

**Cured - but  
at what  
costs?**

# Bio-psycho-social late effects after cancer and cancer treatment

Prevalence, consequences, treatment

# Late effects after cancer and cancer treatment

- Approx. **352,000\*** citizens in Denmark have been diagnosed with cancer
- Higher incidence rates\*\* and more effective treatments
- Cancer treatments are not without costs:
- Approx. **50% of cancer survivors** are expected to experience one or more late effects

*“Late sequelae are health problems that occur during primary treatment and become chronic, or that occur and become manifest months or years after treatment has ended. Late effects include new primary cancers and physical, psychological, or social changes as a consequence of the cancer and/or its treatment”* [The Danish National Board of Health, 2017](#)

\*) 2019 (Cancer.dk), \*\*) 2012-2016 to 2032-2036: 35% (men), 22% (women)

# Late effects after cancer and cancer treatment

Specific, localized symptoms and late effects after surgery and radiotherapy, e.g., lymphedema, and localized pain

General late effects after cancer and cancer treatment

General "biopsychosocial" symptoms and late effects occurring across cancer types and treatments, e.g., fatigue, sleep impairment, pain, cognitive difficulties, depression, fear of cancer recurrence

Specific loco-regional late effects

Specific late effects after systemic treatment

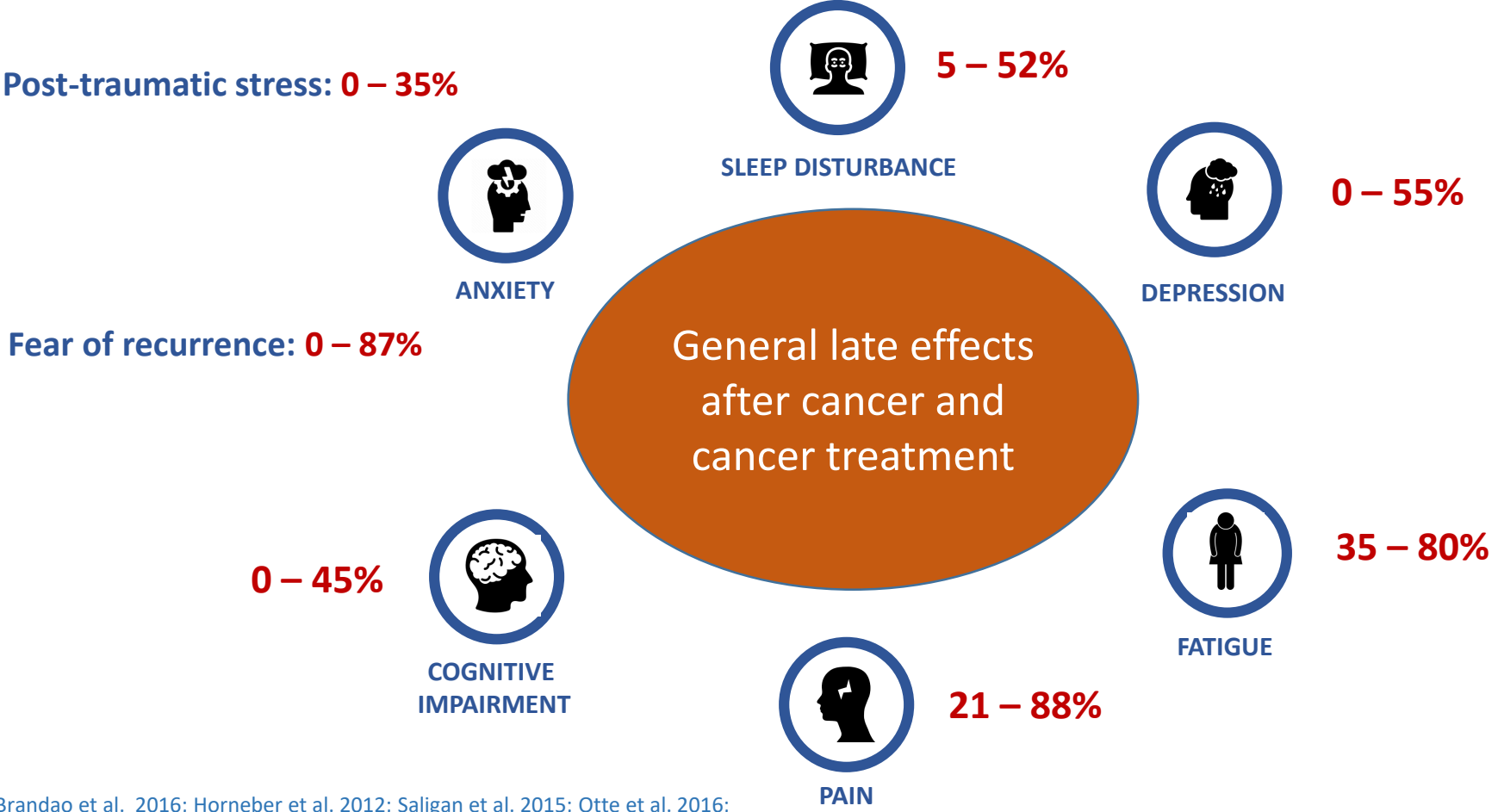
Specific symptoms and late effects after chemotherapy, hormone therapy, biological treatments, e.g., sensory disturbances, neuropathic pain, hot flashes

Secondary treatment-induced disease, e.g., heart disease and new cancer after radiotherapy

