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Underlying disease risk among patients with fatigue:
a population-based cohort study in primary care

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Introduction

Fatigue in Practice

- Fatigue = common & non-specific symptom
- ~1 in 15 GP consultations
- Common causes: depression, insomnia, thyroid, anemia
- Often difficult to triage in primary care
- NICE: CBC, TSH, glucose; no routine cancer screening unless red flags

Current Limitations

- Guidelines list many causes, but:
- Lack risk prioritization
- Based mostly on case–control studies
- No population-based, multi-disease risk ranking

Study Purpose

Estimate 12-month risk of 237 diseases after fatigue

Compare to symptom controls and general population

Stratify by age and sex

Provide actionable data to improve clinical decision-making

methods

Study Design

Retrospective population-based cohort study

Setting: UK primary care (2007–2017)

Aim: Estimate 12-month risk of 237 diseases

Comparison groups: symptom-matched & general population

Data Sources

- CPRD GOLD: primary care data
- HES: hospital admission & diagnostic codes
- NCRAS: national cancer registry
- Linked via NHS patient identifiers

Fatigue Cohort

Aged 30–99 years

First fatigue code within study period

No fatigue in prior 12 months

≥12 months of follow-up

Excluded if recent cancer or palliative care

Comparator Groups

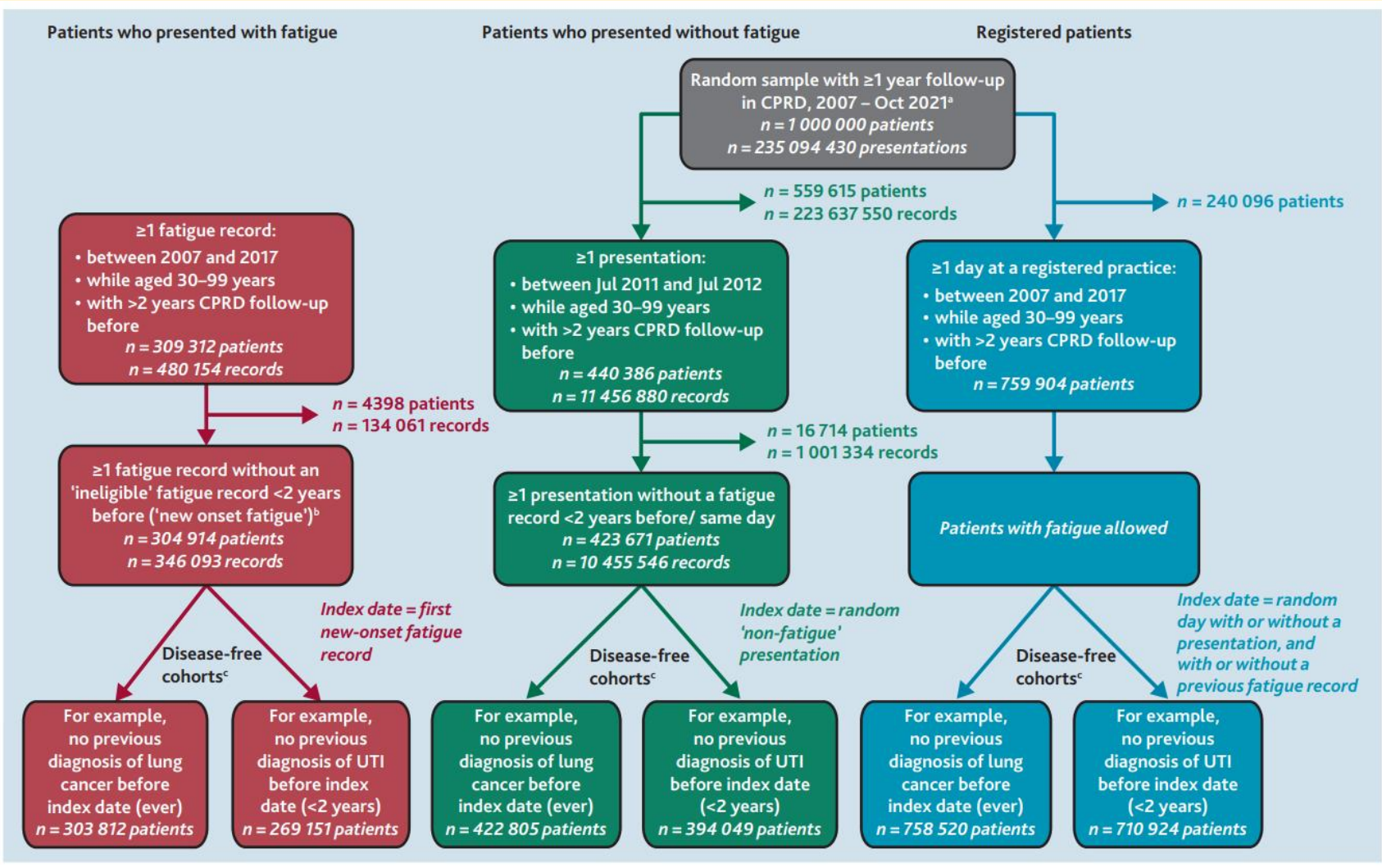
Symptom-matched controls: e.g. cough, headache, dizziness

Matched by age, sex, practice, year

General population comparator: no fatigue

Three groups: fatigue, symptom-matched, general population

Main analysis used symptom-matched controls


Patients who presented with fatigue
Patients who presented without fatigue
Registered patients
Random sample with ≥1 year follow-up in CPRD, 2007 – Oct 2021[a]
n = 1 000 000 patients
n = 235 094 430 presentations
n = 559 615 patients
n = 223 637 550 records
n = 240 096 patients
≥1 fatigue record:
• between 2007 and 2017
• while aged 30–99 years
• with >2 years CPRD follow-up before
n = 309 312 patients
n = 480 154 records
≥1 presentation:
• between Jul 2011 and Jul 2012
• while aged 30–99 years
• with >2 years CPRD follow-up before
n = 440 386 patients
n = 11 456 880 records
≥1 day at a registered practice:
• between 2007 and 2017
• while aged 30–99 years
• with >2 years CPRD follow-up before
n = 759 904 patients
n = 4398 patients
n = 134 061 records
n = 16 714 patients
n = 1 001 334 records
≥1 fatigue record without an 'ineligible' fatigue record <2 years before ('new onset fatigue')[b]
n = 304 914 patients
n = 346 093 records
≥1 presentation without a fatigue record <2 years before/ same day
n = 423 671 patients
n = 10 455 546 records
Patients with fatigue allowed
Index date = first new-onset fatigue record
Index date = random 'non-fatigue' presentation
Index date = random day with or without a presentation, and with or without a previous fatigue record
Disease-free cohorts[c]
Disease-free cohorts[c]
Disease-free cohorts[c]
For example, no previous diagnosis of lung cancer before index date (ever)
n = 303 812 patients
For example, no previous diagnosis of UTI before index date (<2 years)
n = 269 151 patients
For example, no previous diagnosis of lung cancer before index date (ever)
n = 422 805 patients
For example, no previous diagnosis of UTI before index date (<2 years)
n = 394 049 patients
For example, no previous diagnosis of lung cancer before index date (ever)
n = 758 520 patients
For example, no previous diagnosis of UTI before index date (<2 years)
n = 710 924 patients

Follow-Up & Index Date

Index date = fatigue consultation

12-month follow-up

Time to diagnosis recorded

Statistical Methods

- Absolute Risk (AR), Absolute Excess Risk (AER)
- Poisson regression with robust SE
- Stratified by sex
- Age modeled using natural cubic splines

Overview of Diagnoses

- Diagnoses covered 237 diseases
- Most common post-fatigue diagnoses:
- - Infections, Psychiatric disorders
- - Musculoskeletal and Cardiovascular conditions
- Mix of serious and benign conditions

Results

Study Cohorts

309,312 patients presented with fatigue (2007–2017)

Matched 1:1 with symptom-control group (non-fatigue symptoms)

Median age: 58 years; 66% female

Follow-up: 12 months for 237 diagnoses

Absolute vs. Excess Risk

- AR = % of fatigue patients diagnosed
- AER = AR_fatigue – AR_controls
- AER highlights risk truly elevated by fatigue
- Helps prioritize differential diagnoses

Table 1. Demographic characteristics of study cohorts[a]

	Men					
	Fatigue group		Non-fatigue group		Registered patients	
Characteristic	*n*	%	*n*	%	*n*	%
Age group, years						
30–39	13 313	13.20	32 142	16.38	102 064	27.16
40–49	19 285	19.12	44 183	22.52	87 195	23.20
50–59	20 142	19.97	40 463	20.63	69 985	18.62
60–69	19 534	19.36	40 347	20.57	57 440	15.28
70–79	16 838	16.69	25 245	12.87	36 743	9.78
80–89	10 336	10.25	11 971	6.10	19 245	5.12
≥90	1433	1.42	1823	0.93	3127	0.83
Age, years, median	58	—	55	—	49	—
Previous diagnoses						
Any disease studied	92 502	91.69	164 835	84.02	274 199	72.96
Benign neoplasm/CIN	5260	5.21	7169	3.65	10 220	2.72
Cancers	8752	8.68	9772	4.98	14 788	3.94
Diseases of the cardiovascular system	38 437	38.10	55 499	28.29	78 301	20.84
Diseases of the circulatory system	16 880	16.73	19 354	9.87	28 915	7.69
Diseases of the digestive system	39 157	38.82	56 313	28.71	85 005	22.62
Diseases of the ear	14 988	14.86	20 906	10.66	29 239	7.78
Diseases of the endocrine system	14 436	14.31	19 354	9.87	26 559	7.07
Diseases of the eye	16 528	16.38	23 093	11.77	32 606	8.68
Diseases of the genitourinary system	36 543	36.22	50 257	25.62	72 800	19.37
Diseases of the respiratory system	32 951	32.66	48 939	24.95	77 683	20.67
Haematological/immunological conditions	10 782	10.69	10 855	5.53	16 058	4.27
Infectious diseases	27 822	27.58	33 386	17.02	56 034	14.91
Mental health disorders	33 057	32.77	43 987	22.42	72 225	19.22
Musculoskeletal conditions	45 417	45.02	70 993	36.19	101 447	27.00
Neurological conditions	13 369	13.25	17 668	9.01	27 578	7.34
Skin conditions	33 884	33.59	54 052	27.55	83 046	22.10
Subsequent diagnoses						
Any disease studied	64 018	63.46	78 945	40.24	117 421	31.25
Benign neoplasm/CIN	1390	1.38	1529	0.78	2150	0.57
Cancers	2680	2.66	1974	1.01	3735	0.99
Diseases of the cardiovascular system	18 651	18.49	17 787	9.07	27 465	7.31

	Women					
	Fatigue group		Non-fatigue group		Registered patients	
	n	%	*n*	%	*n*	%
	42 246	20.71	40 415	17.77	99 980	26.03
	47 523	23.29	50 312	22.12	80 084	20.85
	36 931	18.10	43 472	19.11	66 349	17.27
	28 867	14.15	41 641	18.30	57 259	14.91
	26 477	12.98	28 725	12.63	41 586	10.83
	18 235	8.94	18 307	8.05	30 248	7.87
	3754	1.84	4625	2.03	8599	2.24
	52	—	54	—	51	—
	193 244	94.71	203 744	89.56	325 963	84.86
	22 544	11.05	21 637	9.51	31 371	8.17
	15 665	7.68	16 307	7.17	25 013	6.51
	52 924	25.94	55 784	24.52	80 927	21.07
	20 313	9.96	17 593	7.73	27 097	7.05
	73 033	35.79	63 521	27.92	93 280	24.29
	23 142	11.34	21 553	9.47	30 053	7.82
	37 353	18.31	32 349	14.22	48 247	12.56
	29 728	14.57	29 748	13.08	43 781	11.40
	79 463	38.95	74 018	32.54	108 916	28.36
	67 999	33.33	61 957	27.23	94 202	24.53
	35 461	17.38	27 560	12.11	41 397	10.78
	76 028	37.26	61 226	26.91	102 393	26.66
	86 770	42.53	71 996	31.65	110 277	28.71
	88 438	43.34	87 693	38.55	123 401	32.13
	38 947	19.09	34 300	15.08	52 930	13.78
	76 676	37.58	75 110	33.02	110 225	28.70
	131 853	64.62	104 520	45.94	157 894	41.11
	3958	1.94	2854	1.25	4308	1.12
	2998	1.47	2159	0.95	3952	1.03
	22 657	11.10	17 478	7.68	27 637	7.20

... continued

Table 2. Excess risk of cancer and diseases with >1% AER in men or women who presented with fatigue compared with patients who did not present with fatigue, ranked by AER

Disease	Overall absolute risk in the fatigue group, % (95% CI)	Overall absolute risk[a] in the non-fatigue group, % (95% CI)	Overall AER[a] in the fatigue group versus non-fatigue group, %	Rank of overall AER[a]	Included in current guidelines[b]
Men					
Depression	3.21 (3.09 to 3.33)	0.83 (0.77 to 0.9)	2.38	1	Yes
Lower RTIs	5.55 (5.40 to 5.70)	3.26 (3.15 to 3.38)	2.28	2	Yes
Hypertension	5.09 (4.93 to 5.26)	2.91 (2.79 to 3.04)	2.18	3	No
Insomnia and sleep disturbances	2.55 (2.45 to 2.66)	0.70 (0.64 to 0.76)	1.85	4	Yes
Ear and upper RTIs	4.96 (4.82 to 5.10)	3.16 (3.05 to 3.28)	1.79	5	Yes
UTIs	3.21 (3.10 to 3.32)	1.71 (1.63 to 1.8)	1.49	6	No
All cancers combined	2.59 (2.49 to 2.70)	1.16 (1.09 to 1.23)	1.43	7	Yes
Other or unspecified infectious organisms	2.56 (2.47 to 2.66)	1.30 (1.23 to 1.37)	1.26	8	Yes
Other anaemias	1.68 (1.6 to 1.76)	0.43 (0.39 to 0.47)	1.25	9	Yes
Erectile dysfunction	2.12 (2.02 to 2.22)	0.93 (0.86 to 0.99)	1.19	10	No
Chronic kidney disease	2.12 (2.02 to 2.21)	0.98 (0.92 to 1.04)	1.14	11	Yes
Anxiety disorders	1.53 (1.45 to 1.62)	0.48 (0.44 to 0.53)	1.05	12	Yes
Diabetes	1.82 (1.73 to 1.91)	0.78 (0.73 to 0.84)	1.04	13	Yes
Connective and soft tissue disorders	2.90 (2.78 to 3.02)	1.88 (1.78 to 1.98)	1.02	14	Yes
Women					
Depression	3.64 (3.54 to 3.73)	1.28 (1.22 to 1.33)	2.36	1	Yes
UTIs	6.66 (6.54 to 6.78)	4.42 (4.32 to 4.52)	2.24	2	No
Ear and upper RTIs	6.64 (6.52 to 6.76)	4.54 (4.45 to 4.64)	2.10	3	Yes
Hypo or hyperthyroidism	2.43 (2.36 to 2.5)	0.67 (0.63 to 0.71)	1.76	4	Yes
Lower RTIs	4.79 (4.70 to 4.89)	3.28 (3.19 to 3.36)	1.52	5	Yes
Insomnia and sleep disturbances	2.25 (2.18 to 2.32)	0.80 (0.75 to 0.84)	1.46	6	Yes
Anxiety disorders	2.08 (2.01 to 2.15)	0.97 (0.92 to 1.01)	1.11	7	Yes
Hypertension	3.06 (2.98 to 3.15)	1.96 (1.90 to 2.03)	1.10	8	No
Iron deficiency anaemia	1.48 (1.43 to 1.54)	0.42 (0.39 to 0.44)	1.07	9	Yes
Other anaemias	1.52 (1.47 to 1.58)	0.48 (0.45 to 0.51)	1.05	10	Yes
Next 10 diseases with <1% AER not shown	—	—	—	—	—
All cancers combined[c]	1.42 (1.36 to 1.47)	0.90 (0.86 to 0.94)	0.52	21	Yes

[a]Adjusting for age differences between the fatigue group and non-fatigue group. [b]Diseases included in current UK diagnostic guidance for fatigue published by either the National Institute for Health and Care Excellence or in BMJ Best Practice.[4,5] [c]Cancer is shown for women despite not having an AER >1%. AER = absolute excess risk. RTI = respiratory tract infection. UTI = urinary tract infection.

Top Diagnoses in Men

1. Depression – 2.38%
2. Lower RTIs – 2.28%
3. Hypertension – 2.18%
4. Insomnia – 1.85%
5. UTIs – 1.49%

Top Diagnoses in Women

1. Depression – 2.36%
2. UTIs – 2.24%
3. Upper RTIs – 2.10%
4. Thyroid disorders – 1.76%
5. Insomnia – 1.64%

Modelled 1-year disease risk in men at selected ages, by cohort.

Becky White et al. Br J Gen Pract
doi:10.3399/BJGP.2024.0093

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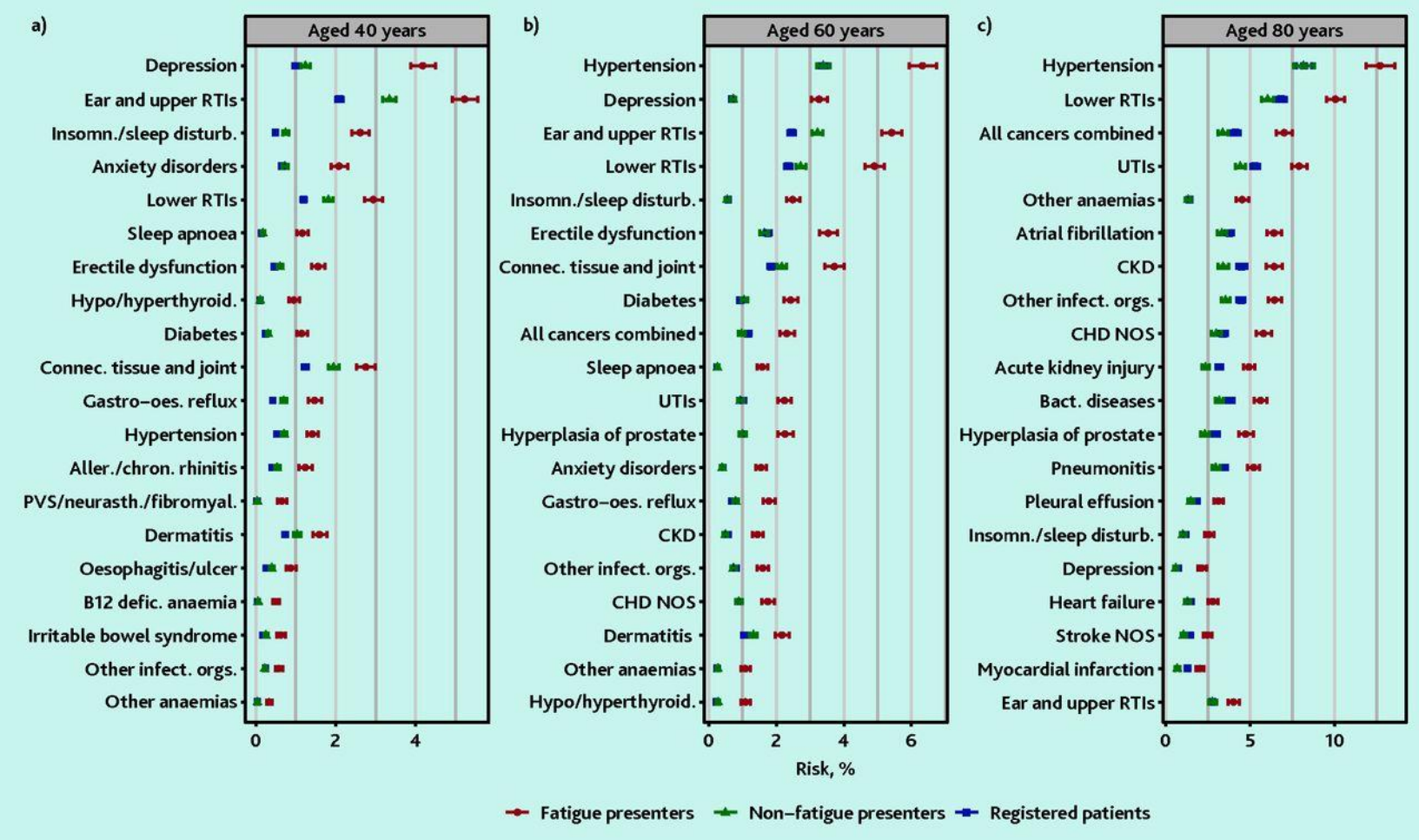
Modelled 1-year disease risk in women at selected ages, by cohort.



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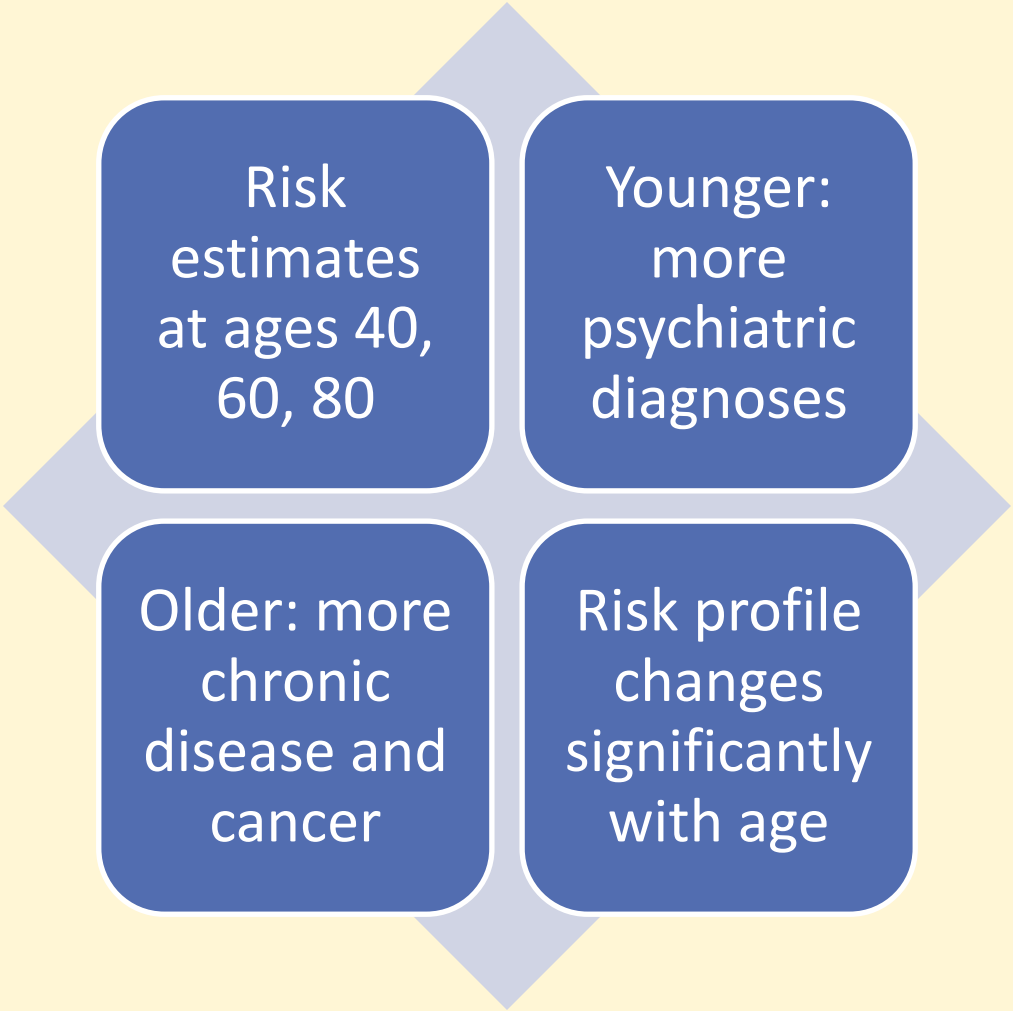
Age-Stratified Results



Sensitivity Analysis

- Shorter follow-up periods repeated
- Same top diagnoses appeared
- Most occurred within first 3–4 months
- Confirms temporal link with fatigue

Highlight: Cancer Risk

- Men: 2.66% (AER = 1.16%)
- Women: 1.53% (AER = 0.57%)
- Most cancers within 3–6 months post-fatigue
- Highest AER in 80-year-old men

Discussion

Summary of Findings

Large cohort study, 12-month risk post-fatigue

>120 diseases with increased risk in men, >150 in women

Risk varies by age and sex

Most diagnoses within 3–4 months

Clinical Interpretation

- Younger patients: psychiatric, minor infections
- Older men: cancer among top 5 diagnoses
- Common diseases not prioritized in guidelines

Importance of Stratification

Risk profiles differ by age and sex

Uniform checklist approach insufficient

Use stratified data for targeted triage

Diagnostic Implications

Younger: focus on mental health, anemia, thyroid

Older: consider malignancy work-up

Risk-based triage can avoid misdiagnosis

Value of AER Rankings

AER HELPS PRIORITIZE COMMON DISEASES

E.G., DEPRESSION AER ~3% (AGE 40), CANCER ~3.7% (AGE 80)

