CHAPTER 172

Personalized medicine for older adults

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Introduction to personalized medicine

Ageing is by far the most important risk factor for developing diseases and injuries. For this reason, older adults frequently have multiple long-term health problems (multimorbidity) and multiple treatments (multitreatment), and multimorbidity is now the most common long-term health problem in healthcare in many countries (Tinetti *et al.*, 2012). The more multimorbidity and multitreatment, the more complicated the clinical analysis.

Types of multimorbidity

Multimorbidity may be divided in two different forms:

- *Primary multimorbidity*: Different manifest health problems exist without any obvious relations (coincidence) according to today's knowledge level. This situation is very common in healthcare and comprise a large and complex mix of different diseases and injuries. An individual may have health problems that may be grouped together as clusters, such as neuropsychiatric cluster, cardiovascular cluster, gastrointestinal cluster, and so on. However, presently it is often not possible to link such clusters to specific pathophysiological processes or genetic mechanisms.
- *Secondary multimorbidity* = comorbidity: One specific organ disease has given rise to numerous associated health problems. This situation represents the natural course of most chronic, progressive diseases such as chronic heart failure, chronic renal failure, diabetes mellitus, rheumatoid arthritis, dementia, HIV, and many others.

In clinical practice, there is a continuous interaction between primary and secondary multimorbidity, which complicates clinical analysis.

Drivers—consequences

Manifest diseases and conditions after injuries (such as hip fracture, myocardial infarction, stroke, and so on) serve as drivers for functional impairment in the cascade shown in Figure 172.1:

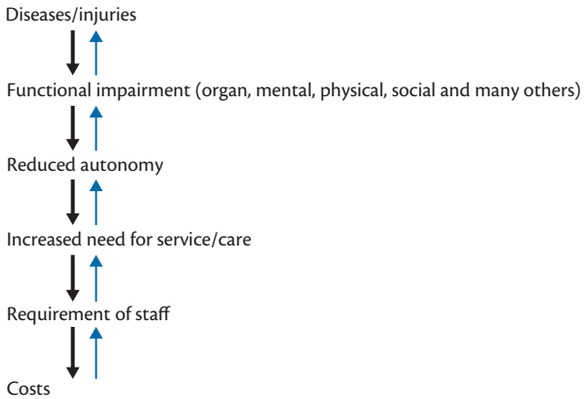

Fig. 172.1 Cascade of events illustrating that manifest diseases and conditions after injuries serve as drivers for functional impairment and need of health care. The cascade is bidirectional, but the net vector is downwards.

The processes is driven top 1–5 down, but the different parts interact with each other in both directions in a complicated manner, and for the individual person in an unpredictable way.

Heterogeneity

The variation in type, degree, and mix of manifest health problems, functional consequences, and risk factor profile is very large and thus, each older person presents with a unique clinical phenotype. This concept is discussed in more detail in Chapters 41 and 42. Clinical heterogeneity calls for a high degree of personalized/individualized approach to geriatric medicine and elderly care, which has implications for both practice and research:

- *Practice*: National guidelines and care programmes based on single-disease management are not appropriate when dealing with multimorbid older people. It is not according to good clinical practice to manage multiple health problems as if they were independent of each other. On the contrary, different health problems interact like communicating vessels and must be managed

from both a single-disease perspective, as well as from an integrated, multidomain perspective. A review from 2005 showed that adhering to current clinical practice guidelines in caring for an older person with multimorbidity may diminish the quality of care (Boyd *et al.*, 2005).

- *Clinical research*: The state-of-the-art method for clinical trials, the randomized controlled trial (RCT) in double-blind design, is not well-suited for multimorbid elderly people, mainly due to large heterogeneity in all measures variables (Engelheart & Akner, 2015) and lack of information of 'potential reversibility' (resilience) regarding the specific treatment(s) being used in the trial. Thus, there is a great need to develop new clinical treatment research methods for older adults with multimorbidity.

Scientific basis

There is a general lack of treatment research for adults aged 75 years and over for both single-disease clinical trials and multimorbidity trials. A report from the Swedish Council on Health Technology Assessment stated that *'The patient groups 65 years and older, who receive the most inpatient care and the most "multiple treatments" are the ones for whom we have the poorest basis of scientific material'* (The Swedish Council on Technology Assessment in Health Care, 2003). The reason for this unfortunate situation is that older adults have often been systematically excluded from clinical trials during the whole modern research era, mainly because of their complex health problems. During the years since this report was initially published, the scientific evidence regarding treatments of health problems in older adults has not improved substantially, particularly not for multiple health problems.

