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Fatigue and the prediction of negative health outcomes: a systematic review with meta-analysis

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Highlights

- 30 papers included providing information on the relationship between fatigue and health outcomes
- Fatigue increases the risk for developing negative health outcome (OR 1,3–3,1 HR/RR 1,0–1,5)
- Fatigue-related physical decline occurs earlier than hospitalization, disease & mortality

Abstract

Introduction: Fatigue is a common complaint among older adults. Evidence grows that fatigue is linked to several negative health outcomes. A general overview of fatigue and its relationship with negative health outcomes still lacks in the existing literature. This brings complications for healthcare professionals and researchers to identify fatigue-related health risks. Therefore, this study gives an overview of the prospective predictive value of the main negative health outcomes for fatigue in community-dwelling older adults.

Methods: PubMed, Web of Knowledge and PsycINFO were systematically screened for prospective studies regarding the relationship between fatigue and negative health outcomes resulting in 4595 articles (last search 5th March 2020). Meta-analyses were conducted in RevMan using Odds ratios (ORs), Hazard ratios (HRs) and relative risk ratios (RR) that were extracted from the included studies. Subgroup-analyses were performed based on (1) gender (male/female), (2) length of follow-up and (3) fatigue level (low, medium and high).

Results: In total, thirty articles were included for this systematic review and meta-analysis encompassing 152 711 participants (age range 40-98 years), providing information on the relationship between fatigue and health outcomes. The results showed that fatigue is related to an increased risk for the occurrence of all studied health outcomes (range OR 1,299 – 3,094, HR/RR 1,038 – 1,471); for example, mortality OR 2.14 [1.74–2.63]; HR/RR 1.44 [1.28-1.62]), the development of disabilities in basic activities of daily living (OR 3.22 [2.05–5.38]), or the occurrence of physical decline (OR 1.42 [1.29–1.57]).

Conclusion: Overall fatigue increases the risk for developing negative health outcomes. The analyses presented in this study show that fatigue related physical decline occurs earlier than hospitalization, diseases and mortality, suggesting the importance of early interventions.

Keywords: Fatigue, Tiredness, Prospective risk outcomes, community-dwelling, elderly, meta-analysis

1. Introduction:

Fatigue is a common complaint among older adults and is associated with functional decline and mortality (Avlund et al., 2002b, Hardy and Studenski, 2008). However, health care professionals often dismiss "non-specific" symptoms, such as fatigue, as an inevitable sign of ageing and old age without any specific treatment(Whitson et al., 2011). Fatigue is defined by the Diagnostic and Statistical Manual of Mental Disorders-5th Edition as a state usually associated with a weakening or depletion of one's physical and/or mental resources, ranging from a general state of lethargy to a specific, work-induced burning sensation within one's muscles. The feeling of being fatigued increases with age and is twice as common in female older adults compared to males(Meng et al., 2010). In general, the prevalence of fatigue is 15-75% in community-dwelling older adults depending on the instrument that was used to evaluate fatigue(Avlund et al., 2003b). Fatigue might be the sign' of age-related decline in reserves and in intrinsic capacity, leading to negative health outcomes. As often in geriatrics, it can be difficult to ascribe fatigue to a disease or to provide a definitive explanation regarding causality. Fatigue is often seen as a marker of aged-related accumulation of deficits indicating that fatigue represents the underlying vulnerability of the individual's homeostatic reserves representing a sign of biological aging. Previously, it has been shown that fatigue and muscle performance are strong prospective predictors for disability in older persons(Vestergaard et al., 2009, Zengarini et al., 2015). In addition, fatigue is one of the early characteristics of frailty as signs of fatigue are already shown approximatively nine years prior to the occurrence of frailty(Stenholm et al., 2019). These results(Stenholm et al., 2019, Zengarini et al., 2015), indicate that fatigue is an important characteristic of aged-related accumulation of deficits, indicating that fatigue represents the underlying vulnerability of the individual's homeostatic reserves representing a sign of biological aging. The presence of fatigue could provide prospective information for negative health outcomes(Zengarini et al., 2015, Eldadah, 2010), however, it can be expected that the predictive value differs according to the different domains and underlying mechanisms of fatigue(Hardy and Studenski, 2010).

Fatigue remains a complex phenomenon due to its multidimensional character and the co-existence of different underlying mechanisms(Hardy and Studenski, 2010), leading to an enlarged risk for negative health outcomes. Thereby, it has been shown that fatigue is an essential parameter in research on frailty(Knoop et al., 2019), reflected by the fact that a loss in physical reserve capacity is a crucial component of all comprehensive frailty scales. Several researchers have studied negative health outcomes that were linked to fatigue. Vestergaard et al. (2009) found in a cross-sectional study that fatigued older adults aged 65 and over have an increased risk for disabilities (OR 4.01 [2.26 – 9.47] for males) and (OR 2.22 [1.14 – 4.32] for females). Fatigue has also been associated with the presence of depression (OR 1.16 [1.08 – 1.26])(Soyuer and Senol,

2011) and reduced physical activity(Egerton et al., 2016, Engberg et al., 2017). Furthermore, older adults who experience tiredness in daily activities measured by the Lower Limb-T fatigue Scale have a 1.7-fold greater risk for the onset of disability (Avlund et al., 2002b, Avlund et al., 2003b). On top, fatigue is associated with reduced intrinsic capacity needed to perform normal physical activities(Gill et al., 2001), also shown in older adults with the presence of comorbid conditions (e.g. osteoarthritis)(Murphy et al., 2013). A general overview of fatigue and its relationship with negative health outcomes is still lacks in the existing literature which results in complications fort healthcare professionals and researchers to identify fatigue-related health risk and to combat fatigue through interventions.

In intervention studies (i.e. physical exercise, pharmacological and nutritional) designed to counter physical frailty, fatigue showed to be non-responsive to the interventions in comparison with other (physical) frailty characteristics (Bendayan et al., 2014, Bibas et al., 2014, Cesari et al., 2015, Pahor et al., 2014, Puts et al., 2017). Other studies have reported interventions to combat fatigue through a variety of pharmacologic(Malaguarnera et al., 2008, Malaguarnera et al., 2007), and nonpharmacologic interventions(Pahor et al., 2014, Gryson et al., 2014, Ho and Ng, 2020). Most effects were seen in physical and behavioural interventions(Ho and Ng, 2020), however the effects of interventions on fatigue were rather low and large scale randomised controlled clinical trials still lack in the literature. Given this perspective, the effectiveness of interventions intended to reduce fatigue will have to start by understanding fatigue and its effect on both symptoms and functions. Better understanding of the predictive value of fatigue will likely translate into the identification of novel therapeutic targets and the development of improved symptomatic interventions. Therefore, this study aims to give an overview of the prospective predictive value of fatigue on negative health outcome in community-dwelling older adults. As prospective evidence will systematically be quantified in this meta-analysis, we expect to provide important information for clinical practice in order to develop in the future adequate interventions to counter the development and outcomes of fatigue.

2. Methods

2.1. Literature search

The databases PubMed and Web of knowledge were systematically screened (last search on March 5th, 2020) using the following combination of keywords ("Aged"[Mesh] OR "Elderly" OR "Elders" OR "Seniors") AND ("Fatigue"[Mesh] OR "Muscle Fatigue"[Mesh] OR "Fatigability" OR "Tiredness" OR "Exhaustion") AND ("Prognosis"[Mesh] OR "Risk"[Mesh] OR "Assessment" OR "Outcome" OR "Predictor") AND ("Cohort Studies"[Mesh]) for PubMed, and (Topic =Aged OR Elderly OR Elders OR Seniors) AND (Topic=Fatigue OR Fatigability OR Tiredness OR Exhaustion) AND (Topic=Prognosis OR Prognoses OR Prognostic OR Risk OR Assessment OR Outcome OR Predictor) AND (Topic=Cohort Studies OR Longitudinal Studies OR Prospective Studies) for Web of Science; based on the following PICO question “Does fatigue (I) predict negative health outcomes (O) in community-dwelling older adults (P)?”. Prospective longitudinal studies were eligible for this review if they investigated fatigue in community-dwelling older persons aged 65 years or older (when only the mean age of the population was reported, the upper limit of the 95% confidence interval for age (calculated as mean age + 1.96 x standard deviation) had to be 65 years or older) and if the occurrence of health outcomes was reported. Studies were included if they were written in English, Dutch, French, or German. No limit was set on the publication date. Articles investigating the effect of fatigue in persons with cancer or neurological disorders were excluded unless cancer was considered as a health outcome. The screening process was performed by 2 independent reviewers blinded for each other’s results. Articles were firstly screened based on title and abstract. Subsequently, full texts were screened. Disagreement was resolved by discussion and consensus method. The systematic literature search ended in March 2020, a total number of 4.595 articles were found, 1.757 articles in PubMed and 2.838 articles in Web of Science (figure 1). Thirty articles were included for this systematic review and meta-analysis. Finally, the full texts, independently read and assessed by at least 2 reviewers, were judged on content and methodological quality.

2.2. Data extraction

The following data were extracted from the included studies: the number of participants tested, length of follow-up (categorized as a= 0-60 months, b= 61-91 months, c= 91-120 months, d= 121-180, e= 181-240, f= >240 months) divided into short (a+b), intermediate (c+d) and long (e+f) follow up period, age of the investigated population, the fatigue assessment tool and its concept (self-perceived or muscle fatigability), the studied negative health outcomes and their assessment method, the predictive statistical measures: odds ratio (OR), Hazard ratio (HR), or relative risk (RR) (all ratios were maximally corrected for potential confounders). Articles were ordered according to the health outcome of the study. When probability ratios were reported in the article, but frequencies were provided, the OR was calculated based on the frequencies of the non-fatigued and fatigued older adults.

2.3. Quality Assessment

Prospective longitudinal cohort studies were assessed using the methodology checklist for prognostic cohort studies from the National Institute for Health and Clinical Excellence (NICE Methodology checklist prognostic studies) to assess the internal validity of the studies by two independent researchers. An overview of the applied checklist and the results per study can be found in supplementary material table 1. A funnel plot for publication bias was generated for the health outcome mortality, since this was the health outcome with most includes studies (see figure S1).

2.4. Meta-Analysis

Meta-analyses were conducted in Review Manager (RevMan) [Computer program], software for advanced meta-analysis from the Cochrane Collaboration (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Meta-analyses were performed separately for OR and the HR/RR. HR and RR were analysed together given their similarity (Deeks J.J., 2008). All OR, RR and HR used in the meta-analysis reported that fatigue influences the OR and the HR/RR compared to a non-fatigue state. The highest predictive values were used in the main meta-analysis. Subgroup-analyses (when relevant) were performed based on (1) gender (males/females), (2) length of follow-up, (3) fatigue level (low, medium and high), (figures for subgroup analysis can be found in supplementary material figures S1.a to S5.a). I^2 (heterogeneity) values with significance level were reported as a measure of the degree of inconsistency in the studies' results, considering a range from 0% (no observed heterogeneity) to 100% (complete heterogeneity) and values of 25% (low), 50% (moderate), and 75% (high)(Higgins et al., 2003).

3. Results

This systematic review was written according to the PRISMA guidelines for transparent reporting of systematic reviews and meta-analyses(Liberati et al., 2009).

3.1. Data extraction and Synthesis

Articles were ordered according to the different health outcomes of the study, multiple health outcomes per study were possible. In total 9 studies described the relationship between fatigue and mortality(Avlund et al., 1998, Avlund et al., 2003a, Basu et al., 2016, Cole et al., 1999, Hardy and Studenski, 2008, Moreh et al., 2009, Moreh et al., 2010, Prescott et al., 2003, Schultz-Larsen and Avlund, 2007b), 9 articles discussed different diseases (Bergelt et al., 2005, Ekmann et al., 2013, Iversen et al., 2012, Just-Ostergaard et al., 2018, Kornerup et al., 2010, Pedersen et al., 2016, Prescott et al., 2003, Volden et al., 2017, Williams et al., 2010) (of which 3 discussed heart disease), 8 articles looked at physical functioning expressed in physical activity(Moreh et al., 2010), physical capacity and gait (Simonsick et al., 2016, Simonsick et al., 2018) while others expressed physical functioning on the Mobility Help scale(Avlund et al., 1995, Idland et al., 2013, Avlund et al., 2003b, Avlund et al., 2003a, Schultz-Larsen and Avlund, 2007b). Four articles described the prospective value of fatigue on disability in Activities of Daily Living (ADL's) (Avlund et al., 1995, Avlund et al., 2002b, Moreh et al., 2010, Mueller-Schotte et al., 2016), 3 investigated hospitalization(Avlund et al., 2001a, Rod et al., 2011, Zaslavsky et al., 2014), and the remaining single articles investigated falls(Kamitani et al., 2017), healthcare utilization(Avlund et al., 2001a), self-reported health(Moreh et al., 2010), depression(Moreh et al., 2010), sleep problems(Moreh et al., 2010), loneliness(Moreh et al., 2010), pain(Aili et al., 2018), dental problems(Avlund et al., 2001b) and cognitive dysfunction(Islamoska et al., 2019). Only self-perceived fatigue instruments were used, no measurement of muscle fatigability was included. Figure 2 shows an overview of the fatigue instruments used per health outcome.

3.2. Fatigue instruments

Eight different fatigue instruments solely focusing on self-perceived fatigue were applied to evaluate the level of fatigue (supplementary table S2). The Mobility Tiredness scale (Mob-T) and Lower Limb Tiredness Scale (Limb-T)(Avlund et al., 1993) designed by Kirsten Avlund, were applied 18 times in this analysis. The Mob-T questionnaire is applied 14 times within 7 different cohorts to evaluate fatigue(Avlund et al., 1998, Schultz-Larsen and Avlund, 2007b, Avlund et al., 2001a, Avlund et al., 2008, Avlund et al., 2003b, Avlund et al., 2003a, Manty et al., 2012, Manty et al., 2014, Ekmann et al., 2013, Avlund et al., 2001b). The Limb-T was used only 4 times in different cohorts (Avlund et al., 1998, Avlund et al., 2001a, Avlund et al., 2002b). Twelve different studies described the Maastricht Questionnaire within 4 large cohorts as a prognostic factor, to predict several diseases including heart diseases (n=3)(Prescott et al., 2003, Rod et al., 2011, Islamoska et al., 2019, Just-Ostergaard et al., 2018, Kornerup et al., 2010, Pedersen et al., 2016, Volden et al., 2017, Bergelt et al., 2005, Williams et al., 2010). Another approach to evaluate fatigue is the 36-item short-form survey (SF-36)(Hays et al., 1993), the vitality subscale of the SF-36 was 6 times applied in the included studies to predict physical functioning, mortality, ADL disability, hospitalization, falls and pain(Aili et al., 2018, Basu et al., 2016, Kamitani et al., 2017, Mueller-Schotte et al., 2016, Zaslavsky et al., 2017). Avlund et al. (2008) derived one question from the 12-Item Short Form Survey (SF-12)(Ware et al., 1996) "*How much of the time during the past four weeks did you have a lot of energy?"* for assessing fatigue(Avlund et al., 2008). Several researchers applied a generic question varying from *"feeling tired most of the time"* to *"feeling generally tired",* to determine the presence or absence of fatigue (Hardy and Studenski, 2008, Moreh et al., 2010, Cole et al., 1999, Steen et al., 2001, Simonsick et al., 2016, Simonsick et al., 2018). The Borg rating of perceived exertion(Borg, 1990) and the Pittsburgh fatigability Scale(Glynn et al., 2015) appeared both once to measure the level of fatigability in measuring functional mobility(Simonsick et al., 2016, Simonsick et al., 2018).

