Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Iron Deficiency, Nocturnal Breathing Symptoms, and Sleep Apnea Diagnosis in Premenopausal Women with Fatigue or Daytime Sleepiness: Cross-Sectional Analyses of NHANES 2005–2023

Birkan Alayci

birkanalayci@gmail.com

Liv Hospital https://orcid.org/0000-0002-8244-0987

Research Article

Keywords: iron deficiency, ferritin, fatigue, daytime sleepiness, sleep apnea, premenopausal women, NHANES, replication

Posted Date: October 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11508928/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: The authors declare no competing interests.

Abstract

Background

Premenopausal women with fatigue or daytime sleepiness are often tested for iron deficiency; sleep-disordered breathing in women often goes unrecognized.

Methods

We analyzed 6,260 premenopausal women in National Health and Nutrition Examination Survey (NHANES) cycles 2005–2010, 2015–2016, 2017–March 2020 (primary sample), and 2021–2023. The outcome was fatigue (Patient Health Questionnaire-9 item 4) and/or daytime sleepiness; fatigue alone in 2009–2010 and 2021–2023. Survey-weighted logistic models adjusted for other candidate explanations. A breathing-symptom index (snoring; snorting or breathing pauses), associated with the outcome in exploratory analyses, was tested in 2005–2008.

Results

In every sample, ferritin < 30 and < 50 ng/mL were similarly common in symptomatic and asymptomatic women and not independently associated with the outcome (adjusted odds ratios [ORs] 0.70–1.28; all 95% confidence intervals [CIs] including 1). Pooled post hoc, replication-sample fatigue ORs were 0.90 (0.72–1.13) and 1.17 (0.93–1.46). With all candidates available, 54.1%–61.8% of symptomatic women with ferritin < 30 ng/mL had another candidate explanation. In 2005–2008, the index was associated with the composite outcome (adjusted OR per point 1.39, 95% CI 1.14–1.69); an association with fatigue alone was not shown (1.22, 0.99–1.49). Of women with frequent breathing symptoms (9.9%), 39.8% had told a doctor about trouble sleeping; 14.0% reported a sleep apnea diagnosis.

Conclusions

A low ferritin did not distinguish women with these complaints, often coexisted with other candidate explanations, and should not end their evaluation. Breathing symptoms were associated with the composite symptom, possibly partly through shared reporting with sleepiness. Few women with frequent breathing symptoms reported diagnosed sleep apnea.

Introduction

Fatigue and daytime sleepiness are common complaints in premenopausal women, and iron deficiency is often the first explanation sought. In primary care, ferritin testing is strongly associated with fatigue and with female sex, and the number of iron-deficiency diagnoses rises steeply as the ferritin cutoff is raised.[1] Iron deficiency without anemia is common in nonpregnant women of reproductive age in high-income

countries.[2] Because low ferritin is so common, finding it in a woman with fatigue does not by itself show that iron deficiency explains the symptom.

The ferritin concentration that defines iron deficiency is also unsettled. Proposed thresholds range from 15 ng/mL to about 50 ng/mL, depending on whether they are anchored to bone-marrow iron, to the onset of anemia and to soluble transferrin receptor, or to the rise in iron absorption in young women.[3–6] Randomized trials show that iron modestly reduces fatigue in non-anemic adults with low ferritin.[7, 8] In contrast, cross-sectional studies that measured ferritin and compared fatigued with non-fatigued people did not, in pooled analysis, show a significant association.[9] A treatment response therefore does not mean that a ferritin result identifies which women have symptoms.

Sleep-disordered breathing is a second explanation that is easily missed in women. Compared with men, women with obstructive sleep apnea (OSA) more often report fatigue, insomnia, headache, and depressive symptoms, and less often report witnessed apneas.[10–12] Women under-report snoring,[13] common screening questionnaires are less sensitive in women,[14] and in a population cohort most women with moderate-to-severe sleep apnea had never been diagnosed.[15] Prevalence estimates in women vary severalfold with the definitions used, and the current US prevalence of OSA is not well established.[16–19] Two analyses of the National Health and Nutrition Examination Survey (NHANES) are close to our question. In non-pregnant women aged 20–49 years, including the 2005–2008 cycles analyzed here, iron deficiency defined by body iron was associated with poorer self-reported sleep quality.[20] In overweight and obese adults, serum ferritin had a U-shaped association with OSA classified from questionnaire data.[21]

We asked whether a low ferritin can be accepted as the explanation for fatigue or daytime sleepiness, and whether nocturnal breathing symptoms deserve attention in their evaluation. Specifically, we (1) tested whether iron deficiency distinguishes premenopausal women with fatigue or daytime sleepiness from those without, in a primary NHANES sample and in the other NHANES cycles from 2005 to 2023 that measured ferritin and asked about fatigue; (2) tested in NHANES 2005–2008 an association between nocturnal breathing symptoms and these complaints that had appeared in exploratory analyses of two other samples; and (3) described how often women with frequent breathing symptoms reported a sleep-disorder or sleep apnea diagnosis, and how much the estimated burden depends on the screening threshold.

Materials and Methods

Design and samples

This is a cross-sectional analysis of NHANES, a continuous, multistage probability survey of the US civilian non-institutionalized population. The analysis had four stages (Fig. 1). First, a primary analysis of NHANES 2017–March 2020 was completed in June 2026. Second, its iron findings were tested in NHANES 2015–2016 and August 2021–August 2023 with the same definitions and models, where the questionnaires allowed. Third, an exploratory analysis of the 2015–2016 and 2017–March 2020 data suggested an association between nocturnal breathing symptoms and the presenting symptom; this association and the iron findings were then tested in NHANES 2005–2006 and 2007–2008, the only other cycles that asked the same snoring, breathing-pause, and daytime-sleepiness questions and measured serum ferritin in women.

Fourth, a check of each NHANES cycle from 1999 to 2023 found one further cycle, 2009–2010, that measured serum ferritin and asked the fatigue item of the Patient Health Questionnaire-9 (PHQ-9) but not the sleep questions (Supplementary Table S7); the iron findings for fatigue were tested there. This stage was not in the analysis plans. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[22] Ethical approval is described under Ethical Considerations.

Participants

Women examined in the mobile examination center were eligible if they were aged 20–49 years (20–50 years in 2017–March 2020, when ferritin was measured in all adults), reported at least one menstrual period in the past 12 months, and were not pregnant at examination; women whose pregnancy status was indeterminate or not assessed were retained. The menstrual-period question is NHANES item RHQ031 (labeled "had regular periods in past 12 months" in most cycles and "at least 1 period" in 2005–2006). Women with missing ferritin, PHQ-9 item 4, body mass index (BMI), age, or, where asked, the daytime-sleepiness item were excluded. The 2017–March 2020 sample was rebuilt from the public data files with these criteria (n = 1,508). The earlier analytic file named in the analysis plans (n = 1,427) could not be reproduced from them; estimates in the two were similar (Supplementary Table S9).

