrition’ is strongly relevant in TP3, but weakly with all other touchpoints, as well. Furthermore, ‘social isolation’, is weakly connected with TP1 and TP2 and strongly with TP3 and TP4. And lastly, the target factor ‘cognitive decline’ is only highly relevant in TP2 and weakly connected to the other touchpoints.

Table 5: Touchpoints and target factors: Connection and Relevance

	TP1	**TP2**	**TP3**	**TP4**
Strong	Falling	Falling	Frailty	Falling
	Frailty	Frailty	Malutrition	Frailty
	Sarcopenia	Cognitive Decline	Social Isolation	Social Isolation
Weak	Malnutrition	Sarcopenia	Falling	Sarcopenia
	Cognitive Decline	Malnutrition	Sarcopenia	Malnutrition
	Social isolation	Social Isolation	Cognitive Decline	Cognitive Decline

10. Discussion

In this narrative literature review, for each target factor (falling, frailty, sarcopenia, malnutrition, social isolation and cognitive decline), several risk factors were identified, as visible in Figure 58. Furthermore, Figure 59 shows the two most important risk factors for each target factor, according to strength of associations. Here, the size of the field is greater for the strongest risk factor compared to the second strongest. Thus, regarding the target factor 'falling', 'orthostatic hypotension' and 'use of assistive devices' are the two most important risk factors. Furthermore, for 'frailty', it is 'malnutrition' and 'sedentary lifestyle', for 'sarcopenia' it is 'female gender' and 'underweight' and for 'cognitive decline', 'elevated plasma homocysteine' and 'anxiety' are the most important factors. Lastly, regarding 'malnutrition' and 'social isolation, it is 'mental disorders' and 'poor oral and dental health' and 'male gender' and 'low income', respectively.

As geriatric syndromes are generally assumed to have a multifactorial nature with complex manifestations, prevention strategies also need to show multifaceted implementations (Inouye et al., 2007). Furthermore, as the development of such conditions is also subject to the amount and type of risk factors a person has, interventions need to be tailored one the one hand to present risks factors, but also to general activities, characteristics or locations of a person. Thus, Figure 60 shows a recommendation regarding prevention strategies, as established due to the findings of this report.

