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Myalgic encephalomyelitis/ chronic fatigue syndrome: Impact on quality of life of partners and family members A prospective multinational, subject-initiated, cross sectional survey

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Title Page

Myalgic encephalomyelitis/ chronic fatigue syndrome: Impact on quality of life of partners and family members

A prospective multinational, subject-initiated, cross sectional survey

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ABSTRACT

Objectives: The aim of this study was to assess the impact of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on the quality of life (QoL) of people with ME/CFS and their relative or partner (family member).
Design: A patient partner, prospective, multinational, subject initiated, cross sectional online survey.
Setting: International survey using ME/CFS charities, support groups and social media
Participants: Self-selected on social media. Inclusion criterion: aged 18 years or over, reported diagnosis of ME/CFS by health professional. 1418 people with ME/CFS and their 1418 family members from 30 countries. Participants with ME/CFS: mean age= 46 years (range 18-81), female=1214 (86% of 1418). Family members mean age =51.9 years (range 18-87), female=504 (36% of 1418). 991 (70% of 1418) family members were partners of the people with ME/CFS.
Interventions: EuroQoL 5 Dimension (EQ-5D-3L) completed by people with ME/CFS, and Family Reported Outcome Measure (FROM-16) questionnaire completed by family members.
Results: The mean overall health status on a visual analogue scale for people with ME/CFS was 33.8 (0=worst, 100=best). People with ME/CFS were most affected by ability to perform usual activities, pain, mobility, self-care and least impacted by anxiety. For family members the overall mean FROM-16 score was 17.9 (0=no impact to 32=worst impact) demonstrating a major impact on QoL. Impact on QoL was significantly correlated between the person with ME/CFS and their family member ($p<0.0001$). Family members were most impacted emotionally by worry, frustration and sadness and personally by family activities, holidays, sex life and finances.
Conclusions: To the best of our knowledge, this is the largest study on the impact of the QoL of persons with ME/CFS and their family members. This research has revealed the significant worldwide burden of ME/CFS on the QoL of people with ME/CFS and on their family members' QoL and has implications for policy and practice.

ARTICLE SUMMARY

Strengths and Limitations of this study

Strengths

- Patient and public involvement in the design of the study
- International study with large number of participants
- Validated Quality of Life questionnaires for persons with ME/CFS and their family members

Limitations

- Recruitment bias towards English speaking participants
- Data on ethnicity was not collected

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INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, debilitating disease, with a negative impact on health-related quality of life (QoL) [1], worse than for many other diseases [2]. There is growing international acknowledgement of the impact of ME/CFS on caregivers [3]: a pilot study, using the Family Reported Outcome Measure (FROM-16), showed that QoL of partners and other family members is greatly impaired, suggesting that ME/CFS impact goes far beyond the affected person [4].

ME/CFS is characterised by multisystem symptoms exacerbated by mild exertion, pain, sleep disruption, orthostatic intolerance, cognitive dysfunction and severe and disabling fatigue not improved by rest [5]. ME/CFS occurs globally with a prevalence of up to 0.89% [6] though prevalence and impact are underestimated in many countries [7]. Often triggered by a virus, the COVID-19 pandemic may increase ME/CFS prevalence [8] and there needs to be improved international recognition of chronic post viral disease burden on QoL of sufferers and families.

This study's aim was to measure the impact of ME/CFS on the QoL of those affected and their partners or family members.

METHODS

This was a prospective, multinational, subject-initiated, cross sectional survey to assess the impact of ME/CFS on the lives of patients and their partner or family member using the EuroQoL 5 Dimension (EQ-5D-3L)[9] and FROM-16 [10] questionnaires. Ethical permission was granted by Cardiff University School of Medicine ethics committee (11th September 2020).

REDCap, a secure web platform [11 12] was used for the survey, which was distributed via ME/CFS websites and social media platforms.

Patient and Public Involvement

The study was co-designed by patients and clinical researchers. Patients with ME/CFS and their family members were involved at all stages of the study design and actively contributed to identifying the research questions and designing the research. Two of the authors, involved have ME/CFS: one is a clinician and the other a patient representative. Patient partners were directly involved in developing the ethics application and disseminating the surveys via patient charities and online. Burden of intervention and time required to participate in the survey was also assessed.

Questionnaires used

EQ-5D-3L
This is a generic instrument measuring an individual's health status[9 13]. It has five dimensions (questions) on mobility, usual activities, self-care, pain and discomfort, and anxiety and depression. Three dimensions have three possible responses: no problems,

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some problems, and inability. The responses for the other two dimensions are: no problems, moderate problems and extreme problems. Each response is coded from 1-,3 and combined as a series of five digits describing the 'EQ-5D self-reported health state' or 'EQ-5D profile'[14]. The EQ-5D-3L has 234 possible health states. EQ-5D profiles can be converted to a single number, the 'EQ-5D value', "1" represents full health and "0" dead[15]. Values <0 indicate a health state worse than death. Overall health status is recorded on a visual analogue scale, from 0 (worst imaginable health) to 100 (best imaginable health).

FROM-16

This questionnaire measures current QoL impact on a healthy person having a partner or family member with a health condition[10]. It can be completed by anyone over the age of 18 years, concerning the impact of the health condition of a patient of any age. There are 16 questions covering the domains "Emotional" (six questions) and "Personal and social life" (ten questions). Each question is scored from 0-2 (0=not at all, 1=a little, 2=a lot), with a score range of 0-32, "0" meaning no impact and "32" meaning greatest possible impact.

Study Design

Multiple survey versions were piloted in November 2020, refining wording for clarity, ease of use and to identify and resolve technical issues. Feedback confirmed that the questionnaires were easy to answer and most persons with ME/CFS completed the EQ-5D questionnaire within five minutes. The preferred order of questionnaires was identified, with the questionnaire for the person with ME/CFS presented first followed by the family member/partner questionnaire, with the option to return later. Following participant comments, a few minor changes were made, for instance to obviate any confusion resulting from having more than one family member with ME/CFS.

Informed consent was obtained via a tick box question for the participant with ME/CFS. Participants completed basic demographic questions including if they had a diagnosis of ME/CFS from a healthcare professional. To ascertain how many met ME/CFS criteria, participants were asked to select their symptoms from a tick box list adapted from the systemic exertion intolerance disease (SEID) US Institute of Medicine criteria for ME/CFS[16], a clinical diagnostic tool comprising five ME/CFS symptoms. The criteria include technical language, hence a plain English version was devised specifically for this study. ME/CFS is diagnosed if all first three symptoms and at least one of the last two are present.

Participants answered the EQ-5D-3L and then chose either their partner or another family member to complete the survey second part. The family member/partner could participate in the study immediately, or was invited via email link by the person with ME/CFS. Similar to the person with ME/CFS, a link to the participant information was provided and consent was given via a tick box question. Family members/partners then completed basic demographic data questions and the FROM-16. All participants were required to be aged 18 years or over

Statistical analysis

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Only data from participants with ME/CFS who had a formal diagnosis by a health care professional (HCP) and their family members were included in the final analysis. Duplicate entries were identified by email address and matching demographics: only the second was analysed. Microsoft Excel, SPSS and GraphPad Prism v9 were used for data handling and statistical analysis, involving descriptive statistics and parametric statistical tests including Item-total correlations, inter-item correlations and Spearman rank correlation coefficient.

RESULTS

The survey was carried out from 1 December 2020 to 31 March 2021. It was started 2980 times. One participant withdrew consent, therefore 2979 records were generated. 2668 participants completed the first part of the survey, including the EQ-5D-3L. 1479 family members/partners completed the second part of the survey. Only the 1479 records that were fully completed by both patient and family members/partners were analysed further. 25 records were excluded either because they were duplicates (n=22) or for other reasons (n=3). From the remaining 1454 records a further 36 were excluded for not having a formal diagnosis of ME/CFS from a health care professional. The final analysis included 1418 survey responses representing 2836 participants (persons with ME/CFS and their family member/partner) (Figure 1).

Demographic Profile of participants

Table 1 shows the participant demographics. Persons with ME/CFS and their family members worldwide participated in the study however most responses came from the UK (58.8%) and other English-speaking countries, including the USA (11.2%), Canada (5%) and Australia (5.8%) (Table 2). The average time since diagnosis of ME/CFS was 13.9 years, (median 11) with 15 patients diagnosed for 1 year and 8 for >50 years. However, 42 participants with ME/CFS and 1 family member did not answer this question. One family member entered an erroneous number.

	Person with ME/CFS	Family Member
Number	1418	1418
Time since diagnosis	13.9 years	n/a
Age	45.82 (18-81)	51.9 (18-87)
Female	1214 (85.6%)	504 (35.5%)
Male	196 (13.8%)	902 (63.6%)

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Other	8 (<1%)	12 (<1%)
Separate Household		149 (10.5%)
Lives alone	158 (11.1%)	
Relationship of person with ME/CFS to family member		
Partner/Spouse		991 (69.9%)
Parent		76 (5.35%)
Sibling		288 (20.3%)
Child		28 (1.9%)
Other		35 (2.5%)
>1 Family member has ME/CFS		160 (11%)
Family member has ME/CFS		49 (3%)

Table 1: Participant demographics

Patient Country	Number
United Kingdom	834
United States of America	159
Australia	82
Canada	71
Norway	40
Germany	34
Netherlands	32

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Sweden	31
Ireland	24
New Zealand	24
Belgium	14
Italy	10
Spain	10
Japan	9
Denmark	8
France	6
South Africa	6
Finland	5
Switzerland	5
Austria	3
Portugal	2
China	1
Croatia	1
Czech Republic	1
Ghana	1
Iceland	1
Poland	1
Senegal	1
Trinidad and Tobago	1

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Uruguay	1

Table 2: Person with ME/CFS country of residence

Reflecting the female preponderance for ME/CFS, far more females responded (85.6%) than male, eight did not answer this question. Only 11.1% (n=158) of participants with ME/CFS lived alone. Those that lived with others mainly shared with a life partner or family member, with only 14 people stating they lived with people outside that description. Most family members who participated lived with the person with ME/CFS, with only 149 living in a separate household and one unknown.

160 family members reported having more than one family member with ME/CFS and 49 family members were themselves ME/CFS sufferers. Two persons failed to answer this question.

All persons with ME/CFS completed five questions based on SEID criteria (Table 3). Most respondents, already diagnosed by a HCP, also met these diagnostic criteria. However, 93 respondents lacked the symptoms for the SEID ME/CFS diagnosis criteria but stated they had a medical diagnosis, and therefore were included in the analysis. 80 participants did not have one or more of the three required symptoms for diagnosis, including less able to do normal things (n=14), symptoms worse after physical, mental or emotional activity (n=12), sleep unrefreshing or disturbed (n=54). 12 stated they did not have two of the three criteria, with one stating they experienced none of the five criteria. Of the 36 (2.5%) people without an ME/CFS medical diagnosis not included in the data analysis, most reported ME/CFS diagnosis criteria symptoms. 604 (42.6%) of the ME/CFS participants reported having another chronic health condition.

Symptom	Yes	No
Less able to do normal things	1404 (99%)	14 (1%)
Worse after physical, mental or emotional activity	1406 (99%)	12 (1%)
Sleep unrefreshing/disturbed	1364 (96.2%)	54 (3.8%)
Brain fog	1382 (97.5%)	36 (2.5%)

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Worse symptoms/dizziness when upright	1103 (77.8%)	315 (22.2%)

Table 3: Person with ME/CFS and the SEID criteria

EQ-5D health profile of persons with ME/CFS

Figure 2 gives the EQ-5D results. Strikingly 98.5% (n=1397) of participants had problems performing their usual activities. Over half (n=775) were unable to perform their usual activities at all. Pain was the next most affected dimension with 93.9% (n=1331) experiencing some (n=976) and extreme (n=355) pain and discomfort. Mobility was affected in 88.6% (n=1256), with participants experiencing some problems (n=1063) with walking or confined to bed (n=193). In terms of self-care, 67.3% (n=954) had some problems or were unable to wash or dress themselves. Anxiety and depression was the least affected dimension, as 40.6% (n=576) participants reported they were not anxious or depressed at all, whilst 59.4% were either moderately (n=678) or extremely (n=164) anxious or depressed. The average EQ-5D VAS score of ME/CFS patients was 33.7, (median 47.5, SD 17.5, range 0-94) (Figure 2b).

Of the possible 234 EQ-5D-3L profiles, participants with ME/CFS expressed 94 unique profiles. Only three participants had a profile 11111, indicating no problems in any dimension. Similarly, 12 participants had a profile 33333 indicating extreme problems in all dimensions. Ten profiles accounted for 56.5% of EQ-5D-3L profiles (Table 4). The profile 22321 was the most frequent (n=128) indicating some problems with mobility and self-care, inability to perform usual activities, moderate pain/discomfort and no anxiety/depression. 22222 and 22322 were found in equal measure (n=117) the only difference is that 22222 means moderate problems in all dimensions whereas 22322 indicates moderate problems in all dimensions and inability to perform usual activities.

	EQ-5D state	EQ-5D Value	Frequency	% Frequency
Least Severe	21221	0.659	72	5.07
	21222	0.596	86	6.06
	22221	0.566	70	4.93
	22222	0.503	117	8.25
	21321	0.394	55	3.87
	21322	0.331	42	2.96

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	22321	0.301	128	9.02
	22322	0.238	117	8.25
	22331	0.214	43	3.03
Most Severe	22332	0.151	77	5.43

Table 4: The 10 most frequent EQ-5D health states of ME/CFS participants, sorted according to EQ-5D value severity

The EQ-5D-3L profile can be converted into a single number or EQ-5D value allowing for comparison with the general population. Our results demonstrate strikingly lower EQ-5D values in each age group for persons with ME/CFS compared to the general UK population[17]. Similarly, persons with ME/CFS reported much higher percentages of 'problems' in each of the EQ-5D dimensions compared to the UK population norm (Figure 3).

Quality of Life of family member/partner of person with ME/CFS

The FROM-16 examined the effects of a person's ME/CFS on their family member's emotions and personal/social life. Family members, on average, scored 7.62 (max=12, median=8, SD=2.81) in the emotional domain and 10.31 (max=20, median=10, SD=4.9) in the personal and social life domain (Figure 4). The average overall FROM-16 score (Figure 5) was 17.93 out of a total of 32 (median=18 SD=6.95) demonstrating a major impact of ME/CFS on family members.

ME/CFS had a significant impact on family member's emotions. Of the 1418 respondents, 96.1% (n=1362) felt worried due to their family member's ME/CFS, making it the most affected emotion. Frustration and sadness with their family member's ME/CFS were also highly prevalent with 93% (n=1369) experiencing frustration and 92.9% (n=1317) experiencing sadness. 84.7% (n=1201) found caring for their family members difficult, 73.4% (n=1041) found it difficult to talk to someone about their thoughts and 70% (n=994) of respondents were a little or a lot angry because of their family member's ME/CFS.

In the personal and social domain, the greatest impact was in the area of family activities with 92% (n=1302) respondents reporting family activities affected. Similarly, 85.3% (n= 1210) experienced problems with holidays. 72.2% (n=1025) stated their sex life was affected and 77.3% (n=1096) felt their finances were impacted in that their family expenses increased. 68.6% (n=973) of respondents found it hard to find time for themselves. Sleep, work or study, and family relationships were almost equally affected with 66.9% (n=948) reporting a negative impact on their sleep, 65.7% a negative impact on their work or study and 63.8% (n=904) found their family relationships with other family members were affected due to their family member's ME/CFS. Everyday travel and eating habits of family members were the least affected of all the areas, with 54.8% (n=777) indicating a problem with everyday travel and 51.8% (n=735) reporting an effect on their eating habits.