Outcomes

The presenting symptom was fatigue (PHQ-9 item 4, "feeling tired or having little energy," on more than half the days or nearly every day)[23] and/or excessive daytime sleepiness (feeling excessively or overly sleepy during the day "often" or "almost always" in the past month). Fatigue alone and sleepiness alone were secondary outcomes. The 2009–2010 and 2021–2023 sleep questionnaires did not include the daytime-sleepiness or breathing-symptom questions, so fatigue alone was the outcome in those cycles.

Iron status

Iron deficiency was defined as serum ferritin < 30 ng/mL (primary) and < 50 ng/mL, with < 15 ng/mL and body iron < 0 mg/kg as secondary definitions. Body iron was calculated with the Cook model from the ratio of soluble transferrin receptor to ferritin,[24] after converting Roche transferrin-receptor values to the enzyme-linked immunosorbent assay scale on which the model was derived.[25] Ferritin values were on the Roche Cobas e601 scale from 2015 to 2023. Values measured on the Roche Elecsys E170 in 2009–2010 and on the Roche/Hitachi 912 in 2005–2008 were converted to the e601 scale with the National Center for Health Statistics (NCHS) bridging equations, so that a threshold of 30 ng/mL corresponds to about 27.6 ng/mL (2009–2010) and 25.5 ng/mL (2005–2008) as originally reported.[26] The proportion of symptomatic women classified as iron-deficient was also mapped across ferritin thresholds from 10 to 70 ng/mL. Sensitivity analyses excluded women with C-reactive protein (CRP) > 5 mg/L or without a CRP result, corrected ferritin for CRP by regression,[27] or, in 2005–2010, used ferritin as originally reported.

Other candidate explanations

Candidate explanations were defined as in the primary analysis: symptom-based OSA risk (Multivariable Apnea Prediction [MAP] index ≥ 0.15, the threshold proposed for premenopausal women[28, 29]); depressive symptoms (PHQ-9 score without the fatigue item ≥ 10); diabetes or prediabetes (glycated hemoglobin ≥ 5.7% or a reported diagnosis)[30]; short sleep (usual sleep < 6 hours); current thyroid disease (self-report); and fatigue-related medication (beta-blocker, sedating antihistamine, or antiepileptic). The MAP index has been adapted to NHANES in other analyses.[31] Here, its symptom score was the breathing-symptom index described below (two items scored 0–3) instead of the original three items scored 0–4, entered with age and BMI into the published equation. In 2009–2010 and 2021–2023, the breathing-symptom items were not asked, so MAP was not available; in 2021–2023, prescription drug names were not collected either, so fatigue-related medication was not available.

As in the primary analysis, a candidate was coded as absent when its input was missing. Women with missing breathing-symptom answers were classified as MAP < 0.15 (21 in 2017–March 2020, 17 in 2015–2016, and 63 in 2005–2008). Between 1 and 5 women per sample with missing PHQ-9 items were classified as without depressive symptoms, and 4 to 13 women per sample who refused or did not know the thyroid questions as without thyroid disease. Other missing inputs affected at most 7 women per sample and candidate.

Nocturnal breathing symptoms and diagnoses

The breathing-symptom index was the mean of two questions about the past 12 months: how often the participant snored, and how often she snorted, gasped, or stopped breathing while asleep, each scored 0 (never) to 3 (5 or more nights a week). If one question was unanswered, the other was used alone (71 women in 2017–March 2020, 61 in 2015–2016, and 158 in 2005–2008). Question wording and response bands were identical across cycles. In 2005–2008, participants were asked whether they had ever told a doctor about trouble sleeping, whether a doctor had ever told them they had a sleep disorder, and, if so, which disorder. The trouble-sleeping question was also asked in 2015–2016 and 2017–March 2020, but doctor contact was analyzed for 2005–2008 only, together with the diagnosis questions.

Statistical analysis

All estimates used the survey design (masked variance strata and primary sampling units, Taylor-series linearization) and the examination or phlebotomy weight relevant to each cycle; the two 2005–2008 cycles were combined with half the 2-year weights, following NCHS guidance. Cycles were otherwise analyzed separately. Associations were estimated as odds ratios (ORs) with survey-weighted logistic regression; 95% confidence intervals (CIs) are Wald intervals on the t distribution with each model's residual degrees of freedom (the design degrees of freedom plus 1 minus the number of model coefficients).

Iron models included one iron-deficiency term with all candidate explanations, age, and BMI. The iron findings were considered replicated when, for both ferritin < 30 and < 50 ng/mL, the prevalence of iron deficiency differed by no more than 10 percentage points between symptomatic and asymptomatic women

and the adjusted OR had a 95% CI including 1 and a point estimate between 0.67 and 1.50. In a post hoc check, iron-deficiency ORs were also estimated without adjustment and with smaller covariate sets.

In a post hoc pooled analysis, the adjusted log ORs for ferritin < 30 and < 50 ng/mL were combined across samples with a DerSimonian–Laird random-effects model,[32] using standard errors derived from each sample's t-based 95% CI. The main pooled analysis used fatigue alone, the only outcome available in every sample, in the four replication samples. Sensitivity analyses used a fixed-effect model, added the primary sample, pooled the composite outcome in the samples with the sleepiness item, and used the Hartung–Knapp interval, which is more conservative when there are few samples.[33] Equivalence was assessed against the margins of the replication criteria (0.67–1.50) and was considered shown if the 90% CI lay within them.

In a post hoc descriptive analysis, we estimated the proportion of symptomatic women with at least one other candidate explanation, and with frequent breathing symptoms (index ≥ 2), separately for women with ferritin < 30 ng/mL and those with higher ferritin. Where MAP or fatigue-related medication was not available, the proportion with another candidate is a lower bound.

In the iron models, the MAP index enters together with age and BMI, which are among its own inputs; this inflates the uncertainty of the MAP term. The exploratory analysis therefore entered the breathing-symptom index directly. In 2005–2008, the composite outcome was regressed on the index, age, BMI, depressive symptoms, diabetes or prediabetes, short sleep, thyroid disease, fatigue-related medication, and ferritin < 50 ng/mL. The association was considered replicated if the lower 95% confidence limit of the OR exceeded 1. Fatigue alone was tested next, only if this criterion was met (fixed-sequence testing). Secondary analyses examined sleepiness alone, replaced the binary depressive-symptom term with a continuous PHQ score excluding the sleep and fatigue items, analyzed each cycle separately, used unconverted ferritin, and replaced the index with MAP ≥ 0.15 in four models without the ferritin term: crude, with depressive symptoms, with the other candidates but not age and BMI, and with the other candidates, age, and BMI. Doctor contact and diagnoses were described by breathing-symptom level (index 0, 0.5–1.5, or ≥ 2) and by MAP ≥ 0.15, and the prevalence of MAP ≥ 0.15 and ≥ 0.50 was estimated. All descriptive proportions were checked against the NCHS data presentation standards for proportions, with Korn–Graubard CIs.[34]

Analyses used R 4.6.0 with the survey package 4.5; earlier runs of the 2005–2008, 2015–2016, and 2021–2023 analyses in R 4.3.3 (survey 4.2-1) gave identical results. Analysis plans are available at osf.io/5jmcf and osf.io/x73sc, and code, derived data, and run logs at [Zenodo DOI to be added]. Claude (Anthropic), a large language model, was used to write and test analysis code and to draft text; the author reviewed all code, output, and text and is responsible for the content.