Treatment-induced secondary disease

Zachariae & Mehlsen (eds.) 2020

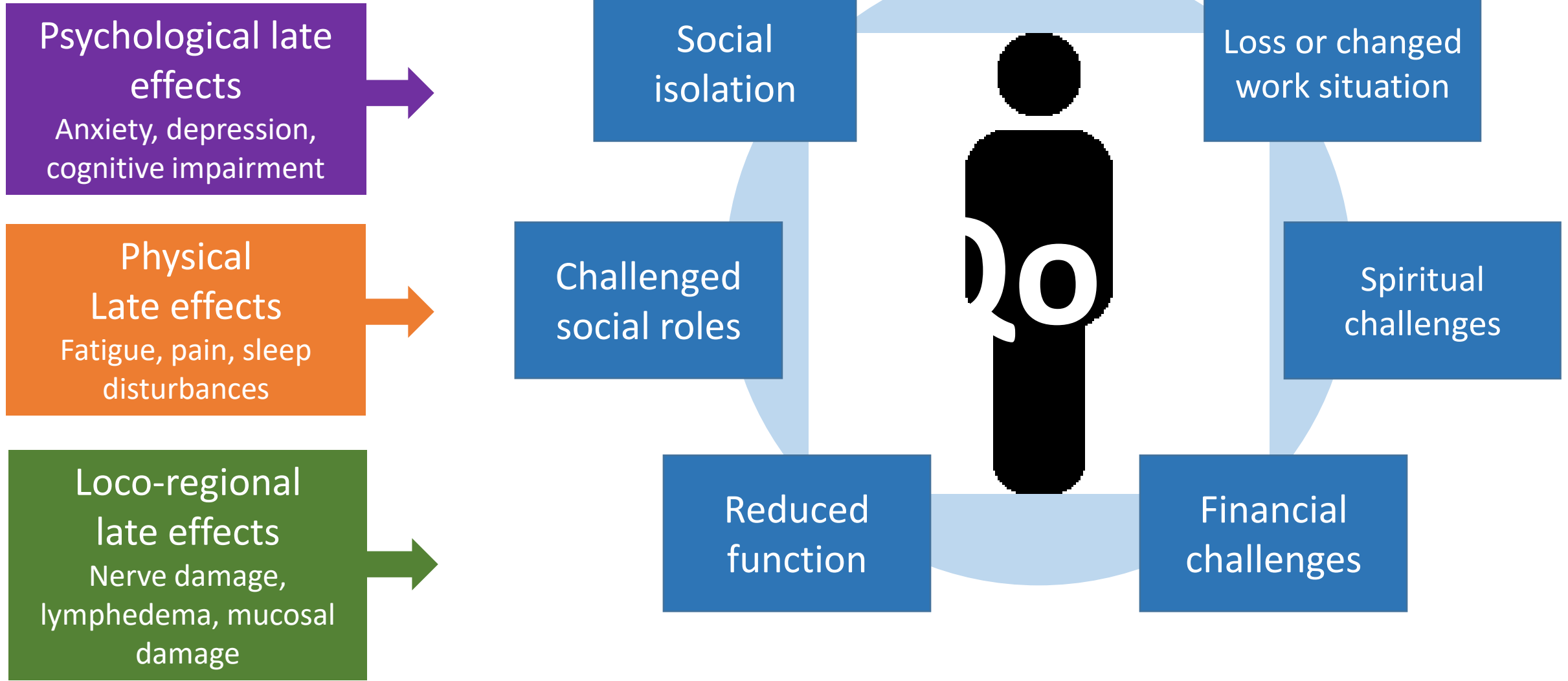
# Common late effects across cancer types and treatments



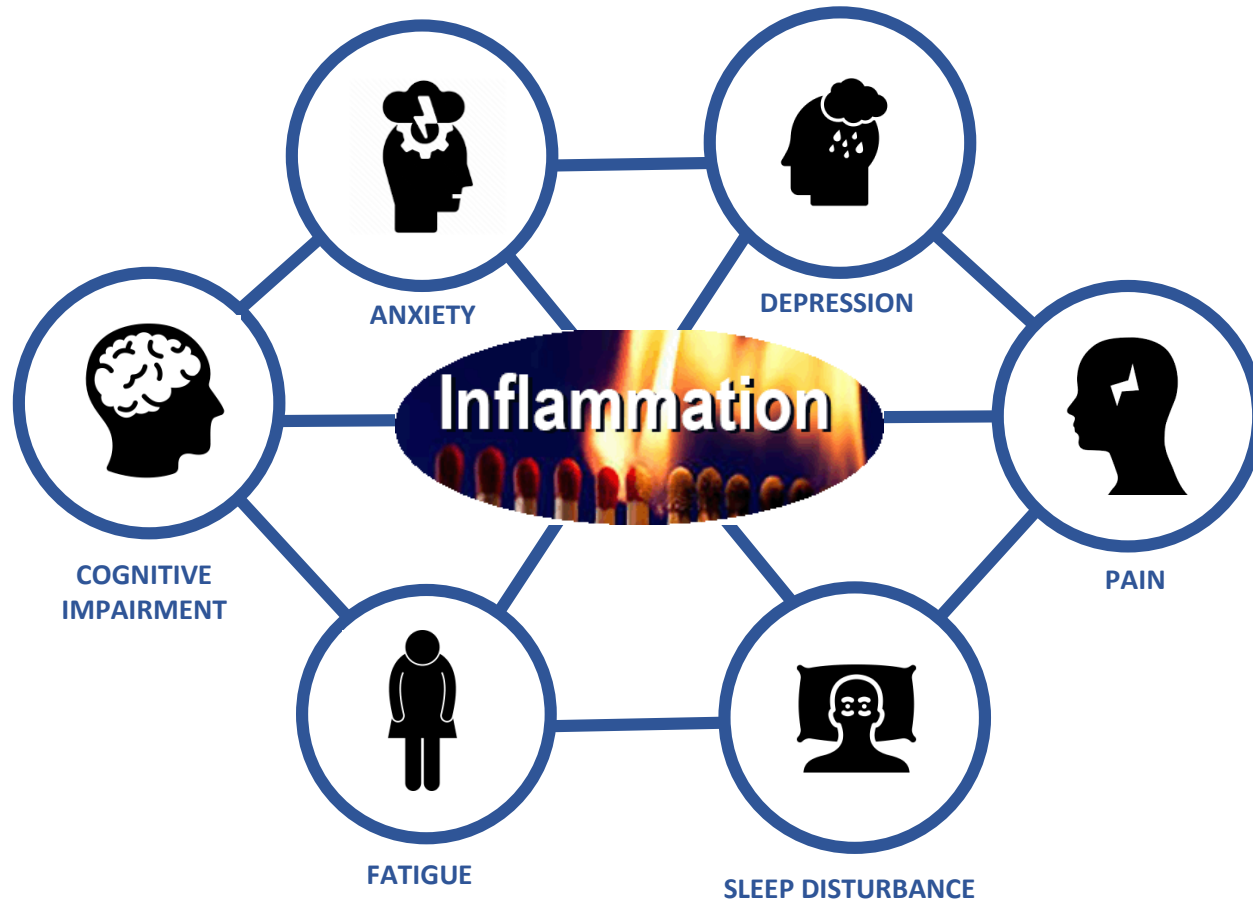
- Prevalence uncertain
- Depends on cancer type, treatment, and time of assessment
- Limited knowledge about predictors, e.g., psychosocial and lifestyle-related
- Lack of large prospective population-based studies
- Quality databases (DMCGs) provide unique opportunities to uncover late effects, causes, patients at risk, and trajectories over time

