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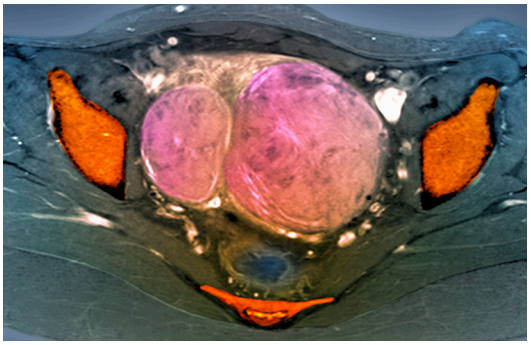

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ORIGINAL RESEARCH Prospective cohort study

Endometriosis and uterine fibroids and risk of premature mortality

Wang Y-X, Farland LV, Gaskins AJ, et al

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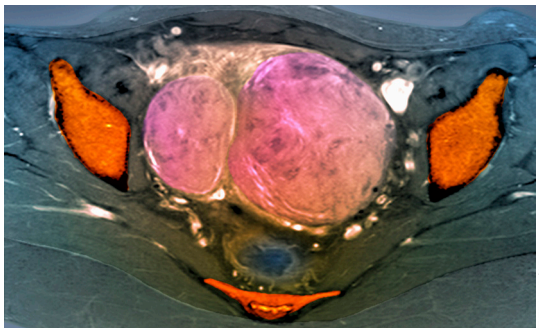
Study question Are endometriosis and uterine fibroids associated with subsequent risk of total and cause specific premature mortality (younger than 70 years)?

Methods The cohort comprised 110 091 women aged 25-42 years in 1989 who were participating in the Nurses' Health Study II (United States) and had no history of hysterectomy before endometriosis or fibroids diagnosis, cardiovascular diseases, or cancer. Women were followed up with biennial questionnaires until 2019. Person years of follow-up were calculated from the return date of the 1989 questionnaires until the end of follow-up (30 June 2019) or death, whichever occurred first. Hazard ratios and 95% confidence intervals (CIs) for total and cause specific premature mortality according to laparoscopically confirmed endometriosis or ultrasound or hysterectomy confirmed uterine fibroids were estimated with Cox proportional hazards models.

Study answer and limitations 4356 premature deaths were recorded during 2 994 354 person years of follow-up (27.2 years per person), including 1459 from cancer, 304 from cardiovascular diseases, and 90 from respiratory diseases. The crude incidence of all cause premature mortality for women with and without laparoscopically confirmed endometriosis was 2.01 and 1.40 per 1000 person years, respectively. In age adjusted models, laparoscopically confirmed endometriosis was associated with a hazard ratio of 1.19 (95% CI 1.09 to 1.30) for premature death; these models were strengthened after also adjusting for potential confounders, including behavioural factors (1.31, 1.20 to 1.44). Cause specific mortality analyses showed that the association was largely driven by mortality from senility and ill-defined diseases (1.80, 1.19 to 2.73), non-malignant respiratory diseases (1.95, 1.11 to 3.41), diseases of the nervous system and sense organs (2.50, 1.40 to 4.44), and malignant neoplasm of gynaecological organs (2.76, 1.79 to 4.26). Ultrasound or hysterectomy confirmed uterine fibroids were not associated with all cause premature mortality (1.03, 0.95 to 1.11), but were associated with a greater risk of mortality from malignant neoplasm of gynaecological organs (2.32, 1.59 to 3.40) in cause specific mortality analyses. An increased risk of premature mortality was also found among women reporting both endometriosis and uterine fibroids. However, endometriosis and uterine fibroids were self-reported, which could have resulted in misclassification and biased risk estimations.

What this study adds Women with a history of endometriosis and uterine fibroids might have an increased long term risk of premature mortality extending beyond their reproductive lifespan. These conditions were also associated with an increased risk of death due to gynaecological cancers. Endometriosis was also associated with a greater risk of non-cancer mortality. These findings highlight the importance for primary care providers to consider both gynaecological disorders in their assessment of women's health.