Results

Samples

The analytic samples comprised 1,508 women in 2017–March 2020 (576 symptomatic), 982 in 2015–2016 (356 symptomatic), 837 in 2021–2023 (197 with fatigue), 1,831 in 2005–2008 (572 symptomatic; 817 from

2005–2006 and 1,014 from 2007–2008), and 1,102 in 2009–2010 (214 with fatigue) (Figure 1). Between 3.8% and 8.5% of eligible women per sample were excluded because of missing data. In 2005–2008, symptomatic women had higher BMI, higher CRP, and more frequent breathing symptoms, depressive symptoms, short sleep, and fatigue-related medication use than asymptomatic women; age, hemoglobin, and the prevalence of iron deficiency were similar (Table 1).

Iron deficiency and the presenting symptom

In each sample, ferritin <30 ng/mL was about as common in symptomatic as in asymptomatic women (38.1% vs 35.2% in 2017–March 2020; 36.0% vs 39.6% in 2015–2016; 30.6% vs 36.4% in 2021–2023, fatigue; 34.1% vs 31.5% in 2005–2008; 34.7% vs 35.1% in 2009–2010, fatigue), and the same was true for ferritin <50 ng/mL (Table 2). Neither definition was independently associated with the outcome in any sample (adjusted ORs 0.70 to 1.28; all 95% CIs including 1). The replication criteria were met in all four replication samples. In 2021–2023, the OR for ferritin <30 ng/mL (0.70) was close to the lower bound of the criterion (0.67). Results were similar after excluding women with CRP >5 mg/L, after correcting ferritin for CRP, and with ferritin as originally reported in 2005–2008 and 2009–2010 (Supplementary Table S1). In the post hoc check, the ORs changed little across covariate sets, and all 95% CIs included 1 (Supplementary Table S6). Of the 12 iron estimates in the primary sample (three outcomes, four definitions), one had a 95% CI excluding 1: ferritin <50 ng/mL with sleepiness alone (adjusted OR 1.46, 95% CI 1.01–2.11). Its 95% CIs included 1 in both CRP sensitivity analyses, and the corresponding ORs were 0.94 in 2015–2016 and 1.00 in 2005–2008 (Supplementary Table S1). Associations of body iron <0 mg/kg varied in direction: inverse in 2015–2016 (composite; adjusted OR 0.66 [95% CI 0.48–0.92]) and 2021–2023 (fatigue; 0.36 [0.20–0.64]), and positive but imprecise in 2009–2010 (fatigue; 1.75 [0.88–3.50]).

In the post hoc pooled analysis of the four replication samples (n = 4,752), the random-effects OR for fatigue was 0.90 (95% CI 0.72–1.13; I^2 28%) for ferritin <30 ng/mL and 1.17 (0.93–1.46; I^2 0%) for <50 ng/mL. The 90% CIs (0.74–1.09 and 0.96–1.41) lay within the equivalence margins; with the Hartung–Knapp method, they were 0.69–1.18 and 0.89–1.53. Fixed-effect estimates, estimates including the primary sample, and estimates for the composite outcome were similar, and all their 95% CIs included 1 (Supplementary Table S8).

At a ferritin threshold of 30 ng/mL, 38.1%, 36.0%, and 34.1% of symptomatic women were classified as iron-deficient in 2017–March 2020, 2015–2016, and 2005–2008, and 22.4%, 25.6%, and 23.3% had no identified candidate explanation. Both proportions changed continuously with the threshold, without a natural cutoff (Figure 3).

In the three samples with all candidate explanations available, 54.1% to 61.8% of symptomatic women with ferritin <30 ng/mL had at least one other candidate explanation, compared with 59.9% to 64.7% of those with higher ferritin; the corresponding proportions with frequent breathing symptoms were 9.6% to 18.5% and 14.0% to 17.6% (Table 5).

Nocturnal breathing symptoms and the presenting symptom

In the exploratory analysis, each 1-point increase in the breathing-symptom index was associated with the composite outcome in 2017–March 2020 (adjusted OR 1.30, 95% CI 1.09–1.55) and 2015–2016 (1.62, 1.13–2.32); for fatigue alone, the 95% CIs included 1 (Table 3; Figure 2).

In 2005–2008 (n = 1,768 with a known index), the index was associated with the composite outcome (adjusted OR 1.39, 95% CI 1.14–1.69; P = .002), meeting the replication criterion. The association with fatigue alone did not meet the criterion (1.22, 0.99–1.49; P = .056). The association with sleepiness alone was 1.25 (1.01–1.55). Estimates for the composite outcome were similar in the secondary analyses (adjusted ORs 1.35 to 1.41; Table 3). With MAP ≥0.15 in place of the index, the crude OR was 1.51 (1.23–1.86). It was 1.32 (1.06–1.64) with depressive symptoms, 1.24 (0.99–1.57) with the other candidates but not age and BMI, and 1.24 (0.83–1.85) in the full model that also adjusts for age and BMI (Table 3).

Doctor contact, diagnoses, and threshold-dependent burden

Frequent breathing symptoms (index ≥2) were reported by 9.9% of women in 2005–2008 (Table 4). Among them, 39.8% had told a doctor about trouble sleeping, 19.8% had been told they had a sleep disorder, and 14.0% reported a sleep apnea diagnosis, compared with 16.2%, 2.1%, and 0.3% among women with no breathing symptoms. Among symptomatic women, 37.4% had told a doctor about trouble sleeping and 3.6% reported a sleep apnea diagnosis. The proportion of women classified at risk was 33.5% with MAP ≥0.15 and 5.5% with MAP ≥0.50. All these proportions met the NCHS presentation standards (Supplementary Table S10).

Discussion

In nationally representative samples from NHANES cycles between 2005 and 2023, iron deficiency was about as common in premenopausal women without fatigue or daytime sleepiness as in those with these complaints, and an independent association was not shown. At least half of symptomatic women with a low ferritin also had another candidate explanation. In contrast, an association of nocturnal breathing symptoms with fatigue and/or daytime sleepiness, first seen in exploratory analyses of 2017–March 2020 and 2015–2016, replicated in 2005–2008. An association with fatigue alone was not shown. Few women who reported frequent snoring or breathing pauses reported a sleep apnea diagnosis, although many had raised sleep problems with a doctor.

