

GULF WAR ILLNESS

[Repeated exposures to diisopropylfluorophosphate result in structural disruptions of myelinated axons and persistent impairments of axonal transport in the brains of rats.](#)

[Naughton SX](#)¹, [Hernandez CM](#)¹, [Beck WD](#)¹, [Poddar I](#)¹, [Yanasak N](#)², [Lin PC](#)², [Terry AV Jr](#)³.

Toxicology. 2018 Jun 9;406-407:92-103. doi: 10.1016/j.tox.2018.06.004. PMID: 29894704. [Epub ahead of print]

Organophosphates (OPs) are found in hundreds of valuable agricultural, industrial, and commercial compounds; however, they have also been associated with a variety of harmful effects in humans. The acute toxicity of OPs is attributed to the inhibition of the enzyme acetylcholinesterase (AChE); however, this mechanism may not account for all of the deleterious neurologic effects of OPs, especially at doses that produce no overt signs of acute toxicity. In this study, the effects of two weeks of daily subcutaneous exposure to the OP-nerve agent diisopropylfluorophosphate (DFP) in doses ranging from 0.125-0.500 mg/kg on whole brain volume, white matter, and gray matter integrity were evaluated in post mortem tissues using histology and magnetic resonance imaging (MRI) methods. The effects of DFP on axonal transport in the brains of living rats were evaluated using a manganese-enhanced MRI (MEMRI) method. DFP was associated with dose-dependent impairments in red blood cell and brain AChE (down to 29 and 18% of control, respectively at the highest dose), 24 h after the last injection. However, there were no visible signs of cholinergic toxicity noted in any portion of the study. Moreover, histological and MRI analysis of post mortem brains did not reveal any pronounced alterations of whole brain, white matter, or gray matter volumes associated with DFP. Electron microscopy did reveal a DFP-related increase in structural disruptions of myelinated axons (i.e., decompactions) in the fimbria region on the corpus callosum. MEMRI indicated that DFP was also associated with dose-dependent decreases in axonal transport in the brains of living rats, an effect that was also present after a 30-day (DFP-free) washout period, when AChE was not significantly inhibited. These results indicate that repeated exposures to the nerve agent, DFP at doses that are below the threshold for acute toxicity, can result in alterations in myelin structure and persistent decreases in axonal transport in the rodent brain. These observations could explain some of the long-term neurological deficits that have been observed in humans who have been repeatedly exposed to OPs.

Note: Although the abstract does not mention GWI, the Introduction for the full text of the article published in [Toxicology](#) states the following: “Lower level, repeated exposures to OPs have also been associated with a variety of adverse symptoms in other contexts. For example, low-level exposures to OP-based insecticides (e.g., chlorpyrifos, dichlorvos) as well as nerve agent-OPs (sarin and cyclosarin) following the destruction of an Iraqi munitions storage complex at Khamisiyah, Iraq, in March 1991 have been implicated in the etiology of Gulf War Illness (GWI), which affects up to one-fourth of the veterans from the first gulf war.”

CHRONIC FATIGUE SYNDROME

[Recent insights into 3 underrecognized conditions: Myalgic encephalomyelitis-chronic fatigue syndrome, fibromyalgia, and environmental sensitivities-multiple chemical sensitivity.](#)

[Hu H](#)¹, [Baines C](#)².

Can Fam Physician. 2018 Jun;64(6):413-415. [Link to full text of this article in [Can Fam Physician](#), with the following introduction] [Note Recommendation #3 in the full text of this article: "Lay the groundwork for a patient-centered system of care"]

The Ontario Ministry of Health and Long-Term Care recently released the interim report of a task force charged with providing recommendations on 3 symptom-based conditions that have both shared and distinctive features: myalgic encephalomyelitis–chronic fatigue syndrome (ME-CFS), fibromyalgia (FM), and environmental sensitivities–multiple chemical sensitivity (ES-MCS).