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In order to determine the relationship between the person with ME/CFS and their family members quality of life, we used linear regression analysis. We found a significant negative correlation between the total FROM-16 score of family members and the patients VAS score ($P<0.0001$, $R=-0.3467$, $R^2=0.1146$) (Figure 6). Furthermore, a similar negative correlation was calculated using the total FROM-16 score and the EQ-5D value of patients ($P<0.0001$, $R=-0.411$, $R^2=0.1668$) (Figure 7), supporting the fact that family member quality of life is significantly impacted by a ME/CFS.

DISCUSSION

To the best of our knowledge this is the largest study on the impact on the QoL of persons with ME/CFS and their family members. Our study confirmed that ME/CFS has a considerable negative impact on QoL. The most common EQ-5D-3L profiles demonstrated that people with ME/CFS experience problems across all domains with similar severity: the problems are not confined or localised to one aspect. None of the ten most frequent profiles in our survey reported a level 3 "a lot" for anxiety. The average EQ VAS score in our study was 33.8 (SD=17.5, median=47.5). The higher the EQ VAS, the better the QoL. The mean EQ VAS for the representative UK population is 82.75. Our data demonstrate that the QoL of family members of persons with ME/CFS is more impaired than in other conditions. In our study, in the Emotional domain of FROM-16, worry was the most frequently impacted item (96.1%, n=1362), frustration was experienced by 93% (n=1319) and sadness by 92.9% (n=1317).

The study strengths include the patient co-design, with patient involvement at the heart of the research team, wide international dissemination of the survey and the very large numbers of participants. There has been controversy over diagnostic criteria for ME/CFS. Participants whose data was included in the analysis were required to have a healthcare professional diagnosis of ME/CFS. Of these participants, 93.4% also fulfilled the SEID criteria for ME/CFS diagnosis. This diagnostic confirmation is a major study strength. Limitations include recruitment bias towards English speaking self-selected people active on social media. Those more severely affected may not have responded because of ME/CFS's debilitating physical effects. Conversely, they may have been more motivated to take part. Online delivery precluded checking whether assistance was given completing forms or whether the family member or patient allowed others to see their responses. Lack of anonymity within the family may have influenced some responses. Data on ethnic background was not collected.

In contrast to the high level of QoL impact revealed in our study, the EQ-5D-3L profiles from a survey in England[17 18] reported that 56.2% of the general public have an EQ-5D profile of 11111, indicating no problems in any dimension. An EQ-5D profile can be converted into an EQ-5D value, with a value of 1 indicating the best possible health. The mean EQ-5D value for persons with ME/CFS in our study was 0.36 (SD=0.21). In comparison, the mean EQ-5D value for the UK representative sample is 0.86 (SD=0.23)[19]. Myers et al[20] in their ME/CFS study reported a mean EQ-5D value of 0.56 (SD=0.35), representing a QoL impact between the UK representative sample and our ME/CFS participants. Hvidberg et al[2] reported an EQ-5D mean value of 0.47 in Danish ME/CFS patients, much lower than the representative Danish

population mean of 0.85. Their study demonstrated that the EQ-5D value for ME/CFS was the lowest of 20 chronic conditions. Nacul et al[21], using the SF-36 in a UK population also demonstrated that the QoL of people with ME/CFS was lower than 10 other chronic conditions. Our findings of greatly impaired QoL are consistent with these studies.
The EQ VAS score in our study was in contrast with a higher VAS score of 54.3 (SD=23.3) in the Meyers study[20]. This discrepancy may be explained by the higher proportion of patients from the UK in our study. Brenna et al[22] conducted a survey of persons with ME/CFS in Italy, Latvia and the UK. Latvian respondents (n=74) reported the least impaired QoL (VAS mean=57.3, SD=16.3), Italian respondents (n=84) had a mean VAS score of 34.6 (SD=20.8) and the UK respondents (n=440) had a mean score of 31.5 (SD=19.8). A Swedish study by Jonsjo et al[23] involving 106 patients with ME/CFS reported a mean EQ-5D value of 0.3 (SD=0.33) and a mean VAS score of 29.8 SD=15.7).

Most previous studies on the impact on family members of persons with ME/CFS have focused on children with ME/CFS[24-26] making comparisons difficult, however in a pilot study, Brittain et al[4] compared the impact of ME/CFS on UK patients and on family members, using WHOQoL-BRef and FROM-16. That study demonstrated that poor QoL of the person with ME/CFS is associated with a high impact on the QoL of family members. There was no significant difference (p = 0.07) between the mean family impact for the Brittain study (mean FROM-16 score = 19.9, n=42) compared with our current international study (mean score = 17.9, n=1418). Chantarasap et al[27] assessed the impact on the QoL of family members of 248 patients diagnosed with various different cancers including hematologic malignancies. The mean FROM-16 score was 11.75 (significantly lower than in our study P<0.0001) with the mean scores in the Emotional domain =4.1, and Personal and social life domain=7.1. The mean FROM-16 scores in our study indicate that family members of patients with ME/CFS have a much lower QoL. In a recent cross sectional international study[28] measuring the impact of COVID-19 on survivors and their partners or family members, the mean FROM-16 score at 15 (n=735) was also high, but significantly less impacted than in our study (p<0.0001). The mean symptom duration for post covid symptoms was 12.8 weeks, but it is clear that a subset of long COVID patients matching ME/CFS diagnostic criteria is now emerging and a repeat study of those who remain symptomatic after a year would be interesting.

ME/CFS needs to be acknowledged as a serious disease, causing significant impact on health and quality of life, not only of the individual but also on their family. Education for healthcare practitioners must be updated to reflect this. It would be possible to screen for these impacts using EQ-5D or FROM-16 in routine clinics. The medical encounter can be vastly improved by acknowledging the impact on family members and providing practical advice and support to both people with ME/CFS and their family members.

Unanswered questions and future research

Not all people with ME/CFS have a family member or partner to complete the FROM-16. Several individuals wrote to the research team explaining their isolation, difficulty maintaining family relationships and/or lack of empathy of family members. Further

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research is needed to understand the wider impact of ME/CFS on families and on individuals.

FROM-16 score meaning descriptors have not yet been developed, therefore a logical arbitrary assumption has been made of the scale of severity as expressed by the FROM-16 scores. Our large dataset may allow further work towards categorising family impact scores and increasing the international validity of FROM-16. A study of this scale provides direction for future qualitative and focus group research to identify why certain aspects of family QoL are impacted more than others and to identify and develop supportive interventions to make the greatest impact. FROM-16 could be used as an outcome measure to assess such novel interventions.

CONCLUSIONS

This research has the potential to have a major and immediate impact on the standard of care and compassion we offer to our patients and families and has implications for policy and practice. The significant worldwide burden of ME/CFS on quality of life for patients and their family members should be a call to arms for biomedical research in this disease.

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Author Statement

JV: Conception of study, study design, data analysis, writing, reviewing and final approval of manuscript
NM: Study design, data analysis, writing, reviewing and final approval of manuscript
RKS: Data analysis, writing, reviewing and final approval of manuscript
RE: Study design, writing, reviewing and final approval of manuscript
AYF: Study design, writing, reviewing and final approval of manuscript

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Association of WA, Far North Coast MECFS Association, ME/CFS/FM Support Association QLD, ACT ME/Chronic Fatigue Syndrome, ME/CFS Australia, Japan ME Association Društvo za fibromialgijo, ACSFCEM, ME/CFS Schweis, The Rocky Mountain CFS/ME & FM Association. We wish to acknowledge MEpedia which was used as a resource to identify national and international ME/CFS organisations.

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Competing Interest statement:

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare no support from any organisation for the submitted work: AYF is joint copyright owner of FROM-16. No royalties from been received for use of FROM-1 in this study. A member of AYF's family is deputy chair of the NICE ME/CFS guideline committee. Outside of this study JV has been on an Advisory board for Amgen and received honorarium from L'Oreal and has been sponsored by UCB Pharma Ltd for a Dermatology conference. NM is Director of Doctors with ME, Chair of CMRC education working group for ME/CFS research collaborative, Member of Forward ME, witness for NICE education, information and support ME, education working groups ICANCME (Canada) and the ME/CFS Centre for Solutions (USA). RE is a member of the Patient Advisory Group to the CMRC, a member of the ME/CFS Friendship group in Gloucestershire and is both a patient with ME/CFS and a family member of a patient with ME/CFS. RKS has nothing to declare.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Sharing:
The authors agree to share data on reasonable request

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List of Figures

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Figure 6: Regression analysis of FROM-16 and VAS score
Figure 7: Regression analysis of FROM-16 and EQ-5D value

FIGURE LEGENDS

Figure 1: A flow diagram demonstrating the basis for participant inclusion/exclusion from the analysis of the study. Following this protocol, 1418 ME/CFS patients and their corresponding family members were identified for analysis.

Figure 2: The EQ-5D health states of the person with ME/CFS. (A) Patients were asked about the following 5 dimensions, each representing a different aspect of health; Usual activities, pain/discomfort, mobility, self-care and anxiety/depression. Each dimension has 3 levels (1= no problem, 2= some problem, 3= extreme problem), with the patient indicating their health state by identifying the level representative of their individual condition. (B) A graph showing the range of patient answers as they were asked to rate their health on a visual analogue scale (VAS), with 0 representing worst imaginable health state and 100 best imaginable health state. The average VAS score of patients with ME/CFS was 33.7.

Figure 3: The EQ-5D results of ME/CFS patients compared to the UK population norm. (A) The average EQ-5D Value of varying age groups for ME/CFS participants of our study, compared to the UK population. (B) The percentage of ME/CFS participants who reported a problem (level 2 or 3) for each of the EQ-5D dimensions as compared to the UK population norm.

Figure 4: FROM-16 score range for the family members of ME/CFS participants in (A) the emotional domain (max score 12) and (B) the personal/social domain (max score 20), with higher scores indicating greater impact on the family members quality of life.

Figure 5: Total FROM-16 scores for the family members of ME/CFS participants. (A) Family members were asked about different aspects of their lives. Each question had 3 responses (0=not at all, 1= a little, 2= a lot). Responses have been sorted from the most impact on family member lives to the least, in both the emotional and personal domains. (B) The FROM-16 score range of family members, with 0 representing no impact on family member quality of life and 32 the greatest impact of patients ME/CFS on family members quality of life. The average score in this study was 17.93 out of a possible 32.

Figure 6: Correlation of total FROM-16 scores with the VAS health state of patients. (A) Scatter plot illustrating the relationship between total FROM-16 scores and patient EQ-5D VAS. The solid line represents the linear fit of data. Figure shows the P value, R and R^2 (B) Residual plot showing the simple linear regression of FROM-16 scores and EQ-5D VAS, as the points are randomly dispersed.

Figure 7: Correlation of total FROM-16 scores with the EQ-5D Values of patients. (A) Scatter plot illustrating the relationship between total FROM-16 scores and patient EQ-5D values. The solid line represents the linear fit of data. Figure shows the P value, R and R^2 (B) Residual plot showing the simple linear regression of FROM-16 scores and EQ-5D values, as the points are randomly dispersed.

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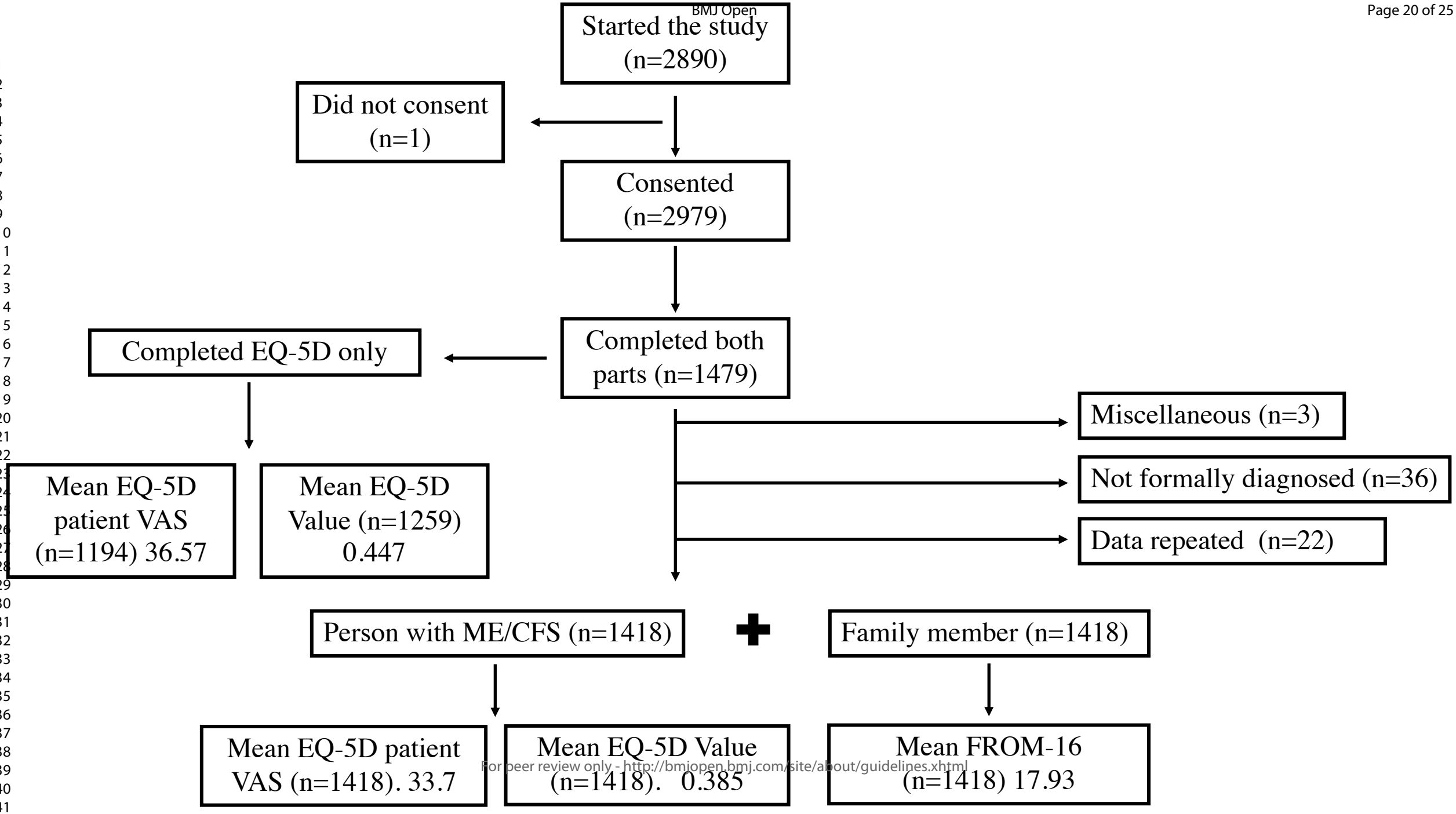

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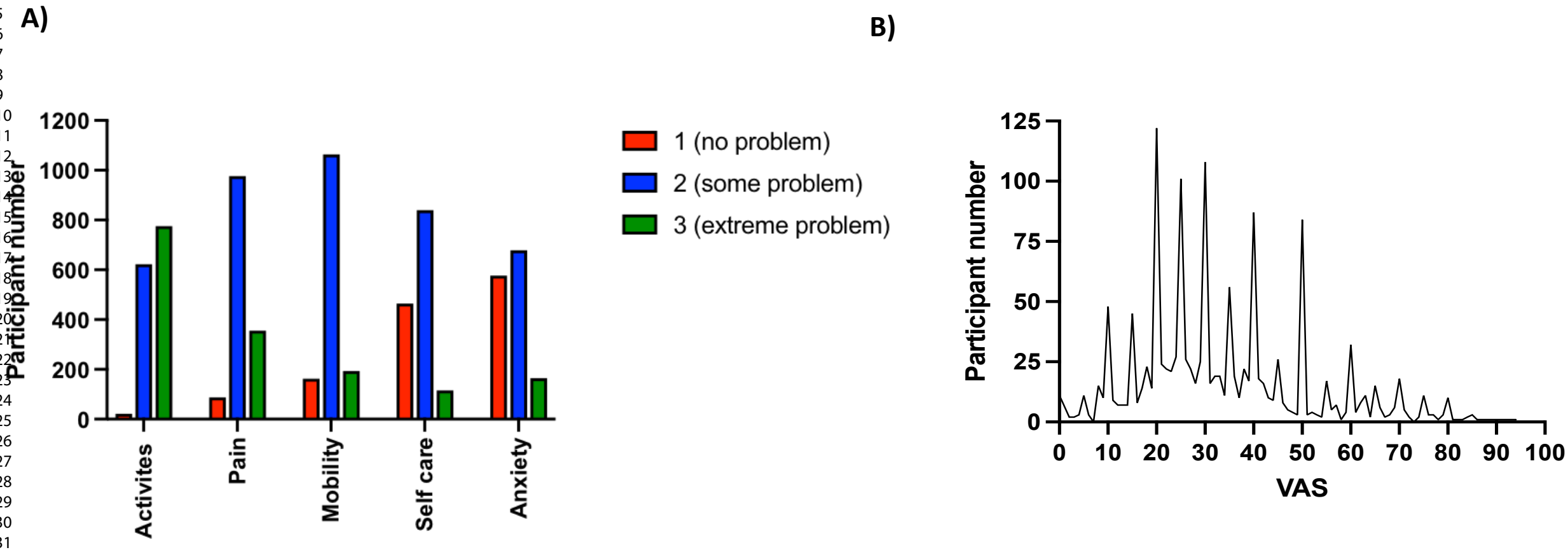
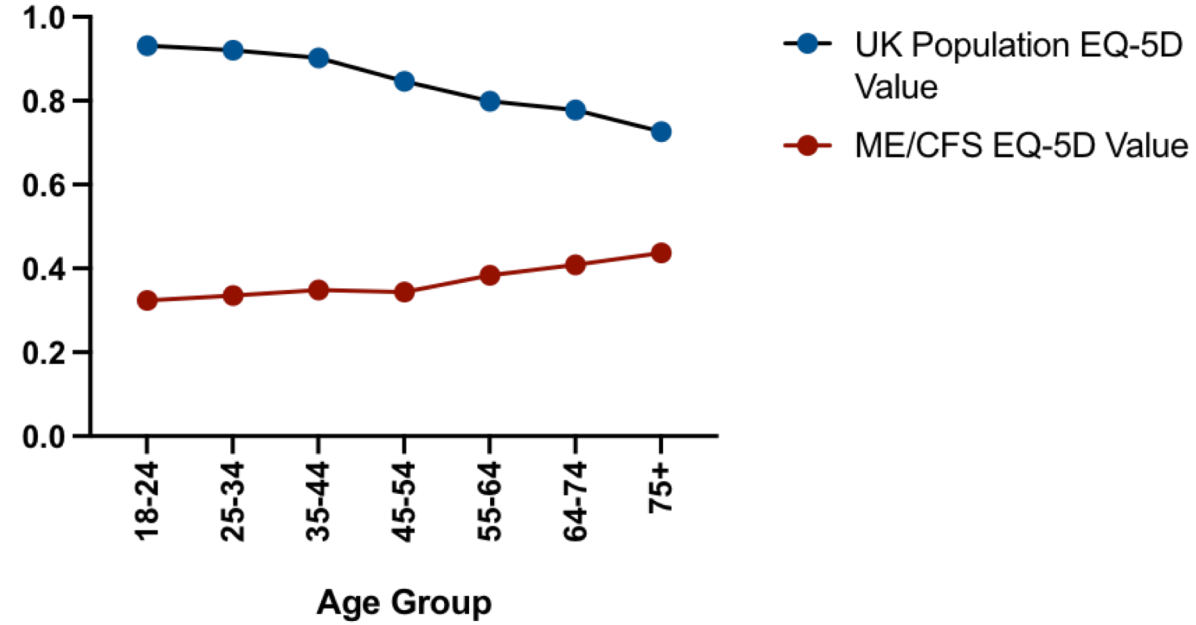
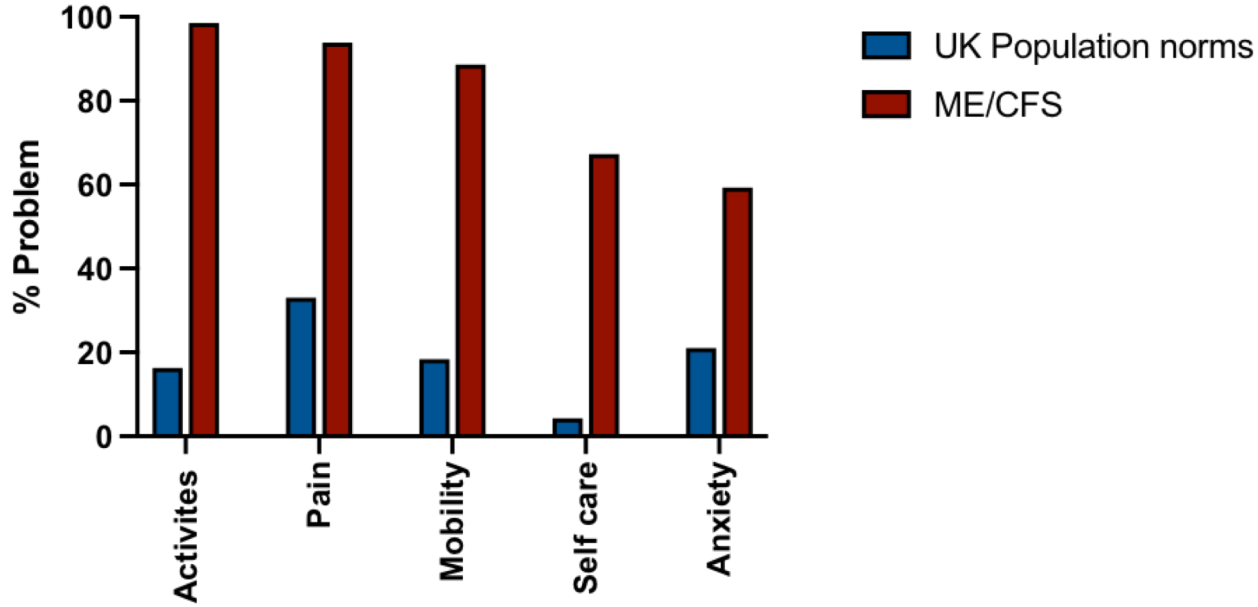

A)
Participant number
1200
1000
800
600
400
200
0
Activites
Pain
Mobility
Self care
Anxiety
1 (no problem)
2 (some problem)
3 (extreme problem)
B)
Participant number
125
100
75
50
25
0
0 10 20 30 40 50 60 70 80 90 100
VAS

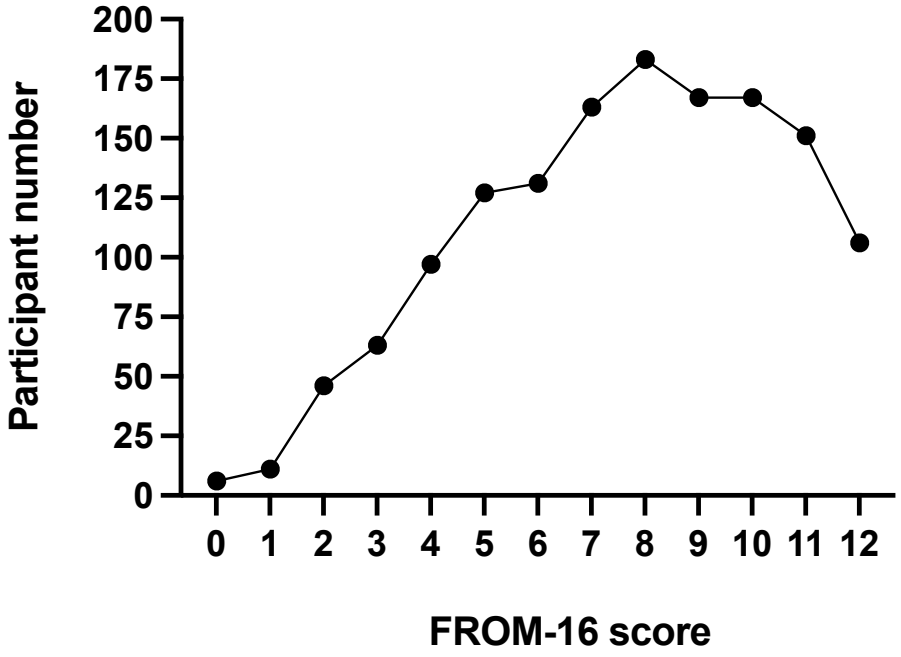
A)


1.0
0.8
0.6
0.4
0.2
0.0
EQ-5D Value
18-24
25-34
35-44
45-54
55-64
64-74
75+
Age Group
UK Population EQ-5D Value
ME/CFS EQ-5D Value

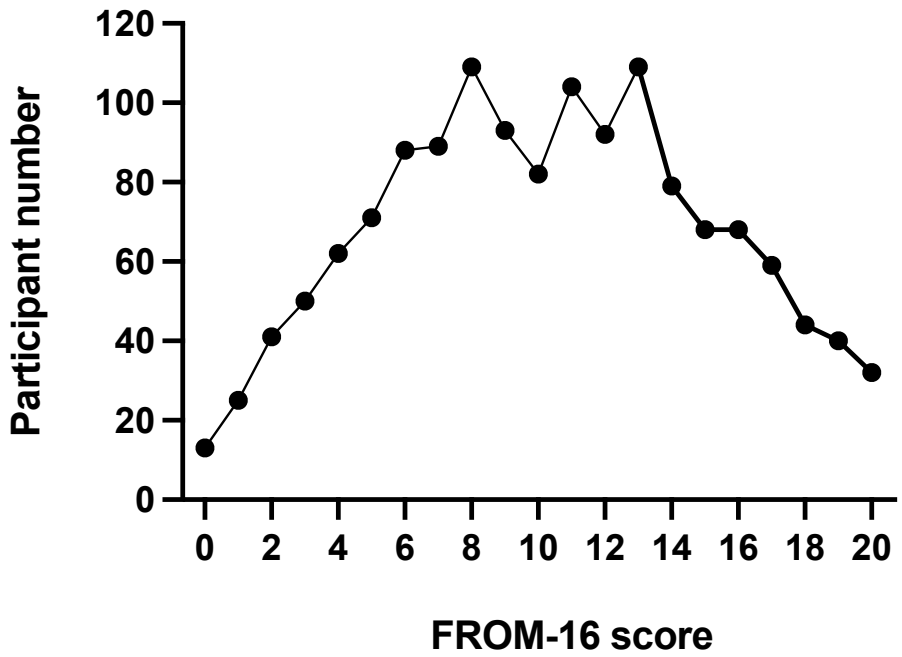
B)


100
80
60
40
20
0
% Problem
Activites
Pain
Mobility
Self care
Anxiety
UK Population norms
ME/CFS

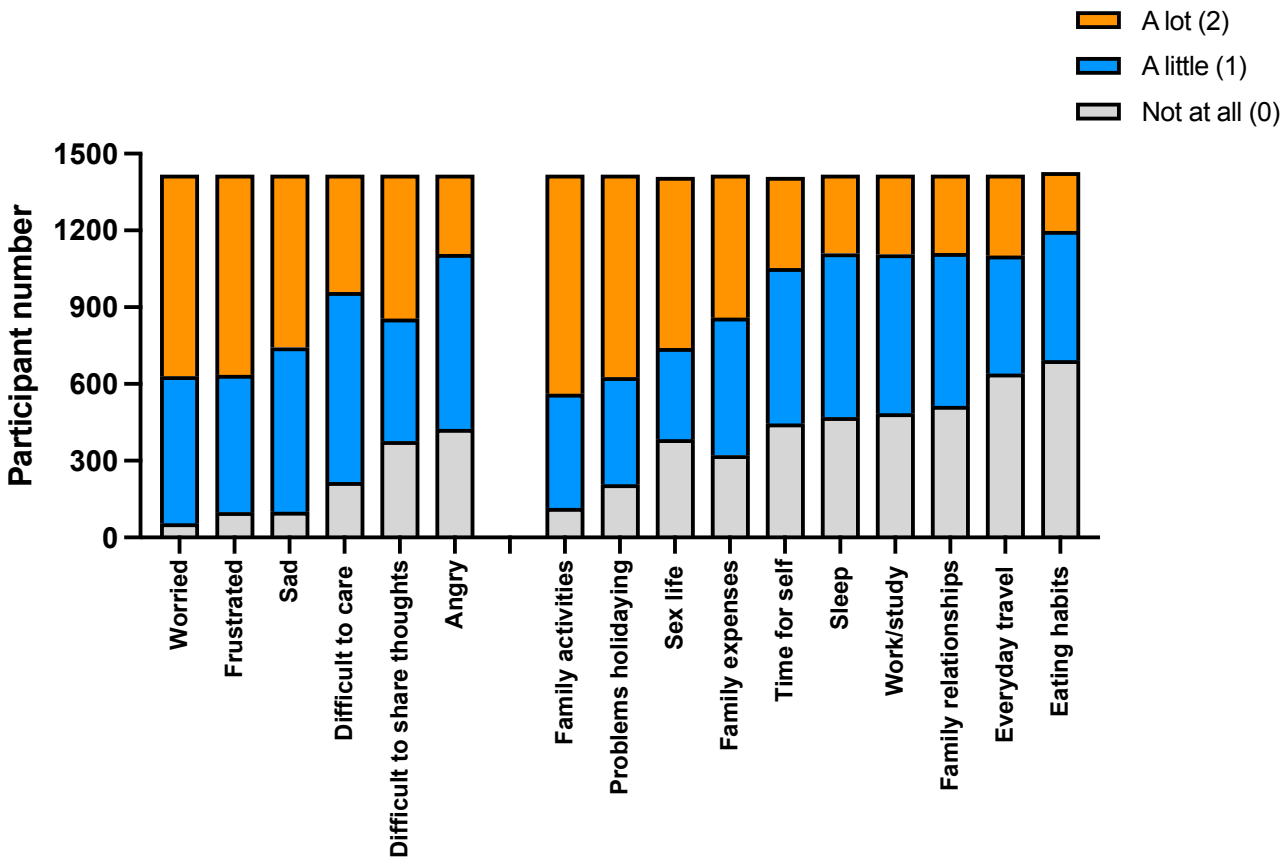
A)


FROM-16 Emotional score
Participant number
200
175
150
125
100
75
50
25
0
0 1 2 3 4 5 6 7 8 9 10 11 12
FROM-16 score

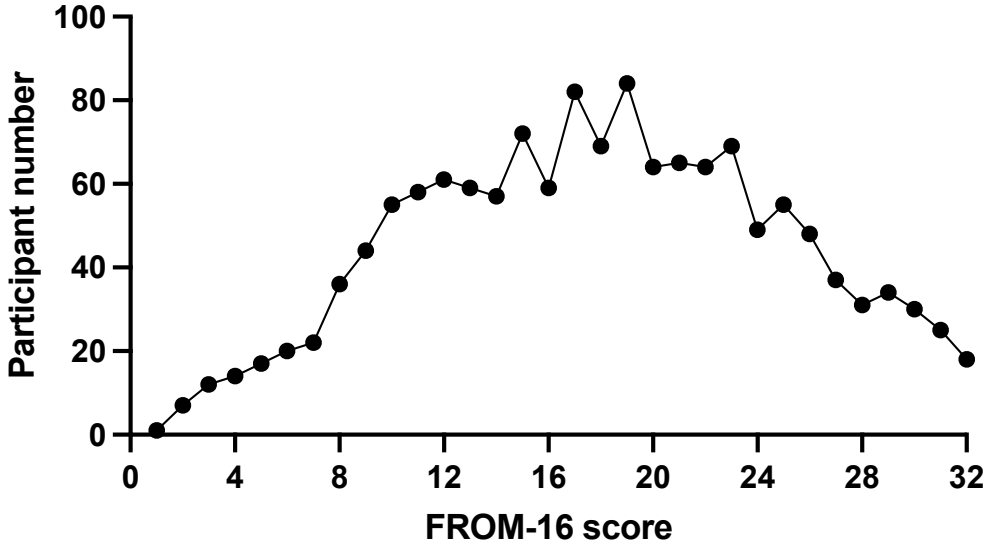
B)

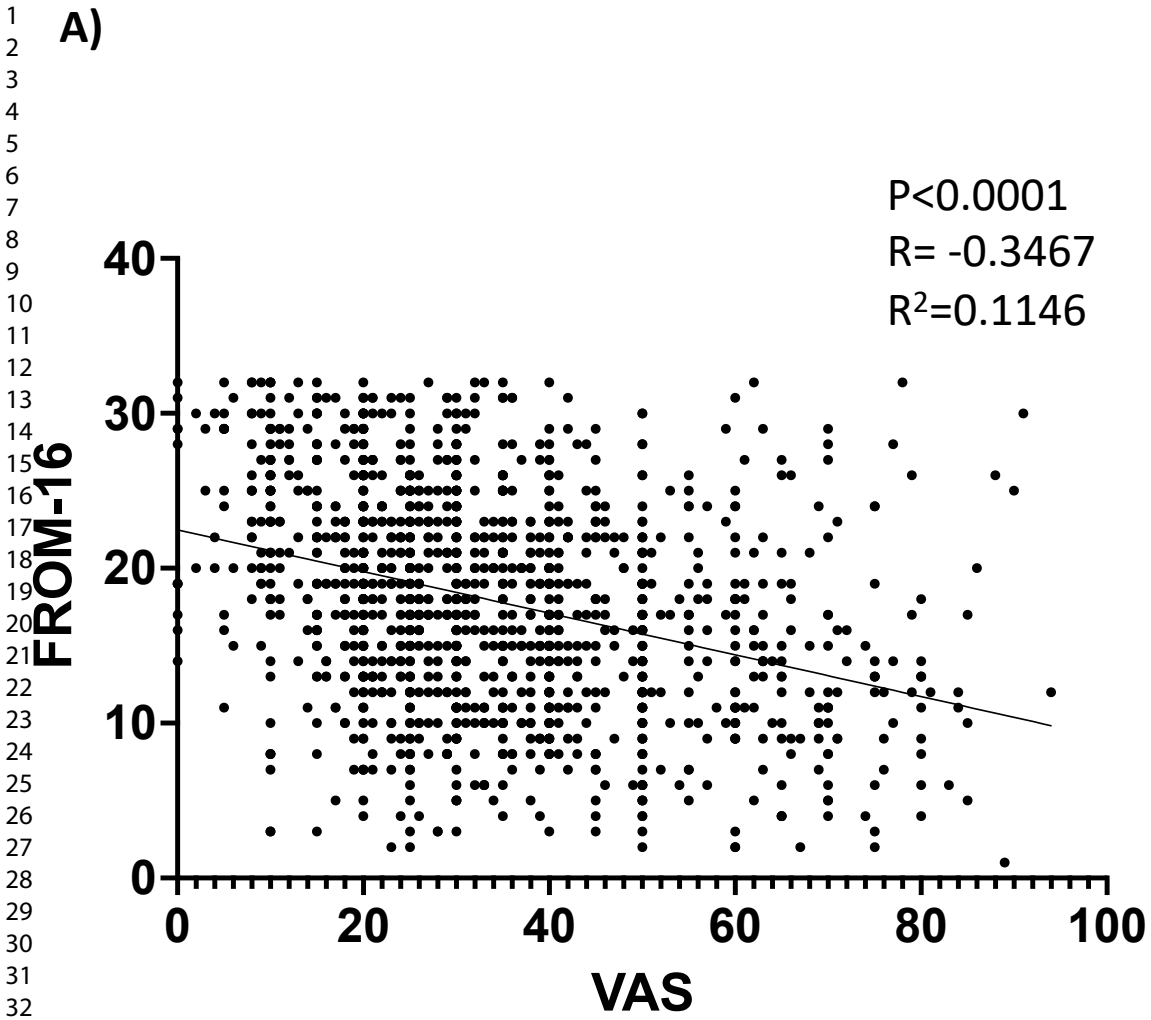

FROM-16 Personal score
Participant number
120
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20
FROM-16 score

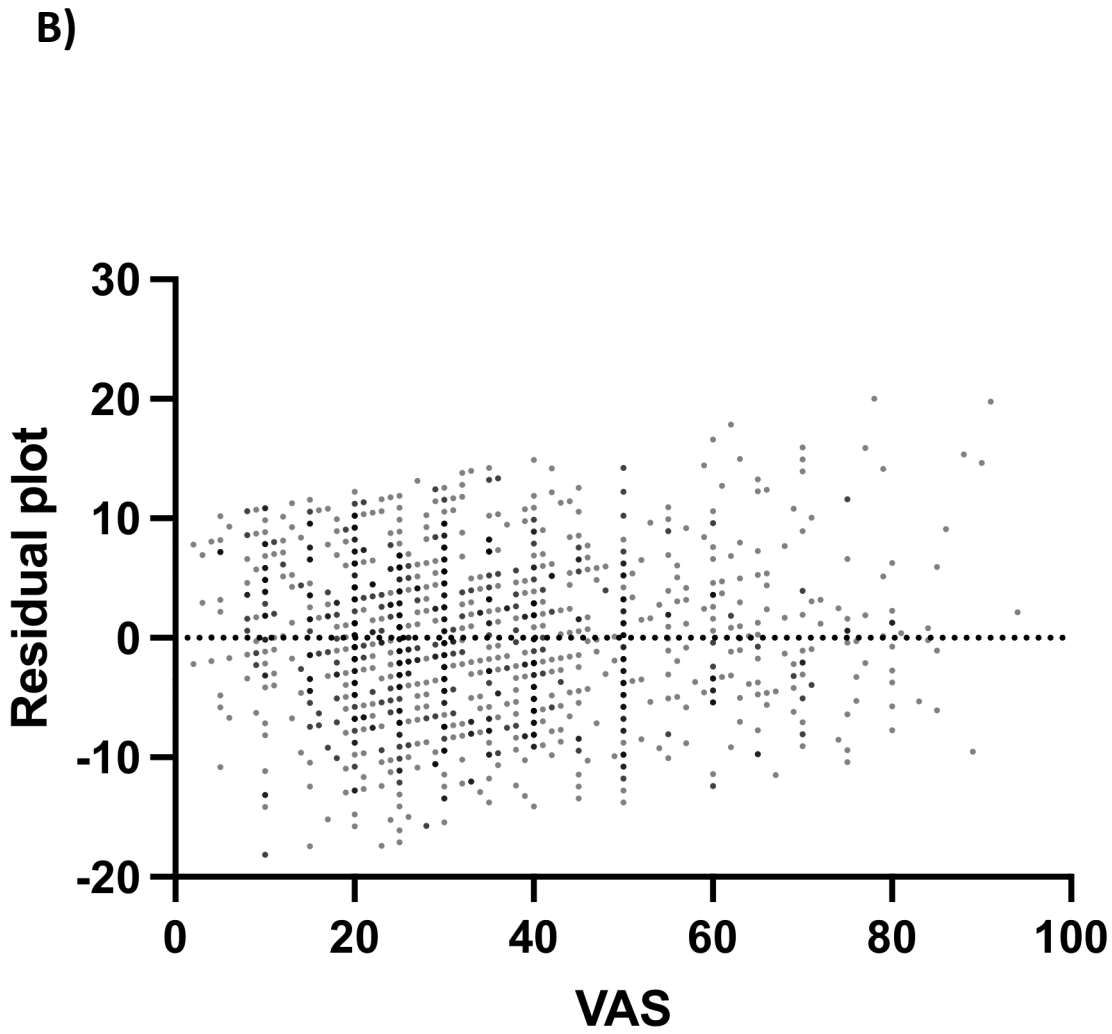
A)


A lot (2)
A little (1)
Not at all (0)
Participant number
1500
1200
900
600
300
0
Worried
Frustrated
Sad
Difficult to care
Difficult to share thoughts
Angry
Family activities
Problems holidaying
Sex life
Family expenses
Time for self
Sleep
Work/study
Family relationships
Everyday travel
Eating habits

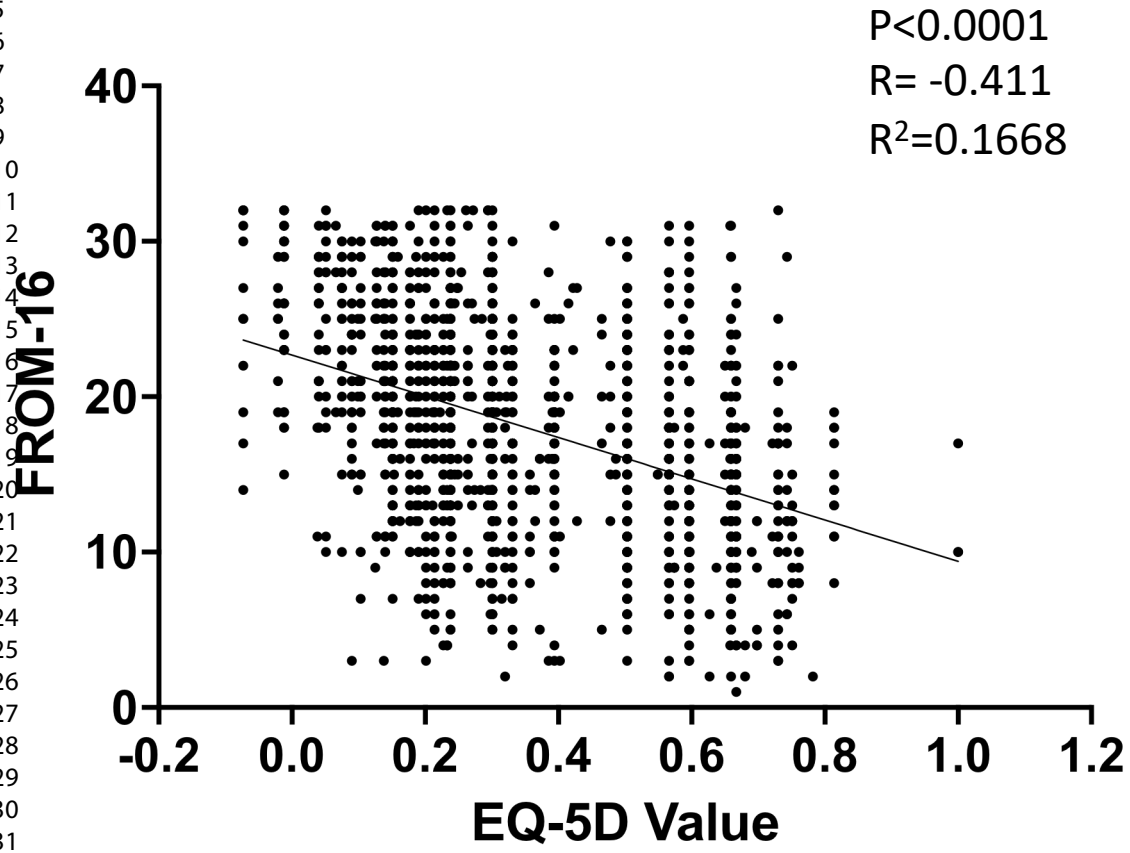
B)


Participant number
100
80
60
40
20
0
0
4
8
12
16
20
24
28
32
FROM-16 score

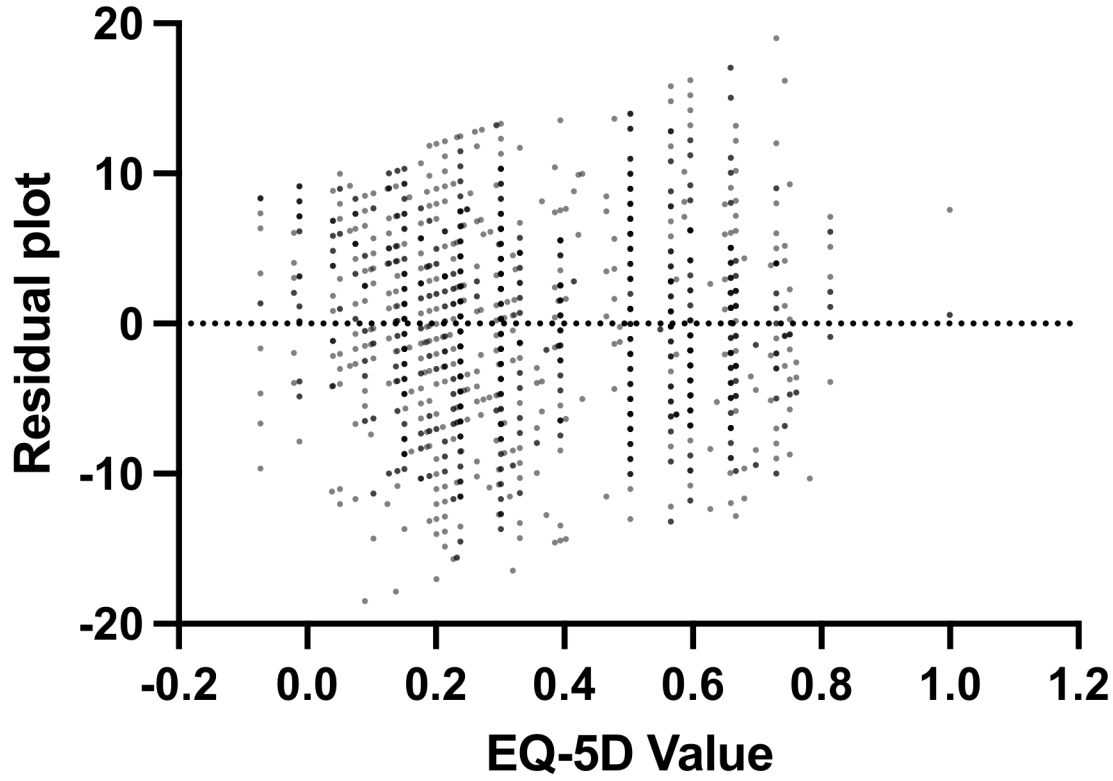

A)
P<0.0001
R= -0.3467
R2=0.1146
FROM-16
VAS
0
10
20
30
40
0
20
40
60
80
100


B)
Residual plot
VAS
-20
-10
0
10
20
30
0
20
40
60
80
100

A)