The iron findings agree with the existing literature when treatment and discrimination are kept apart. Iron supplementation modestly reduces fatigue in non-anemic adults with low ferritin,[7, 8] but cross-sectional studies with measured ferritin and a comparison group have mostly not found that low ferritin distinguishes fatigued from non-fatigued people.[9] Both can be true: iron deficiency may contribute to fatigue in some women and respond to treatment, yet be too common in women without symptoms to identify who has them. Our replications add consistency across cycles, assays, inflammation adjustments, and covariate sets. In the pooled analysis, the 90% CIs excluded associations at or beyond our replication margins (ORs ≤ 0.67 or ≥ 1.50), except with the Hartung–Knapp method for ferritin < 50 ng/mL (upper limit 1.53). A modest association is therefore not excluded, particularly for ferritin < 50 ng/mL (upper 95% limit 1.46). The one iron

estimate in the primary sample with a 95% CI excluding 1, for sleepiness alone, was one of 12 and was not seen in the other samples with the sleepiness item. Associations of low body iron varied in direction across samples; they were secondary findings, and we do not interpret them.

The breathing-symptom finding fits what is known about sleep-disordered breathing in women. Compared with men, women with OSA more often report fatigue, insomnia, headache, and low mood, and less often report witnessed apneas;[10–12] women also tend to under-report snoring,[13] and in a population cohort most women with moderate-to-severe disease had not been diagnosed.[15] Our index therefore relies on symptoms that women tend to under-report. Under-reporting that is similar in women with and without complaints would weaken associations; under-reporting that differs between them could bias them in either direction. In adults in the same 2005–2008 cycles, snorting or breathing pauses on 5 or more nights a week were associated with probable major depression on the PHQ-9.[35] In our data, the association with the presenting symptom remained after adjustment for depressive symptoms, other candidate explanations, and ferritin < 50 ng/mL, and when the depressive-symptom term excluded the PHQ-9 sleep item. Ferritin has been associated with questionnaire-defined OSA in overweight and obese adults;[21] in our iron models, removing the MAP term changed the ORs little (Supplementary Table S6).

Two features limit how far the replicated association can be taken. First, the breathing and sleepiness questions come from the same questionnaire, so part of the composite association may reflect a shared tendency to report sleep problems; the fatigue item comes from a different instrument, and the association with fatigue alone was smaller and its 95% CI included 1. Second, the index is a symptom report, not a diagnosis. NHANES has no sleep studies, so our findings concern nocturnal breathing symptoms, not OSA.

The diagnostic data point in the same direction as earlier cohort studies.[15, 36] Among women with frequent breathing symptoms (index ≥ 2), two in five had told a doctor about trouble sleeping, but only about one in seven reported a sleep apnea diagnosis. In NHANES 2015–2018, 38.7% of native-born citizens with at least one high-risk sleep symptom had reported trouble sleeping to a health care provider.[37] Our figures are self-reports and do not measure undiagnosed OSA. The burden itself is uncertain: the share of women classified at risk changed six-fold between two published MAP thresholds (33.5% vs 5.5%), and the threshold proposed for premenopausal women was derived in a small, selected sample.[29]

These findings bear on a common decision: whether finding a low ferritin can end the evaluation of a premenopausal woman with fatigue or daytime sleepiness. Our data do not support that. A low ferritin was as common in women without these complaints, the share labeled iron-deficient depended on the cutoff, and at least half of symptomatic women with a low ferritin had another candidate explanation. Iron repletion may still be reasonable, but it does not settle the cause. Asking about snoring, snorting, gasping, or breathing pauses is a simple addition. Whether sleep testing in such women would change outcomes cannot be shown with these data. This is case-finding in symptomatic women, not population screening, for which the evidence is insufficient.[19] Common screening questionnaires are less sensitive in women and should not be relied on alone.[14, 29]

Strengths and limitations

Strengths include independent, nationally representative samples spanning 18 years, the same definitions and models in every sample where the questionnaires allowed, explicit replication criteria, and a fixed-sequence test for fatigue alone. The analysis also has limitations. The design is cross-sectional and cannot establish direction or cause. Symptoms were single self-reported items, and the breathing and sleepiness items came from the same questionnaire. There were no sleep studies, women under-report snoring, and the MAP index had to be adapted to two NHANES items. The breathing-symptom association first appeared in exploratory analyses, so those estimates are probably inflated; the 2005–2008 estimate is the one to rely on. The 2009–2010 sample, the pooled analysis, and the analysis of other candidate explanations in women with a low ferritin were not in the analysis plans. The 2017–March 2020 analytic file named in the plans could not be reproduced from the public files; the sample rebuilt with the stated criteria gave similar estimates (Supplementary Table S9). Missing candidate inputs were coded as absent. The 2005–2010 data are older, the ferritin assay changed over time (we converted values with the NCHS bridging equations and repeated the analysis without conversion), and the sleep-duration question differed between cycles; short sleep was reported more often in 2005–2010. Diagnoses were self-reported and were asked only in 2005–2008. Candidate explanations relied on self-report and available laboratory measures and are not confirmed causes; the unexplained share is an upper bound. The study had a single author.

Conclusions

Across NHANES cycles from 2005 to 2023, low ferritin was about as common in premenopausal women without fatigue or daytime sleepiness as in those with these complaints, and an independent association was not shown. At least half of symptomatic women with a low ferritin had another candidate explanation, so a low ferritin should not end the evaluation of these complaints. In 2005–2008, nocturnal breathing symptoms were associated with the composite of fatigue and/or daytime sleepiness, replicating an exploratory finding from two other samples; an association with fatigue alone was not shown, and the composite result may partly reflect shared reporting with the sleepiness item. Few women with frequent breathing symptoms reported a sleep apnea diagnosis. Asking about nocturnal breathing symptoms, in addition to checking ferritin, is a simple step in women with fatigue and/or daytime sleepiness.

Declarations

Ethical Considerations

NHANES protocols were approved by the National Center for Health Statistics (NCHS) Ethics Review Board: Protocol #2005-06 (2005–2006; continued in 2007–2008 and 2009–2010); continuation of Protocol #2011-17 (2015–2016); Protocol #2018-01, preceded until 26 October 2017 by continuation of Protocol #2011-17 (2017–2018); continuation of Protocol #2018-01 (2019–2020); and Protocol #2021-05 (listed by NCHS for 2021–2022). This analysis of de-identified public data required no further ethical approval.

Consent to Participate

NHANES participants gave written informed consent to NCHS at the time of data collection.

Consent for Publication

Not applicable.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this work.

Data Availability

NHANES data are publicly available from the National Center for Health Statistics. Analysis code, derived data sets, test scripts, run logs, figure and supplementary-table scripts, and the download manifests are available at [Zenodo DOI to be added].