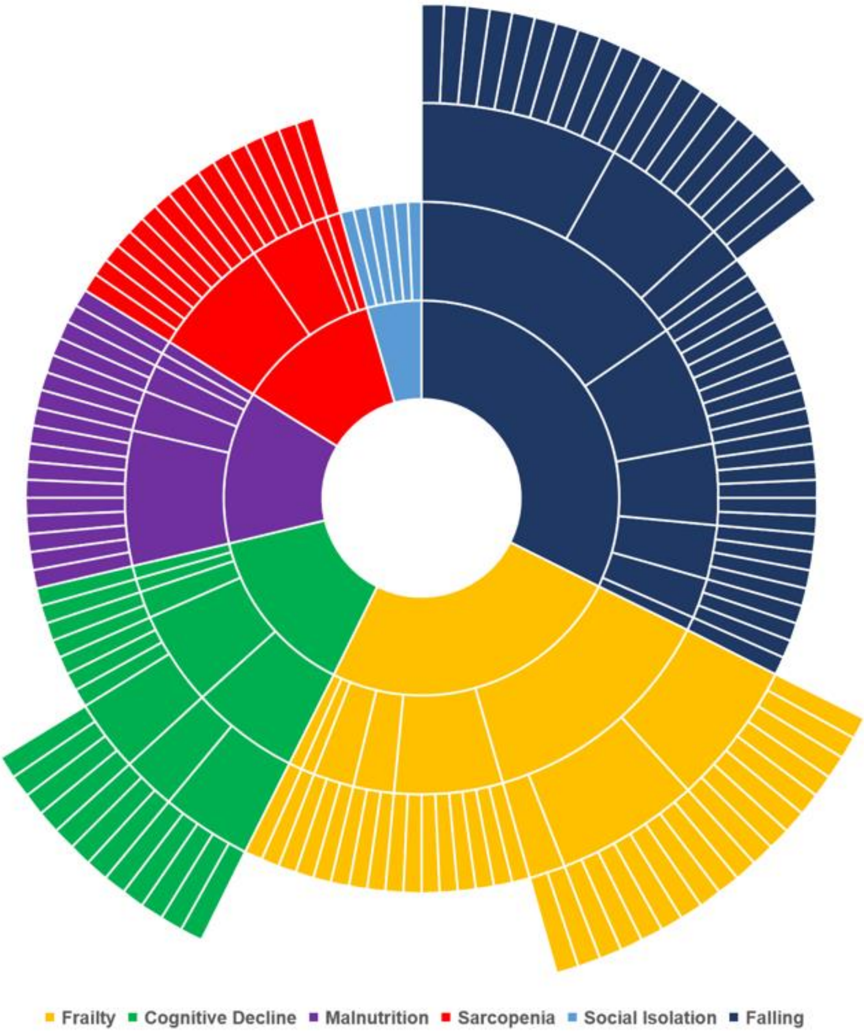

Figure 58: Overview of risk factors for each target factor

Figure 59: Most important risk factors according to target factor

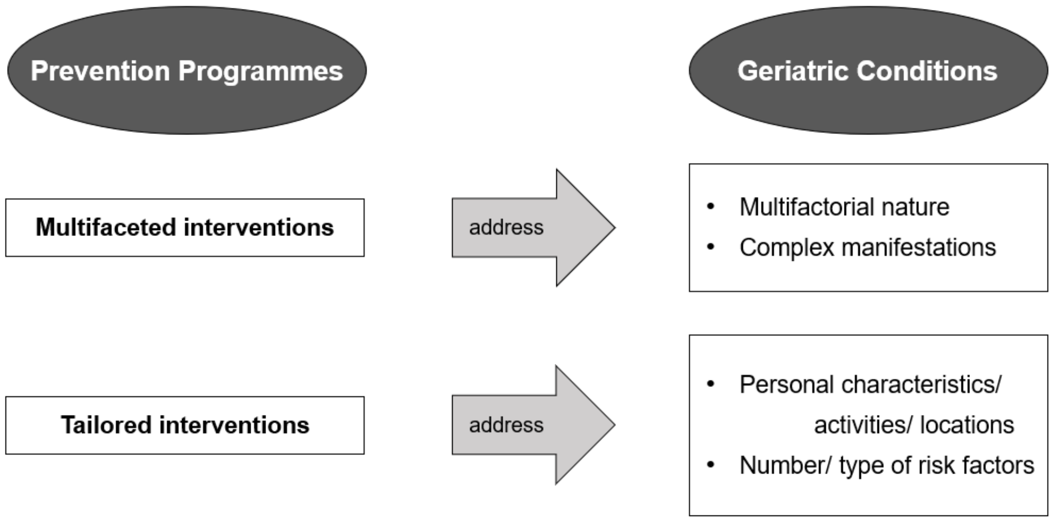

Figure 60: Recommendations for the prevention of geriatric conditions

11. Limitations

This report has several limitations. First, as it is not a systematic review, not all studies generally published on topics regarding the target factors were included. Therefore, the associations between risk and target factors drawn in this report might not represent comprehensive evidence. However, it still can act as a suggestion for important risk factors regarding the targeted geriatric conditions.

Second, although the author followed several rules regarding study search and selection (see 2. Methods), this report might still be prone to selection bias.

Lastly, in this report all risk factors were respected separately regarding their associations with the respective target factors. Thus, possible interactions that might exist between risk factors were not considered.