3.3. Participants

A total of thirty studies, encompassing 152 711 participants were included, which all investigated the impact of fatigue on several negative health outcomes. Participants were healthy community-dwelling older and/ or younger volunteers and were at least 65 years and older (or when 95P is 65 and older). Several cohorts were included, the Copenhagen City Heart study, European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study, Atherosclerosis Risk in Communities Study and Women's Health Initiative Clinical Trial. The EPIC-Norfolk cohort was investigated once in this review(Basu et al., 2016), and is a population-based cohort comprising 18 101 men and women. The participants were followed up for 20 years (mean 16,6 years) using general practice registers in the UK. Nine included studies obtained data from the Copenhagen City Heart Study. This is a longitudinal study initiated in 1976 using an age-stratified random sample of 19 698 men and women

(20-93 years). A physical examination was performed, and the participants were asked to fill in a questionnaire. This cohort is mostly used to investigate the predictive value of fatigue on several diseases(Prescott et al., 2003, Iversen et al., 2012, Bergelt et al., 2005, Volden et al., 2017, Pedersen et al., 2016, Kornerup et al., 2010, Just-Ostergaard et al., 2018), cognitive decline(Islamoska et al., 2019), and hospitalization(Rod et al., 2011). Williams et al. (2010) investigated the predictive value of fatigue on adverse cardiac events based on the Atherosclerosis Risk in Communities Study which encompasses 12 895 males and females (aged 48 to 67 years) in the United States. The Women's Health Initiative Clinical Trial is a large cohort study of American women of 65 years and older and was used to investigate the relation between fatigue and hospitalization(Zaslavsky et al., 2014). There was also one study that only investigated twins followed by the Longitudinal Study of Aging Danish Twins(Ekmann et al., 2013)

3.4 Quality assessment

Internal validity of the thirty prognostic studies was assessed with the NICE methodology checklist for prognostic studies. For 25 studies the 6 items could be a protentional source of bias (see table supplementary material) table S1. Unknown risk of bias is qualified to 11 studies since not all criteria were clearly formulated in the studies. In 4 studies from Avlund et al. (Avlund et al., 1998, Avlund et al., 2001b, Avlund et al., 2001a, Avlund et al., 2002b), and in Moreh et al. (2009) and Schultz-Larsen and Avlund (2007b) was the sample size not clearly represented which is sufficient to limit potential bias to the results. All included articles have sufficiently reported the potential confounders with respect to the prognostic factor fatigue. A funnel plot for mortality was performed (see supplementary material figure S1) and showed that there were 2 studies(Avlund et al., 1998, Moreh et al., 2010) that had a higher risk for publication bias showed by a larger standard error.

3.5 Mortality

Nine prospective studies, comprising 5 different fatigue instruments and 37 454 older adults, described the predictive value of fatigue on mortality and were included in the meta-analysis (Table 1). In all studies, mortality was defined as whether the participant passed away during the follow-up period. The overall OR and HR/RR were calculated and shown separately. Overall, the presence of fatigue significantly increases the likelihood for mortality (OR 2.29 [1.67–3.14]; HR/RR 1.47 [1.34-1.61]) (see figure 3.a and 3.b). Meta-analyses show that the risk for mortality is higher within a follow-up period from 7,5-15 years (OR 2.22 [1.70–2.90]; HR/RR 1.71 [1.10-2.04]) compared to short and long follow-up periods (supplementary figure S2.e and S2.f). When looking at different fatigue levels, high fatigue levels have the highest elevated risk for mortality (HR/RR 1.36 [1.19–1.55]) (see figure 2.c in supplementary material). It seems that males (HR/RR 1.59 [1.46–1.73]), and females (HR/RR 1.53 [1.35–1.73]) show a similar elevated risk for mortality (see figure S2.d in supplementary material). Importantly, no statistically overall heterogeneity was found for HR/RR (I^2= 10,65%, p <0.15) and for OR (I^2= 0,01%, p =0.91).

Two studies(Basu et al., 2016, Cole et al., 1999) described the association between fatigue, cancer-related mortality, and cardiovascular-related mortality. Overall, these studies show that fatigue increases the risk for cancer (HR/RR 1.18 [0.95–1.47]), and for cardiovascular-related death (HR/RR 1.38 [1.06–1.81])(supplementary figure S2.a and S2.b.

3.6 Hospitalization

Only three studies, encompassing 3 different fatigue instruments and 24531 participants described the association between fatigue and hospitalization and were included in the meta-analysis(Avlund et al., 2001a, Rod et al., 2011, Zaslavsky et al., 2014). Overall, these studies show that fatigue increases the risk for hospitalization (HR 1.74 [1.48-2.05]), these results seem to be homogeneous for HR/RR (I^2 0,89%, P 0.34) (see figure 4). No meta-analysis for Avlund et al. (2001a) could be performed as this was the only article reporting odds ratios on hospitalization. However, this study found also evidence that fatigue increases the risk for hospitalization (OR 2.20 [1.10-4.40]). As shown in table 1, Rod et al. (2011), and Zaslavsky et al. (2014) divided the level of fatigue into quartiles, where Q1: slightly exhausted, Q2: exhausted and refers toQ3: highly exhausted measured by the Vital exhaustion questionnaire (1) (Appels et al., 1987). The risk for hospitalization increases when the level of fatigue increases (low (HR/RR 1.28 [1.13–1.45]); medium (HR/RR 1.43 [1.24–1.65]) and high (HR/RR 1.69 [1.36–2.09]) (see figure S3.a in supplementary material). In these studies, a longer follow-up period (HR/RR 1.46 [1.29–1.64]) had a slightly higher risk for hospitalization compared to a short follow up period for hospitalization (HR/RR 1.41 [1.24–1.61]) (figure S3.b in supplementary material).

3.4 Diseases

Nine studies(Bergelt et al., 2005, Ekmann et al., 2013, Iversen et al., 2012, Just-Ostergaard et al., 2018, Kornerup et al., 2010, Pedersen et al., 2016, Prescott et al., 2003, Volden et al., 2017, Williams et al., 2010) encompassed 2 fatigue instruments and 72 094 participants investigated the association between fatigue and several health outcomes (i.e. alcohol use disorder, cancer, diabetes, stroke). Since the investigated diseases are clinically extremely heterogenous no meta-analysis could be performed. Only one meta-analysis reporting on Ischemic Heart diseases(Ekmann et al., 2013, Prescott et al., 2003, Williams et al., 2010), comprising in total 23 793 participants could be performed. Fatigue increases the risk for Ischemic Heart diseases with 60% (HR 1.60 [1.35–1.90]) (see figure s4 and supplementary figure S4.a and S4.b). These findings differed in homogeneity, statistical homogeneity was found HR (I^2= 3,79%, p =0.05).

3.5 Physical functioning

Eight articles discussed physical functioning expressed in different domains such as, physical activity (Moreh et al., 2010), physical capacity, and gait (Simonsick et al., 2016, Simonsick et al., 2018), while the others measured the level of physical functioning with the Mobility Help scale(Avlund et al., 1995, Idland et al., 2013, Avlund et al., 2003b, Avlund et al., 2003a, Schultz-Larsen and Avlund, 2007b). In total, the articles investigated 5918 participants aged between 60 and 89 years. Overall, meta-analysis shows that persons who feel fatigued have 41% more risk to experience limitations in physical functioning (OR 1.41 [1.58–4.08])(figure 6). Two different types of limitation in physical functioning were studied; decline in physical activity and walking problems. Fatigue has a higher risk for reduced physical activity (OR 4.60 [3.38–6.24]) compared to reduced walking ability (OR 2.54 [1.82–3.55]), however, both results are significantly elevated (supplementary material figure S5).

3.6 ADL disability and dependency

The relationship between fatigue and the development of ADL disability was described in 4 articles(Avlund et al., 1995, Avlund et al., 2002b, Moreh et al., 2010, Mueller-Schotte et al., 2016), comprising in total 3015 older adults and 4 different fatigue instruments. Disability in B ADL is generally described as a new onset of problems in 1 daily activity (bathing, dressing, transferring from bed to chair, toileting, and feeding). Fatigue is linked to a 3.7 fold increase for ADL disability (OR 3.70 [2.80–4.87] (figure 7), regardless the time fatigue elevates the risk for ADL disability (0-7,5 year (OR 4.95 [3.42–7.16]) and (15+ years (OR 1.65 [1.02–2.68]) (see figure S6.b, supplementary material 1). The relationship between fatigue and ADL disability is higher in males compared to females (OR 5.41 [3.50–8.37]); (OR 3.26 [1.99–5.33]) (supplementary figure S6.a), however, this can be because Avlund et al. (1995) showed a large confidence interval [7.60–36.70] for males. All studies provide exclusively OR values, enabling a straightforward meta-analysis. One study used IADL as outcome measured by the Stanford Health Assessment Questionnaire and the Modified Katz Questionnaire, to assess BADL the PADL scale(Avlund et al., 1996) was used twice including the items: comb hair, wash upper body, use the toilet, dress upper body, dress lower body, wash lower body, cut fingernails, cut toenails. The scales count the number of items managed without help. One time(Moreh et al., 2010), disability in ADL was defined as a new onset of ADL difficulty but was not measured through a validated instrument. Heterogeneity is significantly high for OR's (I^2 24,94%, P < .001).

3.7 Falls, cognition, pain, dental problems and healthcare utilization

Only one study discussed the relationship between fatigue and the occurrence of falls encompassing 751 older adults. Falls were evaluated as the incidence of at least one fall in the past 2 years(Kamitani et al., 2017). Fatigue was measured by one fatigue scale but with two different versions, the SF 36 vitality scale Japanese version and two items of the SF 36 vitality scale Japanese version(Fukuhara et al., 1998). No meta-analysis could be performed since this was the only study reporting on the risk of falls. However, we see that all hazard ratios show an increased risk for falls, the highest risk could be found in the highest fatigue level (OR 2.15 [1.23–3.76]) and (OR 3.10 [1.58-6.08]).

Also, one single study described the relation between fatigue and cognitive decline(Islamoska et al., 2019), this study used different follow-up periods and evaluated 6807 older adults aged 65+. Since there was only one study reporting on this association with no differences on fatigue levels or follow-up periods, no meta-analysis could be performed.

Aili et al. (2018) is the only study that described the relation between fatigue and widespread pain. Pain was measured by a subjective question "Have you experienced pain lasting more than 3 months during the last 12 months?". The SF-36 questionnaire vitality subscale(1)(Ware and Gandek, 1998) measured the level of fatigue during different follow-up periods. Overall fatigue increases the risk for pain but not significantly (OR 1.56 [0.93–2.59]) (figure 11).

One unique study described the relation between fatigue and the occurrence of dental problems, comprising 325 older adults aged 75 and over(Avlund et al., 2001b). Since the reported data was to heterogeneous, no meta-analysis could be performed. However table 1 shows fatigue to have an increased risk on the number of teeth (OR 1.40 [0.70–2.50]), chewing ability (OR 1.20 [0.60–2.30]) and the frequency of visits to a dentist or denturist (OR 1.90 [1.10–3.20]).

The relation between fatigue and healthcare utilization was examined by (Avlund et al., 2001a), who measured the level of fatigue with the Mobility Tiredness scale (Avlund et al., 1993) and the Lower Limb-T scale (Avlund et al., 1993) over the period of 1 year by 236 participants aged 75 years and older. Health care utilization was measured by the use of help at home yes or no. Fatigue shows to have an increased risk on home help measured by the MOB-T OR 2.40 [1.30–4.40]) and (OR 1.10 [0.60-2.10]) measured by the lower Limb-T scale.

3.8 Loneliness, poor sleep and depression

Each of the outcomes (loneliness, poor sleep, and depression) were investigated by the same study, Moreh et al. (2010) examined the presence of fatigue by a question "Feel generally tired?" on 460 older adults 70+and 858 older adults 78+. The follow-up period ranged from 84 and 96 months. No meta-analysis could be performed. Depression was defined as the onset of a new depression; older adults experiencing fatigue shows to elevate the risk for depression with 100% (OR 2.00 [1.20–3.50]) with a follow up of 84 months. The risk for loneliness when feeling fatigued ranged between (OR 1.80 [0.80–3.70]) and (OR 4.70 [3.00–7.60]). Poor sleep was defined as poor sleep quality and fatigue increased the risk for poor sleep (OR 2.10 [1.00–4.50]) and (OR 1.20 [0.70–2.10]). The change in self-reported health was reported in relation with fatigue and had an increased risk of (OR 2.12 [1.05–4.30]) and (OR 1.00 [0.60–1.80]).

4. Discussion

This systematic review and meta-analysis summarized the literature on the prospective predictive value of fatigue for negative health outcomes among community-dwelling older adults. The results showed that fatigue is (range OR 1,45 – 3,70; HR/RR 1,47 – 1,74) related to the occurrence of several health outcomes, most of these results were significant (except depression, self-reported health, and health care utilization). Research has shown that fatigue is a complex mechanism due to the multidimensional character and the co-existence of different underlying constructs(Hardy and A, 2010). As fatigue causes depletion of reserve capacity, which is related to decrements of intrinsic capacity, the occurrence of negative health outcomes is expected. Results from our meta-analyses are useful for clinical practice as a better understanding of fatigue operationalization and its negative health outcomes hold the promise of better interventions to counter fatigue. Clinicians should be aware of the potential risk of fatigue, as well which instruments can predict the outcome of interest. This is the first meta-analysis examining the association between fatigue and various negative health outcomes. This review included 30 prospective studies. Only self-perceived fatigue was used as a prognostic variable, the most frequently reported outcomes were, physical dysfunction, mortality, diseases, and disability in basal ADL and instrumental ADL. Fatigue was prospectively linked to all outcome measured and frequently studied resulting in a significantly elevated risk for mortality (OR 2.29 [1.67–3.14), HR/RR 1.47 [1.34–1.61]), Ischemic heart diseases (HR/RR 1.60 [1.35–1.90]), physical functioning (OR 1.41 [1.58–4.08]), ADL disability (OR 3.70 [2.80–4.87]) and hospitalization (HR/RR 1.74 [1.48–2.05]). These outcomes have major implications for a person's his/her and their environment. While other health outcomes regarding cognitive decline, psychological disorders such as loneliness and depression have a major impact on a person's well-being but were only studied scarcely in this review.

Fatigue is a sign of age-related decline in reserve capacity(Cesari et al., 2018) and is frequently an early symptom of abnormal processes or diseases(Cho et al., 2012). Insight in underlying mechanisms of fatigue in frail elderly and fatigue operationalization in the frailty scales according to these mechanisms hold the promise of better interventions to counter fatigue and thereby delay the occurrence of negative health outcomes. Fatigue is a state of energy deficiency and may be influenced by several biological changes that are related to aging(Cesari et al., 2018). Research has shown that a reduction in motor unit recruitment and changes in the contractile properties of the muscle but also cardiovascular impairment and the presence of peripheral arterial stiffness are associated with self-perceived fatigue(Allman and Rice, 2002, Alexander et al., 2010, Gonzales et al., 2015). Changes in body composition expressed as the decline in muscle mass and the increase in fat mass enhance the feeling of fatigue(Valentine et al., 2011, Ponti et al., 2019). Decline in muscle mass and muscle function showed to account for up to >20% of the association between fatigue and physical function at higher age(Manty et al., 2012). Higher levels of fat mass are associated with several aspects of fatigue, including general fatigue, physical fatigue, and reduced activity (Valentine et al., 2011, Vgontzas et al., 2006), which may be potentially mediated by chronic systemic inflammation(Santoro et al., 2019). Inflammation is thereby another important process associated with the pathogenesis of fatigue. Research has shown that older patients admitted to an acute geriatric ward with inflammation were significantly weaker and showed significantly higher levels of muscle fatigue compared to those without inflammation(Bautmans et al., 2005). Elevated inflammatory markers in ageing correspond to a chronic low-grade profile (CLIP) (Krabbe et al., 2004, Beyer et al., 2012). Elevated CLIP can lead – besides to fatigue- to many chronic diseases and has been linked to various pathologies such as cancer, loss of mobility, cognitive decline, vascular diseases, and others(Brandt and Pedersen, 2010, Calder et al., 2017, Walston, 2002, Cao Dinh et al., 2019). Low-grade inflammation has been associated to various factors including age, body fat, physical inactivity as well as to comorbidity(Franceschi et al., 2007, Pawelec et al., 2014). In fact, inflammatory markers released in the peripheral blood circulation can cross the blood- brain barrier, causing sickness behaviour and induce fatigue sensations(Dantzer and Kelley, 2007). Inflammation as an underlying mechanism of fatigue could thereby be an important cause of the occurrence of negative health outcomes that were studied in this article. The importance of physical exercise on the inflammatory profile of older adults is well established(Liberman et al., 2017, Cao Dinh et al., 2018). Notably, physical exercise and weight training strategies may need to be evaluated with other known interventions to alter known fatigue determinants. It can be expected that through physical interventions affecting body composition and inflammatory profile will indirectly encounter the feelings of fatigue(Liberman et al., 2017, Emerson et al., 2015).