References

1. Jäger L, Rachamin Y, Senn O, Burgstaller JM, Rosemann T, Markun S (2024) Ferritin cutoffs and diagnosis of iron deficiency in primary care. JAMA Netw Open 7(8):e2425692. 10.1001/jamanetworkopen.2024.25692
2. Auerbach M, DeLoughery TG, Tirnauer JS (2025) Iron deficiency in adults: a review. JAMA 333(20):1813–1823. 10.1001/jama.2025.0452
3. Mei Z, Addo OY, Jefferds ME, Sharma AJ, Flores-Ayala RC, Brittenham GM (2021) Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional study. Lancet Haematol 8(8):e572–e582. 10.1016/S2352-3026(21)00168-X
4. Camaschella C (2019) Iron deficiency. Blood 133(1):30–39. 10.1182/blood-2018-05-815944
5. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW (2021) Iron deficiency. Lancet 397(10270):233–248. 10.1016/S0140-6736(20)32594-0
6. Galetti V, Stoffel NU, Sieber C, Zeder C, Moretti D, Zimmermann MB (2021) Threshold ferritin and hepcidin concentrations indicating early iron deficiency in young women based on upregulation of iron absorption. EClinicalMedicine 39:101052. 10.1016/j.eclinm.2021.101052
7. Verdon F, Burnand B, Stubi CL et al (2003) Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ 326(7399):1124. 10.1136/bmj.326.7399.1124

8. Houston BL, Hurrie D, Graham J et al (2018) Efficacy of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults: a systematic review of randomised controlled trials. BMJ Open 8(4):e019240. 10.1136/bmjopen-2017-019240
9. Yokoi K, Konomi A (2017) Iron deficiency without anaemia is a potential cause of fatigue: meta-analyses of randomised controlled trials and cross-sectional studies. Br J Nutr 117(10):1422–1431. 10.1017/S0007114517001349
10. Romero-Peralta S, García-Rio F, Resano Barrio P et al (2022) Defining the profile of obstructive sleep apnea in women compared to men. J Womens Health (Larchmt) 31(12):1782–1790. 10.1089/jwh.2021.0659
11. Valipour A, Lothaller H, Rauscher H, Zwick H, Burghuber OC, Lavie P (2007) Gender-related differences in symptoms of patients with suspected breathing disorders in sleep: a clinical population study using the sleep disorders questionnaire. Sleep 30(3):312–319. 10.1093/sleep/30.3.312
12. Chervin RD (2000) Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest 118(2):372–379. 10.1378/chest.118.2.372
13. Westreich R, Gozlan-Talmor A, Geva-Robinson S et al (2019) The presence of snoring as well as its intensity is underreported by women. J Clin Sleep Med 15(3):471–476. 10.5664/jcsm.7678
14. Bauters FA, Loof S, Hertegonne KB, Chirinos JA, De Buyzere ML, Rietzschel ER (2020) Sex-specific sleep apnea screening questionnaires: closing the performance gap in women. Sleep Med 67:91–98. 10.1016/j.sleep.2019.10.023
15. Young T, Evans L, Finn L, Palta M (1997) Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 20(9):705–706. 10.1093/sleep/20.9.705
16. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328(17):1230–1235. 10.1056/NEJM199304293281704
17. Heinzer R, Vat S, Marques-Vidal P et al (2015) Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 3(4):310–318. 10.1016/S2213-2600(15)00043-0
18. Senaratna CV, Perret JL, Lodge CJ et al (2017) Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 34:70–81. 10.1016/j.smrv.2016.07.002
19. US Preventive Services Task Force, Mangione CM, Barry MJ, Nicholson WK et al (2022) Screening for obstructive sleep apnea in adults: US Preventive Services Task Force recommendation statement. JAMA 328(19):1945–1950. 10.1001/jama.2022.20304
20. Al Hinai M, Jansen EC, Song PX, Peterson KE, Baylin A (2024) Iron deficiency and vitamin D deficiency are associated with sleep in females of reproductive age: an analysis of NHANES 2005–2018 data. J Nutr 154(2):648–657. 10.1016/j.tjnut.2023.11.030
21. Zhang Y, Zhou P, Xu C et al (2025) Association of serum ferritin levels with obstructive sleep apnea in overweight/obese US populations: a population-based study from the NHANES. Nat Sci Sleep 17:223–238. 10.2147/NSS.S499446
22. Vandenbroucke JP, von Elm E, Altman DG et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 4(10):e297.

10.1371/journal.pmed.0040297

23. Kroenke K, Spitzer RL, Williams JBW (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16(9):606–613. 10.1046/j.1525-1497.2001.016009606.x
24. Cook JD, Flowers CH, Skikne BS (2003) The quantitative assessment of body iron. Blood 101(9):3359–3364. 10.1182/blood-2002-10-3071
25. Pfeiffer CM, Cook JD, Mei Z, Cogswell ME, Looker AC, Lacher DA (2007) Evaluation of an automated soluble transferrin receptor (sTfR) assay on the Roche Hitachi analyzer and its comparison to two ELISA assays. Clin Chim Acta 382(1–2):112–116. 10.1016/j.cca.2007.04.008
26. National Center for Health Statistics (2026) NHANES laboratory data documentation: ferritin, 2009–2010 (FERTIN_F), 2015–2016 (FERTIN_I), and August 2021–August 2023 (FERTIN_L). https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2009/DataFiles/FERTIN_F.htm; https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2015/DataFiles/FERTIN_I.htm; https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2021/DataFiles/FERTIN_L.htm (accessed 24 October
27. Namaste SM, Rohner F, Huang J et al (2017) Adjusting ferritin concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 106(Suppl 1):359S–371S. 10.3945/ajcn.116.141762
28. Maislin G, Pack AI, Kribbs NB et al (1995) A survey screen for prediction of apnea. Sleep 18(3):158–166. 10.1093/sleep/18.3.158
29. Morris JL, Orbell S, Scott PW et al (2023) Risk stratification by sex and menopausal status in the multivariable apnea prediction index. Sleep Breath 27(5):1695–1702. 10.1007/s11325-022-02766-0
30. American Diabetes Association (2021) Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care 44(Suppl 1):S15–S33. 10.2337/dc21-S002
31. Orbell SL, Morris JL, Scott PW et al (2025) The triple overlap of COPD, severe obesity, and high risk of OSA: insights from an NHANES analysis. BMC Pulm Med 25(1):282. 10.1186/s12890-025-03752-4
32. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188. 10.1016/0197-2456(86)90046-2
33. IntHout J, Ioannidis JP, Borm GF (2014) The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 14:25. 10.1186/1471-2288-14-25
34. Parker JD, Talih M, Malec DJ et al (2017) National Center for Health Statistics data presentation standards for proportions. Vital Health Stat 2. ;(175):1–22
35. Wheaton AG, Perry GS, Chapman DP, Croft JB (2012) Sleep disordered breathing and depression among U.S. adults: National Health and Nutrition Examination Survey, 2005–2008. Sleep 35(4):461–467. 10.5665/sleep.1724
36. Lindberg E, Benediktsdottir B, Franklin KA et al (2017) Women with symptoms of sleep-disordered breathing are less likely to be diagnosed and treated for sleep apnea than men. Sleep Med 35:17–22. 10.1016/j.sleep.2017.02.032

37. Weaver GK, Asiedu EA, Liang S, Ngangmeni LN, Liu SH, Soni A (2026) Citizenship status and report of trouble sleeping to a healthcare provider among U.S. adults with high-risk sleep symptoms: NHANES 2015–2018. Sleep Health 12(3):433–439. 10.1016/j.sleh.2026.04.001

Tables

Table 1. Characteristics of premenopausal women by presenting symptom, NHANES 2005–2008 (survey-weighted)