Typical symptoms of ME-CFS, FM, and ES-MCS

Symptoms common to all 3 conditions include the following:

- Fatigue and, to varying degrees, pain, sleep disturbances, and neurologic and cognitive symptoms

Distinct symptoms among each condition include the following:

- The fatigue in ME-CFS is chronic, profound, and not improved by rest, and there is postexertional malaise
- The chronic musculoskeletal pain in FM is widespread
- The symptoms of ES-MCS are provoked by exposure to low levels of multiple (and often unrelated) chemical, biological, or physical agents. Symptoms are usually neurocognitive, and might involve respiratory and other systems, with relief or improvement when inciting agents are removed

ES-MCS—environmental sensitivities–multiple chemical sensitivity, FM—fibromyalgia, ME-CFS—myalgic encephalomyelitis–chronic fatigue syndrome.

None of these conditions has consistent physical or laboratory findings, and the conditions vary in severity. Their underlying biological mechanisms remain unclear. As with many chronic conditions, patients are at risk of anxiety, depression, and other psychological symptoms. The foregoing attributes and the lack of proven treatments and clinical practice guidelines have led to decades of uncertainty regarding diagnosis, unnecessary investigations, ineffective treatment, and unmitigated suffering.

Nevertheless, as noted in the report, recent insights reveal both the need and opportunities for finding solutions. First is evidence underscoring the prevalence of these conditions in Canada and their effect on health care use and employment. Second is mounting evidence of biological mechanisms that might lead to effective treatments. These insights, including those summarized within this article, deserve wide dissemination in the primary care community....

HEADACHE and MIGRAINE

[Linking migraine frequency with family history of migraine.](#)

[Pelzer N](#)¹, [Louter MA](#)^{1,2,3}, [van Zwet EW](#)⁴, [Nyholt DR](#)⁵, [Ferrari MD](#)¹, [van den Maagdenberg AM](#)^{1,6}, [Haan J](#)^{1,7}, [Terwindt GM](#)¹.
Cephalalgia. 2018 Jan 1:333102418783295. doi: 10.1177/0333102418783295. PMID: 29911421. [Epub ahead of print]

Background Migraine is a complex genetic disorder that is brought about by multiple genetic and environmental factors. We aimed to assess whether migraine frequency is associated with genetic susceptibility. Methods We investigated in 2829 migraine patients (14% males) whether 'migraine frequency' (measured as the number of migraine days per month) was related to 'genetic load' (measured as the number of parents affected with migraine) using a validated web-based questionnaire. In addition, we investigated associations with age-at-onset, migraine subtype, use of acute headache medication, and comorbid depression. Results We found an association between the number of migraine days per month and family history of migraine for males ($p = 0.03$), but not for females ($p = 0.97$). This association was confirmed in a linear regression analysis. Also, a lower age-at-onset ($p < 0.001$), having migraine with aura ($p = 0.03$), and a high number of medication days ($p = 0.006$) were associated with a stronger family history of migraine, whereas lifetime depression ($p = 0.13$) was not. Discussion Migraine frequency, as measured by the number of migraine days per month, seems associated with a genetic predisposition only in males. A stronger family history of migraine was also associated with a lower age-at-onset, a higher number of medication days, and migraine with aura. Our findings suggest that specific clinical features of migraine seem more determined by genetic factors.

HEADACHE and MIGRAINE (Continued)

[Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study.](#)

[Tassorelli C](#)¹, [Grazzi L](#)², [de Tommaso M](#)², [Pierangeli G](#)², [Martelletti P](#)², [Rainero I](#)², [Dorlas S](#)², [Geppetti P](#)², [Ambrosini A](#)², [Sarchielli P](#)², [Liebler E](#)², [Barbanti P](#)²; [PRESTO Study Group](#). Collaborators: (52)

Neurology. **2018 Jun 15**. pii: 10.1212/WNL.0000000000005857. doi: 10.1212/WNL.0000000000005857. PMID: 29907608. [Epub ahead of print]

OBJECTIVE: To evaluate the efficacy, safety, and tolerability of noninvasive vagus nerve stimulation (nVNS; gammaCore; electroCore, LLC, Basking Ridge, NJ) for the acute treatment of migraine in a multicenter, double-blind, randomized, sham-controlled trial.