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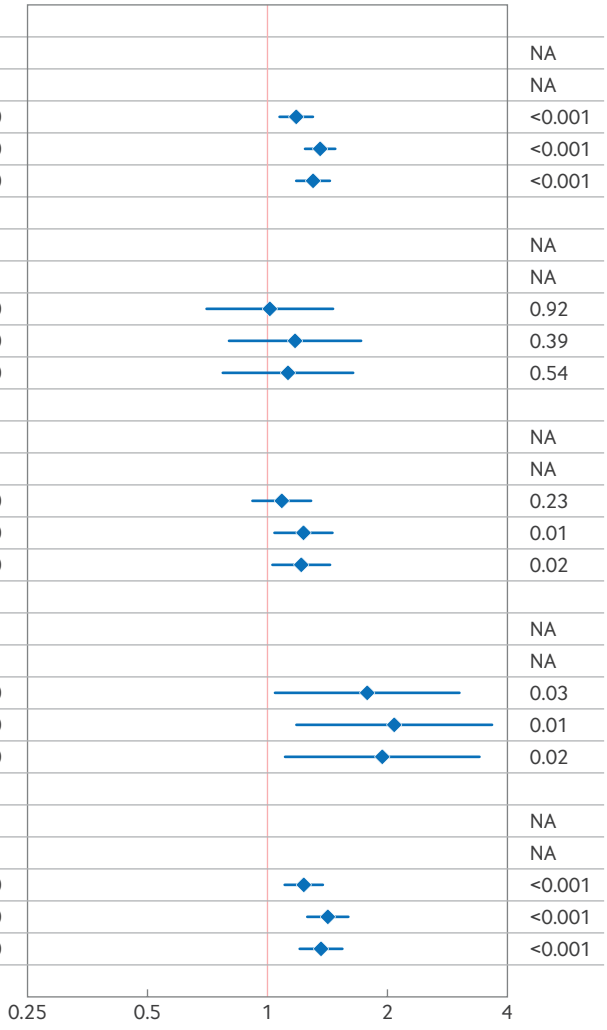
Funding, competing interests, and data sharing
Supported by grants from the National Natural Science Foundation of China and US National Institutes of Health. No relevant competing interests. Data can be obtained by contacting research staff from Nurses' Health Study II.

Causes of death	Laparoscopically confirmed endometriosis: No (n=97 896)	Laparoscopically confirmed endometriosis: Yes (n=12 195)	P value
All deaths			
Deaths/person years of follow-up	3770/2 702 388	586/291 966	NA
Crude incidence per 1000 person years	1.40	2.01	NA
HRs for age adjusted models	1 (reference)	1.19 (1.09 to 1.30)	<0.001
HRs for multivariable models	1 (reference)	1.36 (1.24 to 1.49)	<0.001
HRs for full models adjusted for behavioural factors	1 (reference)	1.31 (1.20 to 1.44)	<0.001
Cardiovascular disease			
Deaths/person years of follow-up	270/2 705 601	34/292 462	NA
Crude incidence per 1000 person years	0.10	0.12	NA
HRs for age adjusted models	1 (reference)	1.02 (0.71 to 1.46)	0.92
HRs for multivariable models	1 (reference)	1.18 (0.81 to 1.71)	0.39
HRs for full models adjusted for behavioural factors	1 (reference)	1.12 (0.77 to 1.63)	0.54
Cancer			
Deaths/person years of follow-up	1282/2 704 647	177/292 337	NA
Crude incidence per 1000 person years	0.47	0.61	NA
HRs for age adjusted models	1 (reference)	1.10 (0.94 to 1.29)	0.23
HRs for multivariable models	1 (reference)	1.24 (1.05 to 1.47)	0.01
HRs for full models adjusted for behavioural factors	1 (reference)	1.22 (1.04 to 1.44)	0.02
Respiratory disease			
Deaths/person years of follow-up	73/2 705 791	17/292 478	NA
Crude incidence per 1000 person years	0.03	0.06	NA
HRs for age adjusted models	1 (reference)	1.79 (1.05 to 3.04)	0.03
HRs for multivariable models	1 (reference)	2.10 (1.20 to 3.68)	0.01
HRs for full models adjusted for behavioural factors	1 (reference)	1.95 (1.11 to 3.41)	0.02
All other causes			
Deaths/person years of follow-up	2145/2 703 926	358/292 177	NA
Crude incidence per 1000 person years	0.79	1.23	NA
HRs for age adjusted models	1 (reference)	1.24 (1.11 to 1.39)	<0.001
HRs for multivariable models	1 (reference)	1.42 (1.26 to 1.60)	<0.001
HRs for full models adjusted for behavioural factors	1 (reference)	1.36 (1.21 to 1.53)	<0.001