Characteristic	Symptomatic (n = 572)	Asymptomatic (n = 1,259)	P
Age, years, mean	34.2	34.9	.192
BMI, kg/m², mean	29.1	27.5	<.001
Systolic blood pressure, mmHg, mean	112.7	113.2	.595
Hemoglobin, g/dL, mean	13.5	13.4	.501
CRP, mg/L, mean	5.1	3.9	.016
Ferritin, ng/mL (e601 scale), mean	53.2	58.2	.080
Breathing-symptom index (0–3), mean	0.9	0.6	<.001
Ferritin <30 ng/mL, %	34.1	31.5	.383
Ferritin <50 ng/mL, %	60.2	56.5	.274
Body iron <0 mg/kg, %	10.6	10.2	.841
Anemia (hemoglobin <12 g/dL), %	8.8	8.0	.695
CRP >5 mg/L, %	29.0	23.8	.063
Frequent breathing symptoms (index ≥2), %	15.1	7.7	<.001
MAP ≥0.15, %	38.8	29.6	<.001
Depressive symptoms, %	16.3	0.6	<.001
Diabetes or prediabetes, %	13.7	10.3	.065
Short sleep (<6 h), %	24.9	7.3	<.001
Current thyroid disease, %	8.7	5.6	.074
Fatigue-related medication, %	7.8	4.5	.015

P values: design-based t tests (means) and Rao–Scott chi-square tests (proportions). Ferritin values from 2005–2008 converted to the Roche Cobas e601 scale. Women with missing breathing-symptom answers (n = 63) are counted as MAP <0.15. Depressive symptoms (PHQ-9 score without the fatigue item ≥10) and the

fatigue item come from the same questionnaire and are therefore strongly related. Characteristics of the other samples are in Supplementary Tables S2–S5. BMI, body mass index; CRP, C-reactive protein; MAP, Multivariable Apnea Prediction index adapted to NHANES; PHQ-9, Patient Health Questionnaire-9.

Table 2. Iron deficiency in symptomatic and asymptomatic premenopausal women, by NHANES sample

Sample (status)	Outcome	n, symptomatic / asymptomatic	Ferritin <30: % symptomatic vs asymptomatic	Adjusted OR (95% CI)	Ferritin <50: % symptomatic vs asymptomatic	Adjusted OR (95% CI)
2017–March 2020 (primary)	Composite	576 / 932	38.1 vs 35.2	1.22 (0.91–1.64)	62.0 vs 57.6	1.27 (0.92–1.77)
2015–2016 (replication)	Composite	356 / 626	36.0 vs 39.6	0.88 (0.63–1.23)	61.6 vs 64.3	0.99 (0.65–1.51)
2021–2023 (replication)	Fatigue	197 / 640	30.6 vs 36.4	0.70 (0.47–1.05)	57.3 vs 58.4	0.90 (0.55–1.48)
2005–2008 (replication)	Composite	572 / 1,259	34.1 vs 31.5	1.19 (0.89–1.61)	60.2 vs 56.5	1.18 (0.88–1.59)
2009–2010 (replication)	Fatigue	214 / 888	34.7 vs 35.1	1.05 (0.70–1.57)	61.9 vs 58.7	1.28 (0.72–2.26)

Composite: fatigue and/or daytime sleepiness. In 2009–2010 and 2021–2023 the sleepiness item was not asked, and the outcome was fatigue alone. Models include one iron term, the candidate explanations available in the cycle, age, and BMI. Replication criteria, for both definitions: prevalence difference ≤10 percentage points, and adjusted OR with a 95% CI including 1 and a point estimate of 0.67–1.50. They were met in all four replication samples. Sensitivity analyses are in Supplementary Table S1 and pooled estimates in Supplementary Table S8. BMI, body mass index; CI, confidence interval; OR, odds ratio.

Table 3. Nocturnal breathing symptoms and the presenting symptom: exploratory and 2005–2008 estimates (adjusted OR, 95% CI)

Analysis	Composite	Fatigue alone	Sleepiness alone
Index, exploratory, 2017–March 2020 (n = 1,487)	1.30 (1.09–1.55)	1.35 (0.91–1.98)	1.39 (1.19–1.62)
Index, exploratory, 2015–2016 (n = 965)	1.62 (1.13–2.32)	1.46 (0.85–2.51)	1.36 (0.96–1.95)
Index, 2005–2008 (n = 1,768)	**1.39 (1.14–1.69)**	**1.22 (0.99–1.49)**	1.25 (1.01–1.55)
Index, 2005–2008: continuous PHQ score without sleep and fatigue items	1.35 (1.12–1.64)	1.17 (0.94–1.47)	1.21 (0.98–1.50)
Index, 2005–2006 alone / 2007–2008 alone	1.38 (0.98–1.96) / 1.41 (1.02–1.95)	—	—
Index, 2005–2008: unconverted ferritin	1.38 (1.13–1.69)	—	—
MAP ≥0.15, 2005–2008 (n = 1,831): crude	1.51 (1.23–1.86)	—	—
MAP ≥0.15: + depressive symptoms	1.32 (1.06–1.64)	—	—
MAP ≥0.15: + other candidates, without age and BMI	1.24 (0.99–1.57)	—	—
MAP ≥0.15: + other candidates, age, and BMI (full model)	1.24 (0.83–1.85)	—	—

Index rows: OR per 1-point increase in the breathing-symptom index, adjusted for age, BMI, depressive symptoms, diabetes or prediabetes, short sleep, thyroid disease, fatigue-related medication, and ferritin <50 ng/mL, in women who answered at least one breathing question. In 2005–2008 (bold), the replication criterion was a lower 95% confidence limit above 1; fatigue alone was tested only if the composite met it (fixed sequence), and sleepiness alone was a secondary outcome. MAP rows: MAP ≥0.15 vs <0.15 in all 1,831 women (missing index counted as MAP <0.15), without the ferritin term; age and BMI are inputs of MAP. Figure 2 shows the estimates in the first three rows. BMI, body mass index; CI, confidence interval; MAP, Multivariable Apnea Prediction index adapted to NHANES; OR, odds ratio; PHQ, Patient Health Questionnaire.

Table 4. Doctor contact and sleep-disorder diagnoses by breathing-symptom level, NHANES 2005–2008 (survey-weighted %, SE)

Group	n	Told a doctor about trouble sleeping	Told of a sleep disorder	Told of sleep apnea
Breathing-symptom index 0	731	16.2 (1.8)	2.1 (0.6)	0.3 (0.2)
Index 0.5–1.5	864	23.0 (2.3)	4.9 (1.0)	0.7 (0.3)
Index ≥2 (frequent)	173	39.8 (5.0)	19.8 (3.8)	14.0 (3.1)
Asymptomatic	1,259	15.2 (1.4)	2.3 (0.6)	0.9 (0.3)
Symptomatic	572	37.4 (2.9)	11.5 (1.5)	3.6 (0.8)
MAP <0.15	1,131	18.8 (1.6)	2.1 (0.6)	0.5 (0.2)
MAP ≥0.15	637	27.7 (3.0)	11.3 (1.8)	4.5 (0.9)

MAP rows include women with a known index. Prevalence among women with a known index (n = 1,768): MAP ≥0.15, 33.5% (SE 1.6); MAP ≥0.50, 5.5% (0.6); index ≥2, 9.9% (0.8). Numbers of women differ slightly between columns because of missing answers. All proportions meet the NCHS data presentation standards for proportions (Supplementary Table S10). MAP, Multivariable Apnea Prediction index adapted to NHANES; NCHS, National Center for Health Statistics; SE, standard error.