A number of factors contributing to fatigue have been identified, but its basic mechanism remains elusive. Research has shown that changes in energy expenditure and sedentary behaviour can increase fatigue but are also leading modifiable risk factors worldwide for cardiovascular disease and all-cause mortality and for other diseases (i.e. diabetes, dyslipidaemia, hypertension, cancer) in young(Park et al., 2020) and in older adults(Sherrington et al., 2020, LaMonte et al., 2020, Lavie et al., 2019, Avlund, 2010). In addition, frailty is more prevalent among older adults who exhibit insufficient levels of physical activity combined with sedentary behaviour (da Silva et al., 2019). It is thereby not clear whether the health outcome is caused by the fatigue or if the health outcome is precipitated by the lifestyle factors that are exacerbated (e.g. sedentary behaviour, eating behaviour) by being fatigued (i.e. a lesser ability to engage in a healthy behaviour). However, in our analysis we have chosen to include the OR and RR/HR that were maximally corrected for potential confounders. Out of the 30 included articles 22 articles included at least 1 (range 1-4 per article) lifestyle factors such as sedentary behaviour (see supplementary table S3)(Avlund et al., 2001a, Avlund et al., 2003b, Avlund et al., 2003a, Bergelt et al., 2005, Cole et al., 1999, Hardy and Studenski, 2008, Islamoska et al., 2019, Iversen et al., 2012, Kamitani et al., 2017, Mueller-Schotte et al., 2016, Pedersen et al., 2016, Prescott et al., 2003, Rod et al., 2011, Volden et al., 2017, Zaslavsky et al., 2014), alcohol use(Basu et al., 2016, Bergelt et al., 2005, Ekmann et al., 2013, Islamoska et al., 2019, Iversen et al., 2012, Pedersen et al., 2016, Prescott et al., 2003, Rod et al., 2011, Zaslavsky et al., 2014), eating behaviour(Basu et al., 2016, Zaslavsky et al., 2014), smoking habits(Avlund et al., 1998, Basu et al., 2016, Cole et al., 1999, Ekmann et al., 2013, Islamoska et al., 2019, Iversen et al., 2012, Moreh et al., 2009, Moreh et al., 2010, Pedersen et al., 2016, Prescott et al., 2003, Rod et al., 2011, Volden et al., 2017, Williams et al., 2010, Zaslavsky et al., 2014) and, BMI as confounders(Basu et al., 2016, Bergelt et al., 2005, Hardy and Studenski, 2010, Islamoska et al., 2019, Iversen et al., 2012, Kamitani et al., 2017, Kornerup et al., 2010, Mueller-Schotte et al., 2016, Prescott et al., 2003, Rod et al., 2011). Even though, there are 8 studies that did not correct for lifestyle factors no significant higher OR or RR/HR were found compared to the studies that corrected for lifestyle factors. This bears the concept that the negative health outcomes are rather caused by fatigue than by the changes in lifestyle.

Different predictive values were found depending on the health outcomes and the different fatigue levels studied. When dividing groups in fatigue level, ranging from low, medium to high, persons with high fatigue levels showed to have enlarged risk for mortality, diseases, low physical functioning, hospitalization, falls and pain compared to those with lower fatigue levels. Data retrieved from Islamoska et al. (2019) who studied 6,807 participants attending the third survey of the Copenhagen City Heart Study in 1991–1994 showed evidence that persons with high fatigue levels have an increased risk on cognitive decline compared to low fatigue(low HR/RR 1.14 [0.97–1.35], high HR/RR 1.41 [1.03–1.93]), however no meta-analysis could be performed. Not all fatigue instruments distinguished between different fatigue levels, these data could only be retrieved from the Maastricht Questionnaire composing 17 items developed by Appels et al. (1987), the SF-36 questionnaire vitality subscale(Ware and Gandek, 1998) and the SF 36 vitality scale Japanese version(Fukuhara et al., 1998). It might be possible that transitions between fatigue status influence the interpretation of the retrieved results. It would be interesting to research the process of reversibility i.e., whether fatigue levels can decrease when an appropriate approach for prevention is applied. It should be further investigated whether other fatigue instruments also show that high fatigue levels appear to be better predictors for these outcomes.

When looking at the different fatigue instruments reported, only one type of instrument was identified: those who only report on self-perceived fatigue. Broadly speaking, fatigue can be divided into self-perceived feeling of fatigue (including sleep problems, depressive feelings, tiredness and performance-based feeling of tiredness) and resistance to physical tiredness which include an “objective” fatigue assessment such as muscle fatigue. Originally, we intended to divide fatigue instruments into self-perceived fatigue and fatigability however, after extracting the data in this review, no measures of fatigability were used in the included articles. Only self-reported fatigue instruments were used in the studies included in this review, which could explain the variability in the results. As there is no clear definition of fatigue, the self-reported measures may explain some of most the likely widely differing individual understandings of the word "fatigue". Recently a systematic review has shown that there is a large heterogeneity of the fatigue definitions that were used in frailty scales, making the link with the underlying pathophysiological mechanisms by which fatigue relates to frailty unclear(Knoop et al., 2019). It seems that muscle fatigability is not used to predict the studied health outcomes, even though an easy non-invasive tool has been developed to assess the level of muscle fatigability(Bautmans and Mets, 2005). However, previously, it has been shown that especially fatigue and muscle performance are strong prospective predictors for disability in older persons(Idland et al., 2013) and that muscle fatigability can help to discriminate robust older adults from those with a higher degree of frailty(De Dobbeleer et al., 2018). Another study showed that changes in muscle fatigability and self-perceived fatigue were related to the energy that is required for physical activities(Buchowski et al., 2013). Physical limitation was studied 8 times in this meta-analysis expressed in reduced physical activity(Moreh et al., 2010), reduced physical capacity and gait limitations (Simonsick et al., 2016, Simonsick et al., 2018), and physical functioning on the Mobility Help scale(Avlund et al., 1995, Idland et al., 2013, Avlund et al., 2003b, Avlund et al., 2003a, Schultz-Larsen and Avlund, 2007b). The lack of the presence of muscle fatigability might give thereby an underestimation on the predictive value of fatigue.

Vital exhaustion was measured with the Maastricht questionnaire developed by Appels and his colleagues(Appels et al., 1987) and studied 12 times in this meta-analysis. This questionnaire consists of 17 items referring to a mental state of psychological distress and covers both somatic and cognitive complaints of unusual fatigue, increased irritability, and demoralization(Appels et al., 1993). Even though this questionnaire measures some aspects of fatigue, but also depressive symptoms we still included this in our analysis. There is a strong relationship between psychological symptoms and self-perceived fatigue but it is unclear whether physiological symptoms are either a cause, a symptom, or a contribution to fatigue (Katz, 2004, Stadje et al., 2016). Moreh et al. (2010) was the only study in this meta-analysis that investigated the predictive value of fatigue on psychological problems expressed as depression and loneliness. Fatigue defined by the question "Feel generally tired" studied by 460 70+ and 858 78+ older adults showed to enlarge the risk for depression (OR 2.00 [1.20–3.50]) and loneliness (OR 4.70 [3.00–7.60]) with 84 months follow up. Even though, the predictive value on depression is not significant it should be taken into consideration as these results are only based on one study. However, we should avoid circular thinking, since the DSM-V criteria incorporate fatigue as one of the symptoms(Soysal et al., 2017). It could be expected that persons who feel fatigued have a lower threshold for measuring depression. Besides, frail older adults who are feeling fatigued experience often depressive symptoms(Ní Mhaoláin et al., 2012, Brown et al., 2017). This relationship could be explained as high levels of pro-inflammatory markers negatively affect the central nervous system which may result in depressive symptoms, fatigue, and other cognitive disorders(Felger and Miller, 2012). Notwithstanding, as fatigue is one of the symptoms that is often assessed in depression scales(Olsen et al., 2003, Radloff, 1991, Haringsma et al., 2004, Yesavage et al., 1982) it would lead to an underestimation when vital exhaustion was not included in this analysis.

The time of follow-up is assumed to be an important factor that determines the risk for an outcome to occur. The follow-up period differed between studies, ranging from 2 years up to over 20 years, possibly affecting the results of the meta-analysis. Therefore, 5 subgroups were created according to the length of follow-up (a = 0-60; b = 61-120; c = 121-180; d = 181-240; e = >241 months). Evidence shows that different results were obtained depending on the time of follow-up. The occurrence of mortality and fatigue was higher with a long follow-up period. For diseases this differed, no big differences were found between the different follow-up categories. This could be since different health conditions were studied and merged under the category "diseases". Therefore, the results might differ, for example, Volden et al. (2017) found that after a follow-up of 12 years the predictive value on alcohol-related hospital admission was (OR 1.17 [0.70–1.94]) higher than for 23 years (OR 0.88 [0.66–1.17]). When looking at more "physical" health outcomes such as ADL functioning, physical performance, and falls we saw that the follow-up period was much shorter ranging between 1-3 years. Because significant odd ratios were found for high fatigue and less with low fatigue it was interesting to divide in fatigue level. Combining this with the follow-up period it showed that for physical problems the highest ratios were found for a short follow up in ADL disability (OR 4.95 [3.42–7.16]). For disabilities in physical functioning, only a short follow up was used, increasing the risk with 41% (OR: 1.41 [1.58-4.08]) These results are important, as it shows that negative health outcomes related to fatigue are progressive. It starts with physical limitations and reduced physical activity and increased fall risk within a short follow up period leading to other health issues such as hospitalization and mortality in long-term. The results of this study show a relationship between fatigue and negative health outcomes. However, for clinicians, it is important to start early preventive interventions when someone feels fatigued and not wait until health problems occur to improve quality of life. Early treatment is thereby necessary to encounter the negative effects of fatigue as the physical problems occur in a short follow-up period. However, to draw conclusions regarding the follow-up period for a certain negative health outcome, not only the range of the ratio but also the 95% confidence interval (CI) should be considered. These intervals are very narrow for some outcomes but very wide for others. For example, fatigue measured by the MOB-T scale shows an increased risk for ADL disabilities within 1 year for woman showed smaller CI (OR 6.70 [3.30–13.40]) than for males (OR 16.70 [7.60–36.70])(Avlund et al., 1995). When subgroup analyses per gender were available, females showed to have a higher risk for the occurrence of mortality, diseases, physical functioning, and hospitalization. This could also be explained by the fact that females are usually more often affected by fatigue compared to men(Avlund, 2010, Liao and Ferrell, 2000). When looking at the underlying mechanism of fatigue, the relation between fatigue and health outcome might be influenced by body composition, inflammation markers(Ronti et al., 2006, Toss et al., 2012). It is known that females have higher fat mass while males have higher muscle and bone mass, muscle strength showed to account for up to >20% of the association between fatigue and physical function at higher age(Manty et al., 2012). Additionally, as adipose tissue expands and muscle and bone tissue decrease during aging for mostly females, there is an increase in pro-inflammatory markers which contributes to local and systematic inflammation. Reduced muscle fatigability might therefore explain the occurrence of fatigue, one of the key characteristics of physical frailty(Fried et al., 2001, Avlund et al., 2002a, Theou et al., 2008) and be more prevalent in females. Opposite results were found for disabilities in ADL, males (OR 5.41 [3.50-8.37]) showed to have a higher risk compared to females (OR 3.26 [1.99-5.33]), these results cannot be explained by sex differences but might be due to low study quality (lack of good statistical analysis and no reports on loss to follow up) of Avlund et al. (1995). This study showed very large intervals, which might have influenced the results. When excluding this study, the overall predictive value of fatigue on ADL decline decreased (OR 2.420 [1.80- 3.25]), no subgroup analysis on sex could be performed after excluding this study.

This review and meta-analysis show convincing evidence for the predictive power of fatigue for the occurrence of all studied negative health outcomes. The importance of the results is portrayed in the need for early interventions as the occurrence of negative health outcomes starts with problems in physical functioning and leads to hospitalization and or mortality. The results showed a causative relationship between fatigue and the studied negative health outcomes; however, it still remains unclear whether fatigue is either a predictor or a symptom of disease. Fatigue is often seen as a symptom of an underlying pathophysiologic process rather than an independent entity. This makes it complicated to isolate a single cause for fatigue(Poluri et al., 2005). Since the included articles are observational in nature, the exact causative role of fatigue on the occurrence of negative health outcomes remains somewhat unsure. Notwithstanding, the prospective design of these studies indicate that the fatigue symptoms proceeded the occurrence of negative health outcomes studied. Preceding on the other side, this does not exclude that specific conditions might already have been present in a subclinical phase explaining the predictive value of fatigue for the occurrence of the health outcomes. Fatigue could be a proxy of an underlying process that causes different health outcomes(Zengarini et al., 2015) accelerating by feeling fatigued. For instance, low grade inflammatory processes have been linked to various pathologies(Calder et al., 2017) and have been reported to be predictive of 10 years all-cause mortality(Varadhan et al., 2014, Giovannini et al., 2011) but can also precipitate fatigue. Physical interventions can reduce the inflammatory markers and have thereby a positive influence on declining the risk for fatigue and the related negative health outcomes(Cao Dinh et al., 2018, Liberman et al., 2017). Physical interventions combined with nutrition could be useful as it is known that obese older adults show higher levels of fatigue(Fantin et al., 2007). Moreover, more fat mass is associated with increased fatigue in this population(Vgontzas et al., 2006, Valentine et al., 2011), therefore changing lifestyle and reducing adiposity may represent a potential target for reducing fatigue in older adults. No meta-analyses regarding interventions for fatigue have been performed for healthy older adults, however, this data is necessary to understand which preventive measures can be taken to prevent the occurrence of negative health outcomes.

Strengths and limitations

The results of this relatively large meta-analysis comprise 30 articles studying 152 711 participants. This large population makes generalization of the results possible. This is the first comprehensive meta-analysis providing evidence stratified by frailty status, frailty instrument, and duration of follow-up. Various operationalizations for the studied negative health outcomes were used and grouped to improve the readability. However, this could also decrease the predictive power and underestimate the results.

All study results were maximally adjusted for confounders, most found confounders were age, sex, education level, sociodemographic covariates, and baseline health status. However, the heterogeneity in most of our meta-analyses were high which could be explained by differences in the study population, confounders, sample size and follow up periods in the individual studies. The age limit was set a priori at 65 years and older or when only the mean age of the population was reported, the upper limit of the 95% confidence interval for age (calculated as mean age + 1.96 x standard deviation) had to be 65 years or older. Some studies regarding fatigue and its negative health outcomes were thereby not included. Fatigue showed to have an increasing age-related trend(Meng et al., 2010). However, these findings are consistent with earlier studies who have investigated negative health outcomes caused by fatigue by a younger population. This review focused on community-dwelling older adults as fatigue is often observed in specific medical diseases. It can be difficult to ascribe fatigue to a single disease or cause, for this reason, we excluded articles with hospitalized patients or patients with specific health conditions. Conceptually, it can be assumed that hospitalized and/or institutionalized older adults are possibly at an already more advanced stage of fatigue. For this reason, results retrieved from those populations may bias the predictive power of frailty in the occurrence of these outcomes at a moment when they are not yet present. However, research in these hospitalized and or institutionalized older adults could be welcome. For this research, many subgroups have been created to analyse the predictive value in as many combinations as possible. This might seem exhaustive, however, this gives clinicians more detailed information on the expected risk their patient has when several factors such as gender, follow-up, and fatigue level. The dissimilarity in ratios and the subgroups may somewhat complicate the interpretation of the results. No meta regression could be performed, since there was not a sufficient number of studies included per health outcome(Deeks J.J., 2008). However, overall meta- analysis for all negative health outcomes shows convincing evidence that fatigue significantly predicts their occurrence. No meta-analysis could be performed for the different diseases due to the clinical heterogeneity, this could have underestimated the risk of fatigue on diseases. The internal validity of the included prognostic studies was overall good. While some studies had a little higher risk due not reporting on the sample size and potential confounders. However overall, we can conclude there was a low risk for bias.