Brandao et al. 2016; Horneber et al. 2012; Saligan et al. 2015; Otte et al. 2016; van den Beuken-van Everdingen et al. 2007; Simard et al. 2013; Zachariae & Mehlsen, 2011; 2020; Moore et al. 2014.

# Consequences



# Symptom clusters!

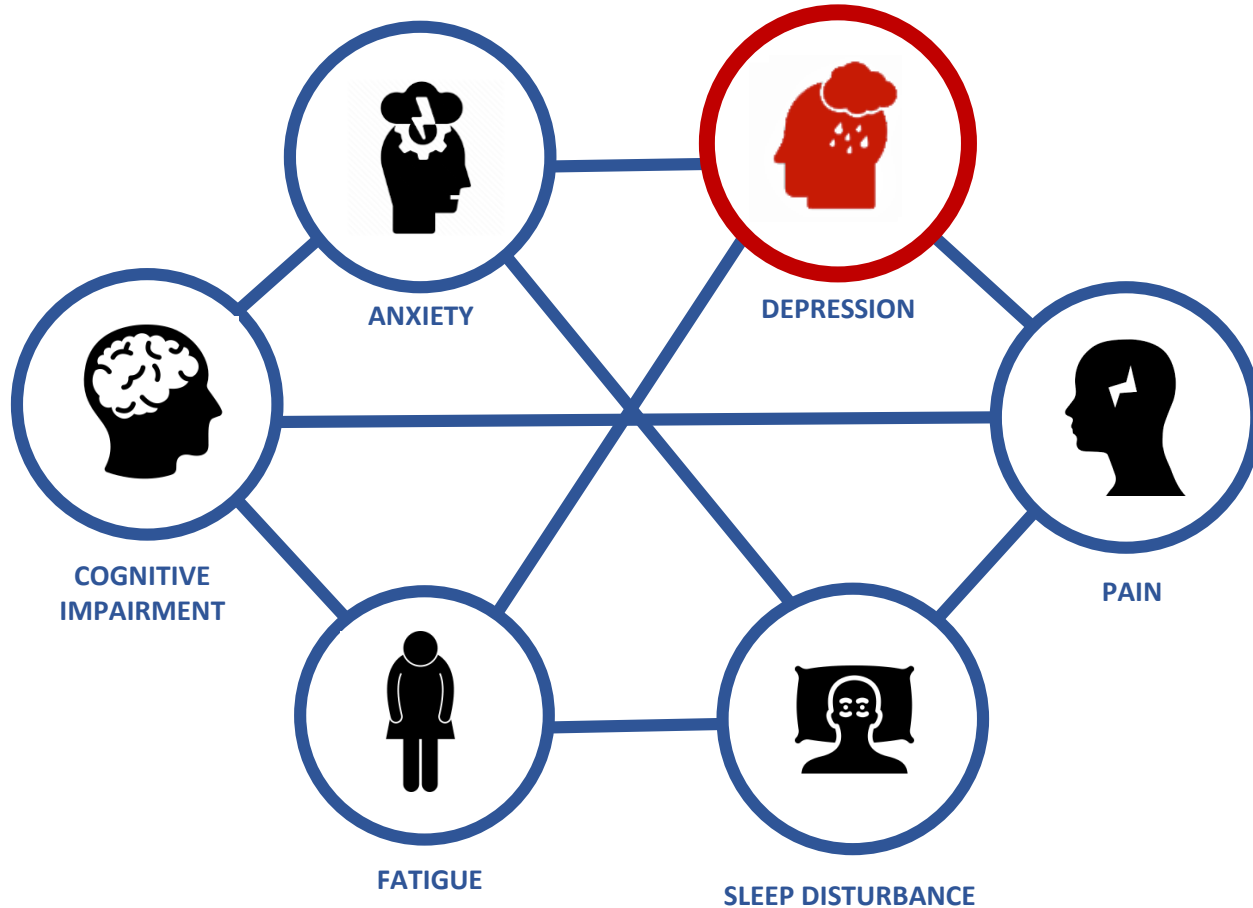


Lee et al. 2004; Irwin et al. 2013; Carlotto et al. 2013; Dong et al. 2014; Fagundes, et al. 2015; Marshall et al. 2017; Xu et al. 2018