METHODS: A total of 248 participants with episodic migraine with/without aura were randomized to receive nVNS or sham within 20 minutes from pain onset. Participants were to repeat treatment if pain had not improved in 15 minutes.

RESULTS: nVNS (n = 120) was superior to sham (n = 123) for pain freedom at 30 minutes (12.7% vs 4.2%; $p = 0.012$) and 60 minutes (21.0% vs 10.0%; $p = 0.023$) but not at 120 minutes (30.4% vs 19.7%; $p = 0.067$; primary endpoint; logistic regression) after the first treated attack. A post hoc repeated-measures test provided further insight into the therapeutic benefit of nVNS through 30, 60, and 120 minutes (odds ratio 2.3; 95% confidence interval 1.2, 4.4; $p = 0.012$). nVNS demonstrated benefits across other endpoints including pain relief at 120 minutes and was safe and well-tolerated.

CONCLUSION: This randomized sham-controlled trial supports the abortive efficacy of nVNS as early as 30 minutes and up to 60 minutes after an attack. Findings also suggest effective pain relief, tolerability, and practicality of nVNS for the acute treatment of episodic migraine.

CLINICALTRIALSGOV IDENTIFIER: [NCT02686034](#).

CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that for patients with an episodic migraine, nVNS significantly increases the probability of having mild pain or being pain-free 2 hours poststimulation (absolute difference 13.2%).

[Color-Selective Photophobia in Ictal vs. Interictal Migraineurs and in Healthy Controls.](#)

[Nir RR](#)^{1,2}, [Lee AJ](#)³, [Huntington S](#)³, [Noseda R](#)^{1,2}, [Bernstein CA](#)^{2,4}, [Fulton AB](#)^{2,5}, [Bertisch SM](#)^{2,6}, [Hovaguimian A](#)^{2,7}, [Buettner C](#)^{2,8}, [Borsook D](#)^{2,9}, [Burstein R](#)^{1,2}.

Pain. **2018 Jun 12**. doi: 10.1097/j.pain.0000000000001303. PMID: 29905657. [Epub ahead of print]

Aversion to light is common among migraineurs undergoing acute attacks. Using psychophysical assessments in episodic migraine patients, we reported that white, blue, amber and red lights exacerbate migraine headache in a significantly larger percentage of patients and to a greater extent compared to green light. This study aimed at determining whether these findings are phase-dependent - namely, manifested exclusively during migraine (ictally) but not in its absence (interictally), or condition-dependent - i.e., expressed uniquely in migraineurs but not in healthy controls. To determine whether the color-preference of migraine-type photophobia is phase- or condition-dependent, we compared the effects of each color of light in each intensity between migraineurs during and in-between attacks and healthy controls. During the ictal and interictal phases, the proportion of migraineurs reporting changes in headache severity when exposed to the different colors of light increased in accordance with elevated light intensities. During the ictal phase, white, blue, amber and red lights exacerbated headaches in ~80% of the patients; however, during the interictal phase light initiated headache in only 16-19%. Notably, green light exacerbated headaches in 40% and triggered headaches in 3% of the patients studied during the ictal and interictal phases, respectively. With one exception (highest red light intensity), no control subject reported headache in response to the light stimuli. These findings suggest that color preference is unique to migraineurs - as it was not found in control subjects - and that it is independent of whether or not the patients are in their ictal or interictal phase.

CHRONIC PAIN

[Pain processing in the human brainstem and spinal cord before, during and after the application of noxious heat stimuli.](#)

[Stroman PW](#)^{1,2}, [Ioachim G](#)¹, [Powers JM](#)¹, [Staud R](#)³, [Pukall C](#)^{1,4}.