The lack of sufficient awareness about the clinical relevance of fatigue significantly affects the robustness of knowledge and effective interventions on this topic. As fatigue is too often seen as rather a symptom than a predictor for a disease no strategies aiming at preventing disabling conditions in our population are performed. Better consideration of fatigue as an abnormal subjective syndrome can bring benefits in the identification of fatigue concerning expected health outcomes. The relevance of potentially modifiable risk factor for negative outcomes is in this article sufficiently recognized in this article. The results of our meta-analyses can be used as a guideline for the prediction of negative outcomes according to fatigue as well as to estimate the time frame and intensity within which these events can be expected to occur.

5. Conclusion

The results of this extensive review and meta-analyses, based on 30 articles investigating 15 negative health outcomes and 152 711 participants, show that overall, fatigue significantly increases the risk for developing all studies' negative health outcomes. The results show that fatigue should be seen as a predictor for negative health outcomes rather than a negligible. symptom. Taken all together, fatigue related physical decline such as reduced physical activity, falls and disability in ADL occurs earlier compared to other health outcomes such as certain diseases, hospitalization, and mortality. This brings benefits in understanding the pathophysiology of fatigue and the importance of early interventions. The analyses presented in this study can be used as a guideline for the prediction of negative health outcomes according to fatigue as well as to estimate the time frame within which these events can be expected to occur.

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Declaration of Interest

None to declare.

Acknowledgements

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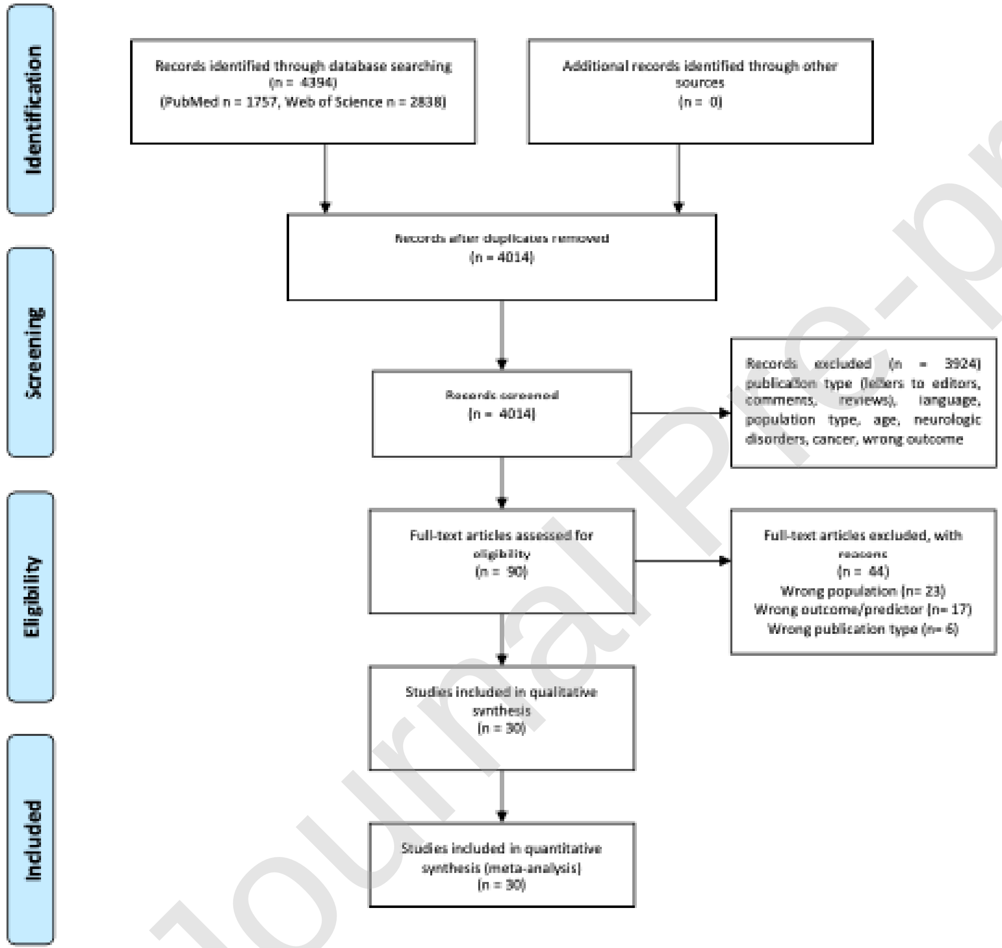

Fig 1. PRISMA Flow diagram

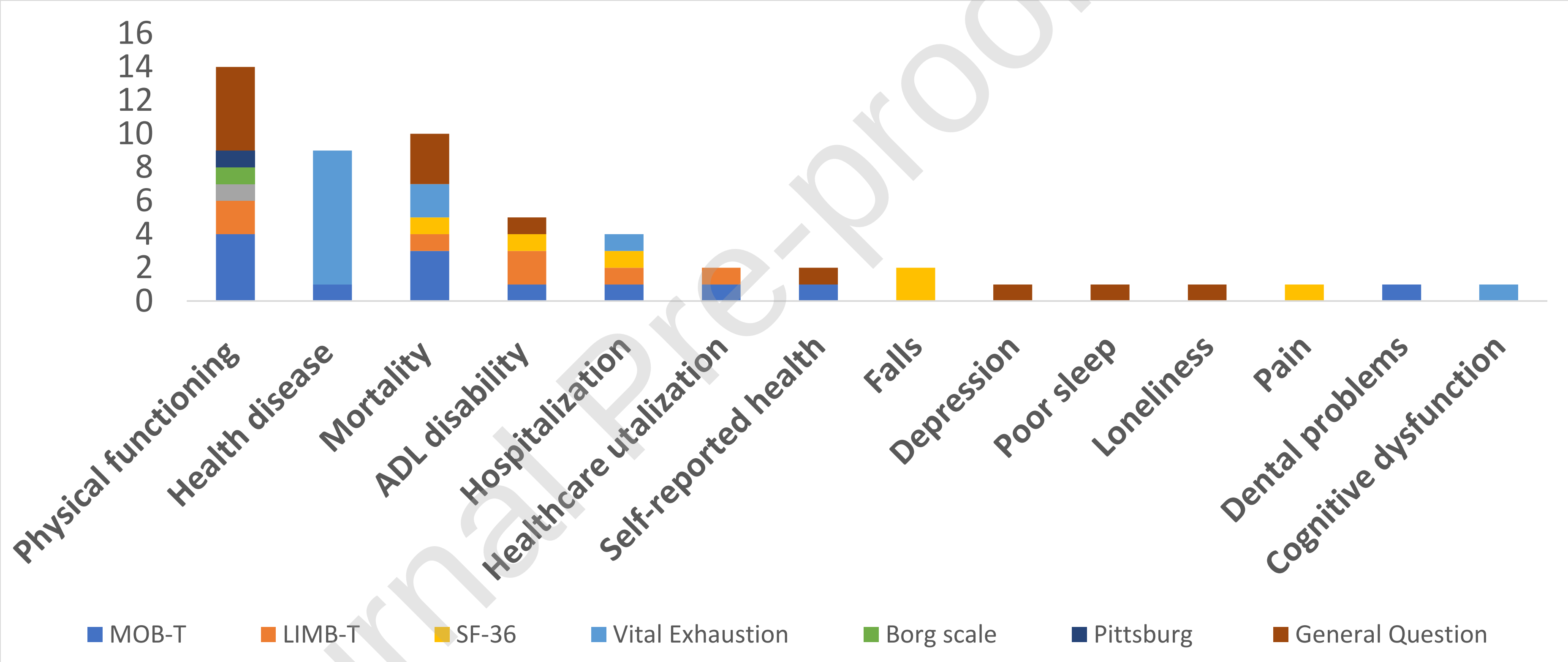

Fig 2. Number and type of fatigue instruments that were used to predict the health outcomes.

Eight different fatigue instruments have been used to predict the health outcomes. The different fatigue instruments were the; Mobility Tiredness scale (MOB-T), and Lower Limb Tiredness Scale (Limb-T), 36-item short-form survey (SF-36) including also question from the 12-Item Short Form Survey (SF-12), Maastricht Questionnaire expressed as Vital exhaustion, the Borg rating of perceived exertion scale and the Pittsburgh fatigability Scale. The general question refers to generic questions varying from *"feeling tired most of the time"* to *"feeling generally tired"*, to determine the presence or absence of fatigue

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Avlund 2003a	0.7885	0.4126	15.2%	2.20 [0.98, 4.94]
Schultz-Larsen 2007	0.8372	0.1748	84.8%	2.31 [1.64, 3.25]
Total (95% CI)			100.0%	2.29 [1.67, 3.14]
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%				
Test for overall effect: Z = 5.16 (P < 0.00001)				

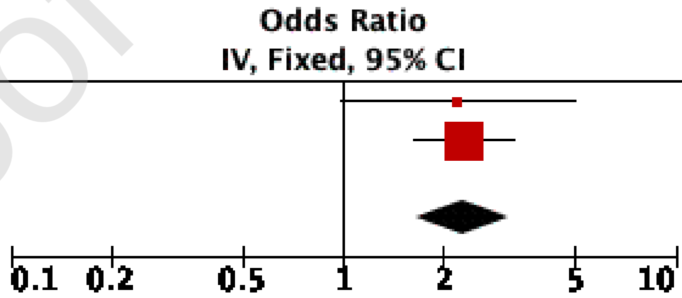

Fig. 3.a Forestplot mortality OR

The vertical line (1) represents no effect, the right side of the line represents more risk and the left side decreased risk. Fatigue increased significantly mortality with an overall effect of 2.29; I^2 = % heterogeneity and corresponding p-value.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Avlund 1998 (F)	0.7885	0.2306	4.3%	2.20 [1.40, 3.46]
Avlund 1998 (M)	0.5878	0.166	8.4%	1.80 [1.30, 2.49]
Basu 2016	0.2311	0.0739	42.2%	1.26 [1.09, 1.46]
Cole 1999	0.6043	0.1986	5.8%	1.83 [1.24, 2.70]
Hardy and Studenski 2008	0.3646	0.1468	10.7%	1.44 [1.08, 1.92]
Moreh 1 2010	0.4383	0.2606	3.4%	1.55 [0.93, 2.58]
Moreh 2009	0.4187	0.2086	5.3%	1.52 [1.01, 2.29]
Prescott 2003	0.4574	0.1074	20.0%	1.58 [1.28, 1.95]
Total (95% CI)			100.0%	1.47 [1.34, 1.61]
Heterogeneity: Chi² = 10.65, df = 7 (P = 0.15); I² = 34%				
Test for overall effect: Z = 7.99 (P < 0.00001)				

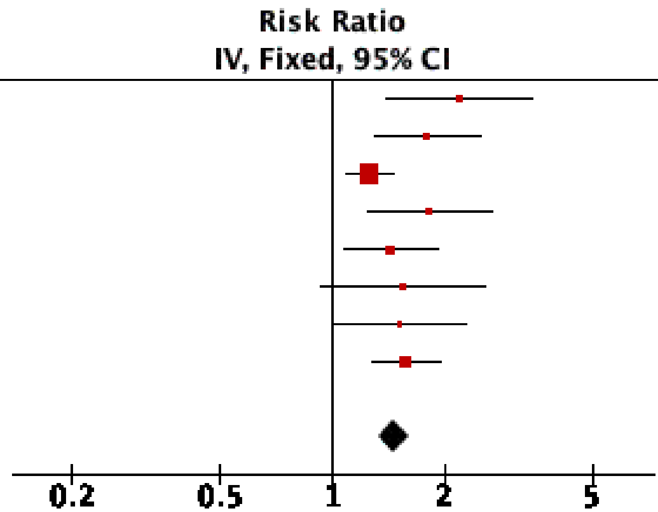

Fig. 3.b Forestplot mortality RR/HR

The vertical line (1) represents no effect, the right side of the line represents more risk and the left side decreased risk. Fatigue increased significantly mortality with an overall effect of 1.47; I^2 = % heterogeneity and corresponding p-value.

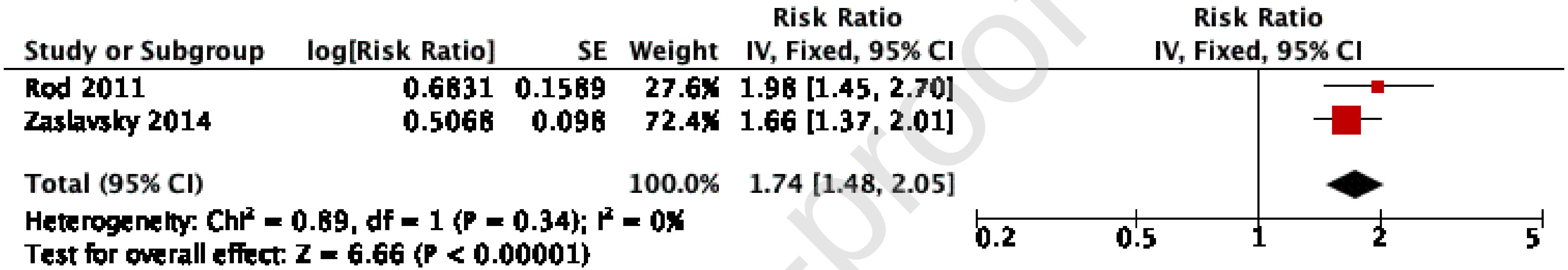

Fig. 4 Forestplot hospitalization RR/HR

The vertical line (1) represents no effect, the right side of the line represents more risk and the left side decreased risk. Fatigue increased significantly mortality with an overall effect of 1.74; I^2 = % heterogeneity and corresponding p-value.