12. Conclusion

In this narrative literature review, risk factors regarding several geriatric conditions (target factors) were analysed. Thus, the most important risk factors for each target factor are: 1. Falling: 'orthostatic hypotension' and 'use of assistive devices'; 2. Frailty: 'malnutrition' and 'sedentary lifestyle'; 3. Cognitive decline: 'elevated plasma homocysteine' and 'anxiety'; 4. Sarcopenia: 'female gender' and 'underweight'; 5. Social Isolation: 'male gender' and 'low income'; 6. Malnutrition: 'mental disorders' and 'poor oral and dental health'.

With regards to the findings of this report, it is suggested for prevention strategies to be implemented in terms of multifaceted and tailored interventions.

All information regarding the REACH project has been obtained from the REACH Deliverables D1.1, Deliverable D1.2 and Deliverable 27 and from consultations with REACH partners.

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Appendix 2: Reviewer Recommendations

REACH 2020: Reviewer Recommendations to be addressed in RP3

Detailed plan/strategy how to address each R

No.	Reviewer Comment + Strategy to address	Lead	Supporters
R9	Consider **scaling down and simplifying the REACH structure**, as well as finding better descriptions of the REACH system components, which is less complex and less technical. It may be useful to revise the structure of the Touchpoints and Engine concept. The notion of "practice cases" as opposed to technical/medical "use cases" should be considered. Strategy how to address it: The REACH structure will be "technically" scaled down to 2-3 interrelated core components for the different use cases ideally extracting a set of universal core-components that are structurally similar cross these use cases. In tune with R13, when scaling down we will streamline REACH towards 2 main user groups: active elderly and patients. Sturrm (which did not participate in the technical development) will lead the task, supported by TUM (systems engineering) and Arjo (marketing). As part of a REACH demo and exhibition in Copenhagen (May 15), the REACH consortium made a first attempt to equip with selected REACH components and in a simplified manner, a home and a rehabilitation room environment and present each with a coherent narrative. Support by Amendment needed: Budget to be shifted consortium-internally to Sturrm to allow for the needed focus.	Sturrm	TUM
R10	Consider consulting additional business and marketing experts across the consortium and its networks in order to formulate effective value propositions and short sales pitches that would grab the attention of stakeholders. This recommendation complements R1 from the angle of external communication. Strategy how to address it: Based on R9, sharp value propositions will be formulated, and short sales pitches will be developed, i.e. modular set of texts, graphics, and presentation elements that the consortium can then use and re-combine in a variety of contexts. Sturrm (which did not participate in the technical development) will lead the task, supported by TUM (systems engineering) and Arjo (marketing). In the context of scaling down the REACH structure and formulating effective value propositions, the economic value of standardisation and standardisation activities, as well as the standardisation activities REACH (CEN, ISO) is involved in, shall be considered as important components. Deliverable: toolkit with modular slides of texts blocks, images, landing pages, etc. Support by Amendment needed: Budget to be shifted consortium-internally to Sturrm to allow for the needed focus.	Sturrm	TUM, DIN
R11	The work towards a **REACH consulting & engineering spin-off** is highly appreciated, since it would be able to create an entity that would allow the consortium as a whole to work together efficiently beyond the projects' duration and at the same time deliver its overall value to society and industry. In this context, the consortium should consider how it can a) develop the young people in the consortium towards	TUM	Sturrm, Tu/e (Hubert), DIN