Pain. **2018 Jun 12**. doi: 10.1097/j.pain.0000000000001302. PMID: 29905656. [Epub ahead of print]

Descending regulation of spinal cord responses to nociceptive signaling has a strong influence on pain perception. Prior studies using functional magnetic resonance imaging (fMRI) have indicated that in addition to reactive responses to nociceptive signals there is a continuous component to regulation, and that it may vary with differences in pain sensitivity. We hypothesize that this continuous regulation component occurs routinely in fMRI studies prior to noxious stimulation, as well as during, and following stimulation. This hypothesis was tested by analyzing data from 59 healthy participants in four prior fMRI studies in our lab employing noxious heat stimuli. Analyses included structural equation modeling (SEM) to identify coordinated blood oxygenation-level dependent (BOLD) signal variations between regions (i.e. connectivity) and Bayesian regression of BOLD time-series responses in relation to pain ratings and stimulus temperatures. The results demonstrate the periaqueductal gray (PAG) - rostral ventromedial medulla (RVM) - spinal cord descending modulation pathway, influenced by input from the hypothalamus, parabrachial nucleus (PBN) and nucleus tractus solitarius (NTS). Connectivity between specific regions is observed to vary in relation to pain sensitivity. The results support the conclusion that homeostatic autonomic control influences the net descending pain regulation, and therefore influences pain sensitivity. The results describe the overall properties of pain processing (specifically pain elicited by heat) in the healthy human brainstem and spinal cord, and mechanisms for variation across individuals. This understanding is expected to be important for studies of how pain processing is altered in chronic pain conditions.

[Gender differences in chronic pain related health care utilization.](#)

[Jonsdottir T](#)¹, [Jonsdottir H](#)², [Gunnarsdottir S](#)^{2,3}.

Scand J Pain. **2017 Dec 29**;8(1):50-51. doi: 10.1016/j.sjpain.2015.04.013. PMID: 29911606.

Aims: To investigate predictors for health-care utilization for chronic pain and whether there are gender differences in variables predicting chronic pain-related health care utilization.

Methods: A postal questionnaire measuring socio-demographic variables, pain characteristics, health related quality of life (HRQoL) and pain related health care utilization, was sent to a sample of 4500 individuals randomly drawn from the national population of Iceland. The relationships between socio-demographic and pain related variables and pain related health care utilization among participants reporting chronic pain (≥ 3 months) were tested by using bivariate and multivariate statistical analysis.

Results: The prevalence of chronic pain among respondents was 47.5%. Among participants reporting chronic pain, 53.2% had consulted a health care provider for pain during the previous six months. Predictors for pain related health care utilization were pain interference with daily life and pain pattern (daily pain) as well as physical components of HRQoL. Even though health care utilization was not related to gender, there were gender differences in pain-related predictors for health care utilization. Interference with daily life and pain pattern were the strongest predictors among women, but interference with life and the physical components of HRQoL were the strongest predictors for men. Pain related health care utilization was not related to socio-demographic variables.

Conclusions: Pain related variables are better predictors of chronic pain related health care utilization than socio-demographics. Even though gender does not predict chronic pain-related health care utilization, there are gender differences in the relationships between pain-related variables and health care utilization. These gender differences warrant further exploration.

CHRONIC PAIN (Continued)

[Recovery of Repressed Memories in Fibromyalgia Patients Treated With Hyperbaric Oxygen - Case Series Presentation and Suggested Bio-Psycho-Social Mechanism.](#)

[Efrati S](#)^{1,2,3}, [Hadanny A](#)^{1,2}, [Daphna-Tekoah S](#)^{4,5}, [Bechor Y](#)¹, [Tiberg K](#)⁶, [Pik N](#)⁷, [Suzin G](#)¹, [Lev-Wiesel R](#)⁸.

Front Psychol. 2018 May 29;9:848. doi: 10.3389/fpsyg.2018.00848. PMID: PMC5987035. eCollection 2018.