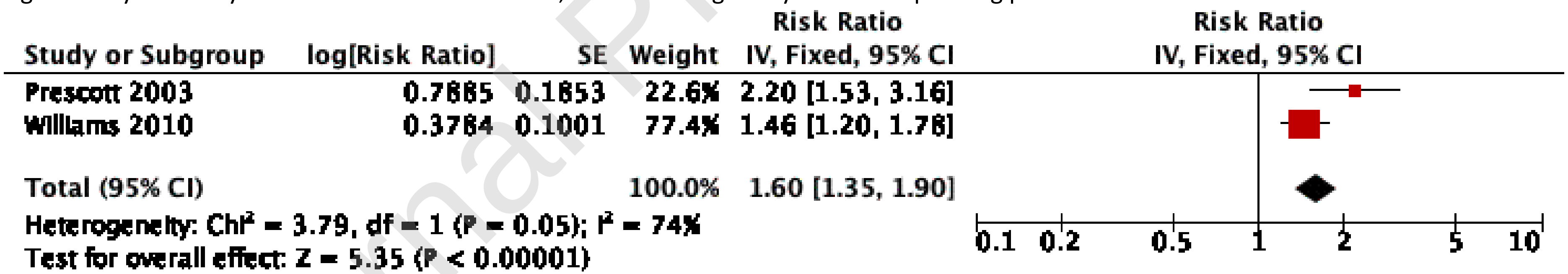

Fig. 5 Heart Diseases RR/HR

The vertical line (1) represents no effect, the right side of the line represents more risk and the left side decreased risk. Fatigue increased significantly mortality with an overall effect of 1.60 ; I^2 = % heterogeneity and corresponding p-value.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Avlund (F) 1995	1.8718	0.4482	1.2%	6.50 [2.70, 15.65]
Avlund (F) 2003b	1.1314	0.3704	1.8%	3.10 [1.50, 6.41]
Avlund (M) 1995	2.3795	0.5605	0.8%	10.80 [3.60, 32.40]
Avlund (M) 2003b	0.8329	0.4787	1.1%	2.30 [0.90, 5.88]
Avlund 2002a	1.1632	0.4218	1.4%	3.20 [1.40, 7.31]
Avlund 2003a	0.47	0.5935	0.7%	1.60 [0.50, 5.12]
Moreh 1 2010	1.6292	0.5038	1.0%	5.10 [1.90, 13.69]
Schultz-Larsen 2007	2.2072	0.3355	2.2%	9.09 [4.71, 17.54]
Simonick 2016	0.174	0.0542	85.4%	1.19 [1.07, 1.32]
Simonsick 2018	0.9322	0.2422	4.3%	2.54 [1.58, 4.08]
Total (95% CI)			100.0%	1.41 [1.28, 1.56]

Heterogeneity: $Chi^2 = 87.27$, df = 9 ($P < 0.00001$); $I^2 = 90\%$

Test for overall effect: $Z = 6.90$ ($P < 0.00001$)

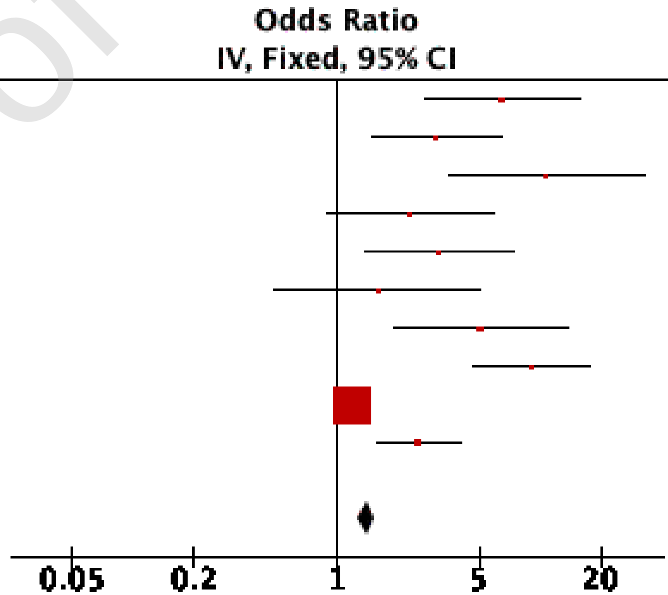

Fig. 6 Forestplot physical functioning OR

The vertical line (1) represents no effect, the right side of the line represents more risk and the left side decreased risk. Fatigue increased significantly mortality with an overall effect of 1.41 ; I^2 = % heterogeneity and corresponding p-value.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Avlund (F) 1995	1.9021	0.3613	15.2%	6.70 [3.30, 13.60]
Avlund (M) 1995	2.8154	0.4017	12.3%	16.70 [7.60, 36.70]
Avlund 2002a	0.7419	0.3785	13.9%	2.10 [1.00, 4.41]
Moreh 1 2010	1.0647	0.3716	14.4%	2.90 [1.40, 6.01]
Mueller-Schotte (F) 2016	1.1909	0.2669	27.9%	3.29 [1.95, 5.55]
Mueller-Schotte (M) 2016	0.5008	0.3506	16.2%	1.65 [0.83, 3.28]
Total (95% CI)			100.0%	3.70 [2.80, 4.87]

Heterogeneity: $Chi^2 = 24.94$, $df = 5$ ($P = 0.0001$); $I^2 = 80\%$
Test for overall effect: $Z = 9.27$ ($P < 0.00001$)

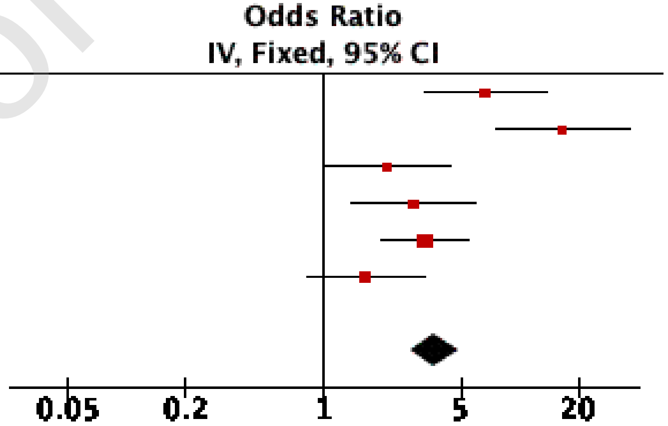

Fig. 7 Forestplot development of disabilities (decline in BADL or IADL) OR
The vertical line (1) represents no effect, the right side of the line represents more risk and the left side decreased risk. Fatigue increased significantly mortality with an overall effect of 3.70 ; I^2 = % heterogeneity and corresponding p-value.

Table 1. Predictive Value of Fatigue on Mortality

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
Mortality					
Avlund et al. (2003a)	Age: 75+, n= 226	Mobility Tiredness scale (1)(Avlund et al., 1993)	60 (a)	Died yes/no	**F vs NF: OR: 2.20 [0.98 – 4.90]**
Schultz-Larsen and Avlund (2007b)	Age 70+, n= 705	Mobility tiredness scale (1)(Avlund et al., 1993)	60 (a) 120 (c) 180 (d)	Died yes/no	F vs NF: OR 1.83 [1.17 – 2.85] F vs NF: OR 2.16 [1.52 – 3.05] **F vs NF: OR 2.31 [1.64 – 3.24]**
					Overall OR 2.29 [1.67-3.14]
Hardy and Studenski (2008)	Age 65+, n = 492	Question: feeling tired most of the time (1)	120 (c)	Died yes/no	**F vs NF: HR 1.44 [1.08 – 1.93]**
Moreh et al. (2009)	Age 70+, n= 461	Question: Feel generally tired (1)	96 (b)	Died yes/no	**F vs NF: HR 1.52 [1.01 – 2.28]**
Moreh et al. (2010)	Age 70+, n= 460 Age 78+, n= 858 Age 85+, n=1162	Question: Feel generally tired (1)	96 (b) 84 (b) 36 (a) 216 (e)	Died yes/no	F vs NF: HR 1.29 [0.79 – 2.11] F vs NF: HR 1.20 [0.90 – 1.70] **F vs NF: HR 1.55 [0.93 – 2.59]** F vs NF: HR 1.31 [0.92 – 1.86]
Avlund et al. (1998)	Age 70 n= 734 ♂ n= 366 ♂ n= 368	Mobility tiredness scale (1)(Avlund et al., 1993) Lower Limb-T scale (1)(Avlund et al., 1993)	120 (c)	Died yes/no	♂ **F vs NF: HR 1.80 [1.30 – 2.70]** ♀ **F vs NF: HR 2.20 [1.40 – 3.60]** ♂ F vs NF: HR 1.30 [0.80 – 2.10] ♀ F vs NF: HR 1.60 [1.00 – 2.60]

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
Basu et al. (2016)	Age 59.0 ± 9.1, n= 18,101$	SF-36 questionnaire vitality subscale(Ware and Gandek, 1998) Q1: (65-75) Q2: (50-64) Q3: (0-49)	240 (e)	Died yes/no Cardiovascular disease related mortality Cancer related mortality	Q1: F vs NF: HR 1.00 [0.87 – 1.15] Q2: F vs NF: HR 1.26 [1.09 – 1.46] **Q3: F vs NF: HR 1.24 [1.05 – 1.46]** Q1: F vs NF: HR 0.84 [0.64 – 1.09] Q2: F vs NF: HR 1.20 [0.92 – 1.56] **Q3: F vs NF: HR 1.26 [0.93 – 1.70]** Q1: F vs NF: HR 1.04 [0.84 – 1.29] **Q2: F vs NF: HR 1.19 [0.95 – 1.51]** Q3: F vs NF: HR 0.86 [0.65 – 1.15]
Cole et al. (1999)	Age 65+, n= 5053 Males	Question "How often do you experience sense of exhaustion (except after exercise)"(1)(Appels et al., 1987)	144 (d)	Died yes/no Cardiovascular disease related mortality Cancer related mortality	**F vs NF: RR 1.83 [1.24 – 2.70]** **F vs NF: RR 2.07 [1.08 – 3.96]** **F vs NF: RR 1.06 [0.43 – 2.60]**
Prescott et al. (2003)	Age 20-93, n= 9202† ♂n= 3961 ♂ n= 5241	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	180 (e)	Died yes/no	♂ Q1: F vs NF: HR 1.23 [1.08 – 1.40] ♂Q2: F vs NF: HR 1.58 [1.35 – 1.85] ♂ Q3: F vs NF: HR 2.50 [2.09 – 2.99] ♀Q1: F vs NF: HR 1.08 [0.88 – 1.32] ♀ Q2: F vs NF: HR 1.43 [1.14 – 1.80] ♀ Q3: F vs NF: HR 2.42 [1.90 - 3.09] Q1: F vs NF: HR 1.09 [0.95 – 1.25] Q2: F vs NF: HR 1.15 [0.96 – 1.37] **Q3: F vs NF: HR 1.58 [1.28 – 1.96]**
				Cancer related mortality Cardiovascular related	Overall HR: 1.47[1.34 – 1.61] Overall HR 1.38 [1.05 – 1.81] Overall HR 1.18 [0.95 – 1.47]
Hospitalization					
Avlund et al. (2001a)	Age 75+, n= 233	Mobility Tiredness scale (1)(Avlund et al., 1993) Lower Limb-T scale (1)(Avlund et al., 1993)	60 (a)	Hospitalization yes/no	F vs NF: OR 2.20 [1.10-4.40] F vs NF: OR 0.90 [0.50-1.90]

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
Rod et al. (2011)	Age 57±15, n= 8487[†] ♂ n= 3700 ♂ n= 4970	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	192 (e)	Heart failure hospitalization yes/no	♂ Q1: F vs NF: HR 1.25 [0.97 – 1.61] ♂ Q2: F vs NF: HR 1.22 [0.84 – 1.76] ♂ Q3: F vs NF: HR 1.53 [0.94 – 2.49] ♀ Q1: F vs NF: HR 1.31 [1.00 – 1.70] ♀ Q2: F vs NF: HR 1.38 [1.01 – 1.90] ♀ Q3: F vs NF: HR 2.32 [1.62 – 3.22] Q1: F vs NF: HR 1.19 [0.98 – 1.46] Q2: F vs NF: HR 1.26 [0.98 – 1.64] **Q3: F vs NF: HR 1.98 [1.45 – 2.71]**
Zaslavsky et al. (2014)	Age 65+, n= 15811[*] Females	SF-36 questionnaire vitality subscale (1)(Ware and Gandek, 1998) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	60 (a)	Hospitalization yes/no	♀ Q1: F vs NF: HR 1.28 [1.07 – 1.53] ♀ Q2: F vs NF: HR 1.50 [1.25 – 1.80] ♀ **Q3: F vs NF: HR 1.66 [1.37 – 2.01]**
					Overall: HR 1.74 [1.48-2.05]
Falls					
Kamitani et al. (2017)	Age 69,9±4,9, n = 751	SF 36 vitality scale Japanese version(1)(Fukuhara et al., 1998) SF 36 vitality scale Japanese 2 item version(1)(Fukuhara et al., 1998) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	24 (a)	Incidence >one fall in past 2 years	F vs NF: OR 1.42 [1.16 - 1.73] Q1: F vs NF: HR 1.60 [0.94 – 2.75] Q2: F vs NF: HR 1.87 [1.12 – 3.11] Q3: F vs NF: HR 2.15 [1.23 – 3.76] F vs NF: OR 1.47 [1.22 - 1.79] Q1: F vs NF: HR 1.73 [1.05 – 2.86] Q2: F vs NF: HR 2.20 [1.39 – 3.48] Q3: F vs NF: HR 3.10 [1.58 – 6.08]
Use of healthcare service					
Avlund et al. (2001a)	Age 75+, n= 236	Mobility Tiredness scale (1)(Avlund et al., 1993) Lower Limb-T scale (1)(Avlund et al., 1993)	60 (a)	Home help yes/no	F vs NF: OR 2.40 [1.30 – 4.40] F vs NF: OR 1.10 [0.60 – 2.10]

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
Development of Disabilities (decline in BADL or IADL)					
(Avlund et al., 1995)	Age 70, n=734 ♂n= 366 ♀n= 368	Mobility Tiredness scale (1)(Avlund et al., 1993) Lower Limb-t scale (1)(Avlund et al., 1993)	60 (a)	PADL Help scale(Avlund et al., 1996)	♀F vs NF: OR 2.30 [1.30 – 4.10] ♂ **F vs NF: OR 16.70 [7.60 – 36.70]** ♀ **F vs NF: OR 6.70 [3.30 – 13.40]**
(Avlund et al., 2002b)	Age 75, n= 429	Lower Limb-t scale (1)(Avlund et al., 1993)	60 (a)	PADL Help scale(Avlund et al., 1996)	**F vs NF: OR 2.10 [1.00 – 4.20]** MF vs NF: OR 2.00 [1.00 – 3.90]
(Moreh et al., 2010)	Age 70+, n= 460 Age 78+, n= 858	Question: Feel generally tired (1)	**96 (b)** 84 (b)	New onset of ADL difficulty	**F vs NF: OR 2.90 [1.40 – 6.10]** F vs NF: OR 0.70 [0.40 – 1.20]
(Mueller-Schotte et al., 2016)	Age (40-79), n= 534 ♂n= 285 ♀n= 249	One question SF-36 (1)	120 (c)	IADL Stanford Health Assessment Questionnaire Modified Katz questionnaire	♂ **F vs NF: OR 3.29 [1.95 – 5.55]** ♀ **F vs NF: OR 1.65 [0.83 – 3.26]**
					Overall OR: 3.70 [2.80-4.87]
Physical limitation and functioning					
(Avlund et al., 1995)	Age 70, n: 734 ♂n= 366 ♀n= 368	Mobility Tiredness scale (1)(Avlund et al., 1993) Lower Limb-t scale (1)(Avlund et al., 1993)	60 (a)	Mobility Help scale(Schultz-larsen and Avlund, 2007a)	♂ **F vs NF: OR 10.80 [3.60 – 32.50]** ♀ **F vs NF: OR 6.50 [2.70 – 15.60]** ♀ F vs NF: OR 3.80 [1.90 – 7.70]
(Avlund et al., 2002b)	Age 75, n= 510	Lower Limb-t scale (1)(Avlund et al., 1993)	60 (a)	Mobility Help scale(Schultz-larsen and Avlund, 2007a)	**F vs NF: OR 3.20 [1.40 – 7.60]** MF vs NF: OR 1.70 [0.80 – 3.80]
(Avlund et al., 2003b)	Age: 74+, n= 1396 M n= 648 F n= 748	Mobility Tiredness scale (1)(Avlund et al., 1993)	18 (a)	Mobility Help scale(Schultz-larsen and Avlund, 2007a)	♂ **F vs NF: OR 2.30 [0.90 – 6.00]** ♂ MF vs NF: OR 2.20 [1.10 – 4.40] ♀ **F vs NF: OR 3.10 [1.50 – 6.50]** ♀ MF vs NF: OR 3.90 [2.30 – 6.60]
(Avlund et al., 2003a)	Age: 75+, n= 136	Mobility Tiredness scale (1)(Avlund et al., 1993)	60 (a)	Mobility Help scale(Schultz-larsen and Avlund, 2007a)	**F vs NF: OR: 1.60 [0.50 – 5.10]**