Risk of all cause and cause specific premature mortality (younger than 70 years) according to the occurrence of endometriosis among 110 091 women (Nurses' Health Study II, 1989-2019). In age adjusted Cox proportional hazard regression models, analyses were stratified jointly by participants' age in months at the start of follow-up and calendar years of the current questionnaire cycle. Multivariable models were further adjusted for history of infertility (yes, no (reference)), body mass index at age 18 years (<18.5, 18.5-24.9 (reference), 25-29.9, 20-34.9, ≥35), menstrual cycle length at age 18-22 years (<26, 26-31 (reference), 32-50, or ≥50 days or too irregular to estimate), age at menarche (<12 (reference), 12, 13, or ≥14 years), time varying postmenopausal hormone therapy (never (reference), former, current), non-aspirin non-steroidal anti-inflammatory drug use (yes, no (reference)), aspirin use (yes, no (reference)), and oral contraceptive use (current or former, no (reference)). Full models were further adjusted for time varying body mass index (<24.9 (reference), 25-29.9, 30-34.9, or ≥35), cigarette smoking status (never (reference), former, current 1-34 cigarettes/day, or current ≥35 cigarettes/day), physical activity (0 (reference), 0.1-1.0, 1.1-2.4, 2.5-5.9, or ≥6 h/week), and Alternate Healthy Eating Index 2010 diet quality scores (fifths, with lowest fifth (reference) representing least healthy diet). CI=confidence interval; HR=hazard ratio; NA=not applicable

Non-hormonal management of vasomotor symptoms of menopause

ORIGINAL RESEARCH Phase 3b randomised controlled trial

Efficacy and safety of fezolinetant for moderate-severe vasomotor symptoms associated with menopause in individuals unsuitable for hormone therapy

Schaudig K, Wang X, Bouchard C, et al

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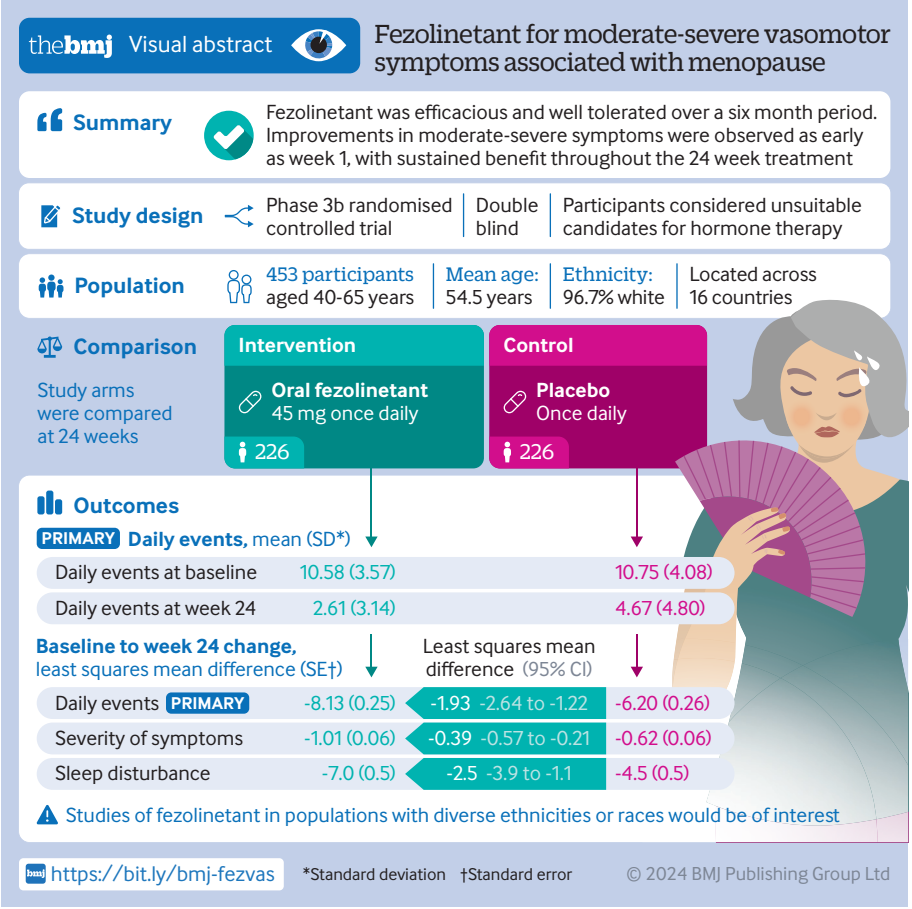
Study question Does the non-hormonal, neurokinin 3 receptor antagonist, fezolinetant, reduce moderate-severe vasomotor symptoms associated with menopause in individuals considered unsuitable for hormone therapy?