Clinical management

Presently, there is no consensus regarding how a personalized/individualized management of multimorbid older adults should be carried out. It is easy to claim in a textbook and in a lecture hall that the care for elderly multimorbid people should be targeted, integrated, and coordinated, however, much harder in clinical practice, and many challenges prevail.

There have been many attempts to develop an organizational framework for management of multimorbid elderly people over time such as Geriatric Evaluation and Management Units (GEMU) (Government South Australia, 2013), Program of All-inclusive Care for the Elderly (PACE) (Lee *et al.*, 1998), Acute Care for the Elders (ACE) units (Landefeld *et al.*, 1995), Care Transition Intervention Models (Coleman *et al.*, 2004), and home-based care (Counsell *et al.*, 2007; Milstein & Gilbertson, 2009; Leff *et al.*, 2005).

The methodological framework of comprehensive geriatric assessment (CGA) originated in Dr. Marjory Warren's work in London/England during the 1940s and 50s (Kong, 2000), and was delineated in a state-of-the art document by the American Geriatrics Society in 1988 (Consensus Development Panel, 1988). The development and utilization of this concept is described in more detail in Chapters 16 and 17.

However, CGA is not a defined method, but rather a set of assessments grouped within a number of health domains that could be used in the assessment of an elderly, multimorbid person. The letter 'A' in CGA implies that the concept is based on multidomain assessment. However, many scientific papers on CGA have also included management, and there is a substantial literature of CGA as an intervention, even though the exact content of CGA varies much between both individual patients and trials. Thus, it seems reasonable to complete the CGA concept with 'management'; CGAM.

A fundamental challenge in the field of managing multimorbid older adults is how a theoretical understanding of the necessity to include assessment of multiple health domains to a suitable depth depending on the individual elderly person, could be translated and adopted to clinical practice and over time.

Below is presented a generic approach to clinical management of individual multimorbid older adults based on the three-part **D**iagnostics, **T**reatment, and **F**ollow-up-model (DTF)) (Akner, 2011) applied in a four-step level of clinical analysis, where the results are tabulated in an analytical matrix that may be put into a multidomain structure to obtain a) an overview of diagnostics and treatments at a certain point in time (cross-sectional) and b) follow-up of all scored measures over time (longitudinal), together allowing for relational analysis as a basis for a targeted treatment and management programme.

DTF-model

The DTF-model represents a generic and easy-to-remember model for all types of problem solving: What is wrong? What should be done? Did it work? (Akner, 2011; 2013). In clinical medicine, physicians have used these principles since ancient times. The reason why the DTF-model needs to be emphasized is that a DTF-structure is not easily recognized in clinical practice and medical records when dealing with multimorbid elderly people over time. It would be a great step forward if the medical records were designed according to the DTF-model.

- **D**iagnostics (dia = through, gnosis = knowledge): This implies analysis and evaluation of the patient's health situation. Diagnostics comprise two parts:
  - *Subjective*: The symptoms experienced by the patient (complaints, ailments, and so on; e.g. day fatigue, nausea, pain) as presented by the patient' s history (self-reported and, if needed, history completed by relatives or staff) are an essential part of the clinical analysis, since they represent the suffering. They constitute the prime entry to the most health analysis and should be a prime outcome measure for evaluation over time.
  - *Objective*: This implies using various work-up methods (e.g. physical body examination, physical function tests, laboratory blood tests, X-ray, spirometry, rating scales, and so on).

The integrated diagnostic assessment implies: a) analysis of possible relations between subjective and objective findings; b) defining ongoing pathological/pathophysiological processes; and c) coding formal diagnoses of diseases and conditions after injuries, as well as their functional consequences.

Besides manifest health problems, the assessment should also comprise a risk factor analysis (see below).

- **T**reatment: This implies planning and agreeing with the patient on a targeted, integrated, and coordinated management programme

that should comprise all current treatment methods (labelled in italics), with their respective components, for example:

- *Medical prescription drugs*
- *Nutrition* (e.g. intake of energy, nutrients and water translated to intake of food/beverages, meal planning, nutritional supplements, help during meals, and so on)
- *Physical activity/exercise* (e.g. gait, balance, endurance, muscle strength, and so on)
- *Medico-technical devices* (e.g. pacemaker, haemodialysis, oxygen concentrator)
- *Technical aids* (e.g. cane, walker, incontinence pads, grip device, dentures, and so on)
- *Social services* = instrumental activities of daily living, iADL
- *Nursing care* = personal activities of daily living, pADL

The planning of treatment should, if possible, take into account the number needed to treat (NNT) and the number needed to harm (NNH) for the various treatment components (Cook & Sackett, 1995). These figures are, however, only occasionally known for the age group 65 years and older (The Swedish Council on Technology Assessment in Health Care, 2003), but there may be some guidance from published treatment trials in younger age groups.