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
(Schultz-Larsen and Avlund, 2007b)	Age 70+, n= 705	Mobility tiredness scale (1)(Avlund et al., 1993)	60 (a) 120 (c) 180 (d)	Mobility Help scale(Schultz-larsen and Avlund, 2007a)	**F vs NF: OR 9.09 [4.71 – 17.54]** F vs NF: OR 1.87 [1.17 – 2.99] F vs NF: OR 1.84 [0.93 – 3.64]
(Simonsick et al., 2016)	Age 60-89, n= 540	1.Fatigability (Borg rating of perceived exertion) (1)(Borg, 1990) 2. Tiredness "in the past month, on average how often have you felt unusually tired?"(1) 3.Energy level "During the past month, what category describes your energy level" (1)	36(a)	Usual gait speed 6 meter walking test Fast gait speed 6 meter walking test HABS PPB(Simonsick et al., 2001) Walking ability Index	**1.F vs NF: OR 1.19 [1.07 – 1.32]** 2. F vs NF: OR 0.71 [0.48 – 1.07] 3. F vs NF: OR 0.96 [0.83 – 1.10] 1.F vs NF: OR 1.13 [1.02 – 1.25] 2. F vs NF: OR 1.20 [0.81 – 1.78] 3. F vs NF: OR 0.95 [0.83 – 1.09] 1.F vs NF: OR 1.17 [1.05 – 1.30] 2. F vs NF: OR 1.09 [0.72 – 1.65] 3. F vs NF: OR 1.00 [0.86 – 1.16] 1. F vs NF: OR 1.14 [1.04 – 1.26] 2. F vs NF: OR 1.53 [1.04 – 2.25] 3. F vs NF: OR 0.78 [0.68 – 0.89]

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
(Simonsick et al., 2018)	Age 60-89, n= 579	1.Pittsburgh Fatigability Scale (1)(Glynn et al., 2015) 1.1 Physical fatigability 1.2 Mental fatigability 2. Tiredness "in the past month, on average how often have you felt unusually tired?"(1) 3. Energy level "During the past month, what category describes your energy level" (1)	48 (a)	Usual gait speed 6 meter walking test Fast gait speed 6 meter walking test Chair stand pace Walking Index	1.1 F vs NF: OR 2.03 [1.33 – 3.09] **1.2 F vs NF: OR 2.54 [1.58 – 4.10]** 2. F vs NF: OR 1.18 [0.80 – 1.73] 3. F vs NF: OR 1.10 [0.96 – 1.25] 1.1 F vs NF: OR 1.43 [0.98 – 2.09] 1.2 F vs NF: OR 1.40 [0.90 – 2.18] 2. F vs NF: OR 1.13 [0.79 – 1.62] 3. F vs NF: OR 1.01 [0.90 – 1.14] 1.1 F vs NF: OR 1.82 [1.17 – 2.83] 1.2 F vs NF: OR 1.58 [0.97 – 2.59] 2. F vs NF: OR 1.30 [0.87 – 1.95] 3. F vs NF: OR 1.13 [0.98 – 1.30] 1.1F vs NF: OR 2.39 [1.52 – 3.78] 1.2F vs NF: OR 1.51 [0.93 – 2.46] 2. F vs NF: OR 1.66 [1.10 – 2.51] 3. F vs NF: OR 1.16 [1.01 – 1.34]
(Moreh et al., 2010)	Age 70+, n= 460 Age 78+, n= 858	Question: Feel generally tired (1)	96 (b) 84 (b)	Change in low levels of physical activity	**F vs NF: OR 5.10 [1.90 – 13.40]** F vs NF: OR 1.30 [0.80 – 2.20]
					Overall OR: 1.41 [1.58-4.08]
Depression					
(Moreh et al., 2010)	Age 70+, n= 460 Age 78+, n= 858	Question: Feel generally tired (1)	96 (b) 84 (b)	New onset of depression	F vs NF: OR 0.65 [0.20 – 2.10] F vs NF: OR 2.00 [1.20 – 3.50]
Self-reported health & health status					
(Moreh et al., 2010)	Age 70+, n= 460 Age 78+, n= 858	Question: Feel generally tired (1)	96 (b) 84 (b)	Change in self-reported health	F vs NF: OR 2.12 [1.05 – 4.30] F vs NF: OR 1.00 [0.60 – 1.80]
Poor sleep					
(Moreh et al., 2010)	Age 70+, n= 460 Age 78+, n= 858	Question: Feel generally tired (1)	96 (b) 84 (b)	Poor sleep quality	F vs NF: OR 2.10 [1.00 – 4.50] F vs NF: OR 1.20 [0.70 – 2.10]
Loneliness					

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
(Moreh et al., 2010)	Age 70+, n= 460 Age 78+, n= 858	Question: Feel generally tired (1)	96 (d) 84 (d)	Change in loneliness yes/np	F vs NF: OR 1.80 [0.80 – 3.70] F vs NF: OR 4.70 [3.00 – 7.60]
Pain					
(Aili et al., 2018)	Age 49±15, n= 1249	SF-36 questionnaire vitality subscale(1)(Ware and Gandek, 1998)	60 (a) (n= 1249) 216 (e) (n= 791)	Question: Have you experienced pain lasting more than 3 months during the last 12 months?	F vs NF: OR 1.93 [0.87 – 4.26] MF vs NF: OR 1.48 [0.70 – 3.15] F vs NF: OR 1.34 [0.69 – 2.68] MF vs NF: OR 0.97 [0.52 – 1.79]
Dental problems					
(Avlund et al., 2001b)	Age 75+, n= 325	Mobility Tiredness scale (1)(Avlund et al., 1993)	60 (a)	Number of teeth Chewing ability Frequency of visits to a dentist or denturist	F vs NF: OR 1.40 [0.70 – 2.50] F vs NF: OR 1.20 [0.60 – 2.30] F vs NF: OR 1.90 [1.10 – 3.20]
Cognitive dysfunction					
(Islamoska et al., 2019)	Age 60,3±11,0, n= 6807†	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	60 (a) 60 (a) 120 (c) 180 (d) 240 (e)	First registration of a dementia diagnosis	Q1: F vs NF: RR 1.144 [0.973 – 1.346] Q2: F vs NF: RR 1.273 [1.025 – 1.580] Q3: F vs NF: RR 1.411 [1.034 – 1.926] F vs NF: RR 1.025 [1.004 – 1.046] F vs NF: RR 1.025 [1.004 – 1.046] F vs NF: RR 1.030 [0.999 – 1.062] F vs NF: RR 1.070 [1.018 – 1.124]
Diseases					
(Just-Ostergaard et al., 2018)	Age 58±16, n= 8956† ♂ n= 3823 ♀ n= 5133	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: Moderate exhaustion Q2: highly exhausted	288 (f)	Alcohol related hospital admission or first-time registration in the Copenhagen Alcohol Cohort	♂ Q1: F vs NF: HR 1.61 [1.05 – 2.46] ♂ Q2: F vs NF: HR 2.46 [1.40 – 4.29] ♀ Q1: F vs NF: HR 1.96 [1.00 – 3.84] ♀ Q2: F vs NF: HR 3.34 [1.62 – 6.85]

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
(Kornerup et al., 2010)	Age 22-99, n= 9186† ♂ n= 3967 ♀ n= 5219	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	108(c)	First stroke (international Classification of Diseases, Tenth, Revision)	♂ Q1: F vs NF: HR 1.30 [0.89 – 1.91] ♂ Q2: F vs NF: HR 0.95 [0.52 – 1.71] ♂ Q3: F vs NF: HR 0.83 [0.35 – 1.96] ♀ Q1: F vs NF: HR 1.04 [0.68 – 1.58] ♀ Q2: F vs NF: HR 1.38 [0.86 – 2.22] ♀ Q3: F vs NF: HR 2.19 [1.31 – 3.66]
(Pedersen et al., 2016)	Age 21-84, n= 3621† ♂ n= 1412 ♀ n= 2209	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	120 (c)	Metabolic syndrome ATP 3 clinical criteria -Abdominal obesity -Triglycerides -HDL cholesterol	♂ Q1: F vs NF: OR 1.09 [0.71 – 1.67] ♂ Q2: F vs NF: OR 0.86 [0.43 – 1.70] ♂ Q3: F vs NF: OR 2.06 [0.92 – 4.60] ♀ Q1: F vs NF: OR 0.85 [0.57 – 1.26] ♀ Q2: F vs NF: OR 1.43 [0.92 – 2.21] ♀ Q3: F vs NF: OR 1.38 [0.76 – 2.52]
(Volden et al., 2017)	Age 21-98, n= 4708† Age 21-98, n= 9075†	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	120 (c) 276(f)	Occurrence of diabetes type 2 by questionnaires Occurrence of diabetes type 2 based on registers	Q1: F vs NF: OR 1.17 [0.70 – 1.94] Q2: F vs NF: OR 1.75 [1.05 – 2.91] Q3: F vs NF: OR 2.56 [1.53 – 4.29] Q1: F vs NF: OR 0.88 [0.66 – 1.17] Q2: F vs NF: OR 0.99 [0.75 – 1.31] Q3: F vs NF: OR 1.31 [0.99 – 1.72]

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
(Bergelt et al., 2005)	Age 21-94, n= 8527†	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	132 (d)	Occurrence of cancer	Q1: F vs NF: HR 0.92 [0.77 – 1.09] Q2: F vs NF: HR 1.00 [0.84 – 1.19] Q3: F vs NF: HR 0.80 [0.66 – 0.96]
				Occurrence of smoking related cancer	**Q1: F vs NF: HR 0.98 [0.74 – 1.31]** **Q2: F vs NF: HR 0.98 [0.73 – 1.30]** **Q3: F vs NF: HR 0.64 [0.46 – 0.90]**
				Occurrence of alcohol related cancer	**Q1: F vs NF: HR 0.87 [0.42 – 1.80]** **Q2: F vs NF: HR 0.98 [0.48 – 2.00]** **Q3: F vs NF: HR 0.87 [0.40 – 1.87]**
				Occurrence of virus and immune related cancer	**Q1: F vs NF: HR 0.51 [0.26 – 0.99]** **Q2: F vs NF: HR 0.58 [0.31 – 1.09]** **Q3: F vs NF: HR 0.51 [0.26 – 0.99]**
				Occurrence of hormone related cancer	**Q1: F vs NF: HR 0.99 [0.70 – 1.39]** **Q2: F vs NF: HR 1.19 [0.86 – 1.65]** **Q3: F vs NF: HR 1.05 [0.75 – 1.49]**
(Iversen et al., 2012)	Age 21-84, n= 4228† ♂n= 1751 ♀n= 2477	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	120 (c)	BMI ≥ 30 kg/m² yes/no	♂ Q1: F vs NF: OR 0.99 [0.62 – 1.57] ♂Q2: F vs NF: OR 1.43 [0.76 – 2.69] ♂ Q3: F vs NF: OR 1.31 [0.54 – 3.20] ♀Q1: F vs NF: OR 2.04 [1.23 – 3.38] ♀ Q2: F vs NF: OR 1.74 [0.97 – 3.12] ♀ Q3: F vs NF: OR 2.40 [1.13 – 5.09]
Heart Disease					
(Ekmann et al., 2013)	Age 70+, n = 1696 Twins	Mobility Tiredness scale (1)(Avlund et al., 1993)	192 (e)	Ischemic Heart Disease incidence	F vs NF: OR 1.47 [1.08– 2.00]
(Williams et al., 2010)	Age 48-67, n= 12895‡	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	156 (d)	Cardiac events	Q1: F vs NF: HR 1.02 [0.82 – 1.27] Q2: F vs NF: HR 1.18 [0.97 – 1.45] **Q3: F vs NF: HR 1.46 [1.20 – 1.79]**

Author	Description of participants	Fatigue instrument and category	Follow-up, mo	Outcome assessment	Results
(Prescott et al., 2003)	Age 20-98, n= 9202† ♂ n= 3961 ♂ n= 5241	Vital exhaustion questionnaire (1) (Appels et al., 1987) Q1: slightly exhausted Q2: exhausted Q3: highly exhausted	180 (d)	Ischaemic heart disease diagnosed?: yes/no	♂ Q1: F vs NF: HR 1.78 [1.31 – 2.42] ♂ Q2: F vs NF: HR 1.94 [1.46 – 2.57] ♂ Q3: F vs NF: HR 2.51 [1.81 – 3.47] ♀ Q1: F vs NF: HR 1.23 [0.85 – 1.79] ♀ Q2: F vs NF: HR 1.98 [1.32 – 2.95] ♀ Q3: F vs NF: HR 2.57 [1.65 - 4.00] Q1: F vs NF: HR 1.56 [1.21 – 2.01] Q2: F vs NF: HR 1.75 [1.29 – 2.38] **Q3: F vs NF: HR 2.20 [1.53 – 3.17]**
					Overall HR: 1.60 [1.35-1.90]

1 = self-perceived fatigue, 2 = muscle fatigability
Follow-up category in months: a = 0-60; b = 61-96; c = 97-120; d = 121-180; e = 181-240; f = >240
F = Fatigues, NF = Not fatigued, MF = Medium fatigued
† Copenhagen City Heart Study; $ EPIC-Norfolk study; ‡ Atherosclerosis Risk in Communities Study; * Women's Health Initiative Clinical Trial
♂ : Males, ♀: Females
Bold: data used in the main analysis

REFERENCES

AILI, K., ANDERSSON, M., BREMANDER, A., HAGLUND, E., LARSSON, I. & BERGMAN, S. 2018. Sleep problems and fatigue as predictors for the onset of chronic widespread pain over a 5- and 18-year perspective. *BMC Musculoskelet Disord,* 19**,** 390.

ALEXANDER, N. B., TAFFET, Ã. G. E., HORNE, M., ELDADAH, B. A., FERRUCCI, L., NAYFIELD, S., STUDENSKI, S. & ÃÃ, M. P. H. 2010. Bedside-to-Bench Conference : Research Agenda for Idiopathic. 967-975.

ALLMAN, B. L. & RICE, C. L. 2002. Neuromuscular fatigue and aging: Central and peripheral factors. *Muscle and Nerve,* 25**,** 785-796.

APPELS, A., FALGER, P. R. J. & SCHOUTEN, E. G. W. 1993. Vital exhaustion as risk indicator for myocardial infarction in women. *Journal of Psychosomatic Research,* 37**,** 881-890.

APPELS, A., HÖPPENER, P. & MULDER, P. 1987. A questionnaire to assess premonitory symptoms of myocardial infarction. *International Journal of Cardiology,* 17**,** 15-24.

AVLUND, K. 2010. Fatigue in older adults: an early indicator of the aging process? *Aging Clin Exp Res,* 22**,** 100-15.

AVLUND, K., DAMSGAARD, M. T., SAKARI-RANTALA, R., LAUKKANEN, P. & SCHROLL, M. 2002a. Tiredness in daily activities among nondisabled old people as determinant of onset of disability. *J Clin Epidemiol,* 55**,** 965-73.

AVLUND, K., DAMSGAARD, M. T., SAKARI-RANTALA, R., LAUKKANEN, P. & SCHROLL, M. 2002b. Tiredness in daily activities among nondisabled old people as determinant of onset of disability. *Journal of Clinical Epidemiology,* 55**,** 965-973.

AVLUND, K., DAMSGAARD, M. T. & SCHROLL, M. 2001a. Tiredness as determinant of subsequent use of health and social services among nondisabled elderly people. *J Aging Health,* 13**,** 267-86.

AVLUND, K., DAVIDSEN, M. & SCHULTZ-LARSEN, K. 1995. Changes in functional ability from ages 70 to 75. A Danish longitudinal study. *J Aging Health,* 7**,** 254-82.

AVLUND, K., HOLM-PEDERSEN, P. & SCHROLL, M. 2001b. Functional ability and oral health among older people: a longitudinal study from age 75 to 80. *J Am Geriatr Soc,* 49**,** 954-62.

AVLUND, K., KREINER, S. & SCHULTZ-LARSEN, K. 1993. Construct validation and the Rasch model: functional ability of healthy elderly people. *Scand J Soc Med,* 21**,** 233-46.

AVLUND, K., KREINER, S. & SCHULTZ-LARSEN, K. 1996. Functional ability scales for the elderly: A validation study. *The European Journal of Public Health,* 6**,** 35-42.