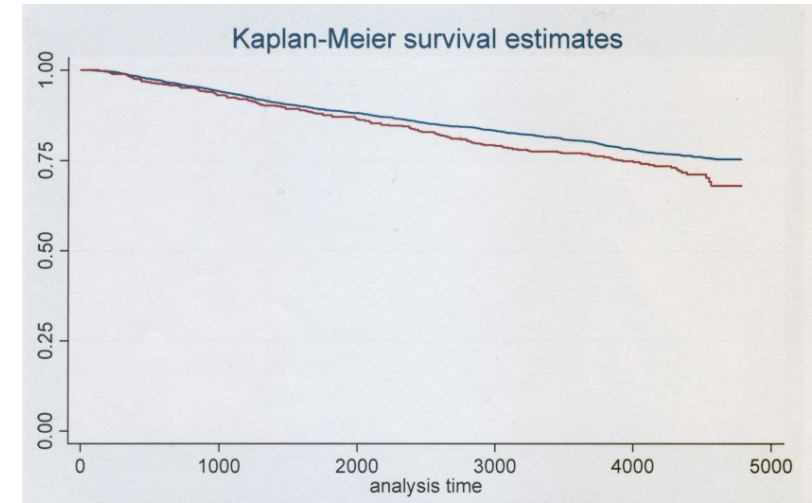


Helgeson et al. 2004

# Depression

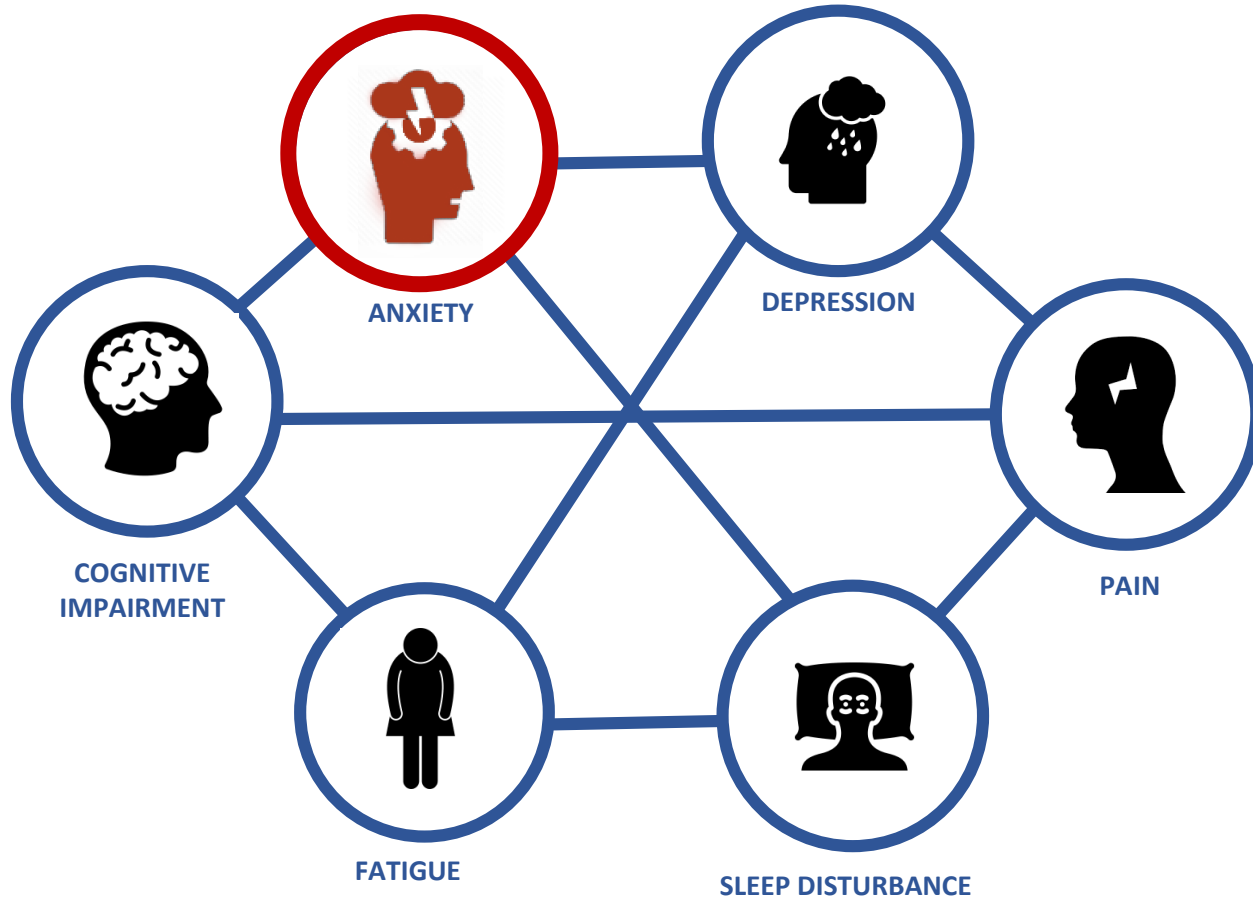


- Persistent clinically significant depressive symptoms associated with poorer prognosis



- 3343 women treated for breast cancer completed questionnaires 3 months and 15 months after surgery
- Depression at **15 months** associated with **54%** increased mortality
- Depression at 3 months *not associated* with mortality (9-10 years FU) (Christensen et al. 2016)

# Anxiety



- **Fear of cancer recurrence (FCR)** is
- Among the 5 most distressing symptoms
- The most common problem that patients want help with (unmet need)
- Associated with increased risk of
  - Depression
  - Reduced QoL
  - Impaired daily function
  - Overuse of health services
  - Underuse of health services
- Systematic review of 130 studies:

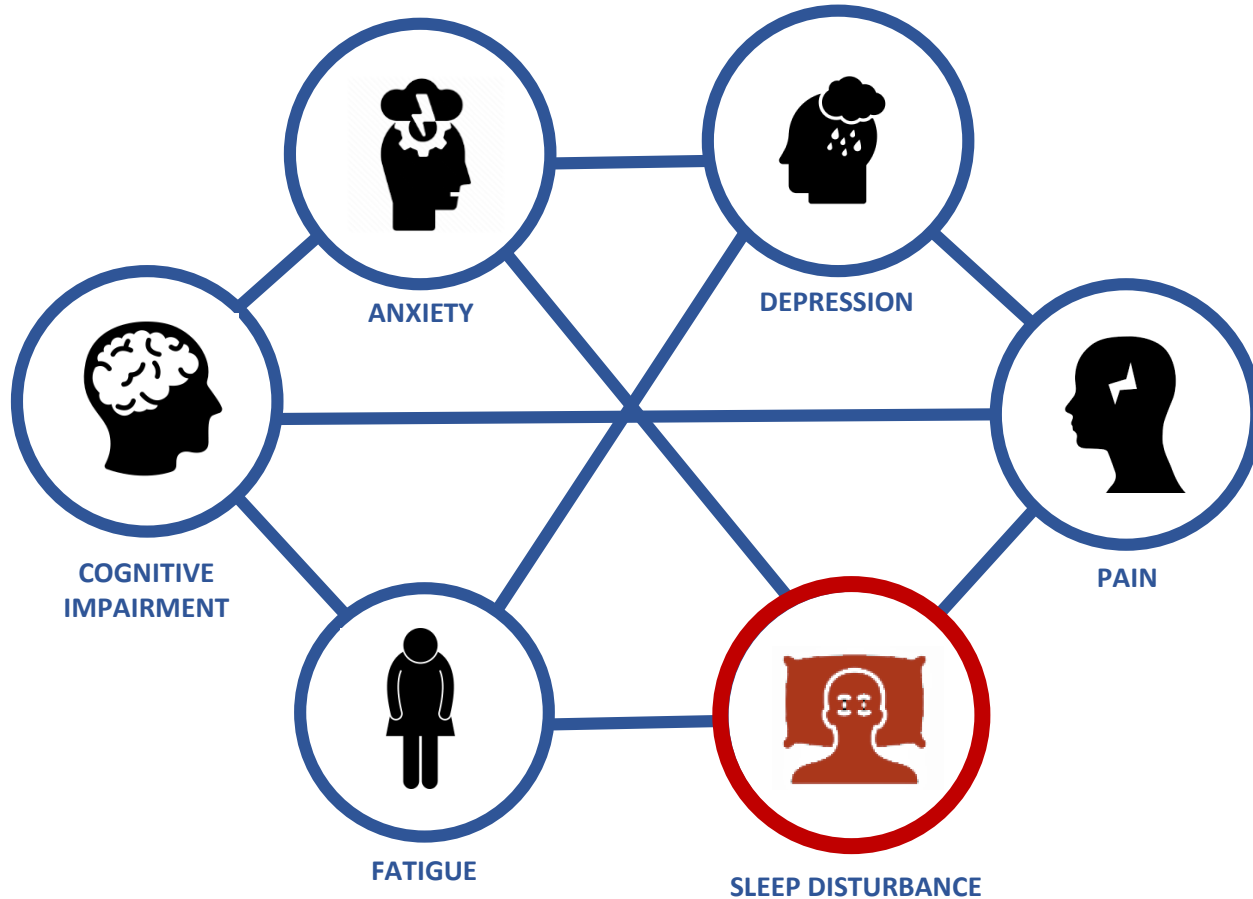
| Fear of recurrence   | Prevalence |
|----------------------|------------|
| To some degree       | 39-97%     |
| Moderate-high degree | 22-87%     |
| Very high degree     | 0-15%      |

- 1890 Danish women 7-9 years after BC-diagnosis: **24%** (pre-menopausal), **17%** (post-menopausal)

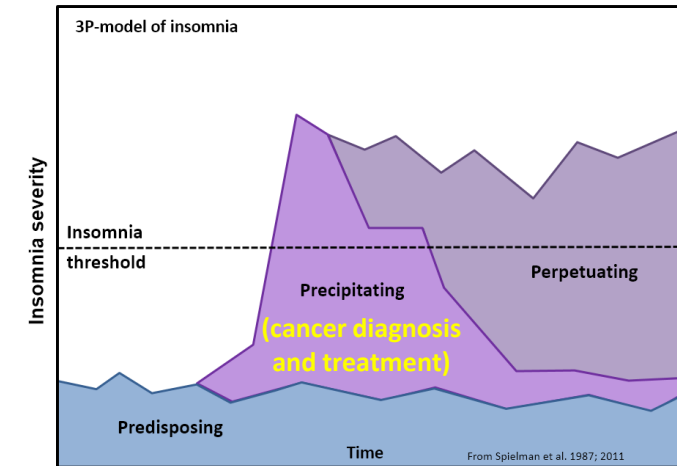
Simard et al. 2014; Thewes et al. 2014



# Sleep disturbance



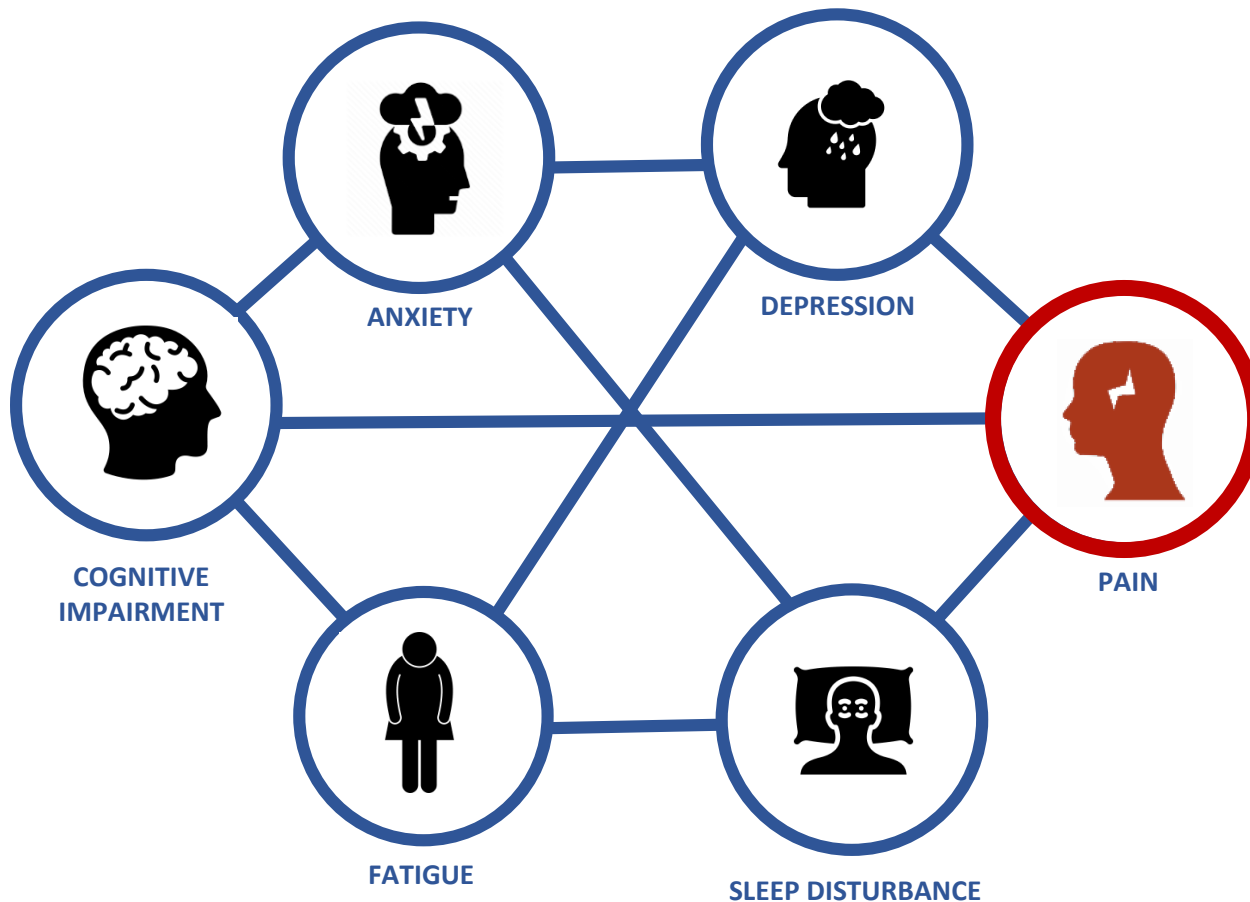
- Cancer patients and survivors have an increased risk of **insomnia**, i.e., persistent difficulty falling asleep and/or maintaining sleep
- **Consequences**: Fatigue, exhaustion, and possibly increased risk of recurrence
- **Amplifies** anxiety, depression, fatigue, pain, and cognitive difficulties
- **Predisposing, precipitating, and perpetuating** factors:



- 3343 Danish women treated for breast cancer: **57.9%** report distressing sleep problems 3 months after diagnosis, **51.9%** 7-9 years after diagnosis. General population: **10-15%**

Savard & Morin, 2001; Savard et al. 2009; Otte et al. 2015; Halle et al. 2017, Colagiuri et al. 2011, 2012; Riemann et al. 2015; Buysse, 2013; Hammersen, 2017

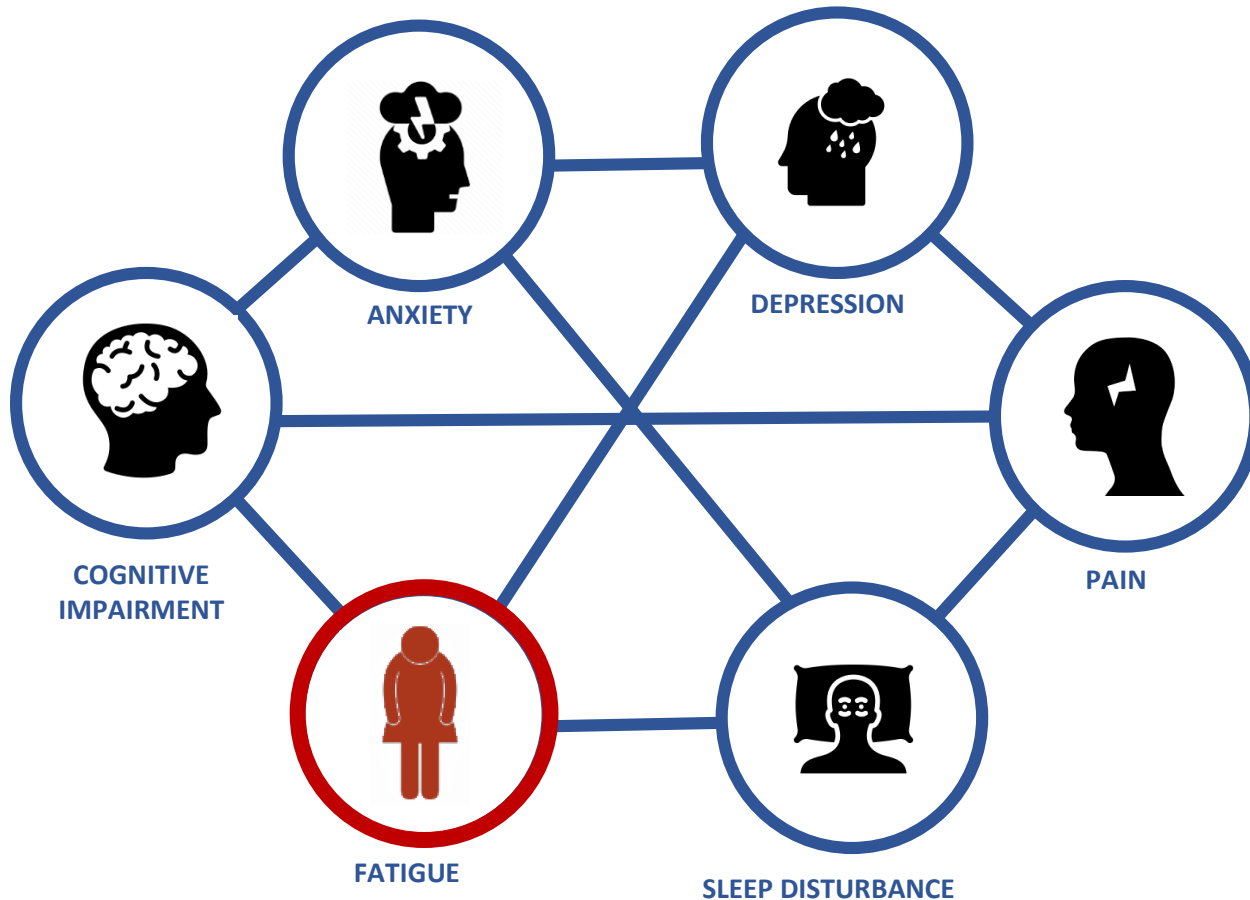
# Pain



- **Pain** is a frequent sequelae of cancer treatment
- **Types of pain:** somatic, visceral and neuropathic
- **Pain dimensions:** the overall experience of pain includes *sensory, emotional, and cognitive* aspects
- **Important to examine:** *intensity, quality, perceived burden, impact on daily function*
- Psychological processes, e.g., tendency to “**catastrophize**”, significant risk factor for chronic pain
- 1905 Danish women treated for breast cancer: Pain “**almost every day**” or “**all the time**”:
- 15 months after diagnosis: **32.7%**
- 7-9 years after diagnosis: **20.4%**
- Independent **risk factors:** Low SES, ALND, endocrine therapy, BMI 30-35, comorbidity, poorer physical function