- **F**ollow-up: This implies monitoring and evaluating the health situation and treatment effects over time, both positive (desired), negative (adverse reactions) and no detectable effect(s). Follow-up therefore represents a re-evaluation of 'D' and 'T' in the DTF-model. There is very little scientific evidence to support how frequent multimorbid elderly patients should be followed up, and thus, how this is carried out varies very much in clinical practice.

The management according to the DTF-model should be planned together with the individual in her/his social context (e.g. family, living conditions, economy), in relation to motivation, health expectations, and prognosis.

Four-step clinical analysis process based on the DTF-model

In older adults with multimorbidity, it is necessary to simultaneously deal with both the individual diseases and a multidomain approach to cover common health problem areas that need to be addressed, even if there are no spontaneous complaints from the patients.

First step

The first step involves listing current symptoms, diagnoses, and treatments, divided in methods and components. Table 172.1 shows an example of an unsorted Diagnostics and Treatment matrix for an 82-year-old woman.

Second step

The second step involves structuring and sorting Diagnostics and Treatment according to health problem areas. Table 172.2 shows the sorted matrix for the same patient as in Table 172.1, where symptoms and help with activities of daily living (ADL) have been omitted since they do not address specific health problem areas.

Figure 172.2 shows how the multimorbidity matrix may be further elaborated by separation into organ, system, and various functional problems (Akner, 2009). Active problem areas for the patient are indicated by bold frames around the boxes.

The multimorbidity matrix of health problems in Table 172.2 and Figure 172.2 also provides an overview of which health areas that are *not* affected ('health factors'), which is valuable for the overall assessment of health risks and for motivation support.

Third step

The third step involves organizing the defined health problem areas into health domains (Fig. 172.3). Earlier proposals of multidomain analysis defined only few health domains (i.e. physiological, psychological, and social) (Rowe & Kahn, 1997). Over time, the multidomain concept has evolved and may now include a number of different health domains, and an example is shown in Figure 172.3.

The reason for expanding the health *problem areas*, based mainly on organs and systems, into *health domains* is the importance to screen older, multimorbid individuals across a number of health domains, since they frequently have multiple health problems without much subjective complaints. Moreover, the multidomain model also serves as a checklist for assessment.

As mentioned above, there is no consensus on which domains should be included and to what depth they should be assessed. A trained clinician may be able to superficially screen many of the domains in Figure 172.3 during a regular clinical consultation. The results of the multidomain screening should preferably be visualized graphically instead of just summarized as text.

Fourth step

The fourth step involves analysis of possible relations between symptoms and diagnoses, including their relative importance. As mentioned above, symptoms represent the suffering and, thus, should be a prime focus for both assessment and evaluation. Still, symptoms are usually non-specific and may have many different possible explanations/relations. Moreover, there may be no plausible explanation for some symptoms, given today's knowledge level in clinical medicine and may thus remain as symptom diagnoses in the final evaluation.

Analysing possible causes/relations between symptoms and diagnoses is of importance for planning a targeted management, both regarding further assessment as well as treatment and follow-up. Figure 172.4 shows possible relations between the symptom 'day fatigue' in the symptom domain and six other health domains.

The clinical analysis should aim to roughly estimate the degree of potential relations between symptoms and diagnoses for the particular patient. Assessed relations should preferably be visualized graphically to allow easy overview and comparison at regular clinical follow-ups. Figure 172.5 shows the clinically estimated relations between the symptom 'day fatigue' and various other health problems in different health domains. The estimated relations are expressed as strong (dark blue), medium (mid blue) and weak (pale blue).

To facilitate the analysis of the health development over time, all measured variables should be visualized graphically, such as symptom scores, diagnose scores, functional assessment scores, rating scale scores, laboratory test-scores, and so on.