	becoming consultants (develop and practice with them the consulting process), b) develop repeatable training modules (e.g. workshops elements, training sessions, presentations, lectures, webinars, videos, etc.) that work towards bringing REACH into the market, and c) manage know-how and knowledge transfer. Based on the outlined structure of the entity a concept for service bundling could be developed. Strategy how to address it: The consortium will intensify its work towards the setting-up of an REACH consulting and engineering spin-off. As part of this R a core group in the consortium (TUM, Sturrm, Tu/e, AM, DIN) – in particular, its "younger" people - will focus on the setting-up of a REACH consulting spin-off. Experienced consultants (Sturrm/C. v. d. Boom, AM/ P. Partyga; TUM/T. Bock), etc.) will give advice to this young group. The New North Zealand Hospital will ideally serve as an initial client which can be used to set up the basic structures of the spin-off. In this context, we will also develop basic (contract) schemata for the flexible involvement of the partners and their know-how (e.g. a contracting structure) into the consulting process. The outcomes of Rs 10 and 11 will be used to shape the offerings of the consulting firm. Furthermore, standardisation expertise shall get an inherent component of the offerings of the consulting firm. Initial attempts will be made to clarify the a) financial, b) legal and c) IP "infrastructures" that need to surround the firm. Ideally, one revenue stream for the firm will come from the project partners for serving as a multiplicator for them. Support by Amendment needed: Slight shift of resources towards WPs 8 and 9, in turn reduction of scope and PMs of selected other tasks		
R12	The consortium should continue to work systematically on the **innovation management** aspects: a) try to develop and work towards securing IP (e.g. related to Machine Learning as part of TPs 2, 3, and 4); b) prepare and/or conduct initial steps towards (medical) certification for market implementation in each TP; c) to allow for faster scale-up, develop a strategy to broaden markets for REACH products and services (e.g. identify markets outside the REACH topics: children, young healthy persons, aviation, transportation industries, etc.). Strategy how to address it: TUM will as part of its work associated with WP9 lead this task and develop an overall strategy for a), b), and c). AM and Sturrm will assist. The consortium has in reporting period 2 developed detailed stakeholder analyses and classifications and has with a systematic tool (IP identification matrix) assessed all technologies and processes. The consortium will build on these materials and take it further when addressing this R. In addition, the consortium will make contact with groups that work on topics outside the ageing society range (e.g. paediatrics, hospital discharge follow-up) and participate in associated workshops and conferences to enter a discussion with them about the applicability of REACH toolkit elements in their filed. The consortium will do this in close coordination with the EIP AHA A3 which also intends to broaden its applicability scope. Support by Amendment needed: Slight shift of resources towards WPs 8 and 9, in turn reduction of scope and PMs of selected other tasks	TUM	AM, Sturrm
R13	The consortium should **focus on 2 user groups: active elderly and patients** in health care systems and shift towards the provisions of solutions and treatments (physicians need solutions, not more data, validations, risks, etc.). An approach should be proposed (within the available resource of the project) towards a component/solution	Philips	Tu/e, TUM, SC, Arjo, AM, CU, HUG

	selection system (matrix or similar) that allows to associate certain medical conditions and needs with REACH system solution components (you may leverage concepts from fields such as mass customisation, modular product platforms, etc.) and certain personalisation levels. <u>Strategy how to address it:</u> Philips has extensive knowledge regarding personalisation for behaviour change as well as connecting to market segmentation. Also, Philips has past experience in driving products and services for the two suggested user groups and will therefore lead this task. Jointly with Tu/e and TUM suitable frameworks that allow a target oriented and case-based selection of REACH components will be developed, also based upon previous knowledge and work done at Philips Design. The consortium has already successfully tested the simplified allocations of its developments to "active elderly" and "patient environments" at the demo event in Lyngby (May 16). The selection system to be developed will link with EIP AHA (https://ec.europa.eu/eip/ageing/blueprint_en), IEC (Syc AAL), and ISO (TC 314), age and age-related conditions and personas classification systems where appropriate. In this context, we will also analyse to what extent we can take further the notion of Touchpoints to a notion of market segments. Likewise, we will work towards integrated service design concepts and scenarios, which integrate different REACH toolkit elements to be used based on the assessment and intervention plan tailored to each user. For practical reasons, the consortium considers focussing on the following 3 user groups/market segments (instead of the 2 mentioned by the reviewers): active elderly (prevention), nursing-home residents (activation for life quality) and patients in health care systems (rehabilitation). As a starting point, we consider a 3-dimensional solution/treatment selection matrix. a) Axis 1: User group (3 possibilities) b) Axis 2: Treatment/medical condition (limited to rehabilitation, frailty, and one other (COPD, Cardiac, e.g.). There will be some medical conditions, which are quite similar but would be addressed with different REACH solutions depending on market/user group c) Axis 3: REACH service solution / scenario Ideally, each solution/treatment (cell in matrix) has evidence-based support as much as possible, or has ongoing activities with regard to that. SC has experience in developing solutions for active elderly monitoring, such as activity tracking as well as patient population tracking, such as detecting and monitoring cardiac arrhythmia and sleep apnea conditions. SC will work with partners to show demonstrators for the market segments in question. CU will contribute to, and support for the development of a classification and selection system for Physical Activity Monitors (PAMs). Also Arjo and AM will support and provide information about practical market segmentation. HUG will feed in information concerning patients and health care professionals in the health care system (rehabilitation) based on the clinical trials run in the hospital. <u>Support by Amendment needed:</u> Slight shift of budgets to Tu/e and CU/DTU to support the generation of inputs based on practice cases in the selection system. Conversion of material budget of Philips into direct personnel cost to involve more highly qualified personnel that has experience and can handle this complex task. Material budget was initially reserved for		

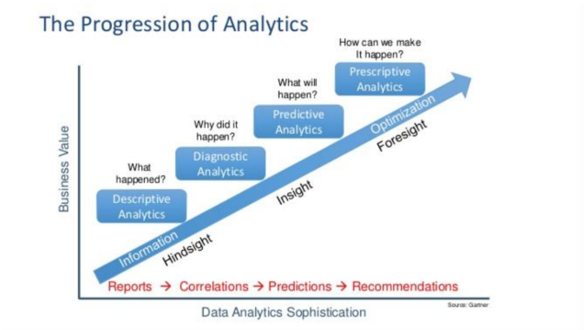
	software purchase, which instead was done as proprietary development; also Philips does not claim travel cost. However, this went to the cost of formalizing the behaviour change results, and connecting it to REACH, as well as delivering more broad guidelines (dissemination) into the world of health tech, leveraging the work done in REACH. This effort still requires substantial energy and resources, so hence at this point we convert material budget into direct personnel cost to be able to make the most impact for REACH (R13) as well as leveraging REACH generated knowledge, insights and proof, through dissemination on behaviour change, into the academic and professional world.		
R14	Please consider the inclusion of weight follow up, Body- Mass Index (BMI), serum albumin as **nutrition markers** and control of nutritional intake (e.g. in the context of TP3). Strategy how to address it: The TP3 core group (Tu/e + BZN) will revise and the Touchpoint 3 system and incorporate the mentioned aspects. The involved core partners will closely cooperate and hold meetings and workshops to integrate their work towards this R. Specifically, HUG will include weight follow up and BMI in MiranaBot, a multiplatform web application with functionalities that allow the users to understand their nutritional habits in terms of variety and regularity, to identify bad eating habits, and to receive personalized recommendations about their diets. Support by Amendment needed: No.	Tu/e	BZN, HUG
R15	Please address the difference between factors and co-factors in terms of prevention out of evidence based medical data, i.e. which is the main factor, what are the co-factors related to a specific event (e.g. Fall and Vit. D). Strategy how to address it: SK and DTU (which led the medical task force) will extract these factors from the available data of the 23 conducted trials, and outline the outcome in an easy to understand graphical from. At SK 1 research associate will perform a systematic literature research for each factor to assess and evaluate the co-factors. Support by Amendment needed: + 1 PM to SK (from TUM)	SK	DTU
R16	**Technical maturation with business aspects in mind for Touchpoint 2**: Touchpoint 2 develops a rehabilitation room (potentially adaptable to and deployable in a variety of care environments: clinics, rehabilitation facilities, care homes, home-care scenarios, etc.) with Human Activity Recognition chain that allows to realize advanced activation and rehabilitation for elderly patients. The room can significantly increase the performance of rehabilitation, patient/elderly empowerment and participation, and safety, as well as reduce cost on individual care (through improvement of processes, and work flows around personalised care). This system is considered as a technologically complex and experimental system that potentially would have an exceptionally high business value. Therefore, the consortium should further work towards the technical maturation and validation of this system, including a) the underlying physical-mechanical aspects (equipment and sensing aspects, modularity, etc.), b) the embedded analytics and machine-learning technology, and c) the seamless incorporation of personalised behaviour changes regimes. As mentioned under INNOVATION & IMPACT, this shall be done with the market and business perspectives in mind.	SK	TUM, Fraunhofer, Tu/e, AM, DTU

	Strategy how to address it: The consortium will address this R through a combination and coordination of the following activities: 1. The overall TP2 group will analyse the potential impacts a full-scale TP2 system may have on the hospital (SK) and the services and therapies it is providing to guide the maturation of this Touchpoint. 2. Tu/e will assist in better including user experience and behaviour change aspects in this TP in order to better capitalise on its technical aspects. 3. AM and SK will jointly conduct practical hands-on testing with the mobility and playful training components of this TP to get "practice case" feedback and present at the end based on these practical and business-oriented solutions for the aging patient market. 4. DTU and TUM will finalize the TP2 and TP4 integration and interfacing with CARP platform. This will provide different REACH partners with an exemplary approach how to store and access their data via the REACH-Engine. 5. DTU is developing and will test in real operations a prototype family alert system comprising sensor-based monitoring of possible critical deviations of daily activities of a single older adult living independently at home. The system transmits via an internet linked dashboard (on smartphone or PC) status, trends and possible alerts to close family member (typically daughter/son of the older adult who are worried about their older family member). The dashboard is available to family members (a new customer segment) and as well professional caregivers (e.g., municipal care organization). Support by Amendment needed: TUM/DTU: • T2.3.5-T2.3.6/D7: slight changes of task description, slight increase of PMs of DTU • SK, TUM, DTU: T6.2/D28: shift of lead from DTU to SK and TUM. • T6.6 and T6.8: slight updates of task descriptions.		
R17	The consortium has already gained a high degree of credibility with regards to the work performed and the soundness of the concept. The final period should be used to extract all aspects of impact - current, future and potential (i.e. outside the scope of this project) and **prepare a visualisation of the roadmap to leverage the impacts** as well as the expected steps and estimated timeframes. Strategy how to address it: A roadmap will be developed, which systematically analyses, outlines, and projects potential impacts over the next 15 years. The consortium will summarize the roadmap and the consortium's capability to make an impact on the ageing population in a special issue of the "Journal of Population Ageing" which will be dedicated to REACH (foreseen publication date: early spring 2020). Support by Amendment needed: Slight shift of resources to fund open access publications for selected partners.	TUM	AM, Sturrm
R18	**Data analytics in Touchpoints 2 (and 3)**: Given the lack of proper data collected in the first 2 reporting periods, and the applied transfer learning approach for analytics model construction, the models will need to be retrained with appropriate in-domain data from the final trials. Consider prolonging the planned duration of the final trials in realistic environments or to run them in 2 batches so that they can be performed also using models trained on valid data collected during the initial batch of the final trials.	Fraunhofer	EPFL, TUM, SK, SC

<table>
<tr><td></td><td>Strategy how to address it:

For TP2, two more batches will be run to adjust the machine learning models to the user group (batch 1) and evaluate its effectiveness (batch 2). In next trials of TP2 data collection will be implemented consisting of in-domain user groups, a) active elderly b) patients. This will improve the learning approach and analytics model construction, which will lead to improved analysis. SC will support the approach for testing in 2 batches, to collect data during the initial batch for training and then performing the testing.

For TP3, it will be analysed if the developed models can be used and developed further on data set of the other TPs, and EPFL will take the system forward towards a recommender system in Touchpoint 3. As per Gartner's "Progression of Analytics" model recommender/ optimisation systems have the highest potential business value. EPFL will build as a "practical solution" an app to generate recommendations for a more active lifestyle. The app will integrate and synthesis previous work of this TP into a solution and concrete business application.