Table 5. Other candidate explanations in symptomatic premenopausal women with and without ferritin <30 ng/mL, by NHANES sample (survey-weighted %, 95% CI)

Sample (outcome)	Ferritin	n	At least one other candidate explanation	Frequent breathing symptoms
2017–March 2020 (composite)	<30 ng/mL	226	54.6 (42.6–66.2)	9.6 (5.4–15.5)
	≥30 ng/mL	350	63.8 (56.8–70.4)	15.7 (10.7–21.9)
2015–2016 (composite)	<30 ng/mL	136	61.8 (51.2–71.6)	18.5 (10.4–29.1)
	≥30 ng/mL	220	59.9 (52.5–67.0)	14.0 (8.7–21.0)
August 2021–August 2023 (fatigue)	<30 ng/mL	63	55.6 (38.7–71.6)†	—
	≥30 ng/mL	134	48.7 (35.9–61.7)	—
2005–2008 (composite)	<30 ng/mL	213	54.1 (46.8–61.2)	10.0 (5.8–15.8)
	≥30 ng/mL	359	64.7 (57.6–71.4)	17.6 (13.0–23.1)
2009–2010 (fatigue)	<30 ng/mL	79	50.0 (26.3–73.7)†	—
	≥30 ng/mL	135	61.8 (49.5–73.1)	—

Post hoc, descriptive. Symptomatic: fatigue and/or daytime sleepiness (composite), or fatigue alone where the sleepiness item was not asked. Other candidate explanations: MAP ≥0.15, depressive symptoms, diabetes or prediabetes, short sleep, current thyroid disease, and fatigue-related medication, as in the main models; MAP was not available in 2009–2010 and August 2021–August 2023, and fatigue-related medication not in August 2021–August 2023, so the proportions there are lower bounds. Frequent breathing symptoms: breathing-symptom index ≥2, among women with a known index; not asked in 2009–2010 and August 2021–August 2023 (—). Korn–Graubard 95% CIs. †Does not meet the NCHS data presentation standards for proportions. CI, confidence interval; MAP, Multivariable Apnea Prediction index adapted to NHANES; NCHS, National Center for Health Statistics.

Figures

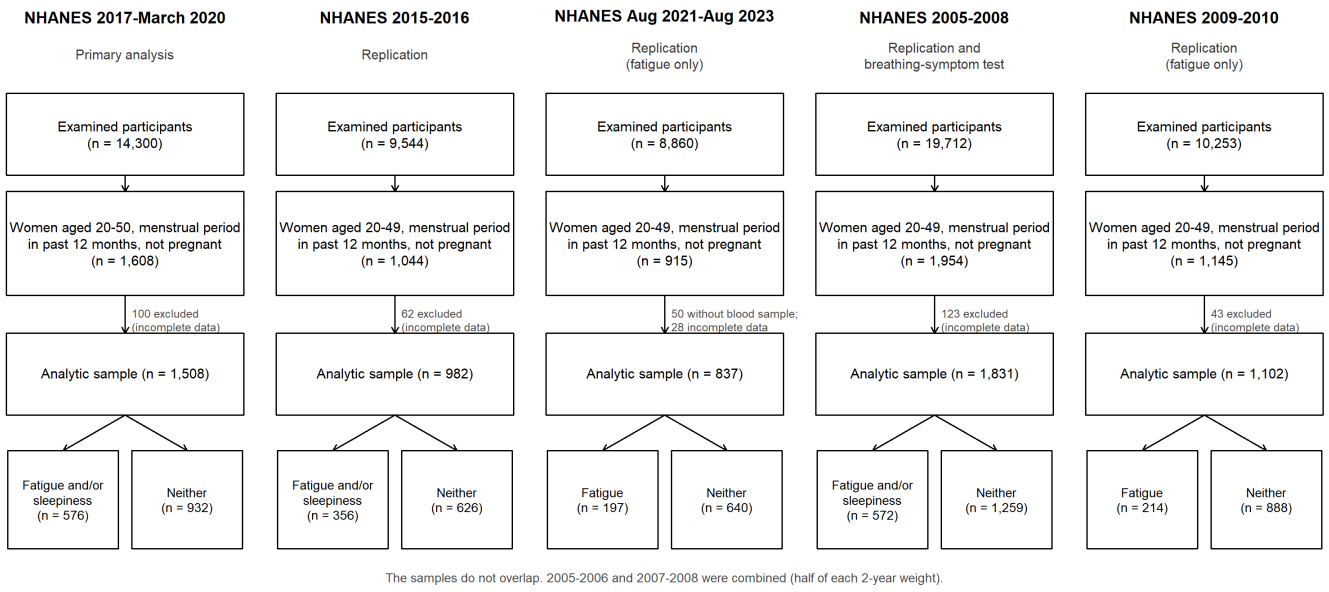


Figure 1

Figure 1. Study stages and participant flow in the NHANES samples. The 2017–March 2020 sample, rebuilt from the public data files, was the primary sample. The iron findings were tested again in 2015–2016, August 2021–August 2023, 2005–2008, and 2009–2010; the outcome was fatigue alone in 2009–2010 and 2021–2023. The breathing-symptom association, first seen in exploratory analyses of 2017–March 2020 and 2015–2016, was tested in 2005–2008.