AVLUND, K., MELHSEN, M., THOMSEN, D., VIIDIK, A. & ZACHARIAE, R. 2008. Physical Functioning and Use of Health Services in a Young and Old Sample. The Influence of Fatigue. *Dan Med Bull,* 55**,** 147-151.

AVLUND, K., PEDERSEN, A. N. & SCHROLL, M. 2003a. Functional decline from age 80 to 85: influence of preceding changes in tiredness in daily activities. *Psychosom Med,* 65**,** 771-7.

AVLUND, K., SCHULTZ-LARSEN, K. & DAVIDSEN, M. 1998. Tiredness in Daily Activities at Age 70 as a Predictor of Mortality During the Next 10 Years. *Journal of Clinical Epidemiology,* 51**,** 323-333.

AVLUND, K., VASS, M. & HENDRIKSEN, C. 2003b. Onset of mobility disability among community-dwelling old men and women. The role of tiredness in daily activities. *Age Ageing,* 32**,** 579-84.

BASU, N., YANG, X., LUBEN, R. N., WHIBLEY, D., MACFARLANE, G. J., WAREHAM, N. J., KHAW, K. T. & MYINT, P. K. 2016. Fatigue is associated with excess mortality in the general population: results from the EPIC-Norfolk study. *BMC Med,* 14**,** 122.

BAUTMANS, I. & METS, T. 2005. A fatigue resistance test for elderly persons based on grip strength: Reliability and comparison with healthy young subjects. *Aging Clinical and Experimental Research,* 17**,** 217-222.

BAUTMANS, I., NJEMINI, R., LAMBERT, M., DEMANET, C. & METS, T. 2005. Circulating Acute Phase Mediators and Skeletal Muscle Performance in Hospitalized Geriatric Patients. *The Journals of Gerontology: Series A,* 60**,** 361-367.

BENDAYAN, M., BIBAS, L., LEVI, M., MULLIE, L., FORMAN, D. E. & AFILALO, J. 2014. Therapeutic interventions for frail elderly patients: Part II: Ongoing and unpublished randomized trials. *Progress in Cardiovascular Diseases,* 57**,** 144-151.

BERGELT, C., CHRISTENSEN, J., PRESCOTT, E., GRONBAEK, M., KOCH, U. & JOHANSEN, C. 2005. Vital exhaustion and risk for cancer: a prospective cohort study on the association between depressive feelings, fatigue, and risk of cancer. *Cancer,* 104**,** 1288-95.

BEYER, I., NJEMINI, R., BAUTMANS, I., DEMANET, C., BERGMANN, P. & METS, T. 2012. Inflammation-related muscle weakness and fatigue in geriatric patients. *EXG,* 47**,** 52-59.

BIBAS, L., LEVI, M., BENDAYAN, M., MULLIE, L., FORMAN, D. E. & AFILALO, J. 2014. Therapeutic interventions for frail elderly patients: Part I: Published randomized trials. *Progress in Cardiovascular Diseases,* 57**,** 134-143.

BORG, G. 1990. Psychophysical scaling with applications in physical work and the perception of exertion. *Scand J Work Environ Health,* 16 Suppl 1**,** 55-8.

BRANDT, C. & PEDERSEN, B. K. 2010. The role of exercise-induced myokines in muscle homeostasis and the defense against chronic diseases. *J Biomed Biotechnol,* 2010**,** 520258.

BROWN, P. J., BADREDDINE, D., ROOSE, S. P., RUTHERFORD, B., AYONAYON, H. N., YAFFE, K., SIMONSICK, E. M., GOODPASTER, B. & HEALTH, A. B. C. S. 2017. Muscle fatigability and depressive symptoms in later life. *Int J Geriatr Psychiatry,* 32**,** e166-e172.

BUCHOWSKI, M. S., SIMMONS, S. F., WHITAKER, L. E., POWERS, J., BEUSCHER, L., CHOI, L., IKIZLER, T. A., CHEN, K. & SHNELLE, J. F. 2013. Fatigability as a function of physical activity energy expenditure in older adults. *Age (Dordr),* 35**,** 179-87.

CALDER, P. C., BOSCO, N., BOURDET-SICARD, R., CAPURON, L., DELZENNE, N., DORE, J., FRANCESCHI, C., LEHTINEN, M. J., RECKER, T., SALVIOLI, S. & VISIOLI, F. 2017. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. *Ageing Res Rev,* 40**,** 95-119.

CAO DINH, H., BAUTMANS, I., BEYER, I., METS, T., ONYEMA, O. O., FORTI, L. N., RENMANS, W., VANDER MEEREN, S., JOCHMANS, K., VERMEIREN, S., VELLA-AZZOPARDI, R., NJEMINI, R. & GERONTOPOLE BRUSSELS STUDY, G. 2019. Association Between Immunosenescence Phenotypes and Pre-frailty in Older Subjects: Does Cytomegalovirus Play a Role? *J Gerontol A Biol Sci Med Sci,* 74**,** 480-488.

CAO DINH, H., NJEMINI, R., ONYEMA, O. O., BEYER, I., LIBERMAN, K., DE DOBBELEER, L., RENMANS, W., VANDER MEEREN, S., JOCHMANS, K., DELAERE, A., KNOOP, V. & BAUTMANS, I. 2018. Strength endurance training but not intensive strength training reduces senescence-prone T-cells in peripheral blood in community-dwelling elderly women. *J Gerontol A Biol Sci Med Sci*.

CESARI, M., ARAUJO DE CARVALHO, I., AMUTHAVALLI THIYAGARAJAN, J., COOPER, C., MARTIN, F. C., REGINSTER, J. Y., VELLAS, B. & BEARD, J. R. 2018. Evidence for the Domains Supporting the Construct of Intrinsic Capacity. *J Gerontol A Biol Sci Med Sci,* 73**,** 1653-1660.

CESARI, M., VELLAS, B., HSU, F. C., NEWMAN, A. B., DOSS, H., KING, A. C., MANINI, T. M., CHURCH, T., GILL, T. M., MILLER, M. E. & PAHOR, M. 2015. A physical activity intervention to treat the frailty syndrome in older persons - Results from the LIFE-P study. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences,* 70**,** 216-222.

CHO, J., MARTIN, P., MARGRETT, J., MACDONALD, M., JOHNSON, M. A., POON, L. W., GEORGIA CENTENARIAN, S., JAZWINSKI, S. M., GREEN, R. C., GEARING, M., WOODARD, J. L., TENOVER, J. S., SIEGLER, I. C., ROTT, C., RODGERS, W. L., HAUSMAN, D., ARNOLD, J. & DAVEY, A. 2012. Multidimensional predictors of fatigue among octogenarians and centenarians. *Gerontology,* 58**,** 249-57.

COLE, S. R., KAWACHI, I., SESSO, H. D., PAFFENBARGER, R. S. & LEE, I. M. 1999. Sense of exhaustion and coronary heart disease among college alumni∗∗This is report no. LXXIV in a series on chronic disease in former college students. *The American Journal of Cardiology,* 84**,** 1401-1405.

DANTZER, R. & KELLEY, K. W. 2007. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun,* 21**,** 153-160.

DE DOBBELEER, L., THEOU, O., BEYER, I., JONES, G. R., JAKOBI, J. M. & BAUTMANS, I. 2018. Martin Vigorimeter assesses muscle fatigability in older adults better than the Jamar Dynamometer. *Exp Gerontol,* 111**,** 65-70.

DEEKS J.J., H. J. P. T., ALTMAN D.G. 2008. *Analysing Data and Undertaking Meta-Analyses. In Cochrane Handbook for Systematic Reviews of Interventions,* Chichester, UK, John Wiley & Sons, Ltd.

EGERTON, T., CHASTIN, S. F., STENSVOLD, D. & HELBOSTAD, J. L. 2016. Fatigue May Contribute to Reduced Physical Activity Among Older People: An Observational Study. *J Gerontol A Biol Sci Med Sci,* 71**,** 670-6.

EKMANN, A., PETERSEN, I., MANTY, M., CHRISTENSEN, K. & AVLUND, K. 2013. Fatigue, general health, and ischemic heart disease in older adults. *J Gerontol A Biol Sci Med Sci,* 68**,** 279-85.

ELDADAH, B. A. 2010. Fatigue and Fatigability in Older Adults. *PMRJ,* 2**,** 406-413.

EMERSON, N. S., STOUT, J. R., FUKUDA, D. H., ROBINSON, E. H., IV, SCANLON, T. C., BEYER, K. S., FRAGALA, M. S. & HOFFMAN, J. R. 2015. Resistance training improves capacity to delay neuromuscular fatigue in older adults. *Arch Gerontol Geriatr,* 61**,** 27-32.

ENGBERG, I., SEGERSTEDT, J., WALLER, G., WENNBERG, P. & ELIASSON, M. 2017. Fatigue in the general population- associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern Sweden MONICA study 2014. *BMC Public Health,* 17**,** 654.

FANTIN, F., DI FRANCESCO, V., FONTANA, G., ZIVELONGHI, A., BISSOLI, L., ZOICO, E., ROSSI, A., MICCIOLO, R., BOSELLO, O. & ZAMBONI, M. 2007. Longitudinal body composition changes in old men and women: interrelationships with worsening disability. *J Gerontol A Biol Sci Med Sci,* 62**,** 1375-81.

FELGER, J. C. & MILLER, A. H. 2012. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. *Front Neuroendocrinol,* 33**,** 315-27.

FRANCESCHI, C., CAPRI, M., MONTI, D., GIUNTA, S., OLIVIERI, F., SEVINI, F., PANOURGIA, M. P., INVIDIA, L., CELANI, L., SCURTI, M., CEVENINI, E., CASTELLANI, G. C. & SALVIOLI, S. 2007. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev,* 128**,** 92-105.

FRIED, L. P., TANGEN, C. M., WALSTON, J., NEWMAN, A. B., HIRSCH, C., GOTTDIENER, J., SEEMAN, T., TRACY, R., KOP, W. J., BURKE, G. & MCBURNIE, M. A. 2001. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol A Biol Sci Med Sci,* 56**,** M146-157.

FUKUHARA, S., BITO, S., GREEN, J., HSIAO, A. & KUROKAWA, K. 1998. Translation, Adaptation, and Validation of the SF-36 Health Survey for Use in Japan. *Journal of Clinical Epidemiology,* 51**,** 1037-1044.

GILL, T. M., DESAI, M. M., GAHBAUER, E. A., HOLFORD, T. R. & WILLIAMS, C. S. 2001. Restricted activity among community-living older persons: incidence, precipitants, and health care utilization. *Ann Intern Med,* 135**,** 313-21.

GIOVANNINI, S., ONDER, G., LIPEROTI, R., RUSSO, A., CARTER, C., CAPOLUONGO, E., PAHOR, M., BERNABEI, R. & LANDI, F. 2011. Interleukin-6, C-reactive protein, and tumor necrosis factor-alpha as predictors of mortality in frail, community-living elderly individuals. *J Am Geriatr Soc,* 59**,** 1679-85.

GLYNN, N. W., SANTANASTO, A. J., SIMONSICK, E. M., BOUDREAU, R. M., BEACH, S. R., SCHULZ, R. & NEWMAN, A. B. 2015. The Pittsburgh Fatigability scale for older adults: development and validation. *J Am Geriatr Soc,* 63**,** 130-5.

GONZALES, J. U., WIBERG, M., DEFFERARI, E. & PROCTOR, D. N. 2015. Arterial stiffness is higher in older adults with increased perceived fatigue and fatigability during walking. *Experimental Gerontology,* 61**,** 92-97.

GRYSON, C., RATEL, S., RANCE, M., PENANDO, S., BONHOMME, C., LE RUYET, P., DUCLOS, M., BOIRIE, Y. & WALRAND, S. 2014. Four-month course of soluble milk proteins interacts with exercise to improve muscle strength and delay fatigue in elderly participants. *J Am Med Dir Assoc,* 15**,** 958 e1-9.

HARDY, S. E. & A, S. S. 2010. Qualities of Fatigue and Associated Chronic Conditions among older adults. *Journal of Pain Symptom Management,* 39**,** 1033-1042.

HARDY, S. E. & STUDENSKI, S. A. 2008. Fatigue predicts mortality in older adults. *J Am Geriatr Soc,* 56**,** 1910-4.

HARDY, S. E. & STUDENSKI, S. A. 2010. Qualities of fatigue and associated chronic conditions among older adults. *J Pain Symptom Manage,* 39**,** 1033-42.

HARINGSMA, R., ENGELS, G. I., BEEKMAN, A. T. & SPINHOVEN, P. 2004. The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. *Int J Geriatr Psychiatry,* 19**,** 558-63.

HAYS, R. D., SHERBOURNE, C. D. & MAZEL, R. M. 1993. The RAND 36-Item Health Survey 1.0. *Health Econ,* 2**,** 217-27.

HIGGINS, J. P., THOMPSON, S. G., DEEKS, J. J. & ALTMAN, D. G. 2003. Measuring inconsistency in meta-analyses. *BMJ,* 327**,** 557-60.

HO, L. Y. W. & NG, S. S. M. 2020. Non-pharmacological interventions for fatigue in older adults: a systematic review and meta-analysis. *Age Ageing,* 49**,** 341-351.

IDLAND, G., PETTERSEN, R., AVLUND, K. & BERGLAND, A. 2013. Physical performance as long-term predictor of onset of activities of daily living (ADL) disability: a 9-year longitudinal study among community-dwelling older women. *Arch Gerontol Geriatr,* 56**,** 501-6.

ISLAMOSKA, S., ISHTIAK-AHMED, K., HANSEN, A. M., GRYNDERUP, M. B., MORTENSEN, E. L., GARDE, A. H., GYNTELBERG, F., PRESCOTT, E. I. B., TOROK, E., WALDEMAR, G. & NABE-

NIELSEN, K. 2019. Vital Exhaustion and Incidence of Dementia: Results from the Copenhagen City Heart Study. *J Alzheimers Dis,* 67**,** 369-379.

IVERSEN, L. B., STRANDBERG-LARSEN, K., PRESCOTT, E., SCHNOHR, P. & ROD, N. H. 2012. Psychosocial risk factors, weight changes and risk of obesity: the Copenhagen City Heart Study. *Eur J Epidemiol,* 27**,** 119-30.

JUST-OSTERGAARD, E., MORTENSEN, E. L., TOLSTRUP, J. S. & FLENSBORG-MADSEN, T. 2018. Vital exhaustion and risk of alcohol use disorders: A prospective cohort study. *J Psychosom Res,* 114**,** 25-30.

KAMITANI, T., YAMAMOTO, Y., KURITA, N., YAMAZAKI, S., FUKUMA, S., OTANI, K., SEKIGUCHI, M., ONISHI, Y., TAKEGAMI, M., ONO, R., KONNO, S., KIKUCHI, S. & FUKUHARA, S. 2017. Longitudinal Association Between Subjective Fatigue and Future Falls in Community-Dwelling Older Adults: The Locomotive Syndrome and Health Outcomes in the Aizu Cohort Study (LOHAS). *J Aging Health,* 31**,** 67-84.

KATZ, I. R. 2004. Depression and frailty: the need for multidisciplinary research. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry,* 12**,** 1-6.

KNOOP, V., COSTENOBLE, A., VELLA AZZOPARDI, R., VERMEIREN, S., DEBAIN, A., JANSEN, B., SCAFOGLIERI, A., BAUTMANS, I. & GERONTOPOLE BRUSSELS STUDY, G. 2019. The operationalization of fatigue in frailty scales: a systematic review. *Ageing Res Rev,* 53**,** 100911.

KORNERUP, H., MAROTT, J. L., SCHNOHR, P., BOYSEN, G., BAREFOOT, J. & PRESCOTT, E. 2010. Vital exhaustion increases the risk of ischemic stroke in women but not in men: results from the Copenhagen City Heart Study. *J Psychosom Res,* 68**,** 131-7.

KRABBE, K. S., PEDERSEN, M. & BRUUNSGAARD, H. 2004. Inflammatory mediators in the elderly. *Exp Gerontol,* 39**,** 687-99.

LAMONTE, M. J., LARSON, J. C., MANSON, J. E., BELLETTIERE, J., LEWIS, C. E., LACROIX, A. Z., BEA, J. W., JOHNSON, K. C., KLEIN, L., NOEL, C. A., STEFANICK, M. L., WACTAWSKI-WENDE, J. & EATON, C. B. 2020. Association of Sedentary Time and Incident Heart Failure Hospitalization in Postmenopausal Women. *Circ Heart Fail***,** CIRCHEARTFAILURE120007508.

LAVIE, C. J., OZEMEK, C., CARBONE, S., KATZMARZYK, P. T. & BLAIR, S. N. 2019. Sedentary Behavior, Exercise, and Cardiovascular Health. *Circ Res,* 124**,** 799-815.

LIAO, S. & FERRELL, B. A. 2000. Fatigue in an older population. *J Am Geriatr Soc,* 48**,** 426-30.

LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GOTZSCHE, P. C., IOANNIDIS, J. P., CLARKE, M., DEVEREAUX, P. J., KLEIJNEN, J. & MOHER, D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ,* 339**,** b2700.

LIBERMAN, K., FORTI, L. N., BEYER, I. & BAUTMANS, I. 2017. The effects of exercise on muscle strength, body composition, physical functioning and the inflammatory profile of older adults: a systematic review. *Curr Opin Clin Nutr Metab Care,* 20**,** 30-53.

MALAGUARNERA, M., CAMMALLERI, L., GARGANTE, M. P., VACANTE, M., COLONNA, V. & MOTTA, M. 2007. L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr,* 86**,** 1738-44.

MALAGUARNERA, M., GARGANTE, M. P., CRISTALDI, E., COLONNA, V., MESSANO, M., KOVERECH, A., NERI, S., VACANTE, M., CAMMALLERI, L. & MOTTA, M. 2008. Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. *Arch Gerontol Geriatr,* 46**,** 181-90.

MANTY, M., DE LEON, C. F., RANTANEN, T., ERA, P., PEDERSEN, A. N., EKMANN, A., SCHROLL, M. & AVLUND, K. 2012. Mobility-related fatigue, walking speed, and muscle strength in older people. *J Gerontol A Biol Sci Med Sci,* 67**,** 523-9.

MANTY, M., EKMANN, A., THINGGAARD, M., CHRISTENSEN, K. & AVLUND, K. 2014. Indoor mobility-related fatigue and muscle strength in nonagenarians: a prospective longitudinal study. *Aging Clin Exp Res,* 26**,** 39-46.

MENG, H., HALE, L. & FRIEDBERG, F. 2010. Prevalence and Predictors of Fatigue Among Middle-Aged and Older Adults: Evidence from the Health and Retirement Study. *Journal of the American Geriatrics …,* 58**,** 2033-2034.

MOREH, E., JACOBS, J. M. & STESSMAN, J. 2009. Feeling tired predicts functional status, physical activity, and mortality in elderly people. *J Am Geriatr Soc,* 57**,** 742-3.

MOREH, E., JACOBS, J. M. & STESSMAN, J. 2010. Fatigue, function, and mortality in older adults. *J Gerontol A Biol Sci Med Sci,* 65**,** 887-95.

MUELLER-SCHOTTE, S., BLEIJENBERG, N., VAN DER SCHOUW, Y. T. & SCHUURMANS, M. J. 2016. Fatigue as a long-term risk factor for limitations in instrumental activities of daily living and/or mobility performance in older adults after 10 years. *Clin Interv Aging,* 11**,** 1579-1587.

MURPHY, S. L., ALEXANDER, N. B., LEVOSKA, M. & SMITH, D. M. 2013. Relationship between fatigue and subsequent physical activity among older adults with symptomatic osteoarthritis. *Arthritis Care Res (Hoboken),* 65**,** 1617-24.

NÍ MHAOLÁIN, A. M., FAN, C. W., ROMERO-ORTUNO, R., COGAN, L., CUNNINGHAM, C., KENNY, R. A. & LAWLOR, B. 2012. Frailty, depression, and anxiety in later life. *International Psychogeriatrics,* 24**,** 1265-1274.

NICE METHODOLOGY CHECKLIST PROGNOSTIC STUDIES. Available: https://www.nice.org.uk/process/pmg6/resources/the-guidelines-manual-appendices-bi-2549703709/chapter/appendix-i-methodology-checklist-prognostic-studies [Accessed May 18, 2020].

OLSEN, L. R., JENSEN, D. V., NOERHOLM, V., MARTINY, K. & BECH, P. 2003. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. *Psychol Med,* 33**,** 351-6.

PAHOR, M., GURALNIK, J. M., AMBROSIUS, W. T., BLAIR, S., BONDS, D. E., CHURCH, T. S., ESPELAND, M. A., FIELDING, R. A., GILL, T. M., GROESSL, E. J., KING, A. C., KRITCHEVSKY, S. B., MANINI, T. M., MCDERMOTT, M. M., MILLER, M. E., NEWMAN, A. B., REJESKI, W. J., SINK, K. M., WILLIAMSON, J. D., INVESTIGATORS, L. S. & FOR THE, L. S. I. 2014. Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE Study randomized clinical trial. *J Am Med Dir Assoc,* 311**,** 2387-2396.

PARK, J. H., MOON, J. H., KIM, H. J., KONG, M. H. & OH, Y. H. 2020. Sedentary Lifestyle: Overview of Updated Evidence of Potential Health Risks. *Korean J Fam Med,* 41**,** 365-373.

PAWELEC, G., GOLDECK, D. & DERHOVANESSIAN, E. 2014. Inflammation, ageing and chronic disease. *Curr Opin Immunol,* 29**,** 23-8.

PEDERSEN, J. M., LUND, R., ANDERSEN, I., CLARK, A. J., PRESCOTT, E. & ROD, N. H. 2016. Psychosocial risk factors for the metabolic syndrome: A prospective cohort study. *Int J Cardiol,* 215**,** 41-6.

POLURI, A., MORES, J., COOK, D. B., FINDLEY, T. W. & CRISTIAN, A. 2005. Fatigue in the elderly population. *Physical Medicine and Rehabilitation Clinics of North America,* 16**,** 91-108.

PONTI, F., SANTORO, A., MERCATELLI, D., GASPERINI, C., CONTE, M., MARTUCCI, M., SANGIORGI, L., FRANCESCHI, C. & BAZZOCCHI, A. 2019. Aging and Imaging Assessment of Body Composition: From Fat to Facts. *Front Endocrinol (Lausanne),* 10**,** 861.

PRESCOTT, E., HOLST, C., GRONBAEK, M., SCHNOHR, P., JENSEN, G. & BAREFOOT, J. 2003. Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. *Int J Epidemiol,* 32**,** 990-7.

PUTS, M. T. E., TOUBASI, S., ANDREW, M. K., ASHE, M. C., PLOEG, J., ATKINSON, E., AYALA, A. P., ROY, A., MONFORTE, M. R., BERGMAN, H. & MCGILTON, K. 2017. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: A scoping review of the literature and international policies. *Age and Ageing,* 46**,** 383-392.

RADLOFF, L. S. 1991. The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *J Youth Adolesc,* 20**,** 149-66.

ROD, N. H., ANDERSEN, I. & PRESCOTT, E. 2011. Psychosocial risk factors and heart failure hospitalization: a prospective cohort study. *Am J Epidemiol,* 174**,** 672-80.

RONTI, T., LUPATTELLI, G. & MANNARINO, E. 2006. The endocrine function of adipose tissue: an update. *Clin Endocrinol (Oxf),* 64**,** 355-65.

SANTORO, A., GUIDARELLI, G., OSTAN, R., GIAMPIERI, E., FABBRI, C., BERTARELLI, C., NICOLETTI, C., KADI, F., DE GROOT, L., FESKENS, E., BERENDSEN, A., BRZOZOWSKA, A., JANUSZKO, O., KOZLOWSKA, K., FAIRWEATHER-TAIT, S., JENNINGS, A., MEUNIER, N., CAUMON, E., NAPOLI, A., MERCATELLI, D., BATTISTA, G., CAPRI, M., FRANCESCHI, C. & BAZZOCCHI, A. 2019. Gender-specific association of body composition with inflammatory and adipose-related markers in healthy elderly Europeans from the NU-AGE study. *Eur Radiol,* 29**,** 4968-4979.

SCHULTZ-LARSEN, K. & AVLUND, K. 2007a. Tiredness in daily activities : A subjective measure for the identification of frailty among non-disabled community-living older adults. 44**,** 83-93.

SCHULTZ-LARSEN, K. & AVLUND, K. 2007b. Tiredness in daily activities: a subjective measure for the identification of frailty among non-disabled community-living older adults. *Arch Gerontol Geriatr,* 44**,** 83-93.

SHERRINGTON, C., FAIRHALL, N., KWOK, W., WALLBANK, G., TIEDEMANN, A., MICHALEFF, Z. A., NG, C. & BAUMAN, A. 2020. Evidence on physical activity and falls prevention for people aged 65+ years: systematic review to inform the WHO guidelines on physical activity and sedentary behaviour. *Int J Behav Nutr Phys Act,* 17**,** 144.

SIMONSICK, E. M., GLYNN, N. W., JEROME, G. J., SHARDELL, M., SCHRACK, J. A. & FERRUCCI, L. 2016. Fatigued, but Not Frail: Perceived Fatigability as a Marker of Impending Decline in Mobility-Intact Older Adults. *J Am Geriatr Soc,* 64**,** 1287-92.

SIMONSICK, E. M., NEWMAN, A. B., NEVITT, M. C., KRITCHEVSKY, S. B., FERRUCCI, L., GURALNIK, J. M., HARRIS, T. & HEALTH, A. B. C. S. G. 2001. Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. *J Gerontol A Biol Sci Med Sci,* 56**,** M644-9.

SIMONSICK, E. M., SCHRACK, J. A., SANTANASTO, A. J., STUDENSKI, S. A., FERRUCCI, L. & GLYNN, N. W. 2018. Pittsburgh Fatigability Scale: One-Page Predictor of Mobility Decline in Mobility-Intact Older Adults. *J Am Geriatr Soc,* 66**,** 2092-2096.

SOYSAL, P., VERONESE, N., THOMPSON, T., KAHL, K. G., FERNANDES, B. S., PRINA, A. M., SOLMI, M., SCHOFIELD, P., KOYANAGI, A., TSENG, P. T., LIN, P. Y., CHU, C. S., COSCO, T. D., CESARI, M., CARVALHO, A. F. & STUBBS, B. 2017. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. *Ageing Res Rev,* 36**,** 78-87.

SOYUER, F. & SENOL, V. 2011. Functional outcome and depression in the elderly with or without fatigue. *Arch Gerontol Geriatr,* 53**,** e164-7.

STADJE, R., DORNIEDEN, K., BAUM, E., BECKER, A., BIROGA, T., BÖSNER, S., HAASENRITTER, J., KEUNECKE, C., VINIOL, A. & DONNER-BANZHOFF, N. 2016. The differential diagnosis of tiredness: A systematic review. *BMC Family Practice,* 17.

STEEN, G., SONN, U., HANSON, A. B. & STEEN, B. 2001. Cognitive function and functional ability. A cross-sectional and longitudinal study at ages 85 and 95 in a non-demented population. *Aging (Milano),* 13**,** 68-77.

STENHOLM, S., FERRUCCI, L., VAHTERA, J., HOOGENDIJK, E. O., HUISMAN, M., PENTTI, J., LINDBOHM, J. V., BANDINELLI, S., GURALNIK, J. M. & KIVIMAKI, M. 2019. Natural Course of Frailty Components in People Who Develop Frailty Syndrome: Evidence From Two Cohort Studies. *J Gerontol A Biol Sci Med Sci,* 74**,** 667-674.

THEOU, O., JONES, G. R., OVEREND, T. J., KLOSECK, M. & VANDERVOORT, A. A. 2008. An exploration of the association between frailty and muscle fatigue. *Appl Physiol Nutr Metab,* 33**,** 651-65.

TOSS, F., WIKLUND, P., NORDSTROM, P. & NORDSTROM, A. 2012. Body composition and mortality risk in later life. *Age Ageing,* 41**,** 677-81.

VALENTINE, R. J., WOODS, J. A., MCAULEY, E., DANTZER, R. & EVANS, E. M. 2011. The associations of adiposity, physical activity and inflammation with fatigue in older adults. *Brain Behav Immun,* 25**,** 1482-90.

VARADHAN, R., YAO, W., MATTEINI, A., BEAMER, B. A., XUE, Q. L., YANG, H., MANWANI, B., REINER, A., JENNY, N., PAREKH, N., FALLIN, M. D., NEWMAN, A., BANDEEN-ROCHE, K., TRACY, R., FERRUCCI, L. & WALSTON, J. 2014. Simple biologically informed inflammatory index of two serum cytokines predicts 10 year all-cause mortality in older adults. *J Gerontol A Biol Sci Med Sci,* 69**,** 165-73.

VESTERGAARD, S., NAYFIELD, S. G., PATEL, K. V., ELDADAH, B., CESARI, M., FERRUCCI, L., CERESINI, G. & GURALNIK, J. M. 2009. Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences,* 64**,** 76-82.

VGONTZAS, A. N., BIXLER, E. O. & CHROUSOS, G. P. 2006. Obesity-related sleepiness and fatigue: the role of the stress system and cytokines. *Ann N Y Acad Sci,* 1083**,** 329-44.

VOLDEN, S., WIMMELMANN, C. L. & FLENSBORG-MADSEN, T. 2017. Does vital exhaustion increase the risk of type 2 diabetes? A prospective study. *J Psychosom Res,* 99**,** 82-88.

WALSTON, J. 2002. Frailty and Activation of the Inflammation and Coagulation Systems With and Without Clinical Comorbidities<subtitle>Results From the Cardiovascular Health Study</subtitle>. *Archives of Internal Medicine,* 162**,** 2333-2333.

WARE, J., JR., KOSINSKI, M. & KELLER, S. D. 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care,* 34**,** 220-33.

WARE, J. E. & GANDEK, B. 1998. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *Journal of Clinical Epidemiology,* 51**,** 903-912.

WHITSON, H. E., THIELKE, S., DIEHR, P., O'HARE, A. M., CHAVES, P. H., ZAKAI, N. A., ARNOLD, A., CHAUDHRY, S., IVES, D. & NEWMAN, A. B. 2011. Patterns and predictors of recovery from exhaustion in older adults: the cardiovascular health study. *J Am Geriatr Soc,* 59**,** 207-13.

WILLIAMS, J. E., MOSLEY, T. H., JR., KOP, W. J., COUPER, D. J., WELCH, V. L. & ROSAMOND, W. D. 2010. Vital exhaustion as a risk factor for adverse cardiac events (from the Atherosclerosis Risk In Communities [ARIC] study). *Am J Cardiol,* 105**,** 1661-5.

YESAVAGE, J. A., BRINK, T. L., ROSE, T. L., LUM, O., HUANG, V., ADEY, M. & LEIRER, V. O. 1982. Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research,* 17**,** 37-49.

ZASLAVSKY, O., COCHRANE, B. B., HERTING, J. R., THOMPSON, H. J., WOODS, N. F. & LACROIX, A. 2014. Application of person-centered analytic methodology in longitudinal research: exemplars from the Women's Health Initiative Clinical Trial data. *Res Nurs Health,* 37**,** 53-64.

ZASLAVSKY, O., ZELBER-SAGI, S., LACROIX, A. Z., BRUNNER, R. L., WALLACE, R. B., COCHRANE, B. B. & WOODS, N. F. 2017. Comparison of the Simplified sWHI and the Standard CHS Frailty Phenotypes for Prediction of Mortality, Incident Falls, and Hip Fractures in Older Women. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences,* 72**,** 1394-1400.

ZENGARINI, E., RUGGIERO, C., PÉREZ-ZEPEDA, M. U., HOOGENDIJK, E. O., VELLAS, B., MECOCCI, P. & CESARI, M. 2015. Fatigue : Relevance and implications in the aging population. *EXG,* 70**,** 78-83.