Johannsen et al. 2015; Mulvey et al. 2017; Brown et al. 2017

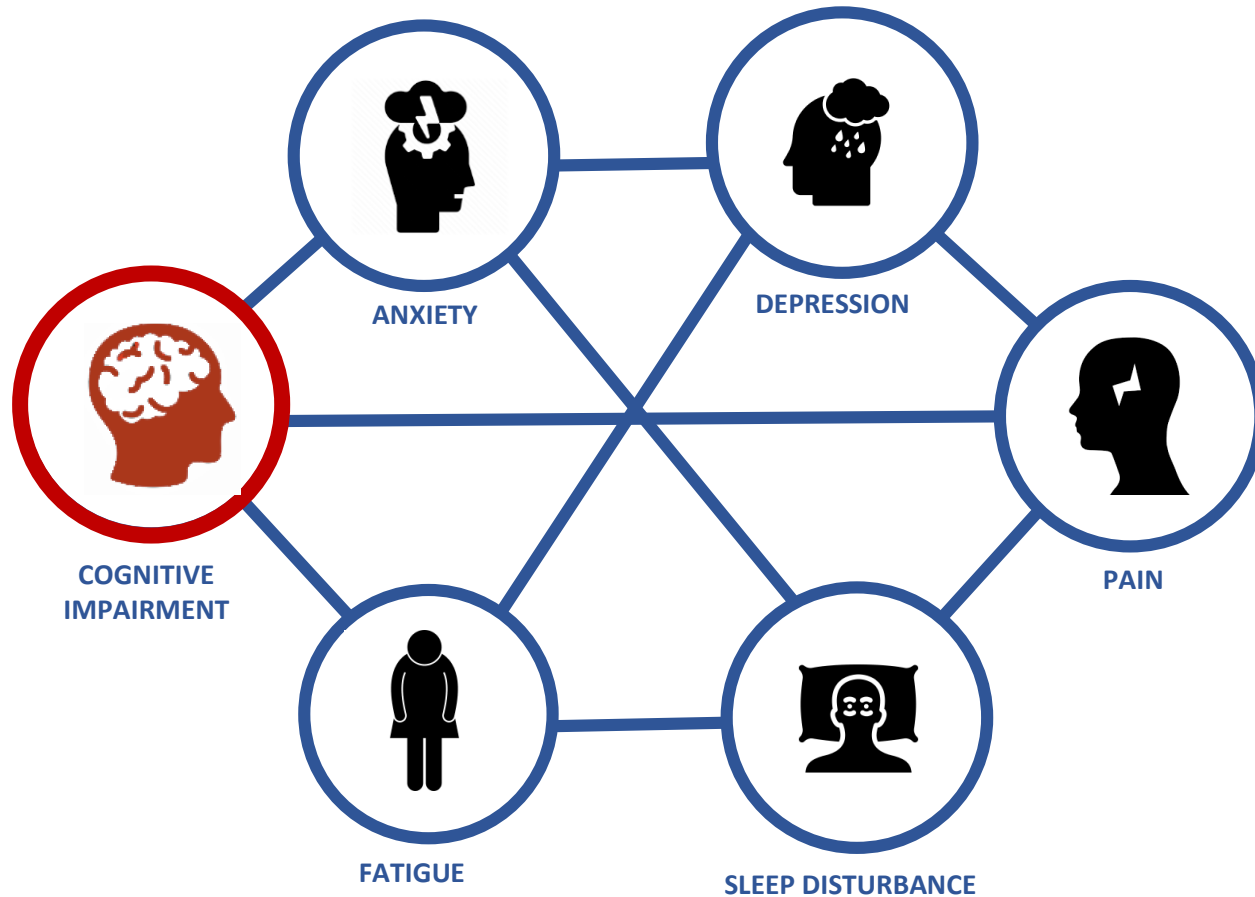
# Fatigue



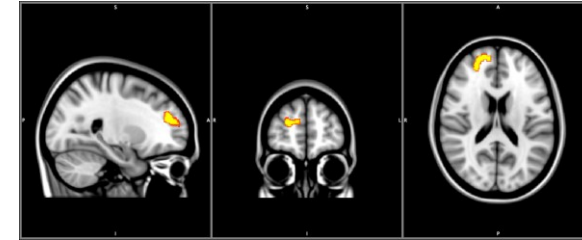
- **Cancer-related fatigue** among the most distressing side and late effects
- **70-90%** of cancer patients receiving chemotherapy
- Up to **30%** of cancer survivors several years after completion of primary treatment
- Factors that independently contribute to cancer-related fatigue:
  - Symptom burden: pain, anxiety, depression
  - Sleep disorders, circadian rhythm disorders
  - Changes in physical function: physical inactivity, physical deconditioning
  - Physiological factors: anemia, comorbidity, e.g., infection, difficulty breathing
  - Medication: painkillers, sleeping pills etc.
  - Cancer treatment: chemotherapy, radiation therapy, surgery, biological treatments, etc.
  - The cancer itself

Ancoli-Israel et al. 2001; Campos et al. 2011; Harris et al. 2014

# Cognitive impairment



- **Cognitive impairment:** High prevalence of self-reported difficulties in women treated for breast cancer (**21% -90%**: meta-analysis of 27 studies)
- Measured with: Self-report, neuropsychological tests, neurophysiological examinations, e.g., MRI, PET. The between-measurement correlations vary.



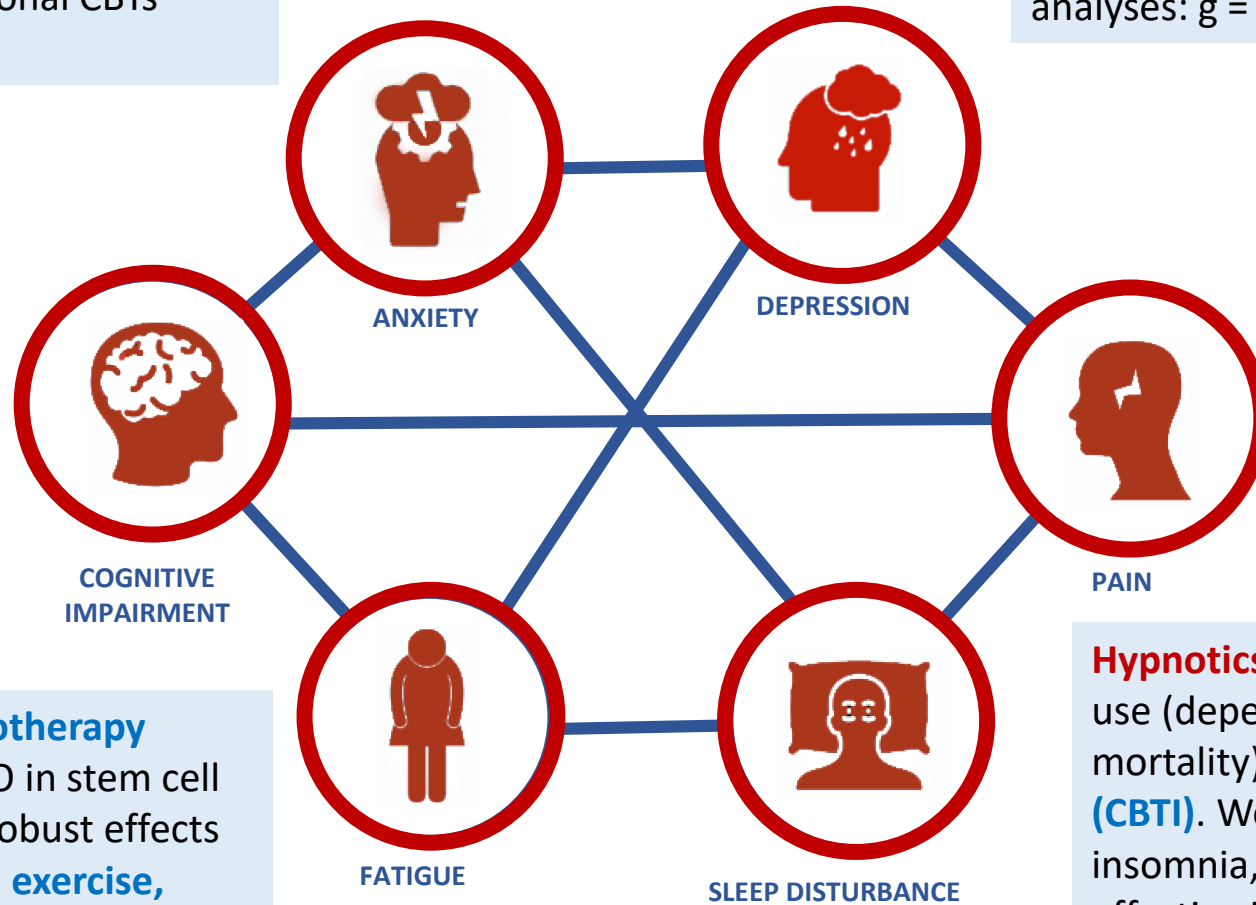
- Even moderate cognitive difficulties can affect quality of life, ability to work, and ability to perform social and societal functions.
- Possible risk factors:
  - Background factors: age, education, genetic factors
  - The cancer: inflammation, hormonal changes
  - Cancer treatment: Chemotherapy, radiation therapy, hormone therapy
  - Behavioral reactions: Sleep disturbances, fatigue
  - Emotional reactions: Stress, depression, anxiety

Calvio et al. 2009; Pullens et al. 2010; Zachariae & Mehlsen, 2011; Amidi et al. 2015; Amidi et al. 2020  
Buskbjerg et al. 2020

**Psychotherapies** for FCR: 23 RCTs, post-treatment ( $g=0.33$ ), follow-up ( $g=0.30$ ). Contemporary CBTs (e.g., ACT, MBTs) more effective ( $g=0.42$ ) than traditional CBTs ( $g=0.24$ ) Tauber et al. 2020

Limited evidence. Treatment options are **cognitive training** and **compensatory strategies**. Meta-analysis (11 studies): memory ( $d=0.21$ ), general cognitive function ( $0.41$ ).

Minimal effects of **pharmacotherapy** ( $g=0.09$ ). An exception is EPO in stem cell transplanted pts. The most robust effects have been found by **physical exercise**, **psychotherapy**, and combinations of the two ( $g=0.30, 0.27, 0.26$ ) Amidi & Zachariae. 2020



0.2 (small), 0.5 (medium), 0.8 (large)  
0.5  $\approx$  clinically relevant

The **antidepressant** literature is limited. **Psychotherapies**, e.g., CBTs and MBTs, including digitally delivered are relatively efficacious. Meta-analyses:  $g = 0.21-0.38$  Cillesen et al. 2019

**Pharmacotherapies**, mixed effects. Depends on pain type. Effects of **psychotherapies**, e.g., CBTs, hypnosis, relaxation, MBTs, guided imagery ( $g = 0.37$ ). Johannsen et al. 2013, 2016, 2018

**Hypnotics** not recommended for long-term use (dependence, side effects, increased mortality). First choice is **CBT for insomnia (CBTI)**. Well-documented effects in comorbid insomnia, e.g., in cancer ( $g = 0.53$ ). Digital CBTI effective in breast cancer ( $g=1.17$ ). Johnson et al. 2016, Zachariae et al. 2016, 2018

# Take-home message

- Late effects are a common problem
- May occur in clusters
- Symptoms maintain and reinforce each other
- No "magic bullet"
- But many different approaches, including physical and psychosocial, can be brought into play
- Several treatments are relatively well-documented, and may also be cost-effective
- But are rarely offered by the healthcare system (costs, number of trained therapists)
- There is a need to clarify the prevalence and trajectories over time, and determine whether there are groups with special needs
- There is also a need to identify women with clinically significant late effects to offer the best available, evidence-based treatment



- Vedvarende smerter efter kræftbehandling
- Kræftrelateret træthed
- Søvnproblemer efter kræft og kræftbehandling
- Kognitive forandringer efter kræft og kræftbehandling
- Psykologiske reaktioner blandt personer behandlet for kræft
- Seksualitet og fertilitet
- Mennesket efter kræftsygdom
- Arbejdslivet efter kræft
- Pårørende



2020