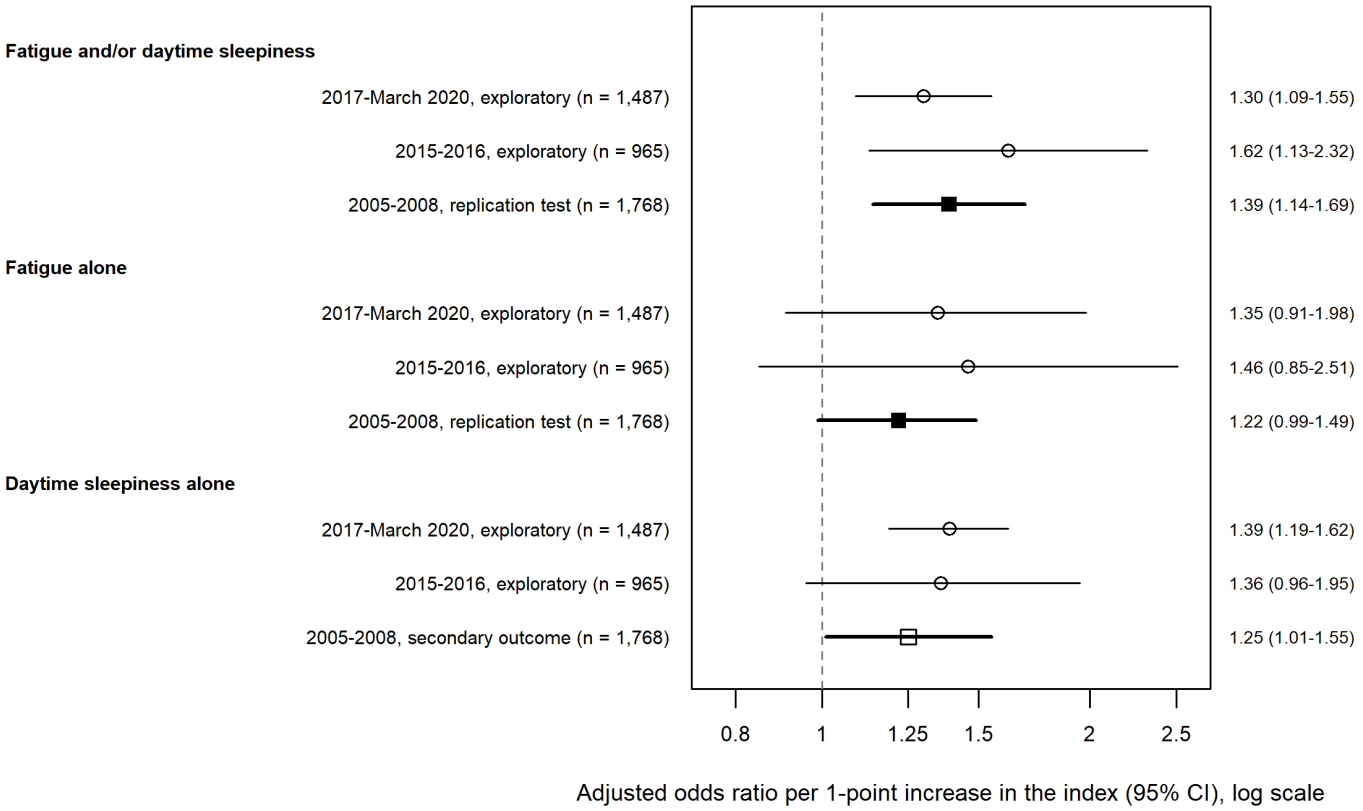


Figure 2

Figure 2. Adjusted odds ratios (95% CI) per 1-point increase in the breathing-symptom index, for fatigue and/or daytime sleepiness, fatigue alone, and daytime sleepiness alone. Open circles: exploratory estimates (2017–March 2020; 2015–2016). Filled squares: replication tests in 2005–2008 (composite; fatigue alone, tested only if the composite association replicated). Open square: secondary outcome in 2005–2008 (daytime sleepiness alone). Models adjust for age, BMI, depressive symptoms, diabetes or prediabetes, short sleep, thyroid disease, fatigue-related medication, and ferritin <50 ng/mL. Log scale.

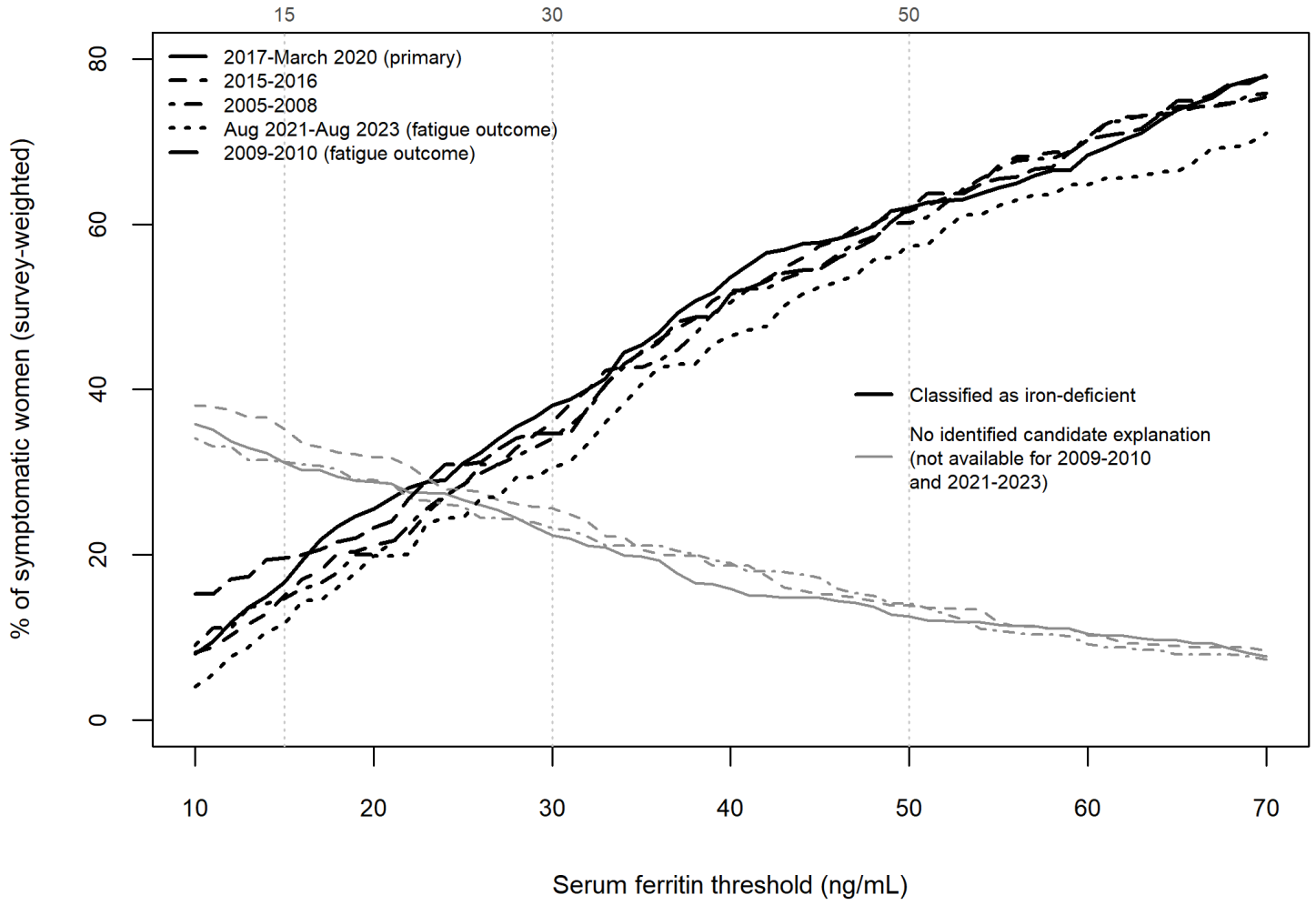


Figure 3

Figure 3. Proportion of symptomatic women classified as iron-deficient (black lines) and proportion with no identified candidate explanation (grey lines) across ferritin thresholds of 10–70 ng/mL, by sample (survey-weighted). In 2009–2010 and August 2021–August 2023, the outcome was fatigue alone, and the no-candidate proportion is not shown because MAP (both cycles) and fatigue-related medication (2021–2023) were not available.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx