



## RESEARCH ARTICLE

# Typing myalgic encephalomyelitis by infection at onset: A DecodeME study [version 1; peer review: 1 approved with reservations, 1 not approved]

Andrew D. Bretherick <sup>1,2</sup>, Simon J. McGrath<sup>3</sup>, Andy Devereux-Cooke<sup>3</sup>, Sian Leary<sup>3</sup>, Emma Northwood<sup>3</sup>, Anna Redshaw<sup>3</sup>, Pippa Stacey<sup>3</sup>, Claire Tripp<sup>3</sup>, Jim Wilson<sup>3</sup>, Sonya Chowdhury<sup>4</sup>, Isabel Lewis<sup>4</sup>, Øyvind Almélid <sup>1</sup>, Sumy V. Baby<sup>1</sup>, Tom Baker<sup>1</sup>, Hannes Becher<sup>1</sup>, Thibaud Boutin<sup>1</sup>, Malgorzata Clyde<sup>1</sup>, Diana Garcia<sup>1</sup>, John Ireland<sup>1</sup>, Shona M. Kerr <sup>1</sup>, Ewan McDowall<sup>1</sup>, David Perry<sup>1</sup>, Gemma L. Samms<sup>1</sup>, Veronique Vitart<sup>1</sup>, Jareth C. Wolfe<sup>1</sup>, Chris P. Ponting <sup>1</sup>

<sup>1</sup>MRC Human Genetics Unit, The University of Edinburgh, Edinburgh, Scotland, EH4 2XU, UK

<sup>2</sup>Pain Service, Ninewells Hospital and Medical School, NHS Tayside, Dundee, Scotland, DD1 9SY, UK

<sup>3</sup>c/o DecodeME, MRC Human Genetics Unit, The University of Edinburgh, Edinburgh, Scotland, EH4 2XU, UK

<sup>4</sup>42 Temple Street, Keynsham, Action For ME, Bristol, England, BS31 1EH, UK

**V1** **First published:** 24 Apr 2023, 3:20  
<https://doi.org/10.3310/nihropenres.13421.1>  
**Second version:** 04 Jul 2023, 3:20  
<https://doi.org/10.3310/nihropenres.13421.2>  
**Third version:** 20 Jul 2023, 3:20  
<https://doi.org/10.3310/nihropenres.13421.3>  
**Latest published:** 21 Aug 2023, 3:20  
<https://doi.org/10.3310/nihropenres.13421.4>

## Abstract

### Background:

People with myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) daily experience core symptoms of post-exertional malaise, unrefreshing sleep, and cognitive impairment or brain fog. Despite numbering 0.2-0.4% of the population, no laboratory test is available for their diagnosis, no effective therapy exists for their treatment, and no scientific breakthrough regarding their pathogenesis has been made. It remains unknown, despite decades of small-scale studies, whether individuals experience different types of ME/CFS separated by onset-type, sex or age.

### Methods:

DecodeME is a large population-based study of ME/CFS that recruited

## Open Peer Review

**Approval Status**

	1	2
<b>version 4</b>		
(revision)		
21 Aug 2023	<a href="#">view</a>	
<b>version 3</b>		
(revision)		
20 Jul 2023	<a href="#">view</a>	
<b>version 2</b>		
(revision)		
04 Jul 2023	<a href="#">view</a>	<a href="#">view</a>
<b>version 1</b>		
24 Apr 2023	<a href="#">view</a>	<a href="#">view</a>

1. **Sarah Tyson**, The University of Manchester, Manchester, UK

2. **Suzanne Vernon** , The Bateman Horne

17,074 participants in the first 3 months following full launch. Their detailed questionnaire responses provided an unparalleled opportunity to investigate illness severity, onset, course and duration.

### Results:

The well-established sex-bias among ME/CFS patients is evident in the initial DecodeME cohort: 83.5% of participants were females. What was not known previously was that females' comorbidities and symptoms tend to be more numerous than males'. Moreover, being female, being older and being over 10 years from ME/CFS onset are significantly associated with greater severity. Five different ME/CFS onset types were examined in the self-reported data: those with ME/CFS onset (i) after glandular fever (infectious mononucleosis); (ii) after COVID-19 infection; (iii) after other infections; (iv) without an identified infectious onset; and, (v) where the occurrence of an infection at or preceding onset is not known.

### Conclusions:

This revealed that people with a ME/CFS diagnosis are not a homogeneous group, as clear differences exist in symptomatology and comorbidity.

### Plain English summary

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) is a chronic disease affecting an estimated 250,000 people in the UK. Its defining symptom is post-exertional malaise, the disproportionate worsening of symptoms following even minor physical or mental exertion. For many people, ME/CFS means a substantial impairment of their activity levels, a high level of disability and a poor quality of life. Research questions recently prioritised by people with ME/CFS and doctors included: "Are there different types of ME/CFS linked to different causes and how severe it becomes? Do different types of ME/CFS need different treatments or have different chances of recovery?" These can begin to be addressed from the questionnaire responses given by more than 17 thousand people with ME/CFS to the DecodeME study.

Results show that people with ME/CFS do not form a single uniform group, because they record clear differences in symptoms and co-occurring medical conditions. For example, if someone reported an infection just prior to getting ME/CFS, then this affects the chance that they report specific symptoms or co-occurring conditions.

It is well known that most people with ME/CFS are females. What was not clear previously was that females tend to have more symptoms and more co-occurring conditions. Also, being female, being older and being over 10 years from ME/CFS onset are associated with greater severity of ME/CFS symptoms.

Center of Excellence, Salt Lake City, USA

Any reports and responses or comments on the article can be found at the end of the article.

These findings could indicate that by studying each ME/CFS type separately – rather than analysing all ME/CFS patients together – it will be easier to understand what has gone wrong in the illness.

### Keywords

Myalgic encephalomyelitis, Post-viral syndrome, Postexertional malaise, Sex-bias, Sub-types

**Corresponding authors:** Andy Devereux-Cooke ([andy@s4me.info](mailto:andy@s4me.info)), Sonya Chowdhury ([sonya.chowdhury@actionforME.org.uk](mailto:sonya.chowdhury@actionforME.org.uk)), Chris P. Ponting ([chris.ponting@ed.ac.uk](mailto:chris.ponting@ed.ac.uk))

**Author roles:** **Bretherick AD:** Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – Review & Editing; **McGrath SJ:** Conceptualization, Writing – Original Draft Preparation; **Devereux-Cooke A:** Conceptualization, Funding Acquisition, Project Administration, Supervision, Writing – Review & Editing; **Leary S:** Conceptualization, Visualization, Writing – Review & Editing; **Northwood E:** Conceptualization, Writing – Review & Editing; **Redshaw A:** Conceptualization, Writing – Review & Editing; **Stacey P:** Conceptualization, Writing – Review & Editing; **Tripp C:** Conceptualization, Writing – Review & Editing; **Wilson J:** Conceptualization, Writing – Review & Editing; **Chowdhury S:** Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing; **Lewis I:** Conceptualization, Project Administration, Writing – Review & Editing; **Almelid Ø:** Resources, Software, Writing – Review & Editing; **Baby SV:** Data Curation, Methodology, Resources, Writing – Review & Editing; **Baker T:** Data Curation, Formal Analysis, Resources, Software, Writing – Review & Editing; **Becher H:** Formal Analysis, Methodology, Writing – Review & Editing; **Boutin T:** Supervision, Writing – Review & Editing; **Clyde M:** Data Curation, Project Administration, Resources, Supervision, Writing – Review & Editing; **Garcia D:** Data Curation, Project Administration, Supervision, Writing – Review & Editing; **Ireland J:** Data Curation, Project Administration, Resources, Software, Writing – Review & Editing; **Kerr SM:** Funding Acquisition, Methodology, Writing – Review & Editing; **McDowall E:** Data Curation, Methodology, Resources, Software, Writing – Review & Editing; **Perry D:** Data Curation, Project Administration, Resources, Software, Writing – Review & Editing; **Samms GL:** Conceptualization, Writing – Review & Editing; **Vitart V:** Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing; **Wolfe JC:** Conceptualization, Resources, Software, Writing – Review & Editing; **Ponting CP:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

**Competing interests:** ADC is a committee member of the Science for ME online support discussion forum. CPP is Deputy Chair of the ME/CFS Research Collaborative and has had PhD studentships funded by Action for ME & the Chief Scientist Office (Scotland), or by ME Research UK. JW is on the ME/CFS Research Collaborative Patient Advisory Group and receives travel expenses for participation in Board Meetings. SC is CEO of Action for ME; Co-Chair, World ME Alliance; and, Non-Executive Director, Curo Group. SL is Head of Advocacy and Communications of the World ME Alliance.

**Grant information:** DecodeME is funded by the National Institute for Health and Care Research (NIHR) and Medical Research Council (MRC), grant number MC\_PC\_20005. The study's Protocol has undergone full external peer review by the MRC as part of the peer review process. The study is also supported by the Medical Research Council University Unit award to the MRC Human Genetics Unit, University of Edinburgh, grant number MC\_UU\_00007/10 (SK, VV) and MC\_UU\_00007/15 (ØA, JCW). ADB would like to acknowledge funding from the Wellcome PhD training fellowship for clinicians (204979, <https://doi.org/10.35802/204979>), the Edinburgh Clinical Academic Track (ECAT) programme. MRC and NIHR facilitated discussions between scientists and people with ME prior to submission of the funding application, but played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**Copyright:** © 2023 Bretherick AD *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Bretherick AD, McGrath SJ, Devereux-Cooke A *et al.* **Typing myalgic encephalomyelitis by infection at onset: A DecodeME study [version 1; peer review: 1 approved with reservations, 1 not approved]** NIHR Open Research 2023, 3:20 <https://doi.org/10.3310/nihropenres.13421.1>

**First published:** 24 Apr 2023, 3:20 <https://doi.org/10.3310/nihropenres.13421.1>

## Plain English summary

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) is a chronic disease affecting an estimated 250,000 people in the UK. Its defining symptom is post-exertional malaise, the disproportionate worsening of symptoms following even minor physical or mental exertion. For many people, ME/CFS means a substantial impairment of their activity levels, a high level of disability and a poor quality of life. Research questions recently prioritised by people with ME/CFS and doctors included: “Are there different types of ME/CFS linked to different causes and how severe it becomes? Do different types of ME/CFS need different treatments or have different chances of recovery?” These can begin to be addressed from the questionnaire responses given by more than 17 thousand people with ME/CFS to the DecodeME study.

Results show that people with ME/CFS do not form a single uniform group, because they record clear differences in symptoms and co-occurring medical conditions. For example, if someone reported an infection just prior to getting ME/CFS, then this affects the chance that they report specific symptoms or co-occurring conditions.

It is well known that most people with ME/CFS are females. What was not clear previously was that females tend to have more symptoms and more co-occurring conditions. Also, being female, being older and being over 10 years from ME/CFS onset are associated with greater severity of ME/CFS symptoms.

These findings could indicate that by studying each ME/CFS type separately – rather than analysing all ME/CFS patients together – it will be easier to understand what has gone wrong in the illness.

## Introduction

Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a chronic multisystem disorder that affects an estimated 0.2–0.4% of the UK population<sup>1,2</sup>. Its core symptoms are post-exertional malaise, pain, fatigue, unrefreshing sleep, cognitive impairment and/or orthostatic intolerance that may change across the life-course<sup>3</sup>. Many people with ME/CFS report an infectious episode prior to their initial symptoms. Up to 10% of people with glandular fever (also known as infectious mononucleosis) are eventually diagnosed with ME/CFS<sup>4,5</sup>, with similar fractions of people with Ross River virus or *Coxiella burnetii* infections also developing ME/CFS<sup>4</sup>. Long COVID, whose symptoms can overlap those of ME/CFS, appears to arise at a similar rate after infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)<sup>6,7</sup>. Onset of ME/CFS can also occur without report of infection<sup>8</sup>. Pathogenesis is unknown, and effective treatment is not available. In one study, the health-related quality of life for people with ME/CFS was worse than 20 other conditions compared, including breast, prostate, colon or lung cancer, type I or II diabetes, stroke, multiple sclerosis and schizophrenia<sup>9</sup>.

One priority from a 2022 priority setting exercise facilitated by the James Lind Alliance<sup>10</sup> was “Are there different types of

ME/CFS linked to different causes and how severe it becomes? Do different types of ME/CFS need different treatments or have different chances of recovery?” To address this question, we took advantage of questionnaire data from DecodeME, a new study launched in the UK in September 2022. Before the end of the year, over 17,000 people with a ME/CFS diagnosis from a health professional, and at least 16 years (y) old, had been recruited and completed the study questionnaire.

Over many decades, ME/CFS studies have addressed similar questions using symptom data for tens or hundreds of participants recruited using various inclusion and exclusion criteria<sup>8,11,12</sup>. However, they remain inconclusive on whether different ME/CFS types exist and whether symptoms are sex-biased. The DecodeME project provided a unique opportunity to perform adequately-powered analyses for detecting differences within a single large ME/CFS cohort, under an assumption that ME/CFS type is delineated by onset type.

## Methods

### Patient and Public Involvement

The DecodeME project grew out of the UK ME Research Collaborative (MERC), formerly known as the CFS/M.E. Research Collaborative or CMRC, which was first established in 2013. The MERC includes people with ME/CFS and carers within a Patient Advisory Group (PAG). As the project evolved in 2018–19, PPI was embedded in every discussion and workshop, resulting in the project becoming a co-production with its grant proposal, aims and outcomes being decided by researchers and PPI in equal measure. In 2020, PPI Steering Group members were selected from across diverse charities and organisations, and for their breadth of experience. In DecodeME, PPI representatives serve on each of its delivery groups, lead on marketing and communication (including social media), and contribute the majority (two of three) members of the decision-making body, the Management Group. People with lived experience of ME/CFS led the co-creation of a new DecodeME questionnaire, making substantial improvements in comprehension and accuracy, thereby boosting recruitment. The project’s name was suggested and decided by PPI members.

DecodeME’s genetics question (“What, if any, significant genetic differences are there between people with—and those without—ME/CFS?”) was identified as a priority first by the MERC and its PAG, before being confirmed as a priority by a wider section of the patient community in the results of the Priority Setting Partnership for ME/CFS<sup>10</sup>. Established participant selection criteria were further refined with PPI throughout. PPI members, through their profound understanding of ME/CFS phenotypes, triggers, severity, symptom range, comorbidities and more, have improved the study’s adherence to our chosen case definition and thus further assured the relevance of genetic associations to ME/CFS lived experience.

A substantial minority of volunteer participants who trialled an initial questionnaire reported difficulties when answering its questions. We then created a new version implementing Canadian Consensus and IOM/NAM criteria<sup>3,13</sup> as well as

criteria introduced in response to peer reviewers' comments. This DecodeME questionnaire is freely available from the DecodeME website. As a co-production, PPI members advised and helped to create both our recruitment strategy and recruitment materials. Further description of DecodeME's recruitment methods and PPI aspects can be found elsewhere<sup>14</sup>. Before study launch public awareness of DecodeME was enhanced using regular podcasts, webinars, blog posts and media interviews. These media channels will be used by PPI members and scientists to disseminate results to the international ME/CFS community. PPI team members maintain extensive input into reporting of the results of the questionnaire (including in this article), providing greater understanding and context, and ensuring accessibility. Our GWAS plan was co-created by researchers and PPI members.

The DecodeME study was reviewed and given a favourable opinion by the North West – Liverpool Central Research Ethics Committee (21/NW/0169). Potential participation bias due to internet use was mitigated by providing a paper questionnaire and providing participants with assistance in completing their online questionnaires. Team members were available to answer phone calls and emails during working hours.

### Cohort

Participants were asked for their sex assigned at birth and about their conditions: "If a health professional has ever told you that you had any of the conditions below, please select all that apply. If the conditions don't apply to you, please do not select any box." Participants indicated whether each condition was Active ("If the condition has given you symptoms in the past 6 months") or not active ("If the condition has not given you symptoms in the past 6 months, either because it has died down or treatment has controlled it"). They were also asked about their symptoms: "In the last 6 months, have you had any of the symptoms below often, repeatedly, or constantly? Please mark any that apply. If none apply, leave all the boxes blank." Questionnaire responses from participants who both consented to participate and self-reported being given a diagnosis of ME, CFS, ME/CFS or CFS/ME by a health professional (as of 19 December 2022) were analysed. Only those whose sex assigned at birth was male or female were analysed due to insufficient numbers of other identities. Participant ages were as of 19 December 2022. Further analyses will be undertaken for the full DecodeME cohort once the recruitment phase of the project is completed.

**Significance testing.** Logistic regression analysis for Figure 6, for example, was of the form: OnsetType ~ age + sex + symptoms + intercept. The analyses conducted were: (i) for 80 symptoms against age and sex – Figure 4; (ii) for each symptom ( $n=80$ ; and, age and sex) against severity – Figure 5; (iii) for each of the 5 onset types against 8 fatigue symptoms plus age and sex – Figure 6A; (iv) for each of the 5 onset types against 72 non-fatigue symptoms (plus age and sex) – Figure 6B; (v) for each of the 5 onset types against 5 illness courses,

relative to 'Fluctuating', the majority response – Figure 6C; and (vi) for each of the 5 onset types against 34 comorbidities (active and inactive) plus age and sex – Figure 7. Analyses used the glm function in R version 4.2.2. Only  $p$ -values that survive Bonferroni correction for multiple tests per analysis are shown.

### Results

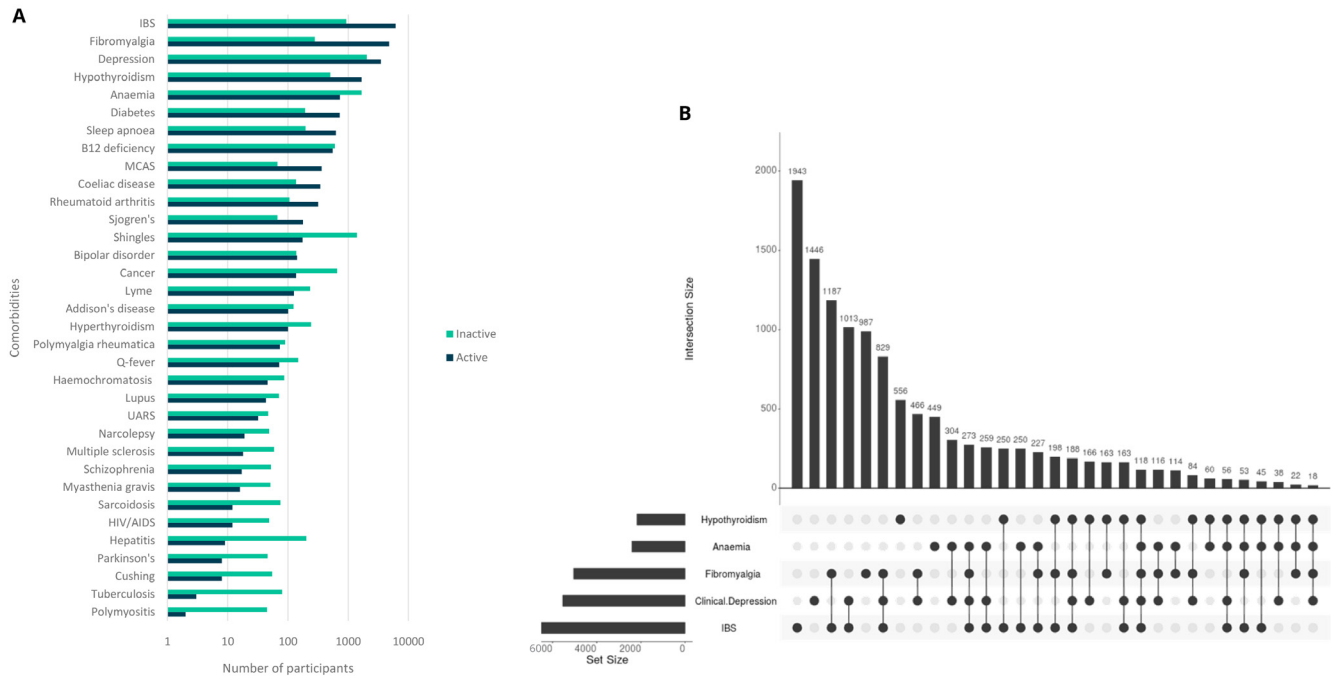
Between its full launch date of September 12, 2022 and a data freeze performed on December 19, 2022, DecodeME recruited 17,074 female or male participants who completed a questionnaire either online (98.1%) or with a paper version (1.9%) and consented to take part. Participants reported being diagnosed with ME/CFS by a health professional and were asked how long they have had their illness. Participants' information included how long they had experienced ME/CFS symptoms, as well as whether they have any of 34 comorbidities (co-occurring conditions; Figure 1) or 82 symptoms (9 fatigue- and 73 non-fatigue symptoms; Figure 2). For each comorbidity, participants could indicate whether this was 'active' or 'inactive', meaning whether or not symptoms had been experienced in the preceding 6 months (Figure 1A).

50.6% of participants reported two or more conditions co-occurring with ME/CFS, most commonly irritable bowel syndrome (IBS; 41.3%), clinical depression (32.4%) and fibromyalgia (29.5%), anaemia (14.1%) and hypothyroidism (12.8%). These results are similar to those of a previous study<sup>15</sup>. Fibromyalgia and IBS occur together with ME/CFS for 18.0% of participants (Figure 1B). 22.6% report no comorbidities.

DecodeME participants' most frequent symptom is post-exertional malaise, a cardinal symptom of ME/CFS<sup>3</sup>, followed by unrefreshing sleep, brain fog, fatigue, muscle pain and gut symptoms (Figure 2). Almost all answered that once they had exceeded their energy limit their change in symptoms lasts "a long time, which can be more than 24 hours" (97.6%) and agreed that their fatigue affected them both physically and mentally (96.2%). For 88.7%, their fatigue occurs more than half of the time and 87.3% report their fatigue as disabling. Most participants (58.0%) indicated that their ME/CFS is "Fluctuating (my symptoms vary day to day but don't go away)", 12.7% describe their symptoms as "Relapsing and remitting (good periods with no symptoms alternating with symptomatically bad periods)" and 15.3% indicate their symptoms are "Getting worse", similar to previous research<sup>15</sup>.

Participants were asked: "Did you have an infection when, or just before, your first ME/CFS symptoms started?" with five possible responses: (i) Yes, glandular fever ( $n=2,936$ ), (ii) Yes, COVID-19 ( $n=380$ ), (iii) Yes, another infection ( $n=7,537$ ), (iv) No ( $n=2,625$ ), or (v) Don't know ( $n=3,596$ ; Figure 3). Proportions of DecodeME participants reporting glandular fever or another infectious disease prior to onset (17.2% or 63.5%, respectively) are similar to those previously reported<sup>11,15,16</sup>. Proportions of people in the first 3 categories reporting a





**Figure 1. Numbers of DecodeME participants reporting conditions co-occurring with ME/CFS (comorbidities); total, 17074 participants.** In (A) numbers are shown in log<sub>10</sub>-scale and those with active or inactive comorbidities are indicated in blue or green, respectively. The UpSet plot<sup>17</sup> (B) shows numbers of participants with five conditions that most frequently co-occur with ME/CFS. These either co-occur together with others (indicated by filled circles linked by lines) or else separately (filled circles not linked by lines).

positive laboratory test of their infection prior to ME/CFS were 68.4%, 50.5% and 25.9%, respectively.

### Demographics

The DecodeME study continues to recruit individuals living in the UK aged 16y and above, with its oldest participant aged over 90y old. Male participants tended to be older than females (median 52y and 48y respectively;  $p < 2.2 \times 10^{-16}$ , Wilcoxon rank sum test). The median age of study participants was 49y, similar to those in previous USA-based studies<sup>18–20</sup>. Only 3.3% of 17,074 participants did not self-report their ethnicity as White, far fewer than the 18.3% in England and Wales who identify as non-White (<https://www.ethnicity-facts-figures.service.gov.uk/>). Participants indicated the duration of their ME/CFS illness by selecting from a set of predefined ranges, for example between 5 and 10 years, or over 10 years, since onset of symptoms. Most (61.3%) DecodeME participants have had ME/CFS for over 10y, and 81.5% over 5y (Figure 3). Together, study participants have experienced over  $1.3 \times 10^5$  years of ME/CFS symptoms.

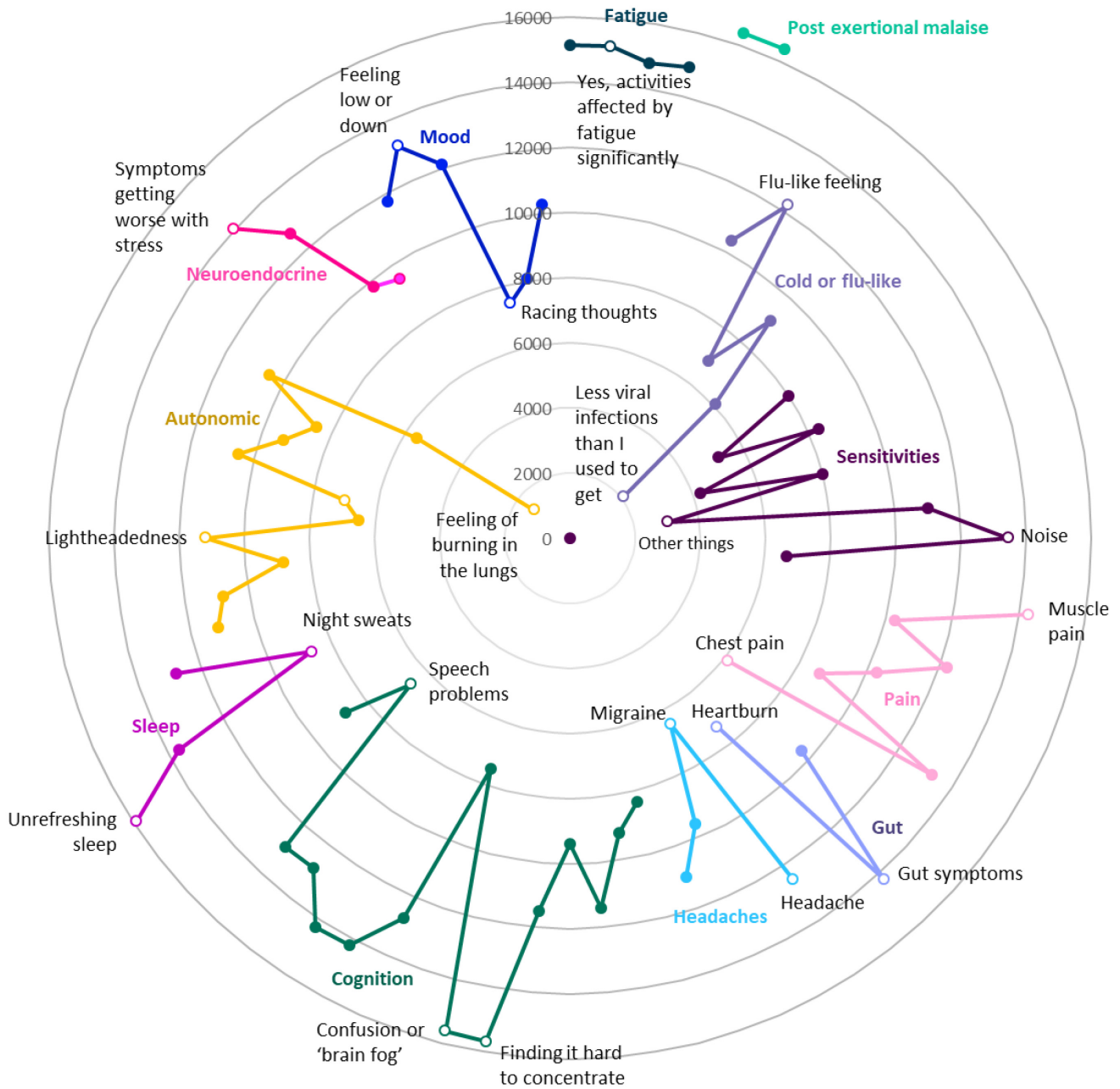
Participants who started their illness within the last 1–3y or 0.5–1y numbered 1,287 or 354, respectively. These numbers are 57% and 21% fewer, per year, than the study’s 1,634 participants from the 3–5y recruitment interval. This paucity of participants with illness duration within 3 years may reflect

how long it usually takes to receive a clinical diagnosis in the UK (median 13–24 months).

To examine the incidence of ME/CFS, we considered 3,150 participants reporting ME/CFS onset within the last 5y. Their median age was 40y, overlapping the peak age (40–59y) of ME/CFS diagnosis in UK primary care<sup>21</sup>. On average, those with glandular fever onset <5y ago were a decade younger than all others (median ages 30.5y and 41y, respectively;  $p < 2.2 \times 10^{-16}$ , Wilcoxon rank sum test). This means that for at least half of our glandular fever onset participants, ME/CFS onset occurred after the age of 25y. This is a decade after peak incidence of glandular fever in the UK between 15 and 19y old<sup>22</sup>. This difference in peak incidence is consistent with adolescents being less likely, than older people, to develop ME/CFS after glandular fever.

### Sex- and age-bias of ME/CFS comorbidities and symptoms

In the DecodeME cohort, females outnumber males by over five-to-one (83.5% females; 16.5% males). This is among the highest female-bias among those with ME/CFS yet reported internationally<sup>3,9,21,23–27</sup>. Despite this strong bias, the substantial number of males participating in DecodeME ( $N=2,827$ ) allowed the study to reveal previously unreported sex-biases in comorbidities or symptoms.

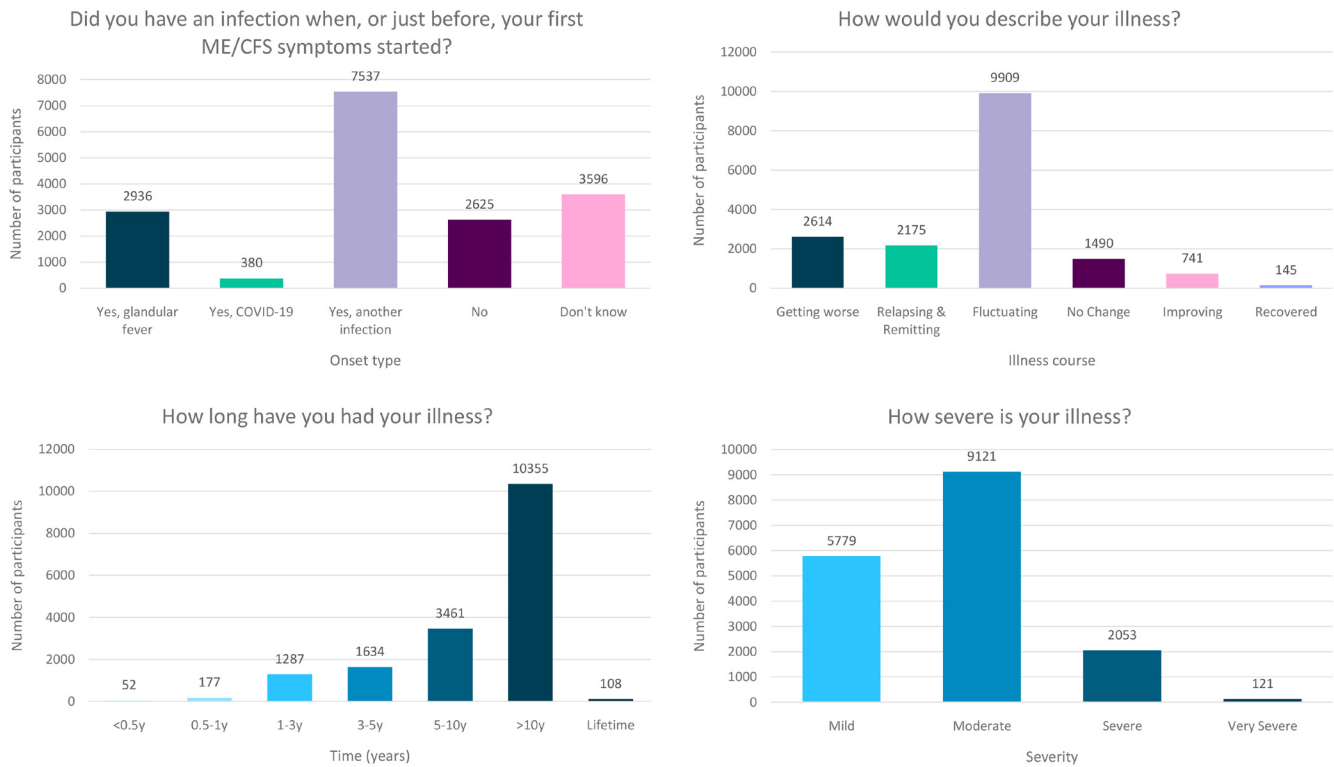


**Figure 2. Numbers of DecodeME participants reporting symptoms (Radar chart); total, 17074 participants.** Most frequently reported symptoms are furthest from these circles' centre. Twelve different groups of questions are indicated in separate colours; for each symptom group, the most and least frequently reported symptoms are listed and indicated as unfilled circles. With reference to the DecodeME questionnaire ([www.decode-me.org.uk/app/uploads/2022/08/DecodeME-Questionnaire.pdf](http://www.decode-me.org.uk/app/uploads/2022/08/DecodeME-Questionnaire.pdf)) the questions (Q) are, clockwise: Fatigue (Q8-answer 3 [Q8-3], Q9-3, Q3-1, Q10-1), Postexertional malaise (PEM, Q12-1 AND Q13-1), Cold or flu-like (Q14-4, -2, -1, -5, -6, -3), Sensitivities (Q15-1, -2, -3, -5, -7, -9, -4, -6, -8), Pain (Q16-4, -6, -5, -3, -2, -7, -1), Gut (Q17-1, -2, -3), Headaches (Q18-1, -4, -2, -3), Cognition (Q19-15, -7, -8, -9, -12, -3, -1, -2, -6, -10, -5, -13, -4, -14, -11), Sleep (Q20-4, -3, -2, -1), Autonomic (Q21-3, -6, -11, -10, -9, -4, -2, -1, -5, -7, -12, -8), Neuroendocrine (Q22-3, -1, -2, -4), and Mood (Q23-2, -3, -1, -5, -6, -4).

Females with ME/CFS reported more comorbidities and symptoms than males in the DecodeME questionnaire. Two-thirds (66.7%) of females, but a half (52.7%) of males, reported at least one active comorbidity; similarly 39.2% of females and 28.6% of males reported at least one inactive comorbidity.

Female participants reported, on average, more symptoms than males (42 versus 36).

To test more formally for an association between age and sex and each symptom we used logistic regression using the



**Figure 3. Onset type, illness course, duration of illness and severity of the DecodeME cohort.** Numbers of DecodeME participants reporting whether they had an infection prior to ME/CFS onset (top left) as well as their illness' course (top right), duration (bottom left) and severity (bottom right;  $n = 17,074$  participants).

Bonferroni correction to adjust for multiple tests (Methods). This identified 62 of 80 symptoms as significantly female-biased, and 61 as biased towards younger age (Figure 4). Female-bias is evident across all symptom types (Figure 4). Females were significantly more likely to report fatigue 'often, repeatedly, or all the time' ( $p=6 \times 10^{-4}$ ; age  $p=1.1 \times 10^{-13}$ ), and more likely to report post-exertional malaise after physical or mental activity ( $p=3 \times 10^{-4}$ ; age  $p=4.2 \times 10^{-7}$ ).

### Severity, comorbidities and symptoms

Participants were asked: "How severe is your illness?" with answer options matching severity definitions from the UK's National Institute for Health and Care Excellence (NICE) guidelines (2021). Most DecodeME participants' severity levels are categorised as Mild or Moderate, but Severe and Very Severe individuals are also represented (Figure 3). Severity categories were consistent with participants' reports of their comorbidities and symptoms (see below).

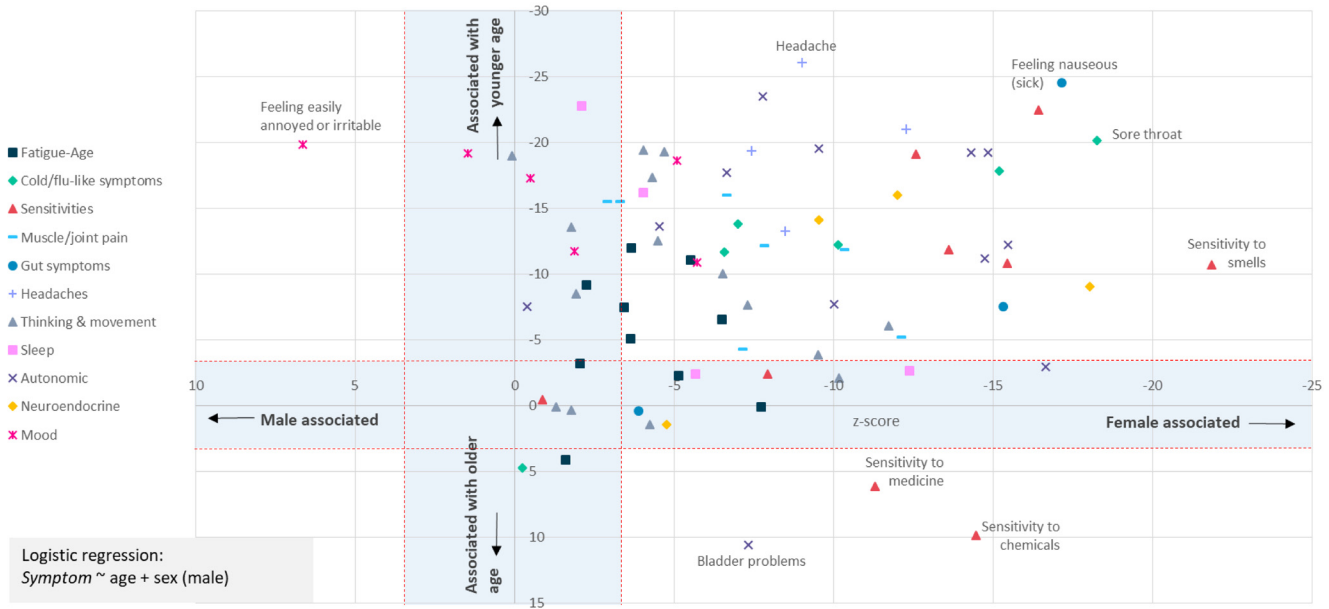
Being female, increasing age and being over 10y from ME/CFS onset are each separately associated with severity in the DecodeME cohort (sex:  $p=4.5 \times 10^{-4}$ ; age:  $p < 2.2 \times 10^{-16}$ ; years since ME/CFS onset:  $p=1.6 \times 10^{-6}$ ). These results are from a comparison of those with mild ME/CFS (34%) against the

remaining 66% with moderate, severe or very severe illness. Testing for all 68 co-occurring (active and inactive) comorbidities, and including both age and sex as covariates in the model, 6 active comorbidities were significantly associated with severity. In order of decreasing significance these were: fibromyalgia ( $p < 2 \times 10^{-16}$ ), clinical depression ( $p < 2 \times 10^{-16}$ ), irritable bowel syndrome ( $p=5.7 \times 10^{-12}$ ), mast cell activation syndrome ( $p=1.8 \times 10^{-11}$ ), diabetes ( $p=9.5 \times 10^{-10}$ ) and sleep apnoea ( $p=5.2 \times 10^{-8}$ ). Severity was also associated with a single inactive comorbidity, hypothyroidism ( $p=1.6 \times 10^{-5}$ ).

Testing all symptoms simultaneously with sex and age, showed strong and independent association between ME/CFS severity and 18 factors including fatigue, age, difficulty remaining standing, and sleep problems (Figure 5). Finally, participants describing their illness as relapsing and remitting were significantly less likely to report their illness as moderate, severe or very severe than those reporting fluctuating symptoms ( $p < 2.2 \times 10^{-16}$ ).

The type of infectious or non-infectious disease onset does not explain these strong and pervasive sex-biases because across the five onset types proportions of females were not significantly different (83.1%-84.5%;  $\chi^2 = 1.707$ ,  $df = 4$ ,  $p = 0.79$ ).





**Figure 4. Most symptoms are strongly associated with female sex at birth and younger age.** The question asked was: “In the last 6 months, have you had any of the symptoms below often, repeatedly, or constantly? Please mark any that apply.” Sex-biased (X-axis) and/or Age-biased (Y-axis) associations in a logistic regression analysis ( $Symptom \sim age + sex + intercept$ ) are shown as data points. Data points within the blue-shaded areas are not significant after accounting for 82 tests ( $p < 0.05/82$ , or  $|Z| < 3.427$ ). Only one symptom (“Feeling easily annoyed or irritable”) was male-biased; 3 symptoms (sensitivities to chemicals or medicine, or bladder problems) were associated with older age. Results for 80 symptoms are shown.

### ME/CFS characteristics by onset type

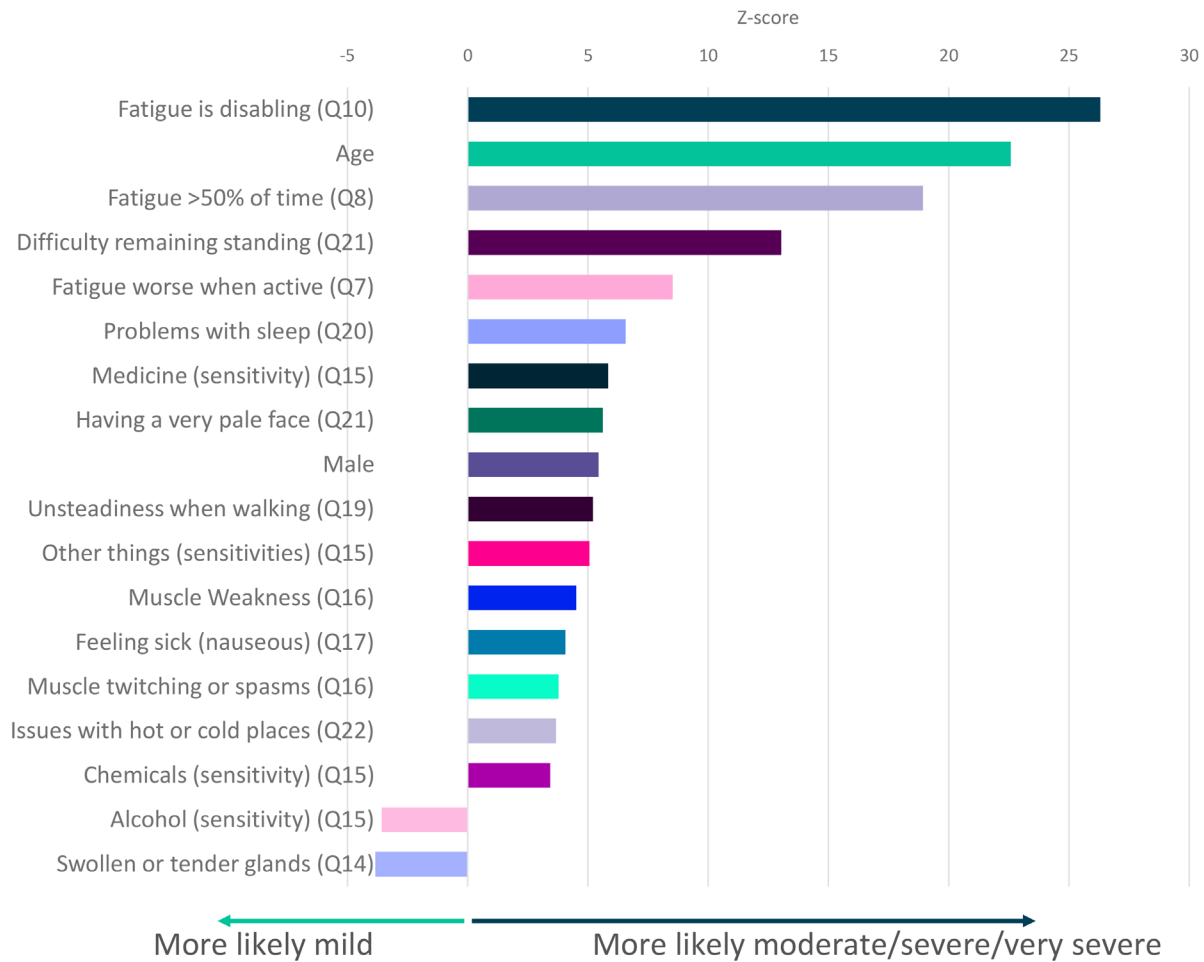
A feature that strongly distinguished among the five onset types was longevity of participants’ ME/CFS symptoms. Participants reporting an infection at onset were more likely to have had ME/CFS symptoms for over 10y than those reporting no infection at onset (67.0% vs. 43.6%). This is despite their similar ages (medians 50y and 46y, respectively).

The statistical significance of this difference is strong. When testing for association between those with an infection prior to ME/CFS onset and duration (<10y vs. >10 years since time of onset), age and sex, only association with duration was significant ( $p = 4 \times 10^{-67}$ ). This relative paucity of participants not reporting an infection prior to onset of their ME/CFS over 10y ago is unexpected, and not easily explained by historic variation in ME/CFS triggers because association with age was not significant in this analysis ( $p > 0.05$ ). When analysed separately, each onset type was not associated with participants’ sex, when including age and ME/CFS duration over 10y in the analysis.

There were significant differences between the 5 ME/CFS onset types and 4 fatigue symptoms (Figure 6A), 16 other symptoms (Figure 6B) and 3 different types of illness course (Figure 6C). Those with glandular fever onset were significantly more likely than others to report swollen or tender glands

and viral infections with long recovery periods within the last 6 months, and to experience relapsing and remitting symptoms (relative to ‘Fluctuating’, the majority response). Others with COVID-19 infection at ME/CFS onset preferentially reported a tight feeling in the chest, sensitivity to alcohol and a feeling of burning in the lungs. Participants with other types of infection onset more frequently reported feeling mentally fatigued, feeling fatigued less than half the time, and difficulties remaining standing, and less frequently reported feeling more sleepy than is normal, having worsening symptoms (relative to ‘Fluctuating’), unusual changes in appetite and mood swings.

Participants reporting an infectious onset (when compared to those who did not) were also significantly more likely to report: improving symptoms, relapsing/remitting, or recovered (relative to ‘Fluctuating’) symptoms, and less likely to report worsening symptoms (again, relative to ‘Fluctuating’). They were more likely, among other things, to report viral infections with long recovery periods, fewer viral infections than they used to get, and having a pale face. Other symptoms that were significantly more likely to be reported by participants without an identified infection at onset were fatigue more than half the time, reduced libido, and unusual changes in appetite. They were also less likely to report symptoms common during infection: flu-like feelings, and swollen or tender glands.



**Figure 5. Questionnaire responses that significantly associate with ME/CFS symptom severity.** Z-scores are shown for symptoms that significantly associate with severity ( $p < 0.05$  after Bonferroni correction for 82 tests, including age and sex). Here severity is defined by self-report of moderate or severe or very severe symptoms versus self-report of mild symptoms (see Figure 3). Responses to questions 14 and 15 (Q14, Q15) are significantly associated with mild symptoms. Responses relate to DecodeME Questionnaire questions (e.g. question 10, Q10).

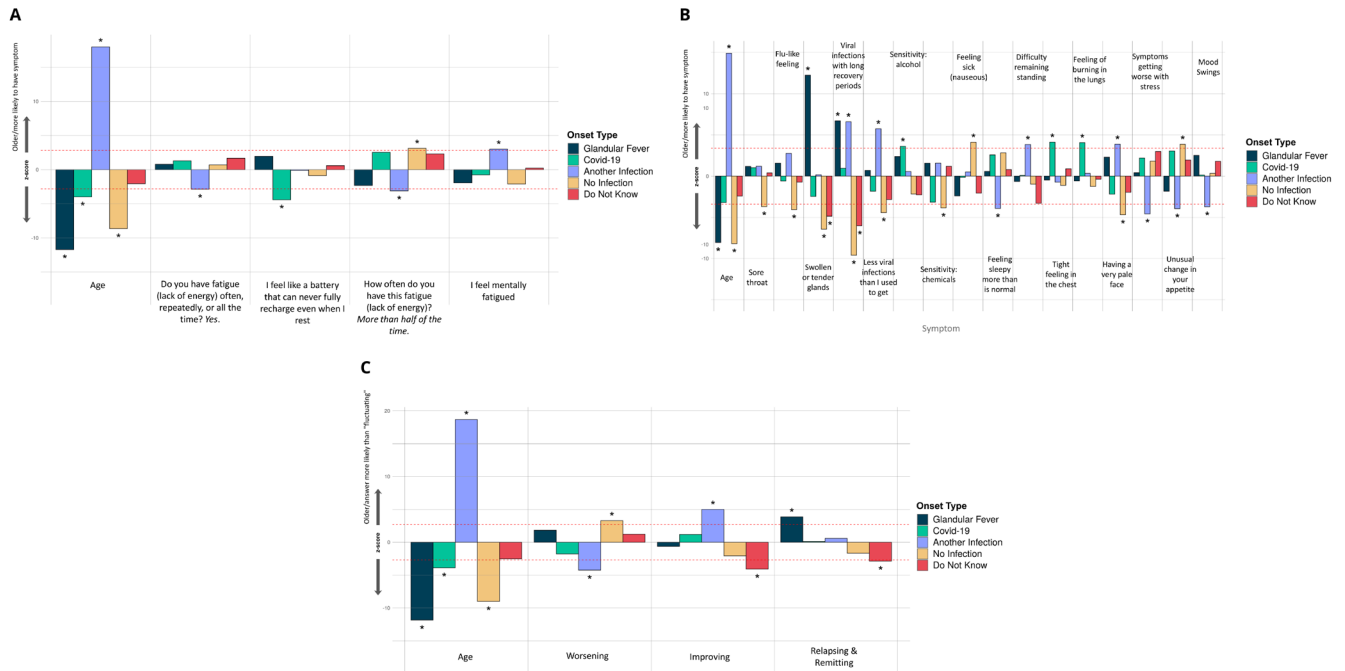
Those with an infection prior to onset of ME/CFS more frequently reported symptoms typical of infection in the last 6 months, whereas those reporting no infection at onset less frequently indicated these symptoms. This was unexpected because of the long time-lag between onset (mostly >10y ago) and participants' recent questionnaire responses. Those with an infection prior to onset of ME/CFS frequently reported symptoms typical of infection in the last 6 months, whereas those reporting no infection at onset infrequently indicated these symptoms. Even though most participants report a long interval between their onset of ME/CFS (mostly >10y ago) and their recent symptoms characteristic of infection, our results cannot distinguish between whether these recent symptoms are a natural consequence of their ME/CFS onset, for example because of viral persistence in some individuals<sup>28</sup>, or else they are independent of onset.

In our last analysis, we tested for association between participants' onset type and their comorbidities, age and sex. Only

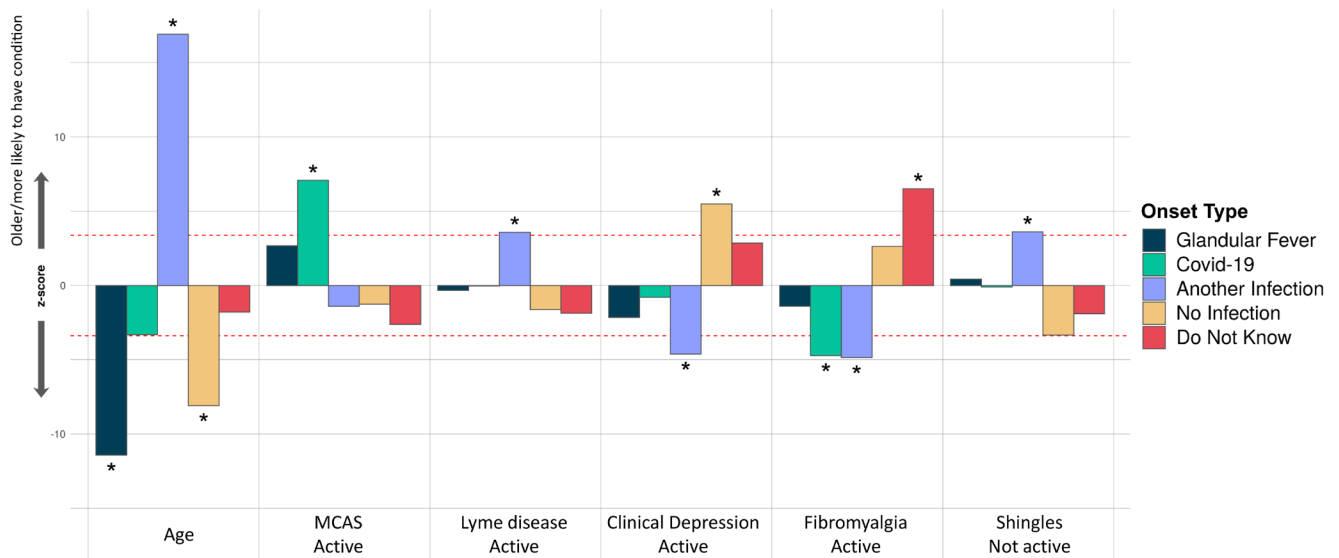
younger age, rather than any comorbidity, was significantly associated with glandular fever onset (Figure 7). Among all onset types, only coronavirus disease 2019 (COVID-19 caused by SARS-CoV-2) infection was significantly associated active Mast Cell Activation Syndrome (MCAS), i.e. MCAS symptoms within the previous 6 months. COVID-19 related onset was also negatively associated with active fibromyalgia. Onset with another infection was positively associated with inactive Shingles or active Lyme disease, and negatively associated with fibromyalgia or clinical depression. Onset without reported infection at onset was significantly associated with recent clinical depression symptoms; and, onset with unknown infection status was significantly associated with active fibromyalgia as a comorbidity (Figure 7).

### Discussion

DecodeME questionnaire responses show how people with ME/CFS do not form a single homogeneous group. Rather, large



**Figure 6.** Associations of symptoms or age to 5 ME/CFS onset types: **(A)** Fatigue symptoms (10 tests), **(B)** Non-fatigue symptoms (74 tests), and **(C)** Illness course descriptions (7 tests). These were considered in a logistic regression model of the form  $\text{OnsetType} \sim \text{age} + \text{sex} + \text{symptoms/descriptions}$  and an intercept. A covariate is only shown if it survived Bonferroni multiple testing correction ( $p < 0.05$ ) per regression for one or more symptom/description. Significant associations are indicated with an asterisk (\*); their Z-scores lie outside of non-significant values, bounded by the red dashed lines, after Bonferroni multiple testing correction. The z-score (Y-axis) is the effect-size estimate in standard deviation units.



**Figure 7.** Associations of comorbidities or age to 5 ME/CFS onset types. Thirty-four comorbidities were considered in a logistic regression model of the form  $\text{OnsetType} \sim \text{age} + \text{sex} + \text{comorbidities}$  and an intercept. A covariate is only shown if it survived Bonferroni multiple testing correction ( $p < 0.05$ ) for one or more onset type. Active and inactive comorbidities were considered independently: Active, if the condition has given symptoms in the past 6 months, or Inactive, if the condition has not given symptoms in the past 6 months, either because it has died down or treatment has controlled it. The z-score (Y-axis) is the effect-size estimate in standard deviation units.

and significant differences exist among five ME/CFS onset types relating to symptoms, comorbidities and illness severity, as well as substantial differences between females and males. Studies involving hundreds of participants previously concluded that ME/CFS exhibits few sex differences in illness patterns<sup>29,30</sup>. Smaller studies indicated older age as associated with greater ME/CFS symptom severity, but other studies found no such association (reviewed in 12,31). These previously limited cohort sizes did not permit comprehensive analysis. In a previous study, three symptoms were reported significantly more often by females than males: fever, swollen glands, and sore throat<sup>30</sup>. In our study, we replicated these findings, and found a further 59 of 80 ME/CFS symptoms that are also female-biased. Our analyses additionally found 61 symptoms biased towards younger age, with only 5 biased towards older age.

The raw number of symptoms may not be meaningful, however, as symptoms can be overlapping, and people with ME/CFS may, over time, pace sufficiently to avoid triggering some symptoms or may begin to describe their symptoms with fewer labels, particularly when interventions are not available to treat each symptom effectively. Indeed, rather than younger participants reporting increased severity, we found that being female, older and over 10y from onset are all risk factors for ME/CFS severity.

Despite its large cohort size (N=17,074), extensive community reach and use of paper, as well as electronic, questionnaires, the analysis presented here – of the December 2022 DecodeME data freeze – has three main limitations. First, recruitment is restricted to participants over the age of 16y, which limited investigation of paediatric ME/CFS. Second, when asking participants if they were diagnosed by a health professional we did not require clinical confirmation of reported answers. Nevertheless, our extensive engagement with participants and the internal consistency of their responses encourage us to believe that questionnaire answers have been given in good faith, noting that inconsistent responses may result from respondents' ME/CFS symptoms including the cognitive dysfunction of 'brain fog'. Thirdly, regrettably DecodeME has not yet been successful in recruiting proportionately from minoritised groups. There is little consensus on whether ME/CFS prevalence differs among these and other groups<sup>32</sup>. Other recruitment and representativeness biases are also possible, as with all research cohorts.

A previous study indicated that ME/CFS onset type associates with severity<sup>33</sup> although this was not replicated by our larger study. Instead, we identified large numbers of comorbidities and symptoms that are each more likely to be reported by participants with a specific onset type. We report significant associations to five onset types derived from participants' responses to the question 'Did you have an infection when, or just before, your first ME/CFS symptoms started?':

1. **'Yes, glandular fever'** (17%): These participants were more likely to report swollen or tender glands and viral infections with long recovery periods, and to experience relapsing and remitting symptoms.
2. **'Yes, COVID-19'** (2%): These participants were more likely to report having Mast Cell Activation Syndrome, a tight feeling in the chest or a burning feeling in the lungs. Mast cell activation symptoms are prevalent in Long-COVID<sup>34</sup> but this condition is rarely diagnosed in people with ME/CFS<sup>35</sup> although perhaps because only recently have MCAS diagnostic criteria been defined<sup>36</sup>.
3. **'Yes, another infection'** (44%): These participants were more likely to be mentally fatigued, to report viral infections needing long recovery periods, and to have had Shingles in the past or symptomatic Lyme disease in the last 6 months. They were also less likely than others to report active clinical depression or fibromyalgia. Over 100 types of infections have been reported to occur at ME/CFS onset<sup>11</sup>.
4. **'No'** (i.e. no infection at onset; 16%): These participants were more likely to report fatigue more than half of the time, to feel nauseous, and to have recent clinical depression symptoms.
5. **'Don't know'** (21%): These were more likely to report fibromyalgia as a comorbidity, and less likely to report cold or flu-like, improving or relapsing and remitting symptoms.

These onset types reveal differences amongst those with ME/CFS regarding their symptoms and comorbidities (Figure 4). However, these distinctions are not absolute. For example, those reporting no infection at onset (Type 4, above) are not cleanly distinguished from all others by active clinical depression. Rather, they were the only onset type that was more likely to report this diagnosis (25.4%) than all other participants were (19.6%). Similarly, Type 3 contains a higher proportion (9.4%) of those who report inactive shingles, than all other participants (7.3%). Shingles is caused by reactivation of latent varicella-zoster virus (a herpesvirus). People with herpes zoster infection are known to have a significantly higher risk of ME/CFS up to at least 6 years<sup>37</sup> fuelling speculation that varicella-zoster virus infection is a cause of ME/CFS that may be prevented by vaccination. 2.5% of ME/CFS cases have been attributed to varicella-zoster virus infection<sup>11</sup>. We note that among those reporting no infection prior to onset (Type 4) some may have developed ME/CFS secondary to an infection without an obvious acute phase, such as can occur with Epstein-Barr virus<sup>38</sup>. However, we are unable to test this hypothesis here.

ME/CFS' poor long-term prognosis, its severe symptoms – especially for older females, its profound impact on the quality of life of people with ME/CFS and family members<sup>9,27</sup>, and its high population prevalence (>0.2%)<sup>1</sup> present formidable healthcare and research challenges. Considering that 63% of DecodeME participants reported an infection prior to onset, any vaccination against the major infectious agents triggering ME/CFS, including Epstein-Barr virus<sup>39</sup>, SARS-CoV-2<sup>40</sup> and influenza viruses<sup>41</sup> may help reduce ME/CFS incidence in the future, especially for individuals more susceptible to severe

disease, or those more likely to be exposed to the infectious agents.

Formal investigation of each onset type's clinical significance is now warranted. To give hope to each of the millions of people worldwide affected by ME/CFS that effective therapeutic interventions will be found within their lifetime, the research community and policy-makers will need to give sustained focus on disease classification and aetiology. It is for this reason that DecodeME is seeking to identify genetic factors causal of altered ME/CFS risk<sup>14</sup> and will do so for infectious versus non-infectious onset participants separately and combined, if final recruitment numbers allow. Recruitment to the DecodeME study is ongoing.

### Data availability

Anonymised data allowing investigation of this study's consented data are available to researchers by managed access via

a Data Access Committee, <https://www.decode.org.uk/faqs/who-will-be-able-to-use-my-data-and-sample/>. This committee consists of a scientist, a patient and a charity representative who strictly control access to the data. DecodeME's anonymised and consented data are only shared with studies that meet high standards and whose academic or industrial researchers agree to treat its data with respect and to keep it secure.

### Acknowledgements

We thank the community of people with ME/CFS and their carers, and Forward-ME for their dedication and steadfast support of the DecodeME project. We also grateful to Professor Sir Stephen T Holgate for his tireless and selfless efforts on behalf of people with ME/CFS, and to the DecodeME Scientific Advisory Board for their critical contributions. DecodeME thanks Helen Baxter (25% M.E. Group) for her dedication when assisting participants to complete their questionnaires. The DecodeME study has been reviewed and given a favourable opinion by the North West – Liverpool Central Research Ethics Committee (21/NW/0169).

### References

- Nacul LC, Lacerda EM, Pheby D, et al.: **Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care.** *BMC Med.* 2011; **9**: 91. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Baker R, Shaw EJ: **Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy): summary of NICE guidance.** *BMJ.* 2007; **335**(7617): 446–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness.** *Mil Med.* The National Academies Collection: Reports funded by National Institutes of Health. Washington (DC). 2015; **180**(7): 721–3. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hickie I, Davenport T, Wakefield D, et al.: **Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study.** *BMJ.* 2006; **333**(7568): 575. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Katz BZ, Shiraiishi Y, Mears CJ, et al.: **Chronic fatigue syndrome after infectious mononucleosis in adolescents.** *Pediatrics.* 2009; **124**(1): 189–93. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sukocheva OA, Maksoud R, Beeraka NM, et al.: **Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome.** *J Adv Res.* 2022; **40**: 179–96. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ayoubkhani D, Bermingham C, Pouwels KB, et al.: **Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study.** *BMJ.* 2022; **377**: e069676. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Reyes M, Dobbins JG, Nisenbaum R, et al.: **Chronic Fatigue Syndrome Progression and Self-Defined Recovery.** *J Chronic Fatigue Syndr.* 1999; **5**(1): 17–27. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hvidberg FM, Brinth LS, Olesen AV, et al.: **The Health-Related Quality of Life for Patients with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS).** *PLoS One.* 2015; **10**(7): e0132421. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Tyson S, Stanley K, Gronlund TA, et al.: **Research priorities for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): the results of a James Lind alliance priority setting exercise.** *Fatigue.* 2022; **10**(4): 200–211. [PubMed Abstract](#) | [Publisher Full Text](#)
- Jason LA, Yoo S, Bhatia S: **Patient perceptions of infectious illnesses preceding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.** *Chronic Illn.* 2022; **18**(4): 901–10. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Cairns R, Hotopf M: **A systematic review describing the prognosis of chronic fatigue syndrome.** *Occup Med (Lond).* 2005; **55**(1): 20–31. [PubMed Abstract](#) | [Publisher Full Text](#)
- Carruthers BM, Jain AK, De Meirleir KL, et al.: **Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.** *J Chronic Fatigue Syndr.* 2003; **11**(1): 7–115. [PubMed Abstract](#) | [Publisher Full Text](#)
- Devereux-Cooke A, Leary S, McGrath SJ, et al.: **DecodeME: community recruitment for a large genetics study of myalgic encephalomyelitis / chronic fatigue syndrome.** *BMC Neurol.* 2022; **22**(1): 269. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chu L, Valencia JJ, Garvert DW, et al.: **Onset Patterns and Course of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.** *Front Pediatr.* 2019; **7**: 12. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Naess H, Sundal E, Myhr KM, et al.: **Postinfectious and chronic fatigue syndromes: clinical experience from a tertiary-referral centre in Norway.** *In Vivo.* 2010; **24**(2): 185–8. [PubMed Abstract](#)
- Lex A, Gehlenborg N, Strobel H, et al.: **UpSet: Visualization of Intersecting Sets.** *IEEE Trans Vis Comput Graph.* 2014; **20**(12): 1983–92. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Jason LA, Richman JA, Rademaker AV, et al.: **A community-based study of chronic fatigue syndrome.** *Arch Intern Med.* 1999; **159**(18): 2129–37. [PubMed Abstract](#) | [Publisher Full Text](#)
- Reyes M, Nisenbaum R, Hoaglin DC, et al.: **Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas.** *Arch Intern Med.* 2003; **163**(13): 1530–6. [PubMed Abstract](#) | [Publisher Full Text](#)
- Reeves WC, Jones JF, Maloney E, et al.: **Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia.** *Popul Health Metr.* 2007; **5**: 5. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Collin SM, Bakken JJ, Nazareth I, et al.: **Trends in the incidence of chronic fatigue syndrome and fibromyalgia in the UK, 2001-2013: a Clinical Practice Research Datalink study.** *J R Soc Med.* 2017; **110**(6): 231–44. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kuri A, Jacobs BM, Vickaryous N, et al.: **Epidemiology of Epstein-Barr virus infection and infectious mononucleosis in the United Kingdom.** *BMC Public Health.* 2020; **20**(1): 912. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bakken JJ, Tveit K, Gunnes N, et al.: **Two age peaks in the incidence of**



- chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008-2012.** *BMC Med.* 2014; **12**: 167.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. Orji N, Campbell JA, Wills K, *et al.*: **Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in Australian primary care patients: only part of the story?** *BMC Public Health.* 2022; **22**(1): 1516.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. Pheby D, Lacerda E, Nacul L, *et al.*: **A Disease Register for ME/CFS: Report of a Pilot Study.** *BMC Res Notes.* 2011; **4**: 139.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Pendergrast T, Brown A, Sunnquist M, *et al.*: **Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome.** *Chronic Illn.* 2016; **12**(4): 292–307.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Vyas J, Muirhead N, Singh R, *et al.*: **Impact of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on the quality of life of people with ME/CFS and their partners and family members: an online cross-sectional survey.** *BMJ Open.* 2022; **12**(5): e058128.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Rasa S, Nora-Krukke Z, Henning N, *et al.*: **Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).** *J Transl Med.* 2018; **16**(1): 268.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Buchwald D, Pearlman T, Kith P, *et al.*: **Gender differences in patients with chronic fatigue syndrome.** *J Gen Intern Med.* 1994; **9**(7): 397–401.  
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Tseng CL, Natelson BH: **Few Gender Differences Exist Between Women and Men with Chronic Fatigue Syndrome.** *Journal of Clinical Psychology in Medical Settings.* 2004; **11**(1): 55–62.  
[Publisher Full Text](#)
31. Joyce J, Hotopf M, Wessely S: **The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review.** *QJM.* 1997; **90**(3): 223–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Dinos S, Khoshaba B, Ashby D, *et al.*: **A systematic review of chronic fatigue, its syndromes and ethnicity: prevalence, severity, co-morbidity and coping.** *Int J Epidemiol.* 2009; **38**(6): 1554–70.  
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Sharpe M, Hawton K, Seagroatt V, *et al.*: **Follow up of patients presenting with fatigue to an infectious diseases clinic.** *BMJ.* 1992; **305**(6846): 147–52.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Weinstock LB, Brook JB, Walters AS, *et al.*: **Mast cell activation symptoms are prevalent in Long-COVID.** *Int J Infect Dis.* 2021; **112**: 217–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Afrin LB, Self S, Menk J, *et al.*: **Characterization of Mast Cell Activation Syndrome.** *Am J Med Sci.* 2017; **353**(3): 207–15.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. Valent P, Akin C, Arock M, *et al.*: **Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal.** *Int Arch Allergy Immunol.* 2012; **157**(3): 215–25.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. Tsai SY, Yang TY, Chen HJ, *et al.*: **Increased risk of chronic fatigue syndrome following herpes zoster: a population-based study.** *Eur J Clin Microbiol Infect Dis.* 2014; **33**(9): 1653–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Womack J, Jimenez M: **Common questions about infectious mononucleosis.** *Am Fam Physician.* 2015; **91**(6): 372–6.  
[PubMed Abstract](#)
39. Zhong L, Krummenacher C, Zhang W, *et al.*: **Urgency and necessity of Epstein-Barr virus prophylactic vaccines.** *NPJ Vaccines.* 2022; **7**(1): 159.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
40. Shaheen N, Shaheen A: **Long-term sequelae of COVID-19 (myalgic encephalomyelitis): An international cross-sectional study.** *Medicine (Baltimore).* 2022; **101**(45): e31819.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Magnus P, Gunnes N, Tveito K, *et al.*: **Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine.** *Vaccine.* 2015; **33**(46): 6173–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)

# Open Peer Review

Current Peer Review Status:  

---

## Version 1

Reviewer Report 25 May 2023

<https://doi.org/10.3310/nihropenres.14555.r29219>

© 2023 **Vernon S.** This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Suzanne Vernon** 

The Bateman Horne Center of Excellence, Salt Lake City, UT, USA

This is a study uses responses to the DecodeME questionnaire to identify ME/CFS subtypes based on self reported type of infection onset that coincided with ME/CFS symptom onset. The choices included "Yes, glandular fever", "Yes, COVID-19", "Yes, another infection", "No", or "Don't know". Responses to this question forms the basis for the symptom analysis and subtyping.

The authors claim that more comorbidity's in females have not been previously reported. However, there are studies by Jason et al <sup>1</sup> and Jones et al <sup>2</sup> that also reported this. Including these important citations would further strengthen the findings of this paper. A couple of citations are provided for your consideration. There are many more that would support these results.

Involvement of patients and the public in the study design is important and adds essential lived experience(s) to the overall DecodeME study design. (This section of the methods should be written more succinctly). However, it is not clear why a standardized and well-validated questionnaire(s), for example the DePaul Symptom Questionnaire (DSQ) was not used rather than or in addition to the DecodeME Questionnaire. The DSQ is validated for ME/CFS, has been used worldwide, and is available in a number of languages. It is also used in the collection of core data elements for ME/CFS (as developed by NIH/NINDS). The use of a new questionnaire that has not been validated for ME/CFS limits the generalizability of these results. Finally, the inclusion of people with comorbid diseases that are exclusionary could explain symptoms limits the ability to replicate these results.

How does a paper questionnaire help decrease or eliminate bias?

The results describe 80+ symptoms yet the DecodeME Questionnaire asks about 12 major symptoms. What accounts for this discrepancy. If each item listed under each major symptom was considered as a separate system, how was collinearity accounted for?

What was the positive test for those that responded "Yes, other infection"?

Duplicated text in the results, 2nd to last paragraph in Results.

The authors point out in the discussion that previous work associated onset type with disease severity and that this study did not find this. Could this be due to the lack of clear severity and frequency assessment of symptoms in the DecodeME Questionnaire?

The major strength of this paper is the >17,000 respondents.

The major weaknesses of this paper are the use of a new ME/CFS questionnaire and the inclusion of exclusionary diseases that could explain the reported symptoms.

### References

1. Jason LA, Helgeson J, Torres-Harding SR, Carrico AW, et al.: Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability. *Eval Health Prof.* 2003; **26** (1): 3-22 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Jones JF, Lin JM, Maloney EM, Boneva RS, et al.: An evaluation of exclusionary medical/psychiatric conditions in the definition of chronic fatigue syndrome. *BMC Med.* 2009; **7**: 57 [PubMed Abstract](#) | [Publisher Full Text](#)

### Is the work clearly and accurately presented and does it cite the current literature?

Partly

### Is the study design appropriate and is the work technically sound?

Partly

### Are sufficient details of methods and analysis provided to allow replication by others?

Partly

### If applicable, is the statistical analysis and its interpretation appropriate?

Yes

### Are all the source data underlying the results available to ensure full reproducibility?

Yes

### Are the conclusions drawn adequately supported by the results?

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Clinical research of ME/CFS and PASC

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 18 May 2023

<https://doi.org/10.3310/nihropenres.14555.r29220>

© 2023 Tyson S. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



### Sarah Tyson

Division of Nursing, Midwifery & Social Work, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, England, UK

The results of the DeCode have been eagerly awaited, even the interim results so there is bound to be a lot of interest in this paper. However I feel it needs some more work to make it as easy to understand as possible. The lack of clarity stems primarily (I think) from a uncertainty about the aim/objective/research questions addressed in this paper. It has a feel of something of a fishing exercise, and having gotten some results, the authors are keen to tell people about them (which is admirable) but aren't really clear about what and why. The methods section, in particular needs more details so the reader can understand what was done, why and how.

To look at each detail in turn:

#### **Abstract**

- The abstract needs a clear aim/objective/res question and further methodological detail. At present there is no info about the questionnaire, except that there was one. An indication of the selection criteria, recruitment methods, and details of the questionnaire (what does it measure, how?) And the analysis methods (which need to be linked research questions) are needed. In the results section there needs to be some data and the unique findings made clearer. It is hardly news that ME/CFS is a heterogeneous condition.
- The plain English summary includes rather lot of jargon. For example – “For many people, ME/CFS means a substantial impairment of their activity levels, a high level of disability and a poor quality of life” rather than “*for many people, ME/CFS means disability and poor quality of life ..*” NB. The PSP included a range of HCPs not just Doctors,

#### **Methods**

- I appreciate that PPI has been central to the DeCode project but there needs to be further details of the actual methods used. The 3<sup>rd</sup> paragraph of the methods isn't really relevant to what was done in this project and can be removed.
- The description of the questionnaire needs to include its aim; an outline of the content (what does it ask about?), its size/length, types of questions and response format(s). The details of how it was developed and validated and any other psychosomatics would be useful. The reader needs to know what data were collected and how, and be reassured that the information obtained was relevant and accurate ie psychometrically robust.
- The paragraph on the ‘cohort’ describes the process of completing part of the questionnaire. It would be easier to understand who was recruited to the study and how by listing the selection criteria, and stating the recruitment strategies- where and how were people recruited? I think it was largely via social media and support groups which is fine. Just say so.

- The paragraph on significance testing needs to be replaced by an explanation of the analysis used, linked to the objectives/ research questions. It might be helpful to get a statistician to help with this. I see that logistic regression model(s) was/were used. This needs further detail, particularly the dependent and independent variables. There is reference to figures which are not explained and I cannot really follow. Also Onset Type, symptoms (in groups with different numbers), severity, illness courses, 'Fluctuating', the majority response, and comorbidities are unexplained, undefined and unconnected to any objective or research question. This section is key to understanding the whole paper so needs to clearly describe what was analysed, why and how.

### **Results**

- The 1<sup>st</sup> paragraph (after the 1<sup>st</sup> sentence) describes what participants did rather than what was found, and so belongs in the method section. The results need to start with a summary description of the sample – the number, mean age; sex ratio; time since diagnosis +/- duration of symptoms. Then the main co-morbidities; frequency of symptoms etc. The text needs to be understandable without the tables/figures and vice versa. The figures /tables add extra detail but there needs to be a summary in the text.
- The results section needs to only include what was found in this study. Reflections on how they relate to other studies (or not) are for the discussion (see paragraph 2).
- In the summary of results, try to avoid copy and pasting the results as they were churned out. Eg rather than "Participants were asked: "Did you have an infection when, or just before, your first ME/CFS symptoms started?" with five possible responses: (i) Yes, glandular fever ( $n=2,936$ ), (ii) Yes, COVID-19 ( $n=380$ ), (iii) Yes, another infection ( $n=7,537$ ), (iv) No ( $n=2,625$ ), or (v) Don't know ( $n=3,596$ ; Figure 3). Proportions of people in the first 3 categories reporting a positive laboratory test of their infection prior to ME/CFS were 68.4%, 50.5% and 25.9%, respectively" – which is lengthy and unfocussed Summarise this for the reader by saying (for example) "*Most ( $n, \%$ ) reported an infectious onset to their symptoms, most commonly glandular fever (17%,  $n=xx$ ) this was glandular fever, followed by covid-19 ( $n, \%$ ). However only 68% and 51% respectively of respondents with these triggers reported a positive laboratory test confirming the diagnosis*".
- Do not include reference/comparison to other studies in the results section; this is for the discussion section.
- Several of the sentences are rather convoluted and a bit more plain English would not go amiss. For example, I eventually managed to work out that "Participants who started their illness within the last 1–3y or 0.5–1y numbered 1,287 or 354, respectively. These numbers are 57% and 21% fewer, per year, than the study's 1,634 participants from the 3–5y recruitment interval." Actually meant "*Most 1,634 ( $xx\%$ ) were diagnosed 3-5 years previously, followed by 1287 ( $x\%$ ) with 1-3 year duration and 354 ( $X\%$ ) were more recently diagnosed (0.5-1 year)*".
- Always include both the number and % of participants being referred to.
- Avoid any interpretation in the results.



- Whenever presenting an average value an indication of the variability (whether standard deviations for means, or inter-quartile ranges for medians) is needed.
- Why was a sub-group used to assess incidence? I don't think 'incidence' is the proper term. The reference to the frequency with which ME/CFS occurs within a defined general population and this dataset does not include that data.
- My comments above also apply to the rest of the results. At present they are difficult to read and to work out the main message from the results. The reader is left to work out the main gist of the results themselves and it is far from easy.

### **Discussion**

- The 1<sup>st</sup> paragraph of the discussion needs to summarise the main findings; the headline news in sufficient detail to the reader to have an insight into the significance of the results. Merely saying ME/CFS is heterogeneous with substantial differences in onset; symptoms, comorbidities and severity and sex differences isn't new, we already know this. The headline news needs some (summary) details about what the differences were.
- Then you compare your findings with previous studies – which is great. Make sure all the comparisons and interpretation are here and not in the results. Also try to include any possible explanation for differing/contrasting results (usually due to sample size, method of data collection or selection criteria)
- The limitations section is good.
- The list of symptoms and other characteristics associated with different onset types are new data and belong in the results section – and would help a great deal to understand the results. Although I am a bit confused - why/how was onset type used to sub-group pwME? why not look at cluster/co-occurrence of symptoms and/or co-morbidities +/- onset? It may be that this was done and onset was the strongest factor, if so it needs to be explained more clearly.
- What is the clinical or significance/ implications of the findings? Are you saying onset is such an important/explanatory factor that it should be used to group different types of ME/CFS? Or that they seem the best bet (if so, I didn't pick that up) or what?
- I'm presuming there isn't a conclusion section where the authors relate the findings to the original objectives /research questions and whether they have been fulfilled, because the journal specifically excludes one. If not, please add a conclusion.

### **Is the work clearly and accurately presented and does it cite the current literature?**

Partly

### **Is the study design appropriate and is the work technically sound?**

Partly

### **Are sufficient details of methods and analysis provided to allow replication by others?**

No

**If applicable, is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** pwME, clinical researcher academic

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.**

---