Fibromyalgia Syndrome (FMS) is a condition considered to represent a prototype of central sensitization syndrome, characterized by chronic widespread pain and along with symptoms of fatigue, non-restorative sleep and cognitive difficulties. FMS can be induced by trauma, infection or emotional stress with cumulative evidence that dissociation is relatively frequent in FMS patients. Two randomized controlled trials have shown that hyperbaric oxygen therapy (HBOT) can induce neuroplasticity and be effective in patients suffering from FMS. In this paper we present, for the first time, case series of female fibromyalgia patients who, in the course of HBOT, suddenly recalled repressed traumatic memories of childhood sexual abuse (CSA). The surfacing of the repressed (dissociative) memories decades after the sexual abuse events was sudden and utterly surprising. No psychological intervention was involved. As the memories surfaced, the physical pain related to FMS subsided. In one patient who had brain single photon emission CT (SPECT) before and after HBOT, the prefrontal cortex appeared suppressed before and reactivated after. The 3 cases reported in this article are representative of a total of nine fibromyalgia patients who experienced a retrieval of repressed memory during HBOT. These cases provide insights on dissociative amnesia and suggested mechanism hypothesis that is further discussed in the article. Obviously, prospective studies cannot be planned since patients are not aware of their repressed memories. However, it is very important to keep in mind the possibility of surfacing memories when treating fibromyalgia patients with HBOT or other interventions capable of awakening dormant brain regions.

OTHER RESEARCH OF INTEREST

[Dementia And Physical Activity \(DAPA\) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial.](#)

[Lamb SE](#)^{1,2}, [Sheehan B](#)³, [Atherton N](#)³, [Nichols V](#)², [Collins H](#)⁴, [Mistry D](#)², [Dosanjh S](#)², [Slowther AM](#)⁵, [Khan I](#)², [Petrou S](#)², [Lall R](#)²; [DAPA Trial Investigators](#).

BMJ. 2018 May 16;361:k1675. doi: 10.1136/bmj.k1675. PMID: PMC5953238. PMID: 29769247.

OBJECTIVE: To estimate the effect of a moderate to high intensity aerobic and strength exercise training programme on cognitive impairment and other outcomes in people with mild to moderate dementia.

DESIGN: Multicentre, pragmatic, investigator masked, randomised controlled trial.

SETTING: National Health Service primary care, community and memory services, dementia research registers, and voluntary sector providers in 15 English regions.

PARTICIPANTS: 494 people with dementia: 329 were assigned to an aerobic and strength exercise programme and 165 were assigned to usual care. Random allocation was 2:1 in favour of the exercise arm.

INTERVENTIONS: Usual care plus four months of supervised exercise and support for ongoing physical activity, or usual care only. Interventions were delivered in community gym facilities and NHS premises.

MAIN OUTCOME MEASURES: The primary outcome was score on the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) at 12 months. Secondary outcomes included activities of daily living, neuropsychiatric symptoms, health related quality of life, and carer quality of life and burden. Physical fitness (including the six minute walk test) was measured in the exercise arm during the intervention.

RESULTS: The average age of participants was 77 (SD 7.9) years and 301/494 (61%) were men. By 12 months the mean ADAS-cog score had increased to 25.2 (SD 12.3) in the exercise arm and 23.8 (SD 10.4) in the usual care arm (adjusted between group difference -1.4, 95% confidence interval -2.6 to -0.2, P=0.03). This indicates greater cognitive impairment in the exercise group, although the average difference is small and clinical relevance uncertain. No differences were found in secondary outcomes or preplanned subgroup analyses by dementia type (Alzheimer's disease or other), severity of cognitive impairment, sex, and mobility. Compliance with exercise was good. Over 65% of participants (214/329) attended more than three quarters of scheduled sessions. Six minute walking distance improved over six weeks (mean change 18.1 m, 95% confidence interval 11.6 m to 24.6 m).

CONCLUSION: A moderate to high intensity aerobic and strength exercise training programme does not slow cognitive impairment in people with mild to moderate dementia. The exercise training programme improved physical fitness, but there were no noticeable improvements in other clinical outcomes.

TRIAL REGISTRATION: Current Controlled Trials ISRCTN10416500.

OTHER RESEARCH OF INTEREST (Continued)**[Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs \(SELECT-NEXT\): a randomised, double-blind, placebo-controlled phase 3 trial.](#)**

[Burmester GR](#)¹, [Kremer JM](#)², [Van den Bosch F](#)³, [Kivitz A](#)⁴, [Bessette L](#)⁵, [Li Y](#)⁶, [Zhou Y](#)⁶, [Othman AA](#)⁶, [Pangan AL](#)⁶, [Camp HS](#)⁶.

Lancet. **2018 Jun 12**. pii: S0140-6736(18)31115-2. doi: 10.1016/S0140-6736(18)31115-2. PMID: 29908669. [Epub ahead of print]

BACKGROUND: Upadacitinib is a selective inhibitor of Janus kinase 1 and was efficacious in phase 2 studies in patients with moderate-to-severe rheumatoid arthritis. We aimed to assess the efficacy of upadacitinib in patients with inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

METHODS: This study is a double-blind, placebo-controlled trial at 150 sites in 35 countries. We enrolled patients aged 18 years or older with active rheumatoid arthritis for 3 months or longer, who had received csDMARDs for at least 3 months with a stable dose for at least 4 weeks before study entry, and had an inadequate response to at least one of the following csDMARDs: methotrexate, sulfasalazine, or leflunomide. Using interactive response technology, we randomly assigned patients receiving stable background csDMARDs (2:2:1:1) to receive a once-daily extended-release formulation of upadacitinib 15 mg or 30 mg, or placebo, for 12 weeks. Patients, investigators, and the funder were masked to allocation. After 12 weeks, patients taking placebo received 15 mg or 30 mg of upadacitinib once daily, according to the prespecified randomisation assignment. The primary endpoints were the proportion of patients at week 12 who achieved 20% improvement in American College of Rheumatology criteria (ACR20), and a 28-joint disease activity score using C-reactive protein (DAS28[CRP]) of 3.2 or less. We did efficacy analyses in the full analysis set of all randomly assigned patients who received at least one dose of study drug, and used non-responder imputation for assessment of the primary outcomes. This study is registered with ClinicalTrials.gov, number [NCT02675426](#).

FINDINGS: Between Dec 17, 2015, and Dec 22, 2016, 1083 patients were assessed for eligibility, of whom 661 were recruited and randomly assigned to receive upadacitinib 15 mg (n=221), upadacitinib 30 mg (n=219), or placebo (n=221). All patients received at least one dose of study drug, and 618 (93%) completed 12 weeks of treatment. At week 12, ACR20 was achieved by 141 (64%; 95% CI 58-70) of 221 patients receiving upadacitinib 15 mg and 145 (66%; 60-73) of 219 patients receiving upadacitinib 30 mg, compared with 79 (36%; 29-42) of 221 patients receiving placebo (p<0.0001 for each dose vs placebo). DAS28(CRP) of 3.2 or less was met by 107 (48%; 95% CI 42-55) patients receiving upadacitinib 15 mg and 105 (48%; 41-55) patients receiving upadacitinib 30 mg, compared with 38 (17%; 12-22) patients receiving placebo (p<0.0001 for each dose vs placebo). Adverse events were reported in 125 (57%) of 221 patients receiving upadacitinib 15 mg, 118 (54%) of 219 patients receiving upadacitinib 30 mg, and 108 (49%) of 221 patients receiving placebo. The most frequently reported adverse events (≥5% of patients in any group) were nausea (16 [7%] of 221 in the upadacitinib 15 mg group; three [1%] of 219 in the upadacitinib 30 mg group; and seven [3%] of 221 in the placebo group), nasopharyngitis (12 [5%]; 13 [6%]; and nine [4%]), upper respiratory tract infection (12 [5%]; 12 [5%]; and nine [4%]), and headache (nine [4%]; seven [3%]; and 12 [5%]). More infections were reported for upadacitinib (64 [29%] of 221 patients receiving 15 mg and 69 [32%] of 219 patients receiving 30 mg) versus placebo (47 [21%] of 221 patients). There were three herpes zoster infections (one [$<1\%$] in the placebo group, one [$<1\%$] in the upadacitinib 15 mg group, and one [$<1\%$] in the upadacitinib 30 mg group) and one primary varicella zoster virus infection (one [$<1\%$] in the upadacitinib 30 mg group), two malignancies (both in the upadacitinib 30 mg group), one adjudicated major adverse cardiovascular event (in the upadacitinib 30 mg group), and five serious infections (one [$<1\%$] in the placebo group, one [$<1\%$] in the upadacitinib 15 mg group, three [1%] in the upadacitinib 30 mg group). No deaths were reported during the trial.

INTERPRETATION: Patients with moderately to severely active rheumatoid arthritis who received upadacitinib (15 mg or 30 mg) in combination with csDMARDs showed significant improvements in clinical signs and symptoms.

FUNDING: AbbVie Inc.

OTHER RESEARCH OF INTEREST (Continued)**[Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants.](#)**

[Hanlon P](#)¹, [Nicholl BI](#)¹, [Jani BD](#)¹, [Lee D](#)², [McQueenie R](#)¹, [Mair FS](#)³.

Lancet Public Health. 2018 Jun 13. pii: S2468-2667(18)30091-4. PMID: 29908859. doi: 10.1016/S2468-2667(18)30091-4.
[Epub ahead of print]

BACKGROUND: Frailty is associated with older age and multimorbidity (two or more long-term conditions); however, little is known about its prevalence or effects on mortality in younger populations. This paper aims to examine the association between frailty, multimorbidity, specific long-term conditions, and mortality in a middle-aged and older aged population.

METHODS: Data were sourced from the UK Biobank. Frailty phenotype was based on five criteria (weight loss, exhaustion, grip strength, low physical activity, slow walking pace). Participants were deemed frail if they met at least three criteria, pre-frail if they fulfilled one or two criteria, and not frail if no criteria were met.

Sociodemographic characteristics and long-term conditions were examined. The outcome was all-cause mortality, which was measured at a median of 7 years follow-up. Multinomial logistic regression compared sociodemographic characteristics and long-term conditions of frail or pre-frail participants with non-frail participants. Cox proportional hazards models examined associations between frailty or pre-frailty and mortality. Results were stratified by age group (37-45, 45-55, 55-65, 65-73 years) and sex, and were adjusted for multimorbidity count, socioeconomic status, body-mass index, smoking status, and alcohol use.

FINDINGS: 493 737 participants aged 37-73 years were included in the study, of whom 16 538 (3%) were considered frail, 185 360 (38%) pre-frail, and 291 839 (59%) not frail. Frailty was significantly associated with multimorbidity (prevalence 18% [4435/25 338] in those with four or more long-term conditions; odds ratio [OR] 27.1, 95% CI 25.3-29.1) socioeconomic deprivation, smoking, obesity, and infrequent alcohol consumption. The top five long-term conditions associated with frailty were multiple sclerosis (OR 15.3; 99.75% CI 12.8-18.2); chronic fatigue syndrome (12.9; 11.1-15.0); chronic obstructive pulmonary disease (5.6; 5.2-6.1); connective tissue disease (5.4; 5.0-5.8); and diabetes (5.0; 4.7-5.2). Pre-frailty and frailty were significantly associated with mortality for all age strata in men and women (except in women aged 37-45 years) after adjustment for confounders.

INTERPRETATION: Efforts to identify, manage, and prevent frailty should include middle-aged individuals with multimorbidity, in whom frailty is significantly associated with mortality, even after adjustment for number of long-term conditions, sociodemographics, and lifestyle. Research, clinical guidelines, and health-care services must shift focus from single conditions to the requirements of increasingly complex patient populations.

FUNDING: CSO Catalyst Grant and National Health Service Research for Scotland Career Research Fellowship.

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