DATA-DRIVEN DECISION-MAKING TOOL

Gaps in Current Guidelines

No ranking in NICE or BMJ lists

High-risk conditions like UTI, HTN not emphasized

Cancer overemphasized in low-risk groups

Cancer Triage Implications

Only 16% had red flag symptoms

Cancer risk still high in older men

Age should guide triage, not red flags alone

Methodological Strengths

- >1.4 million patients
- Linked national datasets
- 237 outcomes across systems
- Matched controls enhance comparison

Limitations

- No fatigue severity/duration data
- No biomarkers or imaging
- 12-month scope only
- UK-only dataset

Lack of Multivariable Adjustment

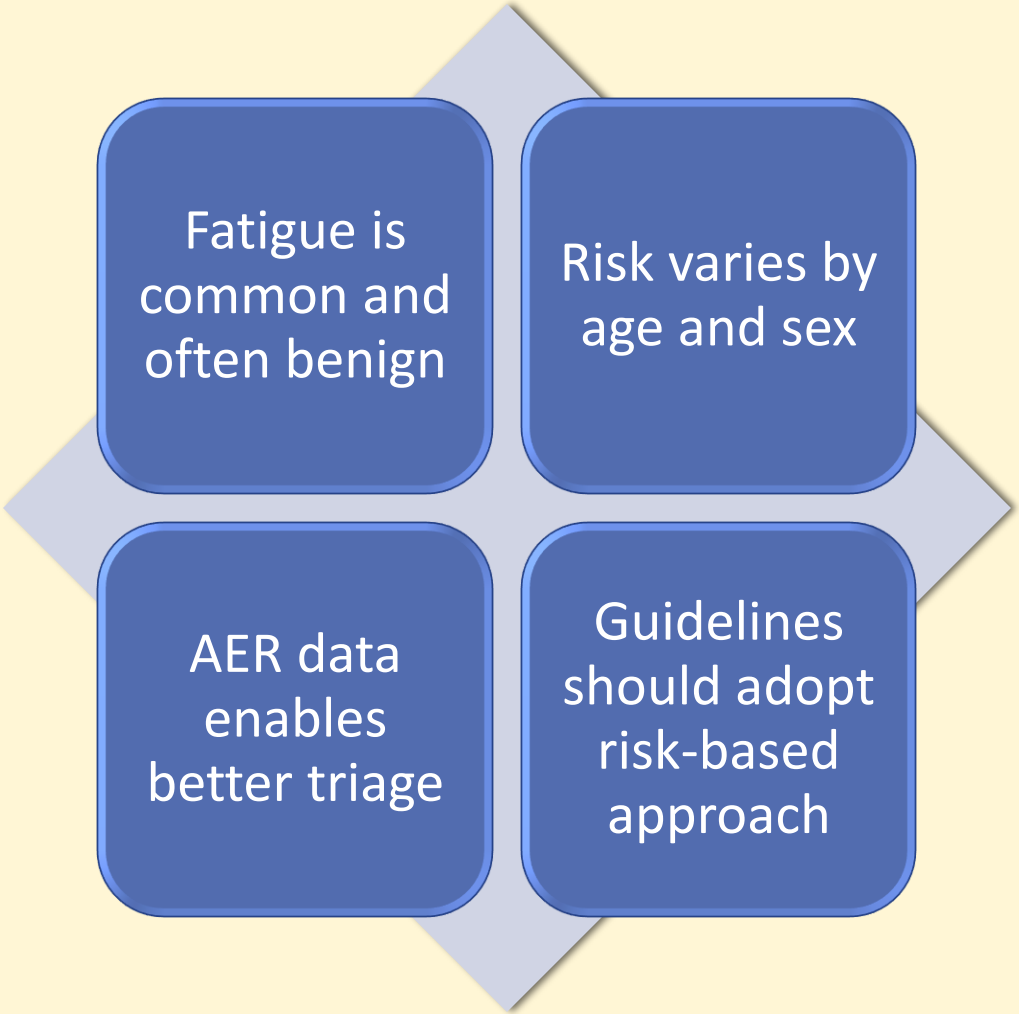
Adjusted only for age and sex

No adjustment for BMI, smoking, comorbidities

Possible uncontrolled confounding

Limits causal interpretation

Final Conclusion



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