Table 172.1 Unsorted matrix of Diagnostics (symptoms and diagnoses) and Treatment divided in 6 methods and 35 components, for an 82-year-old multimorbid woman

Diagnostics		**Treatment (6 methods and 35 components)**						
Symptoms = 18	**Diagnoses of chronic health problems = 24**	**Medical prescription drugs = 13**	**Nutrition = 3**	**Physical activity/ exercise = 2**	**Medico-technical devices = 1**	**Technical aids = 9**	**Activities of daily living (ADL) = 7**	
Thirsty	Chronic heart failure	Calcium/ vitamin D	Dietary advice	Daily walks	Skin wound care	Cane	Instrumental (social services) *ADL=5*	Personal (personal care) *ADL=2*
Day tiredness, fatigue	Parkinson's disease	Metoprolol	Meal order planning	Home training programme		Walker		
Frequent urination	Hearing loss, sensory-neural	polyethylene glycol + KCl	Nutrition suplement			Hearing aid		
Dry mouth	Mild cognitive impairment	Acetyl salicylic acid				Urinary incontinence pads	Shopping	Shower
Body weight reduction, non-voluntary	Urininary incontinence	Citalopram				Multiple handles in appartment	Cooking	Dressing
Impaired memory	Skin wound lower left leg	Levothyroxin				Floor thresholds eliminated	Making bed	
Balance problem, falls x many	Diabetes mellitus type 2	Enalapril				Safety larm	Cleaning	
Hearing problems	Depression	Alendronate				Glasses, reading	Transportation service	
Shortness of breath	Chronic pain syndrome	Zopiclone				Dentures, both jaws		
Tremor	Insomnia	Mirabegron						
Difficulties swallowing	Vitamin B12 malabsorption (atrophic gastritis)	Vitamin B12						
Pain	Dysphagia	Paracetamol						
◆ right shoulder	Body weight reduction, non-voluntary	L-DOPA						
◆ hands, fingers	Hypertension							
Sleeping problems	Status post hip replacement right hip							
Palpitations	Pruritus NUD							
Dry eyes with secretion	Hypothyreosis, primary							
Muscle weekness	Osteoporosis with several fractures							
Cold hands and feet	Balance problem, falling tendency							
	Xerophtalmia							
	Sarcopenia							
	Allergic to penicillin							
	Constipation							
	Xerostomia							

Table 172.2 The same Diagnostics and Treatment matrix as in Table 172.1, sorted according to health problem areas. Symptoms and ADL are omitted from this matrix

Health problem areas	Diagnoses of chronic health problems = 24	Treatment = 28 components (35 if instrumental- and personal ADL are included).				
		Medical prescription drugs = 13	Nutrition = 3	Physical activity/ exercise = 2	Medico-technical devices = 1	Technical aids = 9
Neuro-psychiatric (n = 4)	Parkinson's disease	L-DOPA				
	Mild cognitive impairment					
	Depression	Citalopram				
	Insomnia	Zopiclone				
Cardiovascular (n = 2)	Chronic heart failure	Enalapril				
	Hypertension	Metoprolol				
		Acetyl salicylic acid				
Pulmonary/airways	0					
Gastrointestinal (n = 3)	Xerostomia					Dentures, both jaws
	Dysphagia					
	Constipation	Macrogol + KCl				
Renal/urinary (n = 1)	Urininary overflow incontinence	Mirabegron				Urinary incontinence pads
Gynaecological	0					
Endocrine/metabolism (n = 3)	Diabetes mellitus type 2		Dietary advice	Daily walks		
	Hypothyreosis, primary	Levothyroxin				
	Vitamin B12 malabsorption (atrophic gastritis)	Vitamin B12				
Blood	0					
Joints (n = 1)	Status post-hip replacement right hip					
Muscles (n = 1)	Sarcopenia					
Skeleton (n = 1)	Osteoporosis with several fractures	Calcium/vitamin D				
		Alendronate				
Body weight (n = 1)	Body weight reduction, non-voluntary		Meal order planning			
Fat mass			Nutrition supplement			
Non-fat mass						
Gait/balance (n = 1)	Balance problem, falling tendency			Home-training programme		Cane
						Walker
						Multiple handles in apartment
						Floor thresholds eliminated
						Safety alarm

(*continued*)

Table 172.2 Continued

Health problem areas	Diagnoses of chronic health problems = 24	Treatment = 28 components (35 if instrumental- and personal ADL are included).				
		Medical prescription drugs = 13	Nutrition = 3	Physical activity/ exercise = 2	Medico-technical devices = 1	Technical aids = 9
Skin (n = 2)	Skin wound lower left leg				Skin wound care	
	Pruritus NUD					
Pain (n = 1)	Chronic pain syndrome	Paracetamol				
Eyes/vision (n = 1)	Xerophalmia					Glasses, reading
Ears/hearing (n = 1)	Hearing loss, sensory-neural					Hearing aid
Allergy/oversensitivity (n = 1)	Penicillin					

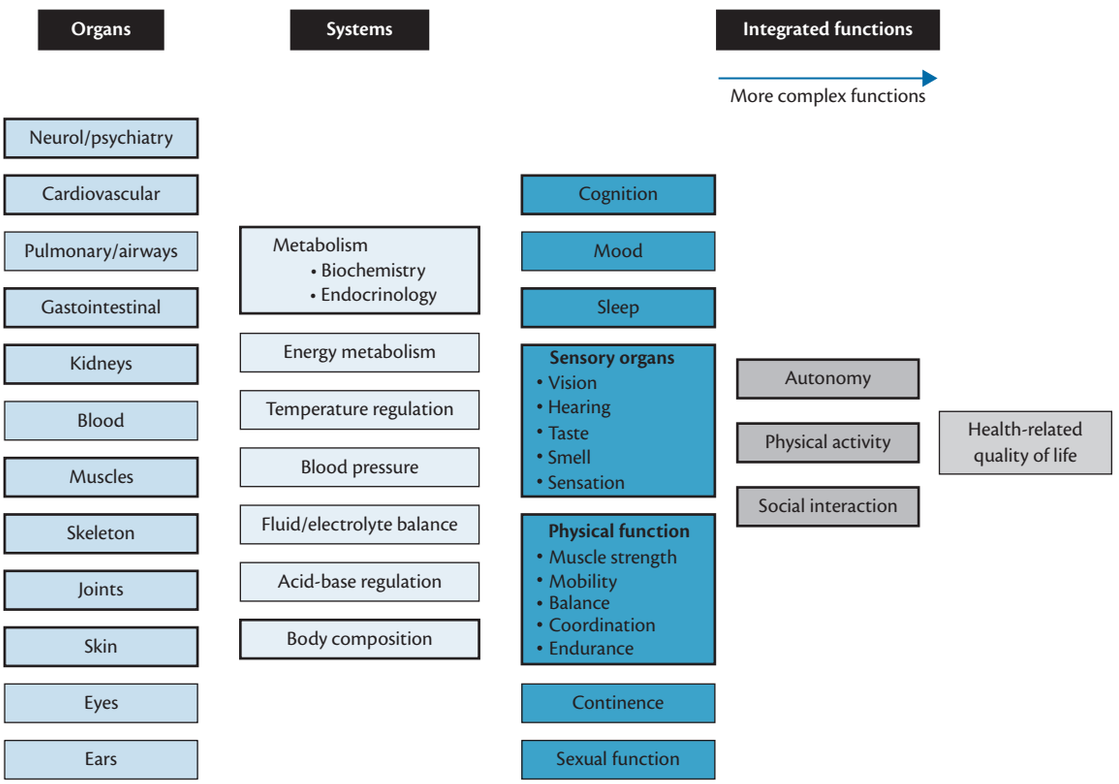

Fig. 172.2 The structure of 'diagnosis of chronic health problems' may be elaborated by separation into organ, system, and various functional problems. Active problem areas for the patient are indicated by bold frames around the boxes.

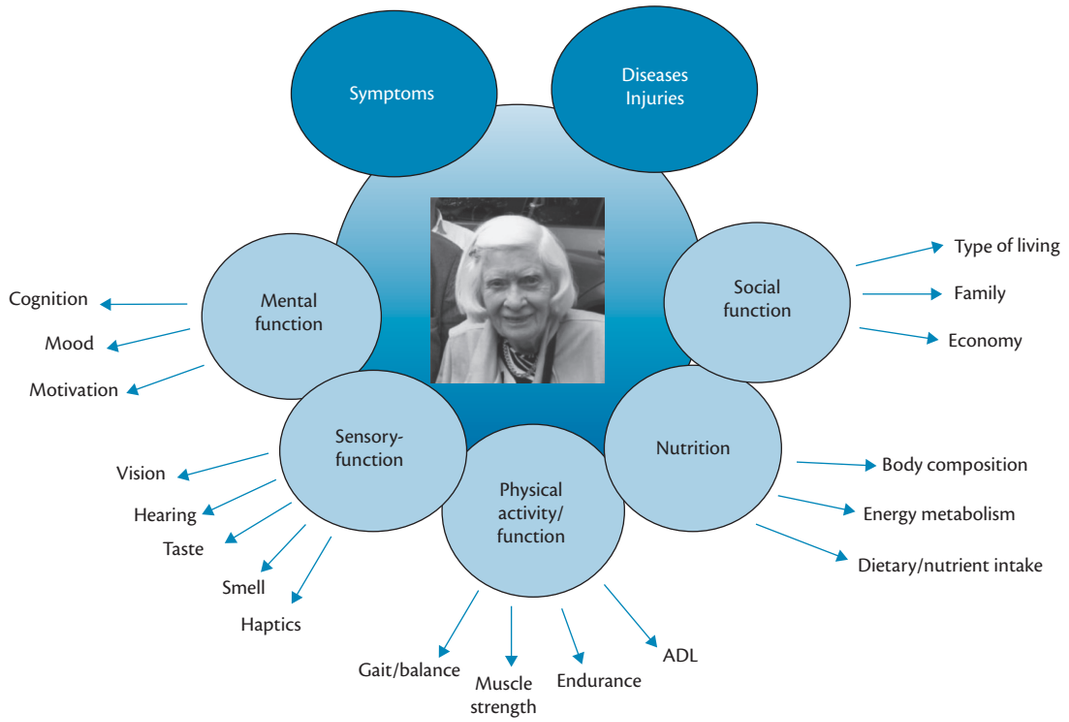

Fig. 172.3 Example of seven health domains, that could be included in an integrated, multidomain health analysis.

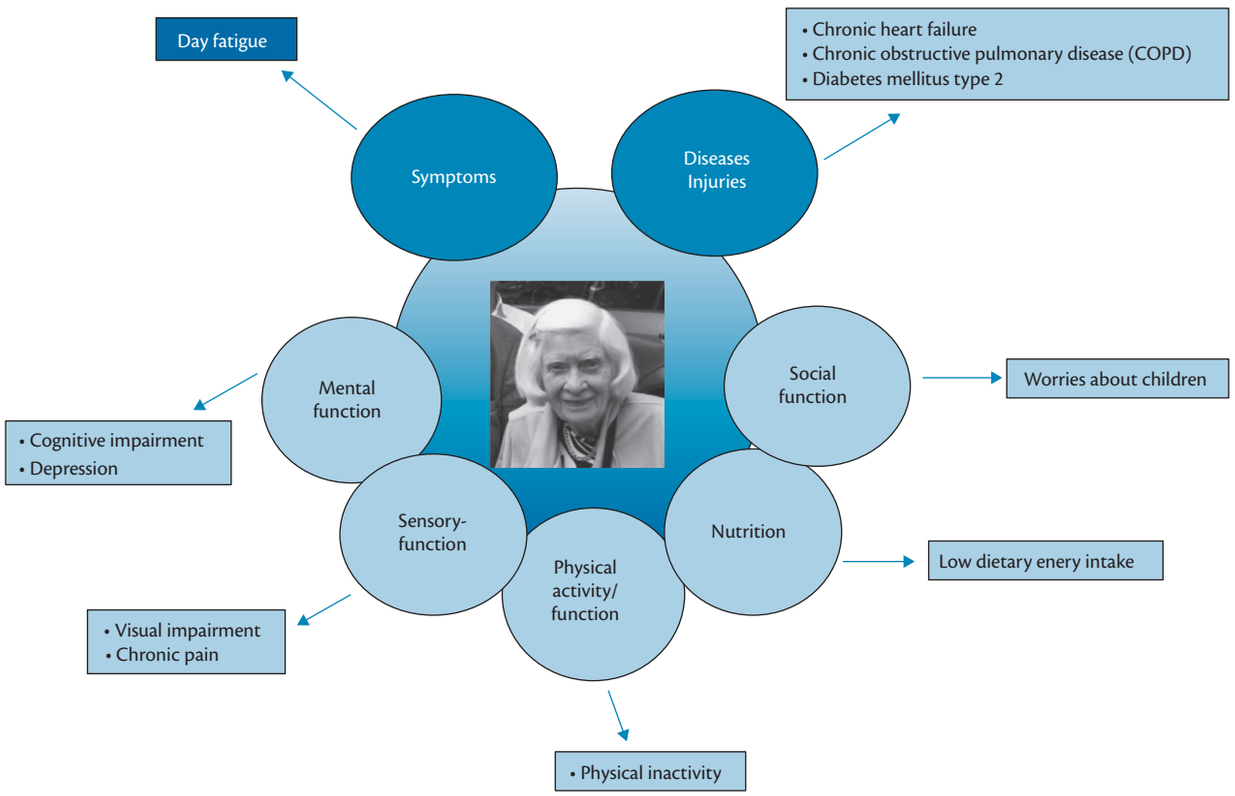

Fig. 172.4 Example of possible relations between the symptom 'day fatigue' in the symptom domain and defined health problems in six other health domains.

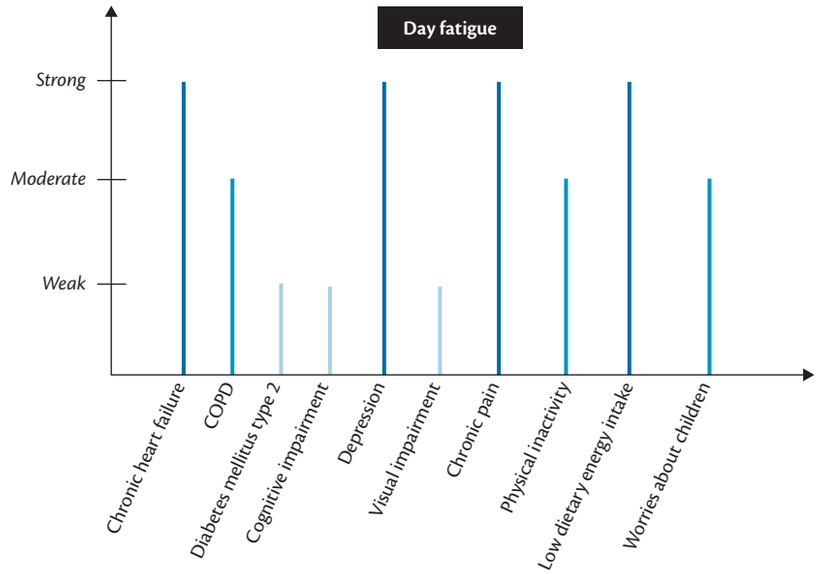

Fig. 172.5 Example of clinically estimated relations between the symptom 'day fatigue' and other health problems in different health domains scored in three degrees: weak (pale blue), moderate (mid blue), and strong (dark blue) relations.

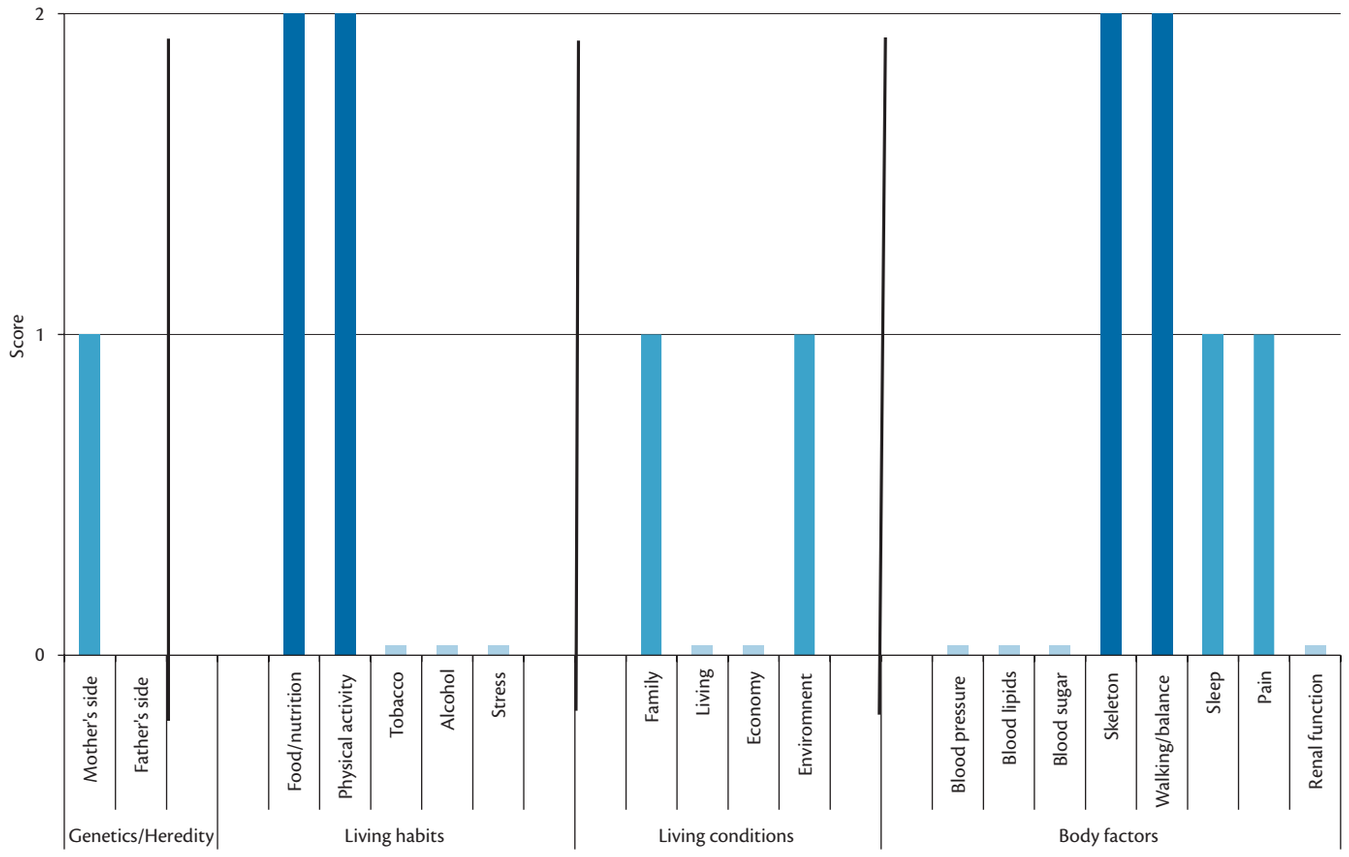

Fig. 172.6 Graphic risk factor profile, where specified risk factors have been divided in four categories and rated by the patient in two degrees; low (mid blue) and high (dark blue) experienced health risks.

Prevention—risk factor profile

The clinical assessment and evaluation should be integrated with an analysis of the individual patient's risk factors. This could be done by defining four categories of risk factors and expressing them graphically as a profile:

- *Genetic risk factors* (e.g. health problems in first-degree relatives, genotyping)
- *Living habit risk factors* (e.g. tobacco smoking, use of alcohol, use of drugs, physical inactivity, poor dietary intake, and so on)
- *Living condition risk factors* (e.g. problems with family, housing, economy, environment, and so on)
- *Body risk factors* (e.g. high/low blood pressure, high/low blood sugar, high blood lipids, low bone mineral density, falling tendency, low skeletal density, and so on)

It is important to realize that most chronic health problems also constitute body risk factors, both regarding progression of the respective health problem, as well as for developing or worsening other health problems. For example, chronic renal insufficiency constitutes a risk factor for cardiovascular disease, chronic pain a risk factor for depression, and many others.

Moreover, medical prescription drug treatment, particularly polypharmacy, also constitutes an important risk factor for adverse drug reactions, drug–drug interactions, and so on.

These and other risk factors could be visualized graphically and a starting point may be the individual patient rating her/his felt degree of health risk for the various risk factors over time, scored in two degrees (weak and strong risk); see Figure 172.6.

From this pedagogical and empowerment-supporting subjective estimate of health risks, it is possible to go further and estimate the patient's prognosis for defined outcomes, such as cardiovascular risk for myocardial infarction, stroke, or death; neuropsychiatric risk for cognitive impairment or suicide; risks for falls or fractures, and so on. The scientific basis for such estimates for age 75+ are weak, but there may be some guidance from published studies in younger age groups.

The risk factor analysis could be complemented by a 'health factor profile' (i.e. health domains and health aspects that are not impaired and thus represents strengths and benefits for the individual).

Facilitators

A DTF-based health analysis including both manifest health problems and risk factors, as discussed above, would be greatly facilitated by:

a) all physicians and staff working with multimorbid, elderly people having a thorough *education and training* in geriatric medicine, including continued medical education in geriatric medicine;

b) an integrated *medical record* structured according to the DTF-model;

c) an integrated *healthcare organization* supporting clinical teamwork over time according to the DTF-model.

The presented four-step clinical analysis process based on the DTF-model serves to operationalize how a comprehensive geriatric assessment could be visualized, thereby serving as a much longed for 'geroscope'.

Healthcare of multimorbid older people should encourage skillful, integrated, and repeated diagnostic assessment, integrated and coordinated treatment/care, repeated follow-up, and easy access to a second opinion.

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