The recommendations provided by the app should be (1) personalized and (2) feasible. For this purpose, we use the data obtained from the TU/e and the machine learning models that were described in the previous Deliverables. We also base our recommendation algorithm on ideas from our previous and current research. Our app uses the inter-personal persuasion profiles to recommend the best intervention for a given user. It pairs the given user with a virtual partner selected from the existing TU/e dataset who can persuade the new user to improve his or her behaviour. We will leverage the work on persuasive messages done cross various TPs in the REACH project in the previous reporting period to choose the best way to present the recommendations to a new user.

Support by Amendment needed:

Reduction of selected other work task and resources in favor of this task/R., i.e.:

• EPFL: Reduction of scope and PMs for the research-oriented task T 3.9 in favour of the above-described work towards practical applications.
• Fraunhofer:
○ T3.5: increase PMs from 8 to 9
○ T3.8: increase PMs from 2 to 3
○ T3.10: increase PMs from 2 to 3
○ T3.11: reduce PMs from 2 to 1
○ T4.3.1: reduce PMs from 1 to 0,5
○ T7.5: reduce PMs from 2 to 0,5 and shift lead to DTU
• Change of deliverable deadlines:
○ D13 deadline from 31 May 2019 to 31 Jan 2020
○ D12 deadline: 31 Jan 2020</td><td></td><td></td></tr>
<tr><td>R19</td><td>Please consider developing a "medical device (MD)" submission strategy that would define whether the marketable result would be an overall platform or a "touchpoint"-specific MD-dossier. This regulatory aspect is of importance before the market dissemination. In addition, CE labels of sensors and devices used in the trials should be reviewed in order to build the MD submission on an European regulatory</td><td>TUM</td><td>SK, Arjo, DIN</td></tr>
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	framework, taking into account national specific requirements. Strategy how to address it: For each TP, a strategy will be developed that sets out a framework for certifying the developments as medical devices and/or against certain national, European, or ISO standards. To develop this strategy the consortium will leverage experience of its partners SK and Arjo, as well as of local certification bodies and certification consultants (e.g. TÜV Süd in Munich). In addition, the consortium will leverage in this context the know-how, insights, and foothold gained as part of its standardisation activities. Support by Amendment needed: No.		
R20	Dissemination and market deployment may need a **demo** that answers the following questions: 1. Who will be the final provider (bearing in mind that the consortium is mainly composed of academics and researchers)? What is the role of the SMEs in the final provision of service? 2. What is the business Model? 3. Who are the final users? 4. Who are prescribers of the services? 5. Any other questions that would help understand the after-project stage. Strategy how to address it: In order to get something „practical" in the last months of REACH, we should get evidence-based support: • that our solutions have a positive impact on users/patients/caretakers which can be proved in real-life settings • that this proof is a right way to commercialisation because we prove that it brings initial sale success. We have managed to get several tests that are being done or are promised to be done with the ActivLive component of TPs 1 and 3. Most of them by aging specialist from outside the REACH (which already shows the strength of interest in the REACH solution): a) HUG is currently conducting a clinical trial that compares the REACH ActivLife system with the standard of care for geriatric patients that are hospitalized for musculoskeletal issues (fracture, prosthesis, falls and low back pain). The RCT measures clinical outcomes, but also evaluates the motivational impact of ActivLife for geriatric patients which benefited from the activLife intervention at the hospital. The study investigates if there are differences in the clinical or motivational outcomes at the hospital and also when the patients are back home. b) Tu/e (Hubert) will to do another test at the activity center with high data accuracy c) SK will test activLife (not iStander) with alzheimer patients and post-stroke patients as hospital rehabilitation device d) Medical University Wrocław does a study on pre-frailty with outpatients coming to family doctor e) Malarden University in Stockholm will do a study on dementia patients at a day care center (probably in better shape than SK alzheimer patients) f) Maxima Medical Center (Cardiac Hospital in Eindhoven) will do a CR study agreed with Warsaw Cardiac Clinic (from which we have already a pilot study) and present results at Cardiac Innovation Congress in Paris g) Warsaw University Hospital will do a study on Parkinson patients (a pilot is already done) h) Medical Academy in Poznań would like to do a study on Mild Cognitive Impairment i) Medical Academy in Łódź would like to do a study on Phase 1 CR at their Cardiac surgery clinic j) Sensor service provider companies including SENS INNOVATION are keenly interested in joining/following the work on ethical guidelines (pre-standard) for safeguarding privacy while using pervasive sensing	AM	Tu/e, HUG, SK, CU, DTU, Lyngby;

	CU will from its ongoing/upcoming large TP4 trial extract information about providers/customers, practical application cases, and business models. DTU will analyse what would be the factors that allow a continued use of REACH solutions beyond the trials in the Lyngby municipality care homes and will target the family members who want to monitor the well-being of older relatives. HUG will feed in information/contributions based on the results of its ongoing RCT. Specifically, the results of the REACH ActivLIfe efficiency (SPPB measurement), functionality (NASA task-load index), motivation and engagement (semi-structured interviews), the analysis of the physical activity data collected by the sensor, and the analysis of the gaming score collected by the mobility equipment. Finally, based on the inputs of the above listed activities for this R, for each TP a standard value chain (graphical outline as a flow chart or similar) will be developed and outlined. Support by Amendment needed: No.		
R21	IPR: as the consortium intends to target non-European markets, such as China, IPR protection needs to be reinforced. In case the production lines are located outside of the EU, IPR protection will be crucial and can also provide a source of revenues. Strategy how to address it: TUM will - based on the in-reporting period 2 developed and used IPR matrix - jointly with partners identify protectable priority items. TUM will facilitate IPR protection activities by AM (patent elements of TP1), Fraunhofer (IPR protection related to the HAR system), Arjo (IPR regarding smart furniture), and DTU (IPR protection on-board ML of TP4). As part of activities to be carried out towards this R, the consortium will work towards the setting up a network spanning cross Europe, Canada, Japan, and Korea (i.e. countries with similar technology capacity and age structures) for the international cross-transfer of know-how, products, and services related to ageing society. Support by Amendment needed: No.	TUM	AM, Fraunhofer, Arjo, DTU
R22	Smart furniture integrating potential sensors (e.g. for epilepsy, sleep apnoea) will benefit from further development. There is a large potential innovative market, and these aspects should be addressed in the final impact considerations. Strategy how to address it: TUM, SK, Arjo, AM, and SC will integrate smart furniture developments conducted cross TPs into a coherent overall furniture kit and demonstrate how from this kit instantiations for practical active elderly and patients use cases can be derived. Ideally in this context, a CBA (Cost-Benefit Analysis Benefit Analysis) can be developed comparing environments equipped with REACH smart furniture with other solutions. Additionally, current development/integration state of sensing modules will be taken forward, towards better communication and integration, which will lead to development of smart furniture. SC has experience in sleep apnea detection and will provide support for CBA analysis and technical feasibility of integrating sensors on furniture to obtain accurate results.	TUM	SK, Arjo, SC

	Support by Amendment needed: Reduction of selected other work task and resources in favor of this task/R; i.e.: • TUM, Deliverable T5.3/D23: slight change of task/deliverable description and slight reduction of PMs of this task in favor of the other wok tasks of WP5.		
R23	The overall issue is “how to translate complexity” into “accessible, easy to use and smart“ solutions for a segmented and large population with different needs and strengths? From a medical point of view the following recommendations could be helpful: 1. To comply with good practice recommendations. 2. To define “niches” and final users: it seems that the project may provide some **personalised “solutions**”. Strategy how to address it: This point will be addressed in conjunction with and as an extension of R13 Support by Amendment needed: No.	Philips	Tu/e, TUM