P<0.0001
R= -0.411
R2=0.1668
FROM-16
EQ-5D Value
40
30
20
10
0
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2

B)


Residual plot
EQ-5D Value
20
10
0
-10
-20
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2

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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

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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

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ABSTRACT

Objectives: The aim of this study was to assess the impact of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on the quality of life (QoL) of people with ME/CFS and their relative or partner (family member).
Design: A patient-partner, multinational, subject-initiated, cross-sectional online survey.
Setting: International survey using ME/CFS charities, support groups and social media
Participants: Participants were self-selected with recruitment via social media. Inclusion criteria were aged 18 years or over and reported diagnosis of ME/CFS by health professional. 1418 people with ME/CFS and their 1418 family members from 30 countries participated in the survey. Participants with ME/CFS had a mean age of 46 years (range 18-81) and were predominantly female (1214 [86%] of 1418). Family members had a mean age of 51.9 years (range 18-87) and were predominantly male (female: 504 [36%] of 1418). 991 (70%) family members were partners of the people with ME/CFS.
Interventions: EuroQoL 5 Dimension (EQ-5D-3L), completed by people with ME/CFS, and Family Reported Outcome Measure (FROM-16) questionnaire, completed by family members.
Results: The mean overall health status on a visual analogue scale for people with ME/CFS was 33.8 (0=worst, 100=best). People with ME/CFS were most affected by ability to perform usual activities, pain, mobility, self-care and least impacted by anxiety. For family members, the overall mean FROM-16 score was 17.9 (0=no impact, 32=worst impact), demonstrating a major impact on QoL. Impact on QoL was significantly correlated between the person with ME/CFS and their family member ($p<0.0001$). Family members were most impacted emotionally by worry, frustration and sadness and personally by family activities, holidays, sex life and finances.
Conclusions: To the best of our knowledge, this is the largest study on the impact of the QoL of persons with ME/CFS and their family members. Whilst open participation surveys are limited by selection bias, this research has revealed a significant worldwide burden of ME/CFS on the QoL of people with ME/CFS and their family members.

Strengths and limitations of this study

- International study with patient and public involvement in the study design.
- Use of validated quality of life questionnaires for persons with ME/CFS and their family members.
- Patients were only included in the data analysis if they reported a healthcare professional diagnosis of ME/CFS.
- However, recruitment was biased towards English-speaking participants
- Open participation can lead to sampling bias, limiting the generalisability of these findings.

INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, debilitating disease, with existing literature demonstrating a negative impact on health-

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related quality of life (QoL) [1], worse than for many other diseases [2]. There is growing international acknowledgement of the impact of ME/CFS on caregivers [3], but there is only a small scale pilot study, using the Family Reported Outcome Measure (FROM-16) which showed that QoL of partners and other family members is greatly impaired, suggesting that ME/CFS impact goes far beyond the affected person [4]. There is therefore very little information about the partner/family impact, a gap in ME/CFS knowledge which this study aims to address.

ME/CFS is characterised by multisystem symptoms exacerbated by mild exertion, pain, sleep disruption, orthostatic intolerance, cognitive dysfunction and severe and disabling fatigue not improved by rest [5]. ME/CFS occurs globally with a prevalence of up to 0.89% [6] though prevalence and impact are underestimated in many countries [7]. Often triggered by a virus, the COVID-19 pandemic may increase ME/CFS prevalence [8] and there needs to be improved international recognition of chronic post viral disease burden on QoL of sufferers and families.

This study's aim was to measure the impact of ME/CFS on the QoL of those affected and expand knowledge by conducting a large-scale international study on the impact on QoL of their partners or family members. In addition we aimed to determine correlation of QoL data between the persons with ME/CFS and their family members.

METHODS

This was a multinational, subject-initiated, cross-sectional survey to assess the impact of ME/CFS on the lives of patients and their partner or family member using the EuroQoL 5 Dimension (EQ-5D-3L)[9] and FROM-16 [10] questionnaires. Ethical permission was granted by Cardiff University School of Medicine ethics committee (11th September 2020 SMREC 20/86).

REDCap, a secure web platform [11 12] was used for the survey, which was distributed via ME/CFS organisations, websites and social media platforms.

Patient and public involvement

The study was co-designed by patients and clinical researchers. Patients with ME/CFS and their family members were involved at all stages of the study design and actively contributed to identifying the research questions and designing the research. Two of the authors, involved have ME/CFS: one is a clinician and the other a patient representative. Patient partners were directly involved in developing the ethics application and disseminating the surveys via patient charities and online. Burden of intervention and time required to participate in the survey was also assessed.

Questionnaires

EQ-5D-3L

This is a generic instrument measuring an individual's health status[9 13]. It has five dimensions (questions) on mobility, usual activities, self-care, pain and discomfort, and

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anxiety and depression. Three dimensions have three possible responses: no problems, some problems, and inability. The responses for the other two dimensions are: no problems, moderate problems and extreme problems. Each response is coded from 1-,3 and combined as a series of five digits describing the 'EQ-5D self-reported health state' or 'EQ-5D profile'[14]. The EQ-5D-3L has 234 possible health states. EQ-5D profiles can be converted to a single number, the 'EQ-5D value', "1" represents full health and "0" dead[15]. Values <0 indicate a health state worse than death. Overall health status is recorded on a visual analogue scale, from 0 (worst imaginable health) to 100 (best imaginable health).

FROM-16

This questionnaire measures current QoL impact on a healthy person of having a partner or family member with a health condition[10]. It can be completed by anyone over the age of 18 years, concerning the impact of the health condition of a patient of any age. There are 16 questions covering the domains "Emotional" (six questions) and "Personal and social life" (ten questions). Each question is scored from 0-2 (0=not at all, 1=a little, 2=a lot), with a score range of 0-32, "0" meaning no impact and "32" meaning greatest possible impact.

Study design

Multiple survey versions were piloted in November 2020, enabling refining wording for clarity, ensuring ease of use and to identify and resolve technical issues. Feedback confirmed that the questionnaires were easy to answer and most persons with ME/CFS completed the EQ-5D questionnaire within five minutes. The preferred order of questionnaires was identified, with the questionnaire for the person with ME/CFS presented first followed by the family member/partner questionnaire, with the option to return later. Following participant comments, a few minor changes were made, for instance to obviate any confusion resulting from having more than one family member with ME/CFS.

The participant eligibility criteria were being a person with ME/CFS aged 18 or over. Participating family members also had to be aged 18 years or over. Data was only analysed if the person with ME/CFS confirmed diagnosis with a health care professional. Informed consent was obtained via a tick box question for the participant with ME/CFS. Participants completed basic demographic questions including if they had a diagnosis of ME/CFS from a healthcare professional. To ascertain how many met ME/CFS criteria, participants were asked to select their symptoms from a tick box list adapted from the systemic exertion intolerance disease (SEID) US Institute of Medicine criteria for ME/CFS[16], a clinical diagnostic tool comprising five ME/CFS symptoms. The criteria include technical language, hence a plain English version was devised specifically for this study. ME/CFS is diagnosed if all the first three symptoms and at least one of the last two are present.

Participants answered the EQ-5D-3L and then chose either their partner or another family member to complete the survey second part. The family member/partner could participate in the study immediately, or was invited via email link by the person with ME/CFS. Similar to the person with ME/CFS, a link to the participant information was provided and consent was given via a tick box question. Family members/partners then completed basic demographic data questions and the FROM-16. The recruitment time window was the only limit to the number of participants.

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Statistical analysis

Only data from participants with ME/CFS who reported a formal diagnosis by a health care professional (HCP) and their family members were included in the final analysis. Duplicate entries were identified by email address and matching demographics: only the second was analysed. Microsoft Excel, SPSS and GraphPad Prism v9 were used for data handling and statistical analysis, involving descriptive statistics and non-parametric statistical tests including Spearman rank correlation coefficient.

RESULTS

The survey was carried out from 1 December 2020 to 31 March 2021. It was started 2980 times. One participant withdrew consent; therefore, 2979 records were generated. 2668 participants completed the first part of the survey, including the EQ-5D-3L. 1479 family members/partners completed the second part of the survey. Only the 1479 records that were fully completed by both patient and family members/partners were analysed further. 25 records were excluded either because they were duplicates (n=22) or for other reasons (n=3). From the remaining 1454 records a further 36 were excluded for not having a formal diagnosis of ME/CFS from a health care professional. The final analysis included 1418 survey responses representing 2836 participants (persons with ME/CFS and their family member/partner) (Figure 1).

Demographic profile of participants

Table 1 shows the participant demographics. Persons with ME/CFS and their family members worldwide participated in the study however most responses came from the UK (58.8%) and other English-speaking countries, including the USA (11.2%), Canada (5%) and Australia (5.8%) (Table 2). The average time since diagnosis of ME/CFS was 13.9 years, (median 11) with 15 patients diagnosed for 1 year and 8 for >50 years.

Table 1: **Participant demographic characteristics**

	Person with ME/CFS	Family member
Number	1418	1418
Time since diagnosis	13.9 years	n/a
Mean Age	45.8 (18-81)	51.9 (18-87)
Female	1214 (85.6%)	504 (35.5%)
Male	196 (13.8%)	902 (63.6%)

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Other	8 (<1%)	12 (<1%)
Separate household		149 (10.5%)
Lives alone	158 (11.1%)	
Relationship of person with ME/CFS to family member		
Partner/Spouse		991 (69.9%)
Parent		76 (5.4%)
Sibling		288 (20.3%)
Child		28 (1.9%)
Other		35 (2.5%)
>1 Family member has ME/CFS		160 (11%)
Family member has ME/CFS		49 (3%)

Table 2: Countries of residence (participants with ME/CFS)

Patient country	Number
United Kingdom	834
United States of America	159
Australia	82
Canada	71
Norway	40
Germany	34
Netherlands	32
Sweden	31

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Ireland	24
New Zealand	24
Belgium	14
Italy	10
Spain	10
Japan	9
Denmark	8
France	6
South Africa	6
Finland	5
Switzerland	5
Austria	3
Portugal	2
China	1
Croatia	1
Czech Republic	1
Ghana	1
Iceland	1
Poland	1
Senegal	1
Trinidad and Tobago	1
Uruguay	1

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Reflecting the female preponderance for ME/CFS, far more females responded (85.6%) than male, eight did not answer this question. Only 11.1% (n=158) of participants with ME/CFS lived alone. Those that lived with others mainly shared with a life partner or family member, with only 14 people stating they lived with people outside that description. Most family members who participated lived with the person with ME/CFS, with only 149 living in a separate household and one unknown.

160 family members reported having more than one family member with ME/CFS and 49 family members were themselves ME/CFS sufferers. Two persons failed to answer this question.

All persons with ME/CFS completed five questions based on SEID criteria (Table 3). Most respondents, already diagnosed by a HCP, also met these diagnostic criteria. However, 93 respondents lacked the symptoms for the SEID ME/CFS diagnosis criteria but stated they had a medical diagnosis, and therefore were included in the analysis. 80 participants did not have one or more of the three required symptoms for diagnosis, including less able to do normal things (n=14), symptoms worse after physical, mental or emotional activity (n=12), sleep unrefreshing or disturbed (n=54). 12 stated they did not have two of the three criteria, with one stating they experienced none of the five criteria. Of the 36 (2.5%) people without an ME/CFS medical diagnosis not included in the data analysis, most reported ME/CFS diagnosis criteria symptoms. 604 (42.6%) of the ME/CFS participants reported having another chronic health condition.

Table 3: Participants with ME/CFS and the SEID criteria

Symptom	Yes	No
Less able to do normal things	1404 (99%)	14 (1%)
Worse after physical, mental or emotional activity	1406 (99%)	12 (1%)
Sleep unrefreshing/disturbed	1364 (96.2%)	54 (3.8%)
Brain fog	1382 (97.5%)	36 (2.5%)
Worse symptoms/dizziness when upright	1103 (77.8%)	315 (22.2%)

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EQ-5D health profile of persons with ME/CFS

Figure 2 gives the EQ-5D results. Strikingly 98.5% (n=1397) of participants had problems performing their usual activities. Over half (n=775) were unable to perform their usual activities at all. Pain was the next most affected dimension with 93.9% (n=1331) experiencing some (n=976) and extreme (n=355) pain and discomfort. Mobility was affected in 88.6% (n=1256), with participants experiencing some problems (n=1063) with walking or confined to bed (n=193). In terms of self-care, 67.3% (n=954) had some problems or were unable to wash or dress themselves. Anxiety and depression was the least affected dimension, as 40.6% (n=576) participants reported they were not anxious or depressed at all, whilst 59.4% were either moderately (n=678) or extremely (n=164) anxious or depressed. The average EQ-5D VAS score of ME/CFS patients was 33.7, (SD 17.5, median 47.5, range 0-94) (Figure 2b).

Of the possible 234 EQ-5D-3L profiles, participants with ME/CFS expressed 94 unique profiles. Only three participants had a profile 11111, indicating no problems in any dimension. Similarly, 12 participants had a profile 33333 indicating extreme problems in all dimensions. Ten profiles accounted for 56.5% of EQ-5D-3L profiles (Table 4). The profile 22321 was the most frequent (n=128) indicating some problems with mobility and self-care, inability to perform usual activities, moderate pain/discomfort and no anxiety/depression. 22222 and 22322 were found in equal measure (n=117) the only difference is that 22222 means moderate problems in all dimensions whereas 22322 indicates moderate problems in all dimensions and inability to perform usual activities.

Table 4: The 10 most frequent EQ-5D health states of ME/CFS participants, sorted according to EQ-5D value severity

	EQ-5D state	EQ-5D Value	Frequency	% Frequency
Least Severe	21221	0.659	72	5.07
	21222	0.596	86	6.06
	22221	0.566	70	4.93
	22222	0.503	117	8.25
	21321	0.394	55	3.87
	21322	0.331	42	2.96
	22321	0.301	128	9.02
	22322	0.238	117	8.25

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	22331	0.214	43	3.03
Most Severe	22332	0.151	77	5.43

The EQ-5D-3L profile can be converted into a single summary number or EQ-5D value allowing for comparison with the general population. Our results demonstrate strikingly lower EQ-5D values in each age group for persons with ME/CFS compared to the general UK population[17]. Similarly, persons with ME/CFS reported much higher percentages of 'problems' in each of the EQ-5D dimensions compared to the UK population norm (Figure 3).

Quality of life of family members/partners of participants with ME/CFS

The FROM-16 examined the effects of a person's ME/CFS on their family member's emotions and personal/social life. Family members, on average, scored 7.62 (SD=2.81, median=8, max=12,) in the emotional domain and 10.31 (SD=4.9, median=10, max=20) in the personal and social life domain (Figure 4). The average overall FROM-16 score (Figure 5) was 17.93 out of a total of 32 (SD=6.95, median=18) demonstrating a major impact of ME/CFS on family members.

ME/CFS had a significant impact on family member's emotions. Of the 1418 respondents, 96.1% (n=1362) felt worried due to their family member's ME/CFS, making it the most affected emotion. Frustration and sadness with their family member's ME/CFS were also highly prevalent with 93% (n=1369) experiencing frustration and 92.9% (n=1317) experiencing sadness. 84.7% (n=1201) found caring for their family members difficult, 73.4% (n=1041) found it difficult to talk to someone about their thoughts and 70% (n=994) of respondents were a little or a lot angry because of their family member's ME/CFS.

In the personal and social domain, the greatest impact was in the area of family activities with 92% (n=1302) respondents reporting family activities affected. Similarly, 85.3% (n= 1210) experienced problems with holidays. 72.2% (n=1025) stated their sex life was affected and 77.3% (n=1096) felt their finances were impacted in that their family expenses increased. 68.6% (n=973) of respondents found it hard to find time for themselves. Sleep, work or study, and family relationships were almost equally affected with 66.9% (n=948) reporting a negative impact on their sleep, 65.7% (n=932) a negative impact on their work or study and 63.8% (n=904) found their family relationships with other family members were affected due to their family member's ME/CFS. Everyday travel and eating habits of family members were the least affected of all the areas, with 54.8% (n=777) indicating a problem with everyday travel and 51.8% (n=735) reporting an effect on their eating habits.

In order to determine the relationship between the person with ME/CFS and their family members quality of life, we used Spearmans Rank Correlation as the data was not normally distributed. We found a significant negative correlation between the total FROM-16 score of

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family members and the patients VAS score (P<0.0001, R=-0.3467) (Figure 6). Furthermore, a similar moderate but significant negative correlation was calculated using the total FROM-16 score and the EQ-5D value of patients (P<0.0001, R=-0.411,) (Figure 6), supporting the fact that family member quality of life is significantly impacted by a family member's ME/CFS.

The inherent biases in the method of recruitment to this study make it difficult to draw any meaningful comparison between FROM-16 scores from different countries or regions of the world. However, when examined, the mean FROM-16 score from UK was 17.79 (SD=6.99, median=18 , n=834), Europe 18 (SD=6.99, median=18, n=228), North America 18.38 (SD=6.92, median=18.5, n=230) and Rest of World 17.96 (SD=6.68, median=18, n=126). The mean EQ5D value from the different regions were also similar with the UK mean of 0.359 (SD=0.218, median= 0.301), Europe mean 0.351 (SD= 0.205, median=0.267), North America mean 0.341 (SD= 0.201, median=0.264) and Rest of World mean EQ-5D value 0.389 (SD=0.217, median=0.264).

DISCUSSION

To the best of our knowledge this is the largest study on the impact on the QoL of persons with ME/CFS and their family members. Our study confirmed that ME/CFS has a considerable negative impact on QoL. The most common EQ-5D-3L profiles demonstrated that people with ME/CFS experience problems across all domains with similar severity: the problems are not confined or localised to one aspect. None of the ten most frequent profiles in our survey reported a level 3 "a lot" for anxiety. The average EQ VAS score in our study was 33.8 (SD=17.5, median=47.5). The higher the EQ VAS, the better the QoL. The mean EQ VAS for the representative UK population is 82.75. Our data demonstrate that the QoL of family members of persons with ME/CFS is more impaired than in other conditions[18] [19]. In our study, in the Emotional domain of FROM-16, worry was the most frequently impacted item (96.1%, n=1362), frustration was experienced by 93% (n=1319) and sadness by 92.9% (n=1317).

The study strengths include the patient co-design, with patient involvement at the heart of the research team, wide international dissemination of the survey and the very large numbers of participants. There has been controversy over diagnostic criteria for ME/CFS. Participants with ME/CFS were only included in the data analysis if they reported a healthcare professional diagnosis of ME/CFS. Of these participants, 93.4% also fulfilled the SEID criteria for ME/CFS diagnosis. The four required symptoms of the 2021 ME/CFS NICE guideline criteria[20] are similar to the three required symptoms, and the first of the two additional symptoms, of the SEID diagnostic criteria. This diagnostic confirmation is a major study strength; however, a limitation of the study was that it was not possible to independently verify that a health care professional diagnosis of ME/CFS had been made. Other limitations include open participation recruitment bias towards English speaking self-selected people active on social media. This may not be representative of the overall ME/CFS population. Those more severely affected may not have responded because of ME/CFS's debilitating physical effects. Conversely, they may have been more motivated to take part. Online delivery precluded checking whether assistance was given completing

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forms or whether the family member or patient allowed others to see their responses. Lack of anonymity within the family may have influenced some responses. Data on ethnic background was not collected.

In contrast to the high level of QoL impact revealed in our study, the EQ-5D-3L profiles from a survey in England[17 21] reported that 56.2% of the general public have an EQ-5D profile of 11111, indicating no problems in any dimension. An EQ-5D profile can be converted into an EQ-5D value, with a value of 1 indicating the best possible health. The mean EQ-5D value for persons with ME/CFS in our study was 0.36 (SD=0.21). In comparison, the mean EQ-5D value for the UK representative sample is 0.86 (SD=0.23)[22]. Myers et al[23] in their ME/CFS study reported a mean EQ-5D value of 0.56 (SD=0.35), representing a QoL impact between the UK representative sample and our ME/CFS participants. Hvidberg et al[2] reported an EQ-5D mean value of 0.47 in Danish ME/CFS patients, much lower than the representative Danish population mean of 0.85. Their study demonstrated that the EQ-5D value for ME/CFS was the lowest of 20 chronic conditions. Nacul et al[24], using the SF-36 in a UK population also demonstrated that the QoL of people with ME/CFS was lower than 10 other chronic conditions. Our findings of greatly impaired QoL are consistent with these studies.
The EQ VAS score in our study was in contrast with a higher VAS score of 54.3 (SD=23.3) in the Meyers study[23]. This discrepancy may be explained by the higher proportion of patients from the UK in our study. Brenna et al[25] conducted a survey of persons with ME/CFS in Italy, Latvia and the UK. Latvian respondents (n=74) reported the least impaired QoL (VAS mean=57.3, SD=16.3), Italian respondents (n=84) had a mean VAS score of 34.6 (SD=20.8) and the UK respondents (n=440) had a mean score of 31.5 (SD=19.8). A Swedish study by Jonsjo et al[26] involving 106 patients with ME/CFS reported a mean EQ-5D value of 0.3 (SD=0.33) and a mean VAS score of 29.8 SD=15.7).

Most previous studies on the impact on family members of persons with ME/CFS have focused on children with ME/CFS[27-29] making comparisons difficult, however in a pilot study, Brittain et al[4] compared the impact of ME/CFS on UK patients and on family members, using WHOQoL-BRef and FROM-16. That study demonstrated that poor QoL of the person with ME/CFS is associated with a high impact on the QoL of family members. There was no significant difference (p = 0.07) between the mean family impact for the Brittain study (mean FROM-16 score = 19.9, n=42) compared with our current international study (mean score = 17.9, n=1418). Chantarasap et al[18] assessed the impact on the QoL of family members of 248 patients diagnosed with various different cancers including hematologic malignancies. The mean FROM-16 score was 11.75 (significantly lower than in our study P<0.0001) with the mean scores in the Emotional domain =4.1, and Personal and social life domain=7.1. The mean FROM-16 scores in our study indicate that family members of patients with ME/CFS have a much lower QoL. In a recent cross-sectional international study[19] measuring the impact of COVID-19 on survivors and their partners or family members, the mean FROM-16 score at 15 (n=735) was also high, but significantly less impacted than in our study (p<0.0001). The mean symptom duration for post covid symptoms was 12.8 weeks, but it is clear that a subset of long COVID patients matching ME/CFS diagnostic criteria is now emerging and a repeat study of those who remain symptomatic after a year would be interesting.

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The median EQ-5D values and FROM-16 scores from the UK, Europe, North America and the Rest of the World are very similar, emphasising the uniform impact experienced by family members across the world. However, it is not possible to be certain of the generalisability of the data due to the recruitment selection bias.

ME/CFS needs to be acknowledged as a serious disease, causing significant impact on health and quality of life, not only of the individual but also of their family. Education for healthcare practitioners must be updated to reflect this. It would be possible to screen for these impacts using EQ-5D or FROM-16 in routine clinics. The medical encounter can be vastly improved by acknowledging the impact on family members and providing practical advice and support to both people with ME/CFS and their family members.

Unanswered questions and future research

Not all people with ME/CFS have a family member or partner to complete the FROM-16. Several individuals wrote to the research team explaining their isolation, difficulty maintaining family relationships and/or lack of empathy of family members. Further research is needed to understand the wider impact of ME/CFS on families and on individuals.

FROM-16 score meaning descriptors have not yet been developed, therefore a logical arbitrary assumption has been made of the scale of severity as expressed by the FROM-16 scores. Our large dataset may allow further work towards categorising family impact scores and increasing the international validity of FROM-16. A study of this scale provides direction for future qualitative and focus group research to identify why certain aspects of family QoL are impacted more than others and to identify and develop supportive interventions to make the greatest impact. FROM-16 could be used as an outcome measure to assess such novel interventions.

CONCLUSIONS

Despite the limitations of selection bias in open participation surveys, this research has revealed the significant worldwide burden of ME/CFS on the QoL of people with ME/CFS and on their family members' QoL. Recognising this impact has the potential to lead to improvements in the standard of care and compassion we offer to our ME/CFS patients and families.

Contributors
JV: conception of study, study design, data analysis, writing, reviewing and final approval of manuscript. NM: study design, data analysis, writing, reviewing and final approval of manuscript. RKS: data analysis, writing, reviewing and final approval of manuscript. RE: study design, writing, reviewing and final approval of manuscript. AYF: study design, writing, reviewing and final approval of manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests

AYF is joint copyright owner of FROM-16 a family member is deputy chair of the NICE ME/CFS guideline committee. JV has been on an Advisory board for Amgen and received honorarium from L'Oreal and support for conference attendance from UCB pharma . NM is Chair of the CMRC education working group for ME/CFS Research Collaborative, member of Forward ME, director of Doctors with ME, witness for NICE education, member of ME education working groups ICANCME (Canada) and the Centre for Solutions (USA), a workshop participant in the James Lind Alliance ME/CFS Priority Setting Partnership and a supporter of Action for ME. NM has received consultancy fees from Learn about ME Project and Ono Pharmaceuticals as well as honorarium from GW4 ME/CFS Carers Project. RE is a member of the Patient Advisory Group to the CMRC, a member of the ME/CFS Friendship group in Gloucestershire, a workshop participant in the James Lind Alliance ME/CFS Priority Setting Partnership, a supporter of Action for ME and is both a patient with ME/CFS and a family member of a patient with ME/CFS. RKS has nothing to declare.

Data availability statement

The authors agree to share data on reasonable request.

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29. Rangel L, Garralda ME, Jeffs J, et al. Family health and characteristics in chronic fatigue syndrome, juvenile rheumatoid arthritis, and emotional disorders of childhood. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005;44(2):150-58.

FIGURE LEGENDS

Figure 1: Participant numbers
Flow diagram demonstrating the basis for participant inclusion/exclusion from the analysis of the study. Following this protocol, 1418 ME/CFS patients and their corresponding family members were identified for analysis.

Figure 2: EQ-5D health profile

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The EQ-5D health states of the person with ME/CFS. (A) Patients were asked about the following 5 dimensions, each representing a different aspect of health; Usual activities, pain/discomfort, mobility, self-care and anxiety/depression. Each dimension has 3 levels (1= no problem, 2= some problem, 3= extreme problem), with the patient indicating their health state by identifying the level representative of their individual condition. (B) A graph showing the range of patient answers as they were asked to rate their health on a visual analogue scale (VAS), with 0 representing worst imaginable health state and 100 best imaginable health state. The average VAS score of patients with ME/CFS was 33.7.

Figure 3: EQ-5D value of ME/CFS vs population norm
The EQ-5D results of ME/CFS patients compared to the UK population norm. (A) The average EQ-5D Value of varying age groups for ME/CFS participants of our study, compared to the UK population. (B) The percentage of ME/CFS participants who reported a problem (level 2 or 3) for each of the EQ-5D dimensions as compared to the UK population norm.

Figure 4: Emotional and Personal and Social domain FROM-16 score
FROM-16 score range for the family members of ME/CFS participants in (A) the emotional domain (max score 12) and (B) the personal/social domain (max score 20), with higher scores indicating greater impact on the family members quality of life.

Figure 5: Overall FROM-16 score
Total FROM-16 scores for the family members of ME/CFS participants. (A) Family members were asked about different aspects of their lives. Each question had 3 responses (0=not at all, 1= a little, 2= a lot). Responses have been sorted from the most impact on family member lives to the least, in both the emotional and personal domains. (B) The FROM-16 score range of family members, with 0 representing no impact on family member quality of life and 32 the greatest impact of patients ME/CFS on family members quality of life. The average score in this study was 17.93 out of a possible 32.

Figure 6: Correlation of FROM-16 scores with VAS and EQ-5D values
Correlation of total FROM-16 scores with (A) VAS health state of patients and (B) the EQ-5D Values of patients. (A) Scatter plot illustrating the relationship between total FROM-16 scores and patient EQ-5D VAS. (B) Scatter plot illustrating the relationship between total FROM-16 scores with the EQ-5D Values of patients. The solid lines represent the linear fit of data. Figures shows the P value and R value as analysed by Spearman's Rank correlation test.

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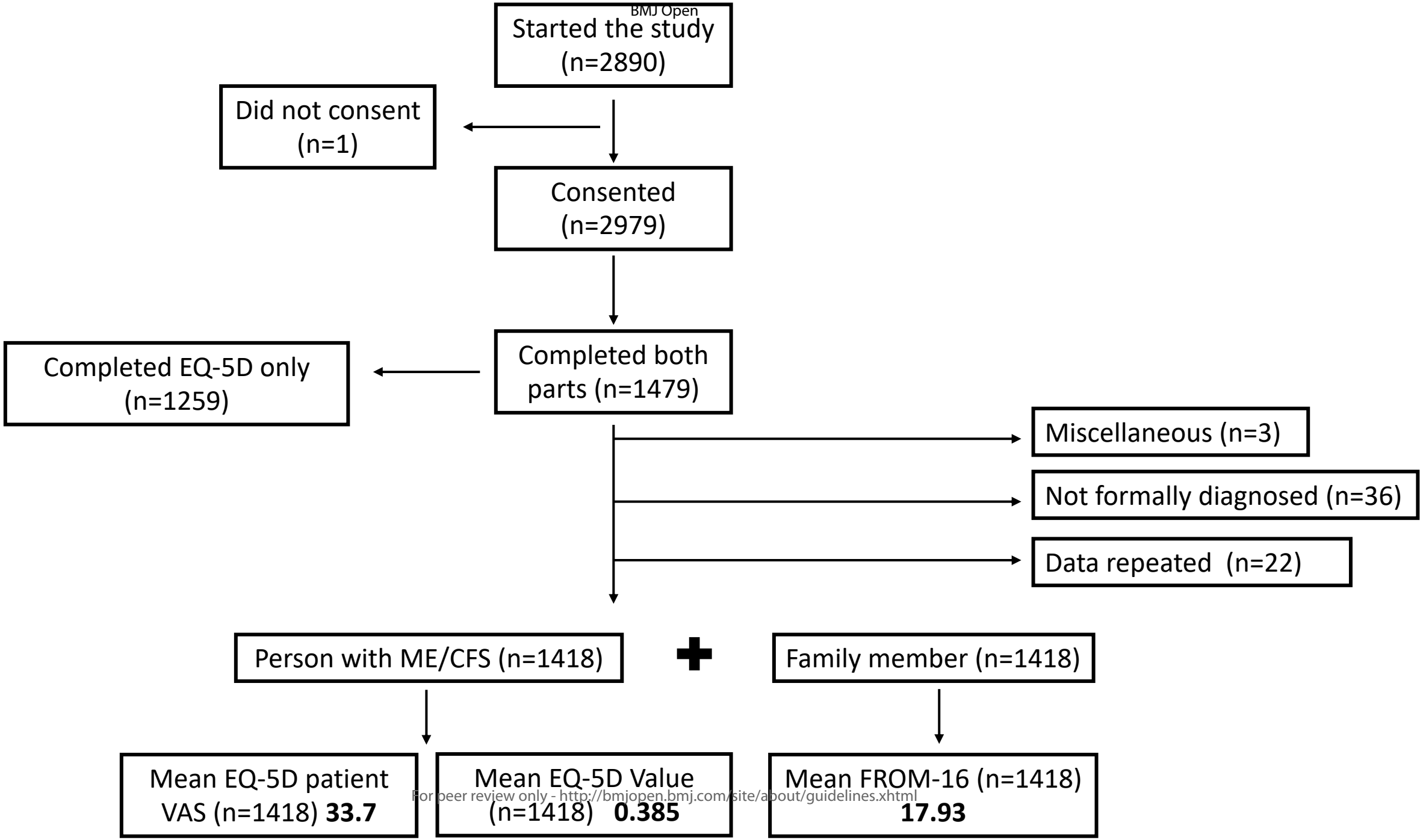

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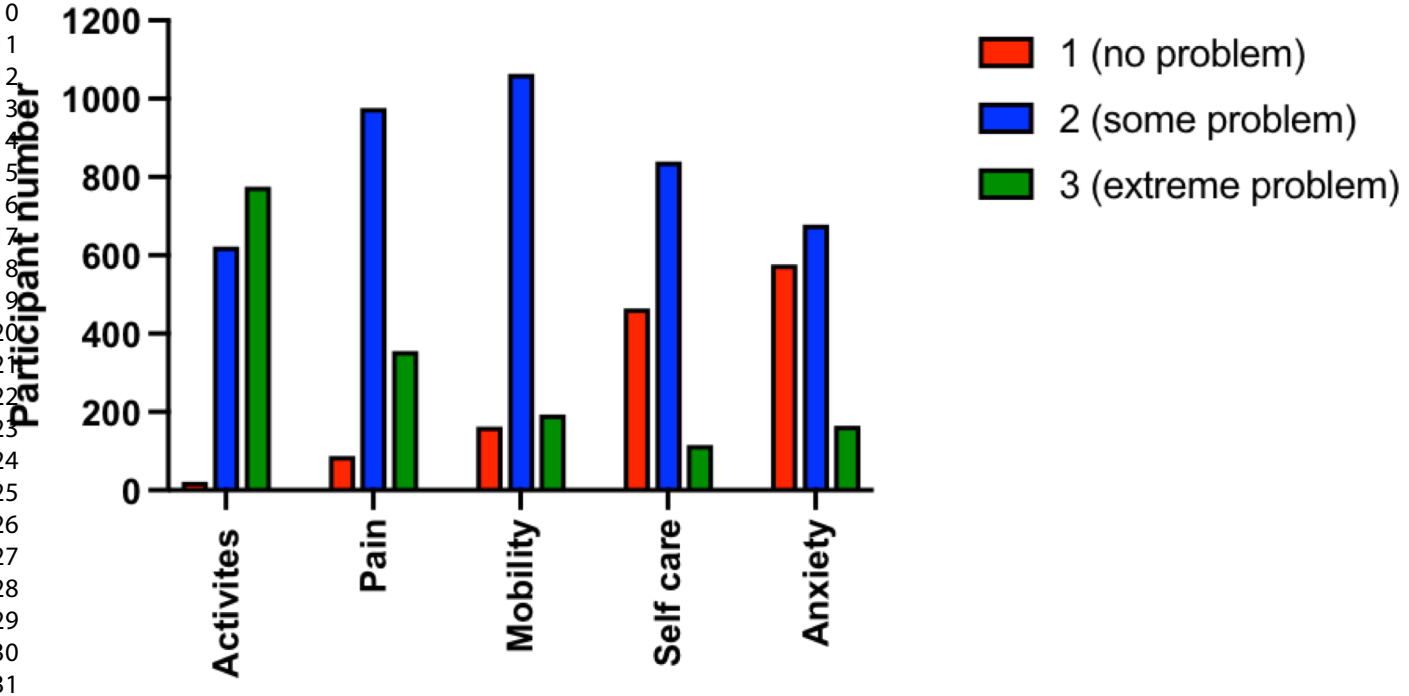
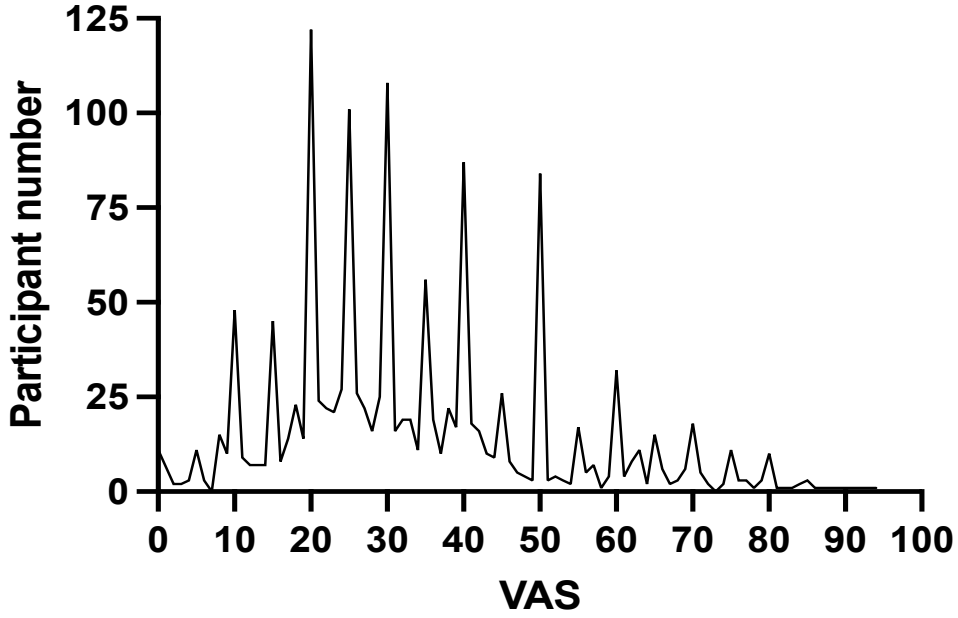
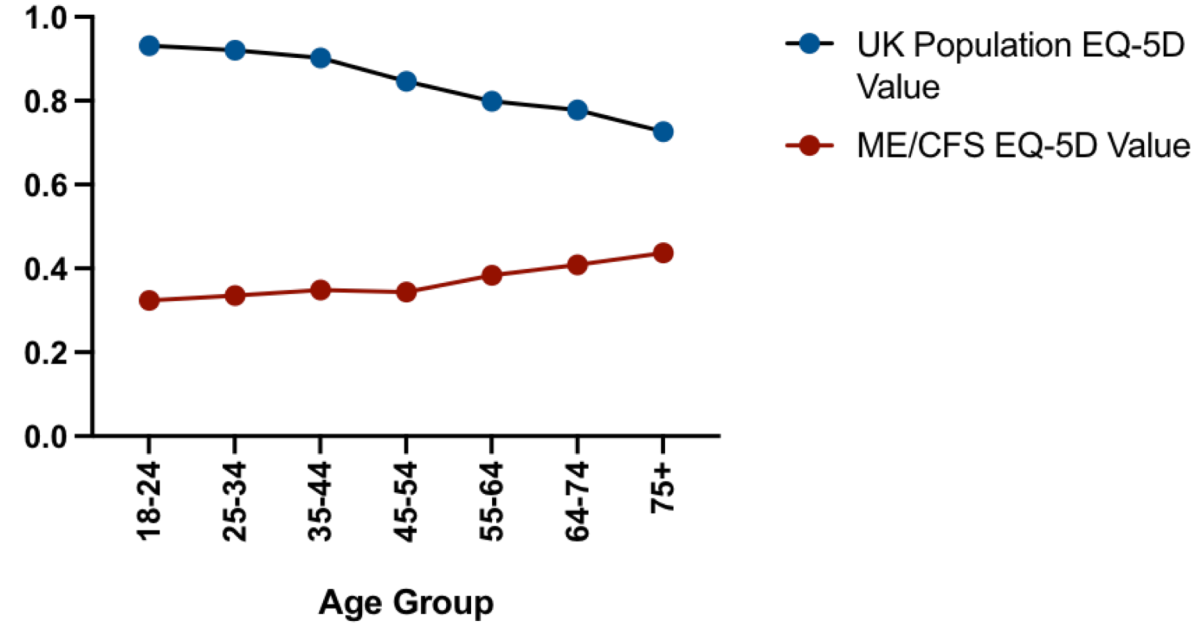
A)


Participant number
1200
1000
800
600
400
200
0
Activites
Pain
Mobility
Self care
Anxiety
1 (no problem)
2 (some problem)
3 (extreme problem)

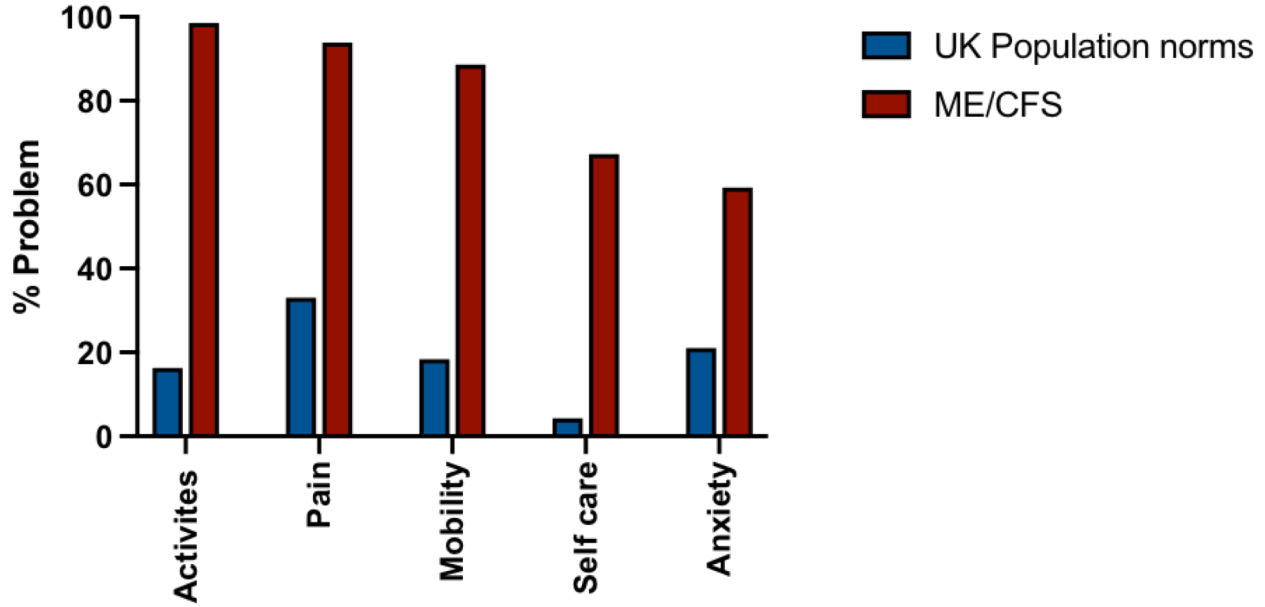
B)


Participant number
125
100
75
50
25
0
0
10
20
30
40
50
60
70
80
90
100
VAS

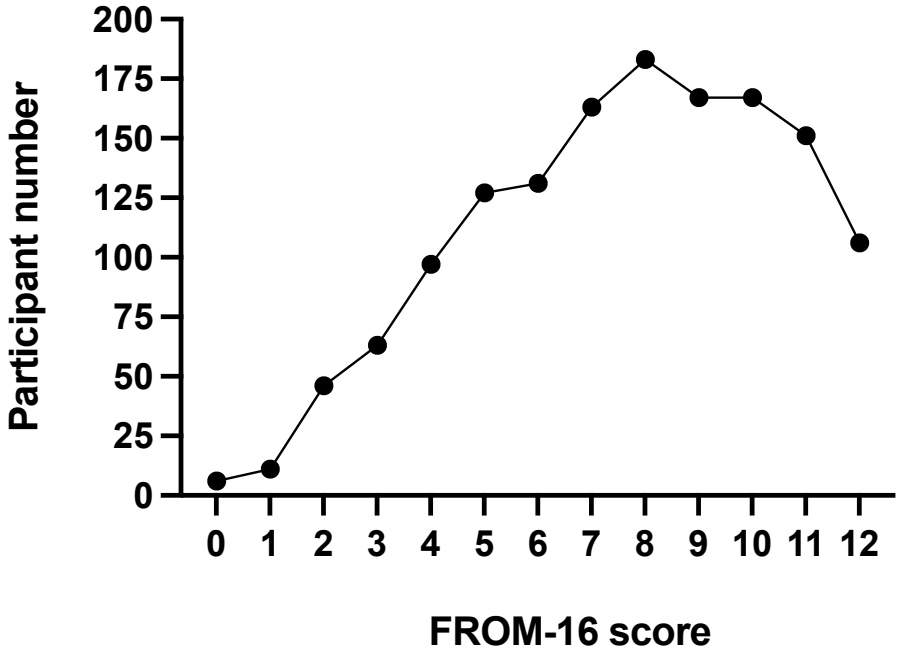
A)


1.0
0.8
0.6
0.4
0.2
0.0
EQ-5D Value
18-24
25-34
35-44
45-54
55-64
64-74
75+
Age Group
UK Population EQ-5D Value
ME/CFS EQ-5D Value

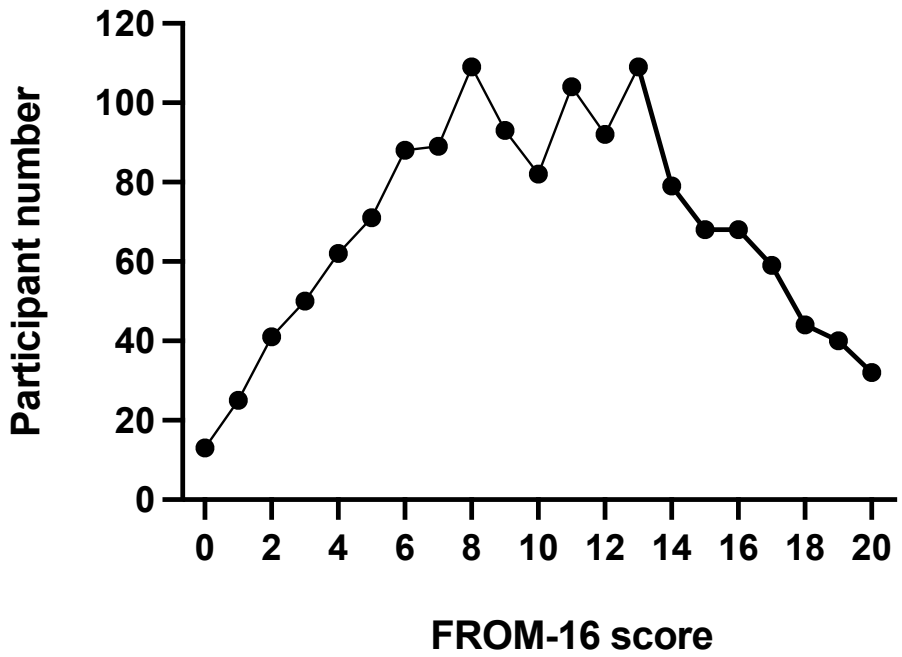
B)


100
80
60
40
20
0
% Problem
Activites
Pain
Mobility
Self care
Anxiety
UK Population norms
ME/CFS

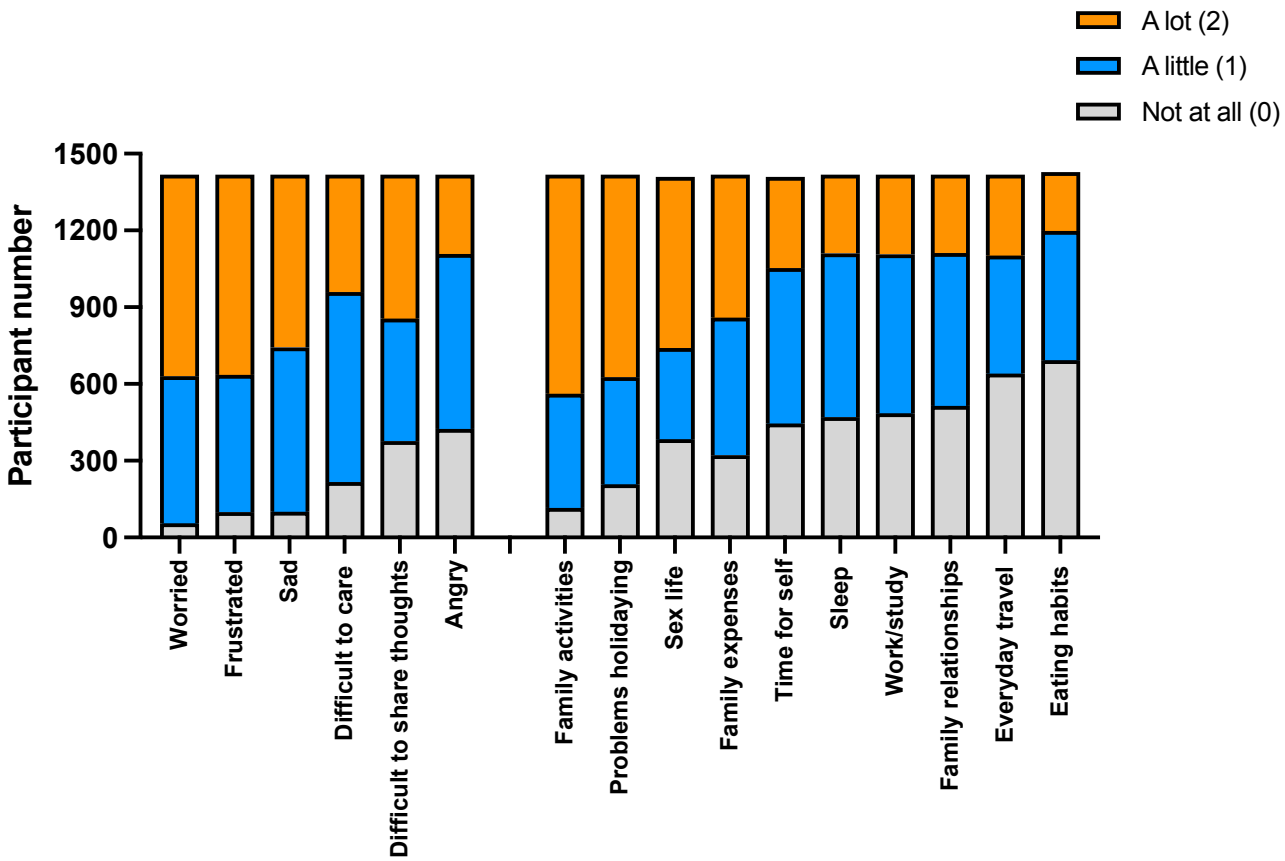
A)


FROM-16 Emotional score
Participant number
200
175
150
125
100
75
50
25
0
0 1 2 3 4 5 6 7 8 9 10 11 12
FROM-16 score

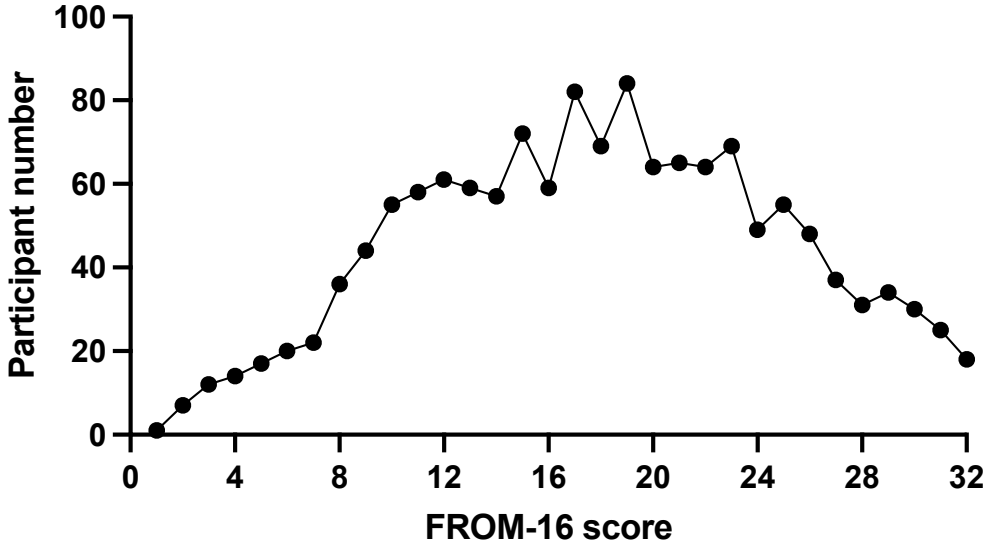
B)

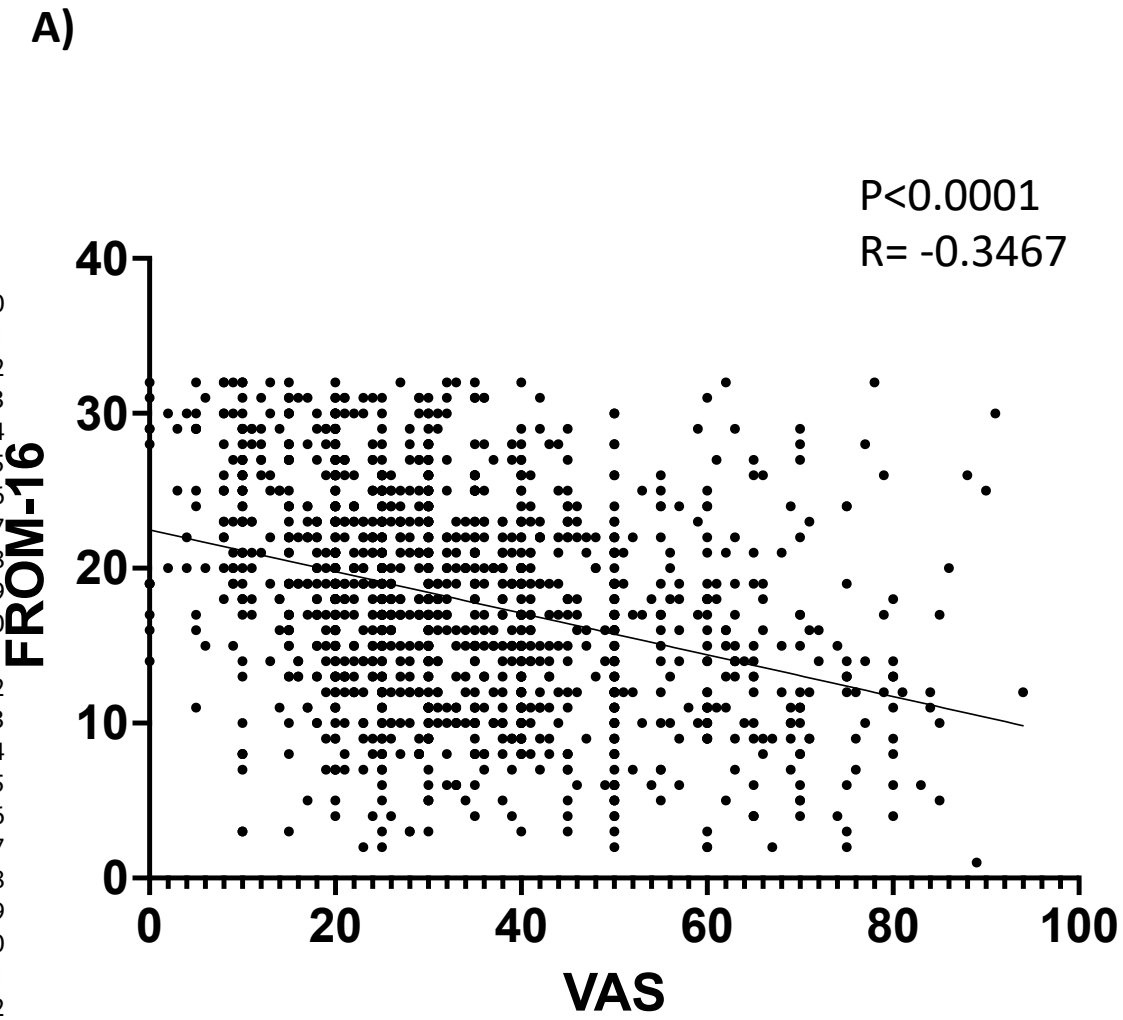

FROM-16 Personal score
Participant number
120
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20
FROM-16 score

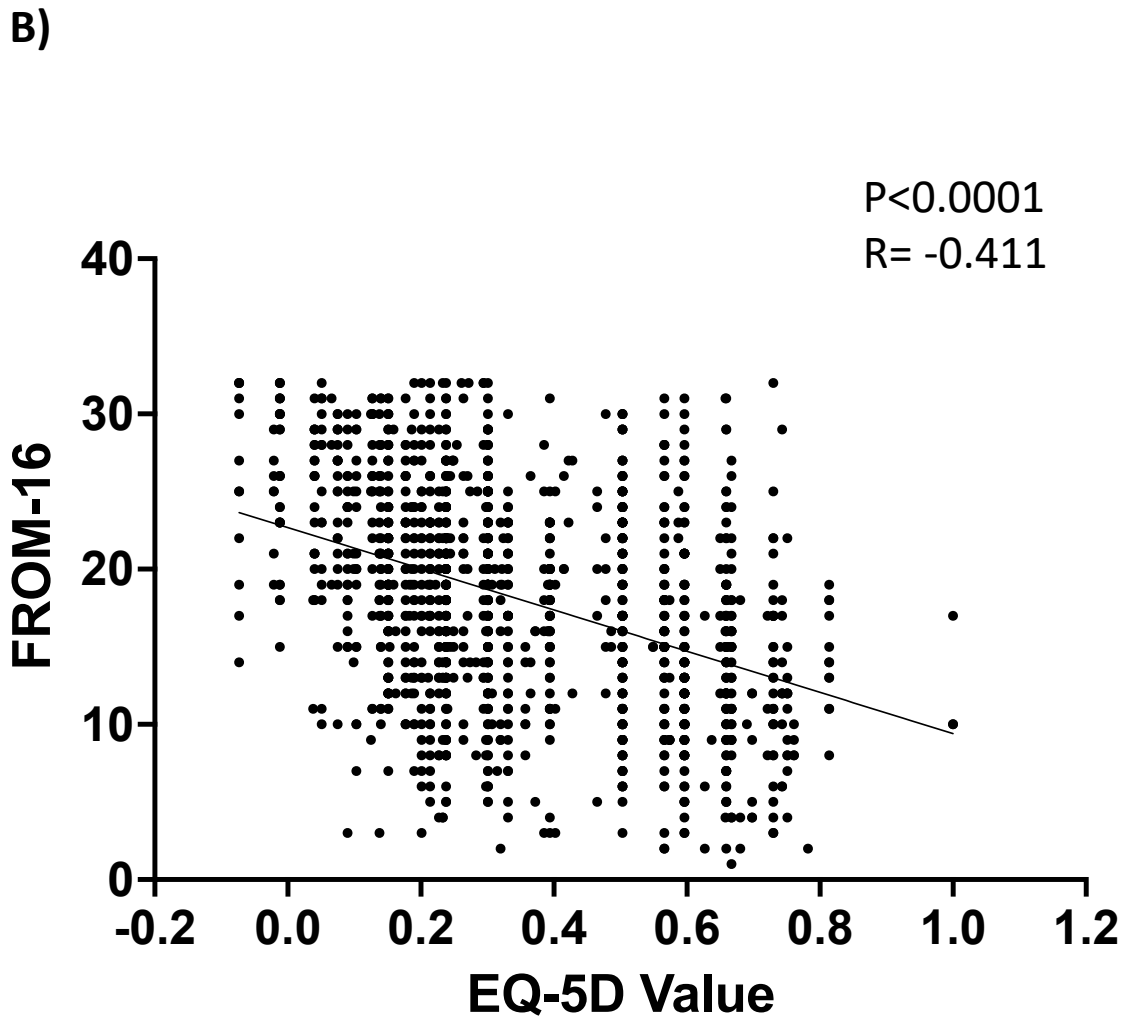
A)


A lot (2)
A little (1)
Not at all (0)
Participant number
1500
1200
900
600
300
0
Worried
Frustrated
Sad
Difficult to care
Difficult to share thoughts
Angry
Family activities
Problems holidaying
Sex life
Family expenses
Time for self
Sleep
Work/study
Family relationships
Everyday travel
Eating habits

B)


Participant number
100
80
60
40
20
0
0
4
8
12
16
20
24
28
32
FROM-16 score


A)
P<0.0001
R= -0.3467
FROM-16
VAS
0
10
20
30
40
0
20
40
60
80
100


B)
P<0.0001
R= -0.411
FROM-16
EQ-5D Value
0
10
20
30
40
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No	Line no
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	7
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	5-31
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	9-17
Objectives	3	State specific objectives, including any prespecified hypotheses	3	27-30
Methods				
Study design	4	Present key elements of study design early in the paper	3	34-41
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 3	26 40-41
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4 3	40-42 34-41
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4	9-27
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4 5	9-27 19-22
Bias	9	Describe any efforts to address potential sources of bias	4 4	31-36 41-42
Study size	10	Explain how the study size was arrived at	5	11-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4	9-27
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5	16-22
		(*b*) Describe any methods used to examine subgroups and interactions	5	19-22
		(*c*) Explain how missing data were addressed	5	27-33
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA	NA
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5	26-35
		(b) Give reasons for non-participation at each stage	NA	NA
		(c) Consider use of a flow diagram	5	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5 6-7	39-43 Table 1, 2
		(b) Indicate number of participants with missing data for each variable of interest	5	26-35 Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	5	26-35

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10	25-33
Discussion				
Key results	18	Summarise key results with reference to study objectives	8 9 10	18-35 Figure 2 1-24 Figure 3-6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	15-25
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13	15-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	12-25
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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