Methods This phase 3b, randomised, double blind study (DAYLIGHT) was performed in 16 countries (Canada, the Netherlands, Belgium, France, Spain, Finland, Hungary, Italy, Czech Republic, UK, Denmark, Sweden, Norway, Poland, Germany, and Turkey) over 24 weeks. Participants were individuals aged 40-65 years with moderate-severe vasomotor symptoms associated with menopause who were considered unsuitable candidates for hormone therapy and categorised as contraindicated, caution (based on medical history), stoppers (previous discontinuation of treatment owing to lack of efficacy, side effects, or medical advice), or averse (an informed choice not to use hormone therapy after discussion with a clinician). Participants were randomised to fezolinetant 45 mg or placebo (1:1) once daily, and vasomotor symptoms were recorded daily using an electronic diary. The primary endpoint was mean change in daily frequency of moderate-severe vasomotor symptoms from baseline to week 24. Mean change in severity of vasomotor symptoms (key secondary endpoint) and safety were also assessed.

Study answer and limitations 453 participants were randomised (fezolinetant n=227, placebo n=226) and 370 (81.7%) completed the study (195 and 175, respectively). The safety and full analysis sets comprised



Fezolinetant once daily was efficacious and well tolerated

452 participants who received at least one dose of study drug. Mean age was 54.5 (standard deviation 4.7) years and most of the participants were white (435 (96.7%)) and categorised as either hormone therapy averse (168 (37.2%)) or caution (165 (36.5%)). At week 24, fezolinetant significantly reduced the frequency (least squares mean difference −1.93, 95% confidence interval −2.64 to −1.22; P<0.001) and severity of vasomotor symptoms (−0.39, −0.57 to −0.21; P<0.001). Improvements over placebo were observed as early as week 1. Both groups showed similar incidences of treatment emergent adverse events (TEAEs, 147 (65.0%) in the fezolinetant group, 138 (61.1%) in the placebo group) and serious TEAEs (10 (4.4%) and 8 (3.5%), respectively). A potential limitation of this study was that most participants self-identified as white thereby restricting the generalisability of the results.

What this study adds Fezolinetant once daily was efficacious and well tolerated as a treatment for moderate-severe vasomotor symptoms in individuals considered unsuitable for hormone therapy.

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Study registration ClinicalTrials.gov NCT05033886; EudraCT 2021-001685-38.

Up to 80% of women experience vasomotor symptoms, including hot flushes and night sweats, during menopausal transition.[1-7] These symptoms can persist for years before and after menopause, substantially impacting quality of life by impairing sleep, mood, and cognitive functioning.[2-12] An effective treatment of vasomotor symptoms is hormonal therapy, but this treatment is not appropriate for everyone and only about 10% of women worldwide with vasomotor symptoms report using hormonal therapy.[2-15] Contraindications to hormonal therapy and concerns for adverse effects with prolonged hormonal therapy use may contribute to its low use.[2-9] Non-hormonal alternatives to manage vasomotor symptoms are available but these alternatives are generally considered less efficacious than hormonal therapy.[6-14] Fezolinetant represents a newer non-hormonal option for management of moderate-to-severe vasomotor symptoms associated with menopause and is approved for this indication in Europe, the United States, and Australia. Fezolinetant is a neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) from binding on kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the hypothalamus to moderate the neural activity in the thermoregulatory centre.[2-14]

In their paper, Schaudig and colleagues report the results of the DAYLIGHT trial, a multicentre, randomised, double blind, phase 3b trial designed to assess the safety and efficacy data of fezolinetant for the treatment of moderate-to-severe vasomotor symptoms.[7] This trial specifically included women who were considered unsuitable for hormonal therapy (ie, women who were contraindicated, cautious, or averse) and randomly assigned 453 women to receive 45 mg of oral fezolinetant daily (n=227) or placebo (n=226). DAYLIGHT's placebo controlled duration of 24 weeks was longer compared with previous 12 week phase 3 trials, although those shorter trials also had a 42 week extension period.[7-17]

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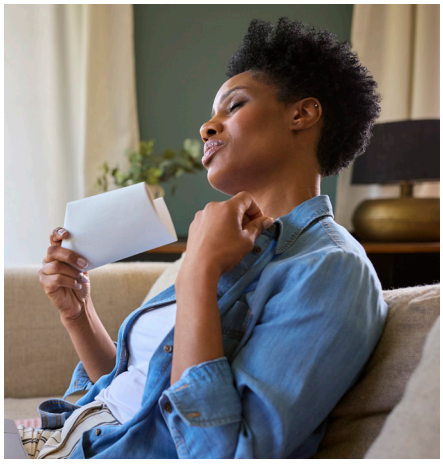

Fezolinetant has potential to address the unmet need for women with vasomotor symptoms who are deemed unsuitable for or averse to hormonal therapy

Beneficial effects

The efficacy data of the DAYLIGHT trial corroborates the findings of the pivotal phase 3 randomised controlled trials and shows that by week 24, compared with placebo, fezolinetant is effective in reducing the frequency (primary endpoint) and potentially severity (secondary endpoint) of moderate-to-severe vasomotor symptoms and could improve associated sleep disturbances (secondary endpoint).[7-17] Consistent with the SKYLIGHT trials, these beneficial effects were observed within one week of treatment.

The tolerability and safety data from DAYLIGHT is in line with those observed in the previous phase 3 trials. Treatment emergent adverse events leading to discontinuation of treatment were low (5.5%). During the six month treatment period of DAYLIGHT, a high frequency of mild to moderate treatment emergent adverse events was reported in both fezolinetant (65.0%) and placebo (61.1%) groups; however, no significant between group differences were noted. The proportion of patients who had serious treatment emergent adverse events was 4.4% in the fezolinetant group while the proportion was 3.5% in the placebo group.[7] The most common treatment emergent adverse events in the fezolinetant group were covid-19 (13.3%), headache (8.8%), and fatigue (5.8%).[7] Treatment emergent adverse events of special interest with fezolinetant included one case with a potential causal relationship to liver test elevations with no drug induced liver injury, six patients with uterine bleeding, one patient with endometrial hyperplasia or a disordered proliferative endometrium, and no patients with thrombocytopenia.[7] Together, the data from all published phase 3 trials continue to support a favourable safety profile of fezolinetant.

Safety profile

The DAYLIGHT study expanded on existing literature by showcasing fezolinetant as an efficacious and well tolerated option for vasomotor symptoms.[2-14] This study also supports fezolinetant's previously described safety profile among women who were considered unsuitable for hormonal therapy, which was shown by the low incidence of treatment emergent adverse events resulting in treatment withdrawal or discontinuation.[2-12] It is important to note that the efficacy of fezolinetant has not yet been compared head-to-head with hormonal therapy or other non-hormonal treatment choices in randomised controlled trials. Also, when reviewing fezolinetant's safety data, DAYLIGHT did not compare fezolinetant's safety profile with other non-hormonal options. This assessment may have been restricted by the limited safety data available for some non-hormonal options.[2] While the DAYLIGHT trial was conducted in 16 European and North American countries, the population predominantly included white women and therefore the findings may not be directly generalisable to other populations.

The data from DAYLIGHT support the clinical value of fezolinetant as a non-hormonal option for management of moderate-to-severe vasomotor symptoms. With its high efficacy and safety profile, fezolinetant has potential to address the unmet need for women with vasomotor symptoms who are deemed unsuitable for or averse to hormonal therapy.[5-15] The data from DAYLIGHT conducted across 69 centres in 16 countries throughout Europe and North America and also soon from the Moonlight trial of fezolinetant among Asian women (unpublished, NCT0423204) further strengthens fezolinetant's place as the first-in-class non-hormonal treatment of vasomotor symptoms in women worldwide.[7]

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